FLUOTHANE SENSITIZATION OF DOG HEART TO ACTION OF EPINEPHRINE

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Fluothane is a potent, volatile, nonexplosive anesthetic agent. Because of its halogenation, one of its possible toxic effects, theoretically, would be similarity to chloroform in sensitizing the heart to the action of epinephrine.

Raventós has described ventricular fibrillation in experimental animals during Fluothane anesthesia when epinephrine was given intravenously (1). There have been several reports in the literature of the use of subcutaneous or intramuscular epinephrine concurrently with Fluothane in humans; Marrett (2), Junkin *et al.* (3), MacKay (4), Burn (5), and Brindle *et al.* (6) reported no serious effects from epinephrine in doses from 0.1 to 1.0 mg.

The following experiments were set up to study the role of Fluothane in epinephrine-induced arrhythmias of the dog heart.

Method

Thirty-seven mongrel dogs in good health were used; they were unselected as to sex, and weighed from 6.8 to 13.2 kg. All dogs were anesthetized with thiopental or Fluothane and their tracheas immediately intubated. They were then transferred from the kennels to the laboratory where various recording instruments were connected.

Respirations were monitored using an endotracheal nonrebreathing system (breathing room air) with the respiratory gases passing through a wire screen flow meter which was connected by means of a Statham pressure transducer, model P-97, to a Sanborn model 150 amplifier-recorder system (7). The nonrebreathing system was attached to a Palmer Ideal pump in such a manner that the spontaneous respiration could be converted immediately to passive hyperventilation by simply turning on the pump, the static resistances being identical in both cases. In this series of experiments, expiration alone was measured. The maximum error in measurement of the minute volume was caused by error of planimetry of ± 4 per cent, although reproducibility fell within ± 2 per cent. The concentration of Fluothane delivered by a Heidbrink Trilene bottle, and in the later experiments by the Fluotec vaporizer, was calculated as previously reported (7).

Blood pressure was monitored by means of a 2 mm. (inside diameter) polyethylene catheter inserted through the femoral artery into

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the abdominal aorta and connected to a Statham transducer, model P-23 AA, which was in turn connected to the Sanborn amplifier-recorder. The tip of the catheter, as verified by autopsy, in most cases fell between the bifurcation of the aorta and the renal arteries. Similarly, a venous catheter of the same size was inserted through the femoral vein into the inferior vena cava. The tip of this, as verified by autopsy, usually fell just below the diaphragm. A slow drip (5 to 10 cc./kg./hour) of glucose 5 per cent in water (just enough for a constant urinary output during light anesthesia) was maintained. This catheter was also used for the administration of the epinephrine solutions.

Lead 2 of the electrocardiogram was recorded continuously. The heart rate was counted from the blood pressure record and electrocardiogram. The fronto-occipital electroencephalogram was also monitored continuously on the Sanborn recorder. A polyethylene catheter was placed in the urinary bladder and the urine output recorded intermittently; the rectal temperature was measured intermittently.

The anesthesia was lightened as much as possible and "control" values were obtained. Anesthesia was then reinduced with either Fluothane or thiopental and allowed to achieve, as nearly as possible a steady state. The level of anesthesia was that necessary for a quiet animal during the femoral surgery, approximately equal to plane 2 of stage 3. When stabilized, all of the physiological parameters were carefully measured and the epinephrine or norepinephrine was administered.

The epinephrine used was Adrenaline (Parke, Davis & Company) assayed as 99.9 per cent pure (8), while the norepinephrine used was Levophed (Winthrop Laboratories) assayed as free of epinephrine (9). The epinephrine or norepinephrine in volumes of 1 cc. or less was introduced by means of a three-way stopcock into the polyethylene catheter in the vena cava. These were then immediately washed in with 4 to 6 cc. of 5 per cent glucose in water, a procedure taking no more than five seconds. This technique was used in order to administer a large dose of the drug directly to the myocardium. In this manner, primary cardiac effects were seen (usually 5 to 10 seconds postinjection) before secondary effects occurred. This separation of primary and secondary effects was not possible with the Meek technique, which consists of injecting 2 μg./kg./10 seconds through the radial vein (10). The assumption was made that with the present technique fairly good mixing was obtained in the right heart and pulmonary circuit before the drug reached the myocardium by way of the coronary arteries. It was assumed, also, that there was no direct effect on the pulmonary bed, which may not have been the case. However, the physiological effects seemed remarkably reproducible with this technique. Geometrically increasing doses (2 to 2½ times the previous dose) were given and enough time allowed to elapse between doses for all of the recorded parameters to return to normal. An attempt was made to find as an

end point, a dose which would produce ventricular tachycardia without fibrillation, although in some cases an unexpected fibrillation occurred.

The dogs were divided into 4 groups, as follows:

Group 1.—Nine dogs received thiopental in a foreleg vein for induction, intubation of their tracheas, and as a continuous intravenous drip to produce a steady state of anesthesia for trial with intravenous epinephrine. The average total dose of thiopental was 74 mg./kg. administered over an average period of three hundred and thirteen minutes. The thiopental drip was then stopped, and, an average of forty-two minutes later, when the dogs seemed nearly awake, Fluothane was begun. The same experiment was then repeated using Fluothane instead of thiopental, in supposedly the same plane of anesthesia (as estimated clinically and by the electroencephalogram).

Group 2.—Seventeen dogs were given a minimal amount of thiopental (21.6 mg./kg.), just enough for tracheal intubation, and then maintained on open drop Fluothane until they could be connected to a Fluothane vaporizer. Intravenous testing with epinephrine was carried out using Fluothane alone. These dogs differed from those in group 1 by undergoing only a very brief period of thiopental anesthesia. An average of one hundred and twenty-one minutes elapsed between the intubation under thiopental and the time when trial with epinephrine was begun.

Group 3.—Seven dogs from groups 1 and 2 were given intramuscular doses of epinephrine or norepinephrine after the arrhythmic threshold for intravenous doses was determined. These injections were made at several sites in the very vascular muscles surrounding the cranium; the total volume of each injection was less than 2 cc. These dogs were maintained at the same plane of anesthesia with Fluothane as for the intravenous injections, judging clinically, by the electroencephalogram, and by the vaporizer setting. The intravenous tests were resumed an average of forty-nine and one-half minutes after the final intramuscular dose, when recovery seemed complete as judged by the recorded parameters.

Group 4.—Eleven other dogs were treated at first exactly as were the 17 dogs in group 2. Following intravenous testing with epinephrine, with spontaneous respirations, the respiratory pump was turned on, and the dogs passively hyperventilated. At this point it was usually necessary to reduce the Fluothane concentration in order to maintain the same level of anesthesia. When the anesthesia seemed stabilized, trial with intravenous epinephrine was repeated. Anesthesia was then educed * by turning off the Fluothane. Small doses of succinylcholine were used to prevent movement (average total dose: 4.9 mg./kg.), and for this purpose a second intravenous drip was begun using a foreleg vein. Intravenous epinephrine was tested a third time;

* Eduction: A term indicating the opposite of induction and used since terms such as "awakening" do not fully cover all of the physiological processes involved. Educe is not a new word; its medical usage has been traced as far back as Bayne, in 1617 (11).

no Fluothane had been given for an average of one hundred and four minutes. Except for any possible effect of the hyperventilation or succinylcholine, the dogs were essentially awake, and the recorded parameters seemed stable.

Then the dogs were reanesthetized with Fluothane to the same level of anesthesia as previously, and the experiment repeated a fourth time.

If the dogs survived this procedure, they were allowed to return to spontaneous respirations at the same level of Fluothane anesthesia and testing with epinephrine was carried out a fifth time.

Results

Figure 1 shows the effect of a subarrhythmic dose of epinephrine in a dog under Fluothane anesthesia. From the time relationship of the injection and responses, it can be seen that the primary effect is an increase of blood pressure and a decrease in pulse pressure. This is usually accompanied by a tachycardia. There is a small, secondary, relative hypotension and increased pulse pressure. In figure 1, this is

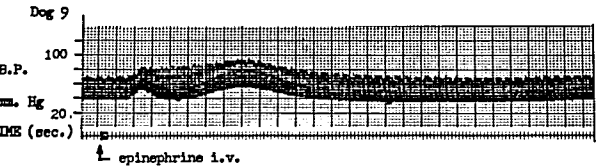

FIG. 1. This shows a typical effect of a subarrhythmic dose of epinephrine in a dog which had been receiving 1.81 per cent Fluothane for thirty-five minutes. The arrow points to an artifact in the time line which indicates exactly when 5 μg. (0.46 μg./kg.) of epinephrine were introduced into the inferior vena cava. See figure 2B.

most apparent in the diastolic pressure. There is sometimes a tertiary pressure response.

Figure 2 shows two examples of ventricular fibrillation, both demonstrating the onset of this arrhythmia ten to fifteen seconds after the epinephrine injection, one showing a lack of any marked hypertension before the fatal arrhythmia.

Figure 3 shows two examples of the spontaneous reversion of ventricular fibrillation to an atrial rhythm. This must be rare. The blood pressure curve during ventricular fibrillation suggests fibrillation (rather than multiple ectopic beats or ventricular tachycardia) even before a diagnosis of fibrillation is certain by electrocardiogram.

Of the 9 dogs in group 1, none died under thiopental anesthesia when tested with intravenous epinephrine, but 7 died of ventricular fibrillation under Fluothane anesthesia when tested with intravenous epinephrine. The average fatal dose of epinephrine was 4.63 μg./kg., and the average concentration of Fluothane in the inspired air was 1.0 per cent. Fibrillation occurred unexpectedly in 1 of these dogs (table

1). That is, the previous dose of epinephrine produced no arrhythmias, warning of ventricular fibrillation with the next higher dose. The dose of epinephrine given them while under thiopental anesthesia was an average of 8.3 times greater than the fatal dose they received while under Fluothane anesthesia.

All but one of the 17 dogs in group 2 died of ventricular fibrillation under Fluothane anesthesia. Thirteen died with an average epinephrine dose of 5.10 μg./kg. Six dogs were administered norepinephrine and 3 of them died with an average fatal dose of 24.6 μg./kg. (This latter group is too small a series to be significant quantitatively.) The dogs in group 2 had an average concentration of 1.36 per cent of Fluothane in the inspired air. Thirty-three per cent of the dogs in group 2 died of ventricular fibrillation unexpectedly (table 1). This is compared with 11 per cent unexpected fibrillations in group 1, where a larger dose of thiopental had been given (table 1). However, the fatal dose of epinephrine was nearly the same in the thiopental-Fluothane dogs as in the Fluothane-only dogs (4.63 and 5.10 μg./kg., respectively).

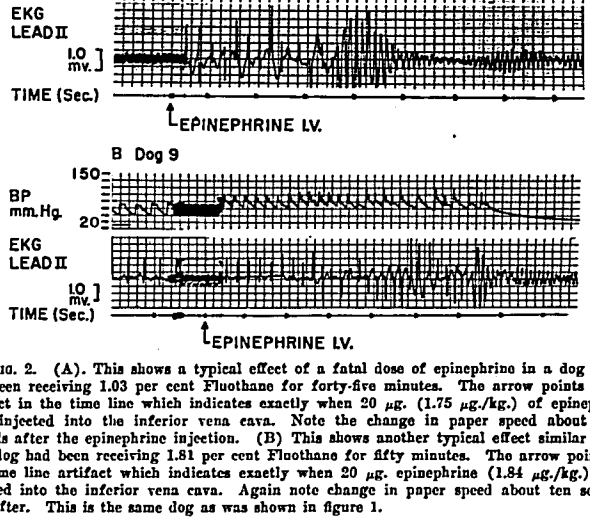

FIG. 2. (A). This shows a typical effect of a fatal dose of epinephrine in a dog which had been receiving 1.03 per cent Fluothane for forty-five minutes. The arrow points to the artifact in the time line which indicates exactly when 20 μg. (1.75 μg./kg.) of epinephrine were injected into the inferior vena cava. Note the change in paper speed about eight seconds after the epinephrine injection. (B) This shows another typical effect similar to A. This dog had been receiving 1.81 per cent Fluothane for fifty minutes. The arrow points to the time line artifact which indicates exactly when 20 μg. epinephrine (1.84 μg./kg.) were injected into the inferior vena cava. Again note change in paper speed about ten seconds thereafter. This is the same dog as was shown in figure 1.

Six of the dogs from groups 1 and 2 were given epinephrine intramuscularly with an average maximum dose of 262 μg./kg. (table 2).

The most severe arrhythmia occurred within three to four minutes and showed improvement within ten to twenty minutes after the injection.

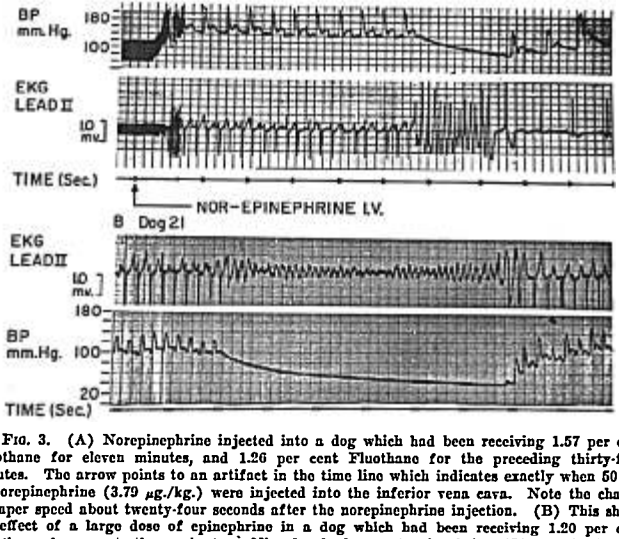

FIG. 3. (A) Norepinephrine injected into a dog which had been receiving 1.57 per cent Fluothane for eleven minutes, and 1.26 per cent Fluothane for the preceding thirty-four minutes. The arrow points to an artifact in the time line which indicates exactly when 50 mg. of norepinephrine (3.79 μg./kg.) were injected into the inferior vena cava. Note the change in paper speed about twenty-four seconds after the norepinephrine injection. (B) This shows the effect of a large dose of epinephrine in a dog which had been receiving 1.20 per cent Fluothane for seventy-three minutes. Nine hundred μg. of epinephrine (76.3 μg./kg.) were given ten seconds (not shown) before the beginning of this excerpt. This dog had previously been tested during thiopental anesthesia, and recovery from fibrillation might represent a tolerance to epinephrine. A total of 1,060 mg. of thiopental had been given, the last eighty-four minutes before this dose of epinephrine.

TABLE 1

SENSITIVITY TO EPINEPHRINE AND NOREPINEPHRINE DURING ANESTHESIA

Group	Thiopental mg./kg.	Unexpected Fibrillation	
		Epinephrine (per cent)	Norepinephrine (per cent)
Thiopental only (9 dogs) (group 1)	74.0	0/9 = 0	—
Thiopental, then Fluothane (group 1)	the same	1/9 = 11	—
Fluothane (17 other dogs) (group 2)	21.6	5/15 = 33	2/6 = 33

This table shows the incidence of unexpected ventricular fibrillation in dogs which had received thiopental only (group 1), thiopental and then Fluothane (group 1) and Fluothane only (group 2). The numerators in the fractions in the last 2 columns give the number of dogs that died of ventricular fibrillation unexpectedly. The denominator indicates the total number of dogs in the experiment.

TABLE 2

Intramuscular Epinephrine and Norepinephrine During Fluothane Anesthesia

Dog No.	Fluothane in Air (per cent)	Epinephrine (µg./kg.)		Norepinephrine (µg./kg.)	
		Fatal I.V. Dose	Max. I.M.	Fatal I.V. Dose	Max. I.M.
5	1.25	4.06	163	—	—
6	1.13	3.80	—	—	152
9	1.70	16.90	170	—	170
10	1.07	5.00	200	—	100
11	1.53	—	611	61.1	244
17	.81	—	231	—	—
26	.50	5.00	200	—	—
Averages	1.14	6.95	262	61.1	167

Results from intramuscular epinephrine or norepinephrine in 7 dogs. The second column from the left lists the percentage of Fluothane, in air, which the dogs had been breathing for an average time of forty-five minutes. The fourth and sixth columns list the maximum intramuscular doses.

None of the dogs died of ventricular fibrillation, but all of them had severe arrhythmias such as occurred on the prefibrillatory intravenous doses. The average fatal intravenous dose of epinephrine for the same dogs was 6.95 µg./kg. If the dogs had had ventricular fibrillation on the intramuscular doses, it could be said that the safety factor between intramuscular and intravenous doses was 39. Since the dogs survived the intramuscular doses, however, these doses should be compared with the intravenous doses producing the severe, but not fatal, arrhythmias. This gives a safety factor of 159. That is to say, an intramuscular dose 159 times greater than a given intravenous dose produced the same physiological effect. This seemed to be a constant ratio. One hundred and sixty-seven µg./kg. of norepinephrine produced similar results in 4 dogs (table 2).

In order to study any possible effect of hypoxia or hypercapnia due to the respiratory depressive effect of Fluothane anesthesia, the minute volumes of the 16 dogs in group 2 at the time of the fatal dose are shown in table 3. It can be seen that there was a large individual "control" variation with an average minute volume of 4.42 l./minute. Under Fluothane anesthesia, just prior to the injection of epinephrine, the average minute volume ratio was 0.91 with a range of 0.62 to 1.48. (Ratio indicates experimental/control.)

To study this further, 11 additional dogs in group 4 were treated, at first, just as were the dogs in group 2. In step 1, (table 4) the 11 dogs, which were intentionally not taken beyond the subfatal dose (in that series 1.54 µg./kg.), had an average minute volume ratio of 0.80. They were then passively hyperventilated with an average minute volume ratio of 1.70, or double that on spontaneous respirations (step 2). Four of the 11 dogs died of ventricular fibrillation when tested with epinephrine, the dose being 4.04 µg./kg. The 7 surviving dogs

TABLE 3

RESPIRATION PRIOR TO FATAL DOSES OF EPINEPHRINE AND NOREPINEPHRINE

Dog	Fluothane in Air (per cent)	Fatal Dose (μg./kg.)		Minute Volume	
		Epinephrine	Norepinephrine	Control, Liters/Minute	Ratio
1	1.39	5.0		2.49	1.15
2	1.65	2.2		4.45	.62
3	1.03	1.8		5.20	.86
4	.88	.9		3.84	.75
5	.83	4.1		5.24	.99
6	1.13	3.8		2.25	1.48
7	1.89	—	8.5	4.42	.86
8	.96	—	4.1	4.77	.73
9	1.81	16.9		3.32	1.22
10	1.10	5.0		2.99	.64
11	1.64	—	61.1	2.91	.83
12	1.66	3.9		4.57	.70
13	1.81	1.8		3.01	.73
14	1.07	15.7		12.90	1.29
15	1.34	4.4		6.00	.86
16	1.50	.9		2.32	.88
Averages	1.36	5.1	24.6	4.42	.91

The respiration of group 2 dogs under Fluothane anesthesia at the time of fatal doses of epinephrine and norepinephrine. The column which is second from the right lists the "control" minute volumes in liters/minute when the dogs were "awake" prior to induction with Fluothane. The right-hand column indicates the minute volume ratio (experimental/control) immediately prior to the injection of epinephrine or norepinephrine

were then educed and kept on passive hyperventilation with the aid of succinylcholine (step 3). The minute volume ratio averaged approximately 1.80. The average maximum dose of epinephrine was increased to 55 μg./kg. with no fatalities. In step 4, anesthesia was reinduced, the dogs still being passively hyperventilated, with a minute volume ratio of 1.70. Six of these 7 dogs then died of fibrillation with an average epinephrine dose of 10.19 μg./kg. In step 5, the one hardy survivor was allowed to return to spontaneous respirations, and anesthesia was deepened to the point that the minute volume ratio was only 0.15. This dog died of ventricular fibrillation after a dose of 122 μg./kg. of epinephrine. Fluothane in the inspired air in step 1 averaged 1.33 per cent; step 2, 0.96; step 4, 1.01 per cent; and step 5, 2.15 per cent.

Table 5 shows blood pressure data from the 30 dogs dying of ventricular fibrillation after administration of epinephrine during Fluothane anesthesia. Both the systolic and diastolic blood pressure ratios show a depression of about 25 per cent due to Fluothane anesthesia with a fairly wide individual variation. The maximum blood pressures before the onset of fibrillation show an increase of about 25 per cent with a decrease of pulse pressure, again with a wide individual variation. The maximum blood pressure rise in subfatal doses, however, was in the same range as in the case of the fatal doses.

TABLE 4

ROLE OF VENTILATION IN SENSITIVITY TO EPINEPHRINE DURING FLUOTHANE ANESTHESIA

Experimental Condition	Number of Dogs	Fluothane in Air, Average (per cent)	Minute Volume, Average Ratio	Epinephrine, Average Fatal Dose (μg./kg.)
1. Fluothane, spontaneous respiration	11	1.33 ± .39	.81 ± .19	(none died; no maximum dose) 1.25 ± .22)
2. Fluothane, hyperventilation	11	.97 ± .18	1.66 ± .58	4.04 (N = 4)
3. Fluothane off; succinylcholine on, then off	7	0	1.80	(none died; no maximum dose) 55.5)
4. Repeat Step 2	7	1.01	1.77	10.19 (N = 6)
5. Repeat Step 1	1	2.51	.15	12.2 (N = 1)

The dogs were carried through 5 steps as indicated in the left-hand column. As can be seen in the next column, 11 dogs survived the first step, and 4 of them died during the second step. All the remaining 7 dogs survived the third step and 6 of them died during the fourth step. The one remaining survivor died during step 5. The third column from the left indicates the average per cent of Fluothane, in air, which the dogs were breathing in each step. The fourth column gives the average minute volume ratios. Ratio indicates experimental/control, experimental being the minute volume immediately prior to the epinephrine injection, and "control" being the "awake" minute volume. The ± symbols indicate standard deviation. The right-hand column indicates the average fatal dose of epinephrine in μg./kg. In steps 1 and 3, since none of the dogs died, the maximum dose given was indicated, instead of the fatal dose. In this column, "N" indicates the number of dogs that died in each step.

DISCUSSION

There are many ways in which an anesthetic drug may exhibit its toxicity on the heart. One of these is by increasing the irritability of the heart muscle, or by increasing the automaticity of specialized tissues, particularly in the ventricle. Epinephrine provides a useful tool to study this, since it can be used to produce a standard degree of cardiac irritability. When added to the effect of drugs such as the halogenated hydrocarbons, severe ventricular arrhythmias may occur (10).

TABLE 5

Time	Blood Pressure (Ratio)	
	Systolic	Diastolic
Before fatal dose	.74 ± .13	.75 ± .25
Maximum after fatal dose, but before onset of fibrillation	1.25 ± .27	1.34 ± .36
Maximum after subfatal doses; no fibrillation	1.25 ± .27	1.27 ± .32

The hypertensive effect of a fatal dose of epinephrine in 30 dogs under Fluothane anesthesia. Ratio indicates experimental/control. The first line indicates the blood pressure ratio just before the fatal epinephrine injections.

The experiments presented here suggest that Fluothane did increase the sensitivity of the heart to the effect of epinephrine and norepinephrine. This is in agreement with Raventós, who placed Fluothane between cyclopropane and chloroform in this regard (1). It can be seen that thiopental did not increase the irritability of the dog heart as did Fluothane, at least at similar anesthetic levels.

From a practical standpoint, one might wonder if there are drugs other than epinephrine which will give desirable surgical results with local infiltration, without producing increased cardiac irritability. As some believe that norepinephrine does not increase cardiac irritability (12), this drug was tested in the same manner as epinephrine. In the 6 dogs tested in this series, norepinephrine and epinephrine had similar effects during Fluothane anesthesia. Surks and Luger, however, used norepinephrine infusions during cyclopropane anesthesia in humans without any cardiac arrhythmias. They used an infusion rate of 8–24 μg./minute, but did not have a comparable series with epinephrine (13).

There were no fatal arrhythmias in the 7 dogs tested with intramuscular epinephrine, although the injections were made into very vascular areas. From the ratio of 1:159 between intravenous and intramuscular doses, one might predict that an intramuscular dose of 159 mg. would give the same blood level as would 1 mg., intravenously, with this technique.

The results in tables 3 and 4 suggest that hypoxia and hypercapnia did not play a significant role in the increased sensitivity of the heart to the effect of epinephrine in this series. Severe hypoxia and hypercapnia, however, as were probably present in the dog in step 5, table 3, probably do contribute to this sensitivity. It seemed unlikely that the arrhythmias were secondary to hypertension, as suggested by Raventós (1). Whether the combination of epinephrine and Fluothane interferes in any way with the coronary blood flow, however, remains to be investigated.

On the basis of the present experiments, one might estimate the fatal intravenous dose of epinephrine in an average (70 kg.) man to be 350 μg. (1/3 mg.). If used intramuscularly, this fatal dose would then become about 55 mg., unless accidental intravenous injection occurred. However, it is well known that the human heart is much less prone to fibrillation than is the dog heart. The effect of intramuscular epinephrine during Fluothane anesthesia in chimpanzees is being investigated in this laboratory, and no arrhythmias have resulted so far. These experiments will be reported later. The chimpanzee heart is probably more like that of man and less irritable than the dog heart. Since the large doses of epinephrine mentioned above would never be used clinically, there is probably no absolute contraindication to using Fluothane and epinephrine concurrently. A series of neurosurgical patients receiving intramuscular epinephrine, and Fluothane, is being observed

in this laboratory. The electrocardiogram and blood pressure are being carefully observed during and immediately following the injections. No arrhythmias have been found to date. However, it is suggested that this combination be withheld in any patient with cardiovascular disease until further experience has been gained.

Summary

Intravenous and intramuscular doses of epinephrine and norepinephrine were given to 37 dogs under various conditions. Fluothane increased the sensitivity of the dog heart to the effect of epinephrine and norepinephrine. Under similar conditions, thiopental did not increase the sensitivity of the dog heart to the effect of epinephrine.

Intramuscular administration of epinephrine and norepinephrine produced serious, but never fatal, arrhythmias in dogs under Fluothane anesthesia. It required 159 times the intravenous dose to produce a similar effect intramuscularly.

The respiratory depression from Fluothane anesthesia and the hypertensive effects of the epinephrine did not seem to play a significant part in the increased cardiac sensitivity.

There does not seem to be an absolute contraindication to using Fluothane and epinephrine in normal, healthy patients. It is suggested, however, that epinephrine be omitted in the presence of cardiovascular disense.

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