STUDIES ON THE EFFECT OF THE ACTION OF DIGITALIS ON THE OUTPUT OF BLOOD FROM THE HEART.

II. The Effect on the Output of the Hearts of Dogs Subject to Artificial Auricular Fibrillation

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That an effect of giving digitalis to normal unanesthetised dogs is to decrease cardiac output and size, and to increase the extent of ventricular contractions has previously been reported (1). To study in dogs, phenomena comparable with heart failure with edema in human beings, experiments were undertaken employing several methods. The one finally adopted was to bring about, artificially, insufficiencies of the mitral valve (2). After a lesion had been made by operation, the hearts increased in size. The dogs exhibited no signs of heart failure, however, and were able to run on a treadmill as normal dogs do. When digitalis was given to them, the results were similar to those occurring in normal dogs. These were decrease in cardiac output and cardiac size, and increase in the extent of ventricular excursions (2). A situation was, however, still wanting, in which to test the effect of giving digitalis to animals the hearts of which were in a poor state functionally, a situation, in short, in which the output of blood per minute from the heart was diminished and the heart dilated. Stewart and Gilchrist (3) and Stewart and Crawford (4) have shown that such a situation could be managed. They found that when the hearts of normal dogs were made subject to auricular fibrillation, artificially induced, the volume output of blood per minute from the heart diminishes (3), and dilatation of the heart, detected by increase in size of its shadow in x-ray photographs, may occur (4). These changes, decrease in output and increase in size of the heart, were already present one hour after the onset of auricular fibrillation. Here then was a preparation suitable for testing in dogs the effect of giving digitalis when the functional capacity was diminished. In this report there are described, accordingly, observations on the effect of giving digitalis on the cardiac output per minute, cardiac size, ventricular and femoral pulse rates per minute in unanesthetized trained dogs during auricular fibrillation.

METHODS

All the dogs were trained to breathe in a Benedict-Roth spirometer for 20 to 30 minutes a day for ten days to two weeks before they were used. At the end of this time they lay quietly on the table without emotional disturbance, while measurements of oxygen consumption were made and other procedures were carried out. It was possible to decide at the first or second trial whether a given dog was a satisfactory subject. In the technique of measuring oxygen consumption, the rubber mask described by Blalock was used (5).

The operative procedure has already been described (6). Briefly, wire electrodes were sutured to the right auricle (Figure 1). The opera-

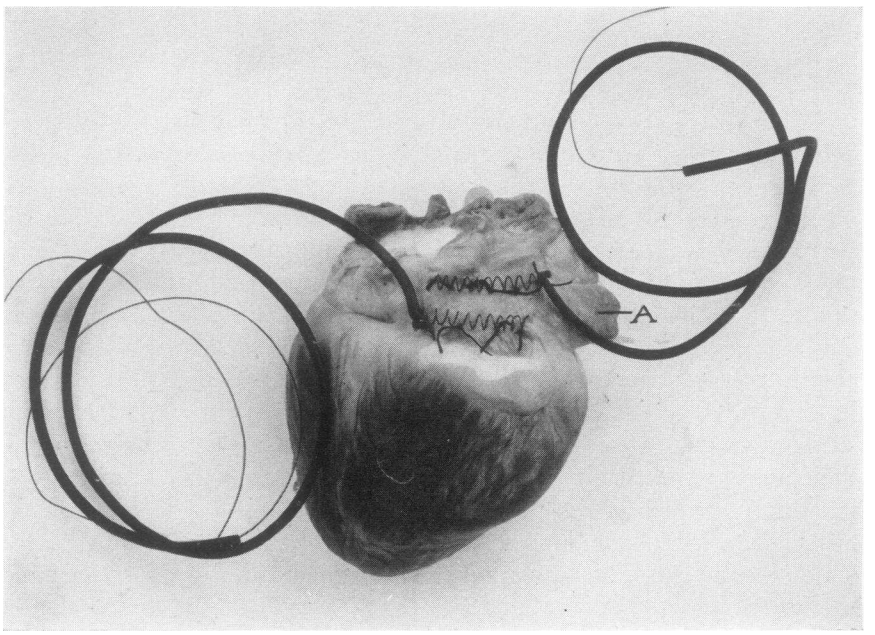


FIG. 1. THIS FIGURE SHOWS THE MANNER IN WHICH THE SPIRAL WIRE ELECTRODES WERE SUTURED TO THE RIGHT AURICLE
A is the right auricular appendix.

tions were performed with sterile precautions, the dogs being anesthetized with ether given by the intratracheal method. After recovery from the preliminary operation, the auricles of the heart were made to fibrillate by stimulating them through these electrodes with faradic current obtained from one to three dry cell batteries placed in the primary circuit of a DuBois-Reymond induction coil. In order to be certain that the auricles were fibrillating, as well as to calculate the number of effective beats, a tracing of the femoral pulse was recorded simultaneously on the same film with an electrocardiogram (Figure 2)(7). The femoral pulse was

transmitted by rubber tubing from a rubber cuff applied to the right hind-leg through an Erlanger capsule modified by Kolls (8), and Kubie (9), to a Frank capsule placed in front of the camera. The rubber cuff on the leg was inflated with air to a pressure near the diastolic level. The movements of a beam of light focused on a mirror glued to the membrane of the Frank capsule were reflected to the lens of the camera and were traced on the moving sensitive film simultaneously with the electrocardiogram. Nonpolarizable electrodes were placed on the right fore-leg and the left hind-leg for the derivation of Lead II of the electrocardiogram.

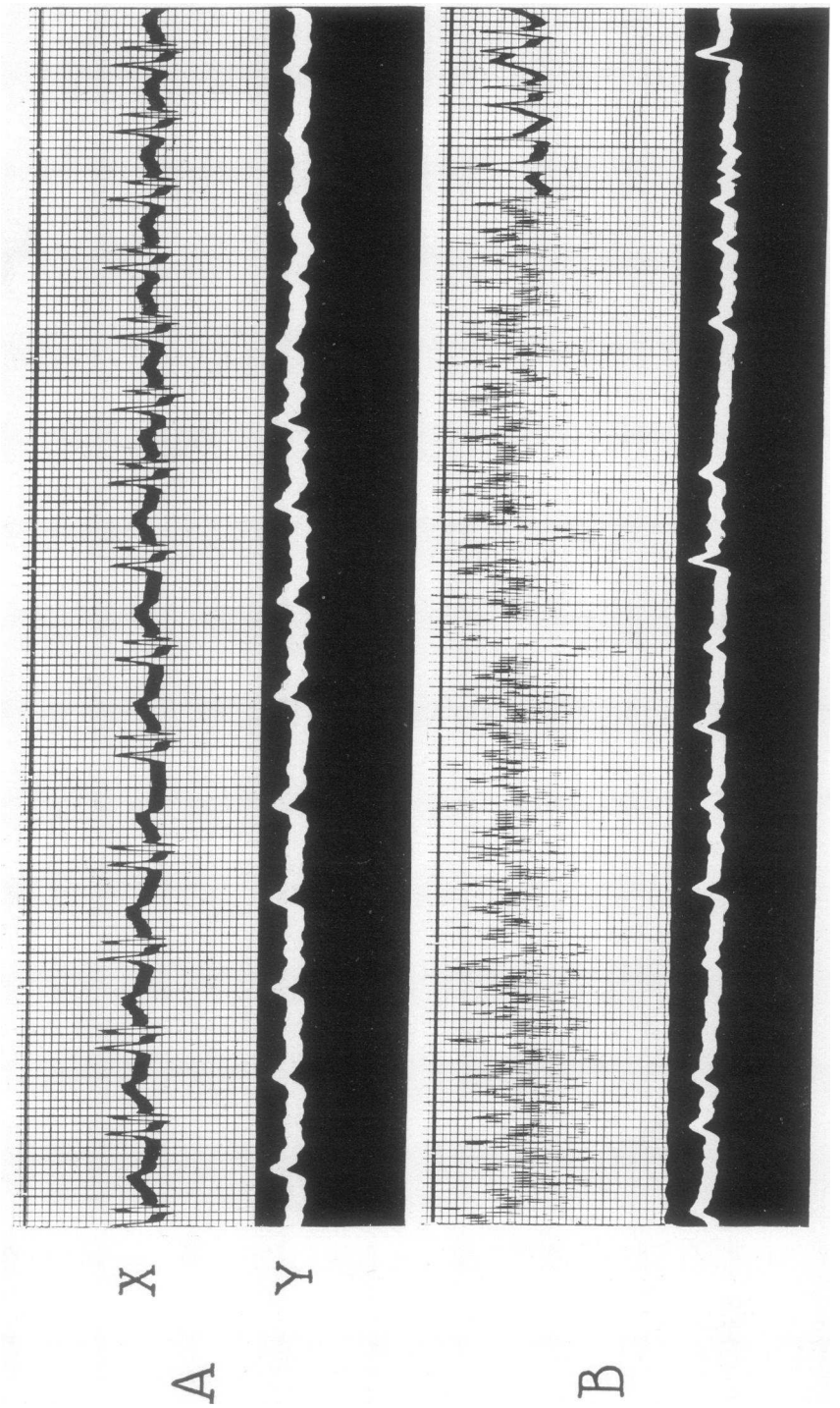
Samples of arterial blood were drawn from a femoral artery and those of mixed venous blood from the right ventricle by a special cannula inserted into that chamber through the right external jugular vein (10). The oxygen contents of these samples were estimated by the Van Slyke and Neill manometric method (11) for calculation of the arteriovenous oxygen differences. Immediately after the blood samples were drawn, the oxygen consumption was measured with a Benedict-Roth spirometer equipped with a graphic recording drum. Data were available, therefore, for calculating the minute volume output of the heart according to the Fick principle (12).

X-ray photographs of the heart taken at a distance of 2 meters were made according to the method described by Stewart for obtaining photographs of the hearts of dogs under uniform conditions. The x-ray shadows of the heart were traced on thin paper and the areas measured with a planimeter (13).

Plan of observations

The day after the preliminary operation the following observations were made. The dogs, in a basal metabolic state, lay quietly on the table without anesthesia. A set of observations consisting of: an x-ray photograph of the heart, samples of arterial and of mixed venous blood, measurement of oxygen consumption, and electrocardiograms together with simultaneous femoral pulse tracings, was taken during the period of normal cardiac rhythm, hereafter called the "period of normal rhythm." Taking a complete set of observations required usually 30 to 45 minutes. The right auricle was then made subject to fibrillation. At the end of approximately one hour, designated the "period of auricular fibrillation," while the auricles were still fibrillating, a second set of observations was made. Then, while this rhythm was maintained by continuing faradic stimulation, tincture of digitalis (Upsher Smith) was injected intravenously in an amount calculated to be 25 to 30 per cent of the lethal dose.[1]

[1] This amount was chosen because Robinson and Wilson (14) found the therapeutic dose of digitalis for cats to be 30 per cent of the calculated lethal dose, and because Cohn (15) found that the dose for cats must be multiplied by the factor 1.16 to arrive at a comparable quantity for dogs. We have accordingly injected this amount of the tincture. To several dogs we administered digifoline (Ciba) 0.5 cc. per kilogram of body weight (16, 17). The same phenomena resulted irrespective of the preparation that was given.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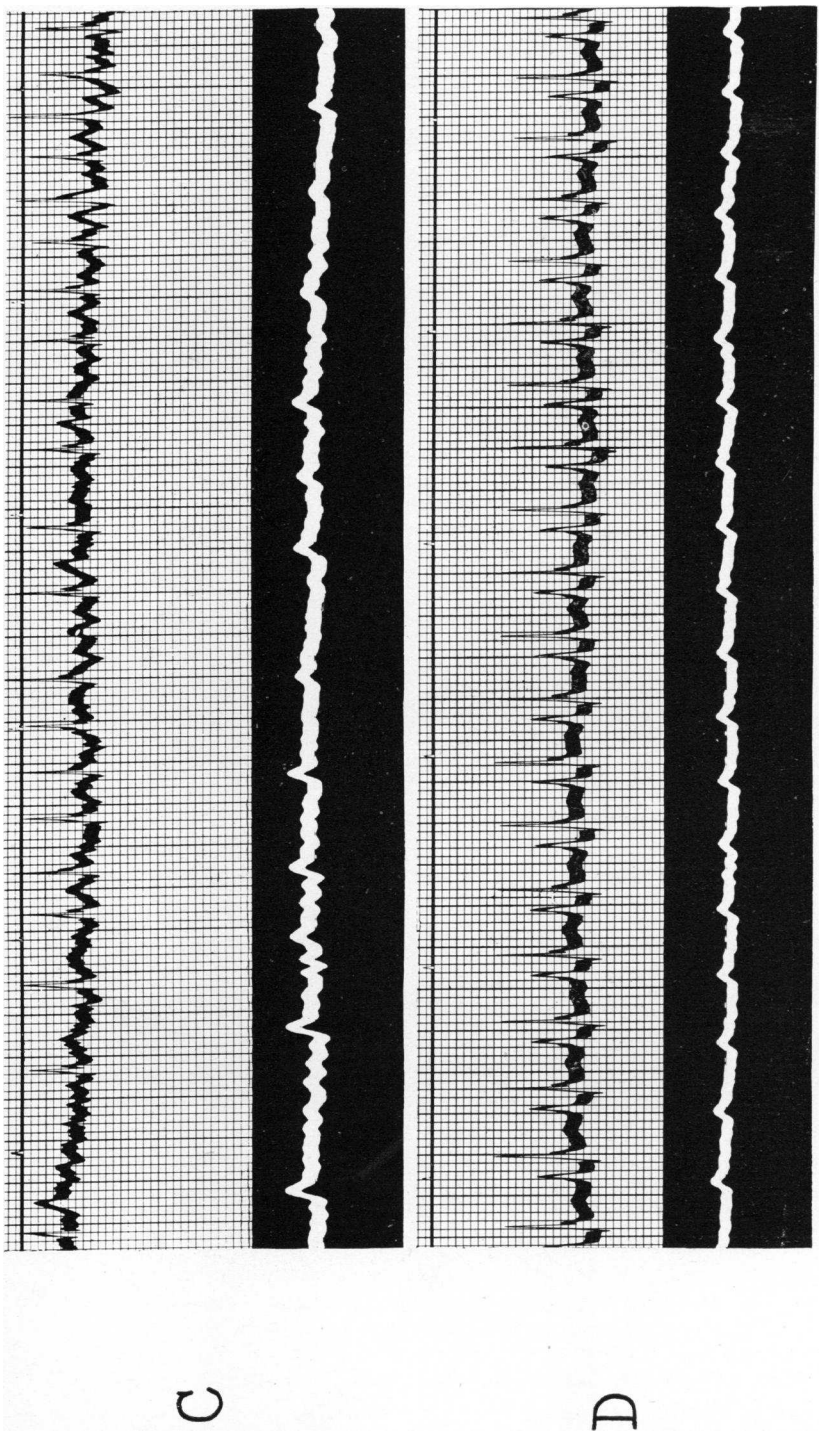

FIG. 2. IN THIS FIGURE ARE SHOWN THE RECORDS OF DOG 231, TAKEN ON APRIL 14, 1927

A was taken when the rhythm was normal; *B*, during and after auricular fibrillation had been present 71 minutes; *C*, 200 minutes after the onset of auricular fibrillation and 105 minutes after the injection of tincture of digitalis (Upsher Smith) 2.0 cc. intravenously; and *D*, 81 minutes after the return to the normal rhythm, and 210 minutes after injecting digitalis. *X* is the electrocardiogram (Lead II) and *Y* the femoral pulse tracing. A short time interval elapses between the beginning of the QRS complex of the electrocardiogram and the corresponding femoral pulse, due partly to the time required for transmission of impulses from the heart to the femoral artery, and partly to that from the rubber cuff to the Frank capsule. In the femoral pulse tracing taken during auricular fibrillation (*B* and *C*) attention is called to the variation in the excursion of the femoral pulse from beat to beat. In this figure divisions of the ordinates equal 10^{-4} volts; divisions of the abscissae equal 0.04 of a second. The original curves are sharply contrasted black and white; no half tones are lost by the method of reproduction. The curves are reproduced full size.

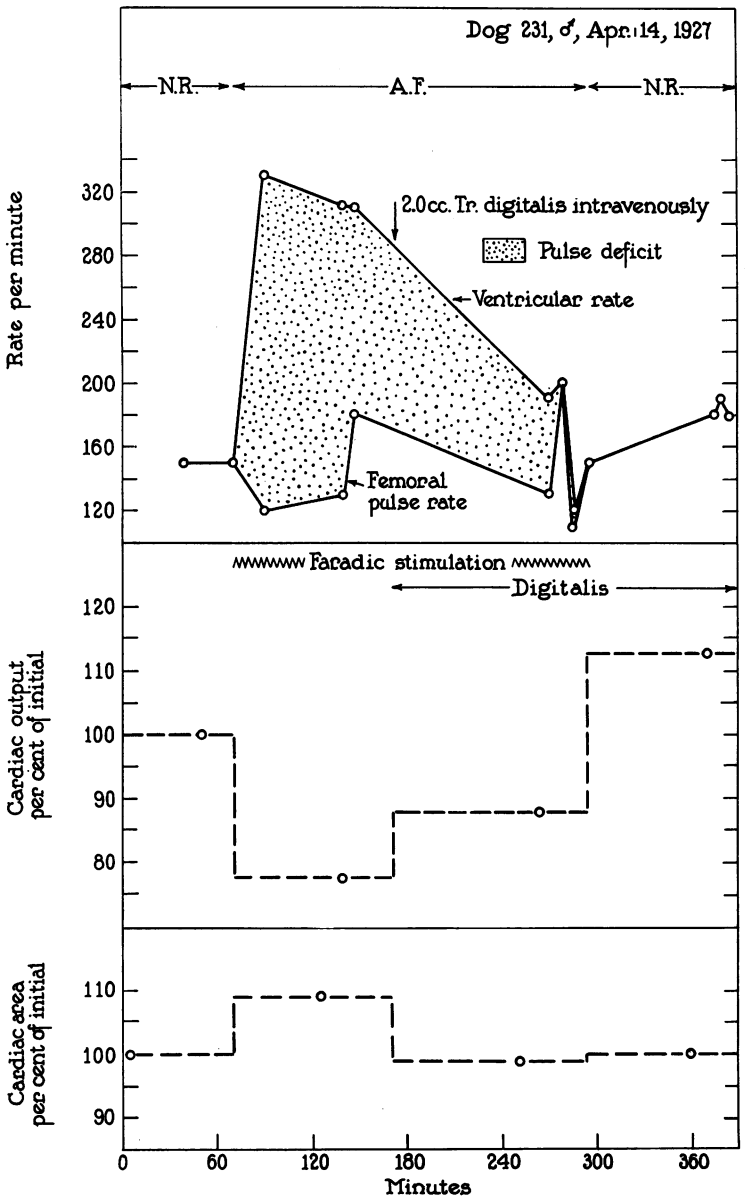

FIG. 3. IN THIS FIGURE IS SHOWN THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE, VENTRICULAR RATE AND FEMORAL PULSE RATE PER MINUTE IN DOG 231 (APRIL 14, 1927) DURING ARTIFICIAL AURICULAR FIBRILLATION.

In this figure as well as in Figure 4, the points on the curves show the exact time (abscissa) at which each observation was made. In order to bring into relief the relations between the various situations at these times, the curves are drawn in dotted straight lines as though these relations existed throughout the various periods. In this figure and in Figure 4, N.R. indicates normal rhythm and A.F., auricular fibrillation.

TABLE 1

The effect of giving digitalis on the cardiac output, cardiac size, and ventricular rate in dogs subject to artificial auricular fibriliation

Dog number and sex	Date	Time with reference to faradic stimulation ‖	Time with reference to administration of digitalis ††	Weight	O_2 content		Arterio-venous oxygen difference	O_2 consumption	Cardiac output	Cardiac output per cent of initial	Cardiac area	Cardiac area per cent of initial	O_2 capacity	Ventricular rate*	Corresponding femoral pulse rate *	Digitalis	Rhythm of heart
					Arterial blood	Mixed venous blood											
	1927	*minutes*	*minutes*	*kgm.*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc. per minute*	*cc. per minute*	*per cent*	*sq. cm.*	*per cent*	*volumes per cent*	*per minute*	*per minute*	*cc.*	
231 ♂	Apr. 14	0–65 B	B	10.45	25.24	17.88	7.36	82	1112	100	36.5	100	26.05	150	150		N.R.†
														150	150		
		60–75 A	B		25.49	15.77	9.72	84	864	78	39.6	109	26.05	330	120		A.F.¶
														300	130		
														330	180		
																2.0‡	
		180–220 A	85–120 A		24.62	15.30	9.32	91	976	88	36.0	99	24.95	190	130		A.F.
														200	200		
														120	110		
														150	150		
		64–89 E	190–230 A		23.77	16.71	7.06	89	1261	113	36.5	100	26.19	180	180		N.R.
														190	190		
														180	180		
	Apr. 21	0–45 B	B	9.15	15.79	9.63	6.16	95	1542	100	40.2	100	15.72	100	100		N.R.
														90	90		
		60–100 A	B		16.24	5.47	10.77	119	1105	72	42.5	106	16.53	270	170		A.F.
														290	150		
																4.66§	
		175–205 A	90–95 A		15.57	5.38	10.19	125	1227	80	39.5	98	15.95	180	170		A.F.
		60–90 E	180–185 A		15.46	6.52	8.94	104	1163	75	37.6	94	16.02	170	170		N.R.
														170	170		

TABLE 1 (*continued*)

Dog number and sex	Date	Time with reference to faradic stimulation ‖	Time with reference to administration of digitalis ††	Weight	O_2 content		Arterio-venous oxygen difference	O_2 consumption	Cardiac output	Cardiac output per cent of initial	Cardiac area	Cardiac area per cent of initial	O_2 capacity	Ventricular rate*	Corresponding femoral pulse rate *	Digitalis	Rhythm of heart
					Arterial blood	Mixed venous blood											
	1927	*minutes*	*minutes*	*kgm.*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc. per minute*	*cc. per minute*	*per cent*	*sq. cm.*	*per cent*	*volumes per cent*	*per minute*	*per minute*	*cc.*	
229 ♀	Mar. 25	0–75 B	B	11.8	20.81	12.34	8.47	145	1716	100	48.1	100	21.28	150	150		N.R.
														150	150		
		60–85 A	B		20.31	8.80	11.51	141	1220	71	50.0	104	21.26	340	140		A.F.
														340	130		
														310	180		
														360	180		
		160–210 A	55–105 A		19.80	10.53	9.27	144	1554	90	46.7	97	21.64	240	200	2.5‡	A.F.
		65–110 E	170–215 A		19.58	11.38	8.27	123	1487	86	45.4	95	20.68	240	240		
														190	190		N.R.
														190	190		
192 ♂	Mar. 29	0–35 B	B	19.1	23.63	15.93	7.70	220	2853	100	59.3	100	24.46	200	200		N.R.
														200	200		
		70–105 A	B		23.29	13.55	9.74	220	2258	79	65.8	111	23.86	300	170		A.F.
														360	240		
														310	140		
														330	150		
														330	120		
														300	150		
														300	180		
		180–225 A	60–110 A		21.35	12.32	9.03	223	2469	87	63.3	107	23.16	240	230	4.0‡	A.F.
														240	240		
		57–98 E	172–219 A		22.74	13.06	9.68	190	1963	69	58.5	98	22.65	190	190		N.R.
														190	190		
		60–85 A**	150–185 A		22.24	12.52	9.72	223	2294	80	61.1	103	23.83	200	200		A.F.

TABLE 1 (*continued*)

Dog number and sex	Date	Time with reference to faradic stimulation‖	Time with reference to administration of digitalis ††	Weight	O_2 content		Arterio-venous oxygen difference	O_2 consumption	Cardiac output	Cardiac output per cent of initial	Cardiac area	Cardiac area per cent of initial	O_2 capacity	Ventricular rate*	Corresponding femoral pulse rate*	Digitalis	Rhythm of heart
					Arterial blood	Mixed venous blood											
	1927	*minutes*	*minutes*	*kgm.*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc. per minute*	*cc. per minute*	*per cent*	*sq. cm.*	*per cent*	*volumes per cent*	*per minute*	*per minute*	*cc.*	
234 ♀	Apr. 28	0–49 B	B	15.2	24.86	14.07	9.99	113	1131	100	50.0	100	25.69	200 190	200 190		N.R.
		60–80 A	B		25.49	13.73	11.76	104	884	78	53.0	106	26.32	300 330	180 150	8.0§	A.F.
		140–170 A	45–75 A		24.86	17.96	6.88	108	1569	138	48.0	96	24.32	220	220		A.F.
		60–95 E	153–185 A		24.03	16.44	7.59	112	1449	127	46.3	93	25.98	190 190	190 190		N.R.

‖ B = before beginning stimulation, A = after beginning stimulation, E = after ending stimulation; see text "Plan of Observations."

†† B = before injecting digitalis, A = after injecting digitalis.

* In this table as well as in Table 2, the ventricular rate and the corresponding femoral pulse rate were counted in the electrocardiographic record and simultaneous femoral pulse tracing.

† N.R. = normal rhythm.

¶ A.F. = auricular fibrillation.

‡ Tincture of digitalis (Upsher Smith) given intravenously.

§ Digifoline (Ciba) given intravenously.

** In this dog observations were made during a second "period of auricular fibrillation with digitalis."

Approximately one hour later, during the "period of auricular fibrillation with digitalis," the auricles still fibrillating, a third set of observations was made. Stimulation of the auricles was then discontinued and the rhythm of the heart became normal again. After another hour, designated the "period of normal rhythm with digitalis," a fourth set of observations was made. Deviation from this schedule, whenever it occurred, is shown in the tables.

There are complete observations in four dogs. The results secured in the case of dog 231 serve to illustrate the course of events (Table 1, Figure 3). When the heart was beating normally at a rate of 150 per minute its output was 1112 cc. per minute, and the area of the heart measured 36.5 sq. cm. (Table 1, April 14, 1927). One hour after the onset of auricular fibrillation and while this rhythm was still present, the ventricular rate being 300 to 330 (Figure 2) and the femoral pulse rate 120 to 180 per minute, the cardiac output fell to 864 cc. per minute or 78 per cent of its initial value (Table 1, Figure 3), and the area of the heart measured 39.6 sq. cm., an increase to 109 per cent of its initial size. While the auricles were fibrillating, tincture of digitalis (Upsher Smith) 2.0 grams was given intravenously. Eighty-five minutes later, under the influence of digitalis, the ventricular rate decreased further from 200 to 120, and the corresponding femoral pulse rate from 200 to 110 per minute, the pulse deficit being smaller; the heart was, in short, still beating irregularly but more slowly and more forcibly, there being only a few ineffective beats. The cardiac output *increased* to 976 cc. per minute (88 per cent of its initial value) and its size *decreased* to 36.0 sq. cm. (99 per cent of its initial size). Then stimulation of the auricles was discontinued and the rhythm of the heart again became normal. One hour later the cardiac rate was 190 to 200 per minute, the heart still being under the influence of digitalis. Since there was no longer a pulse deficit, the cardiac output increased to 1261 cc. per minute (113 per cent of the initial) though the area of the heart remained unchanged (36.5 sq. cm., 100 per cent). When the observations were repeated one week later (April 21, 1927) similar results were obtained (Table 1), with this exception that cardiac output and cardiac size both diminished when the rhythm of the heart became regular again in the final (fourth) period.

Summary: With the onset of auricular fibrillation the cardiac output decreased and the heart dilated. When digitalis was given the size diminished and the output increased; that is to say, the capacity of the heart to expel blood increased. The results in the three other dogs were similar to these. The most frequent effect observed after the end of stimulation, when the rhythm again became regular, was further decrease in the size of the heart and a decrease in output. In other instances, as in the one described in detail, cardiac size remained unchanged from that in the fibrillatory state and the cardiac output increased.

TABLE 2

The effect of giving digitalis on the relative blood flow, cardiac size, and ventricular rate in dogs subject to artificial auricular fibrillation

Dog number and sex	Date	Time with reference to faradic stimulation ‖	Time with reference to administration of digitalis ††	Weight	O_2 content		Arterio-venous oxygen difference *	Blood flow per cent of initial	Cardiac area	Cardiac area per cent of initial	O_2 capacity	Ventricular rate	Corresponding femoral pulse rate	Digitalis †	Rhythm of heart
					Arterial blood	Mixed venous blood									
		minutes	*minutes*	*kgm.*	*mM.*	*mM.*	*mM.*	*per cent*	*sq. cm.*	*per cent*	*mM.*	*per minute*	*per minute*	*cc.*	
226 ♀	February 11, 1927	0–13 B	B	14.75	11.25	8.17	2.99	100	45.2	100	11.81	200	200		N.R.¶
												190	190		
												190	190		
		70–105 A	B		11.80	6.72	5.08	59	50.7	112	12.04	350	160		A.F.§
												340	160		
												350	150		
														2.8	
		170–189 A	60–79 A		11.07	7.70	3.37	89	47.0	104	12.22	270	270		A.F.
												210	210		
		60–80 E	150–170 A		11.11	7.08	4.03	74	42.8	95	12.06	190	190		N.R.
												200	200		
												190	190		
214 ♀	December 16, 1926	0–50 B	B	13.88	10.47	7.14	3.33	100	44.4	100	9.84	230	230		N.R.
		73–143 A	B		10.56	5.29	5.27	63	50.4	113	10.75	340	190		A.F.
														3.0	
		208–268 A	60–120 A		10.52	6.91	3.61	92	44.8	101	10.36	200	200		A.F.
		60–68 E	202–210 A		10.89	6.30	4.59	72	41.6	94	11.15	210	210		N.R.

TABLE 2 (*continued*)

Dog number and sex	Date	Time with reference to faradic stimulation ‖	Time with reference to administration of digitalis ††	Weight	O_2 content		Arterio-venous oxygen difference *	Blood flow per cent of initial	Cardiac area	Cardiac area per cent of initial	O_2 capacity	Ventricular rate	Corresponding femoral pulse rate	Digitalis †	Rhythm of heart
					Arterial blood	Mixed venous blood									
		minutes	*minutes*	*kgm.*	*mM.*	*mM.*	*mM.*	*per cent*	*sq. cm.*	*per cent*	*mM.*	*per minute*	*per minute*	*cc.*	
220 ♀	January 19, 1927	0–22 B	B	10.2	11.10	8.36	2.74	100	34.3	100	11.21	130	130		N.R.
												140	140		
		60–90 A	B		11.21	6.84	4.37	62	37.8	110	11.40	300	210		A.F.
												350	240		
												340	210		
														2.3	
		180–210 A	60–90 A		10.29	6.53	3.76	73	34.6	100	10.40	160	150		A.F.
		210–270 A‡	135 A		10.74	6.92	3.82	72			11.45	200?	190		A.F.
		75–100 E	360–385 A		11.08	6.63	4.45	61	31.3	91	11.39	180	180		N.R.
												190	190		
223 ♀	February 3, 1927	0–40 B	B	11.0	11.09	8.84	2.25	100	39.2	100	11.88	160	160		N.R.
		40–60 A	B		11.70	6.77	4.93	46	42.5	109	11.90	340	180		A.F.
														2.0	
		115–150 A	47–82 A		11.04	6.96	4.08	55	41.9	106	12.39	180	180		A.F.
		60–80 E	137–157 A		11.47	6.50	3.97	57	40.9	104	12.17	170	170		N.R.

‖ B = before beginning stimulation, A = after beginning stimulation; E = after ending stimulation; see text "Plan of Observations."

†† B = before injecting digitalis, A = after injecting digitalis.

* Oxygen removed from each liter of blood.

† Tincture of digitalis (Upsher Smith) given intravenously.

¶ N.R. = normal rhythm.

§ A.F. = auricular fibrillation.

‡ In this dog observations were made during a second "period of auricular fibrillation with digitalis."

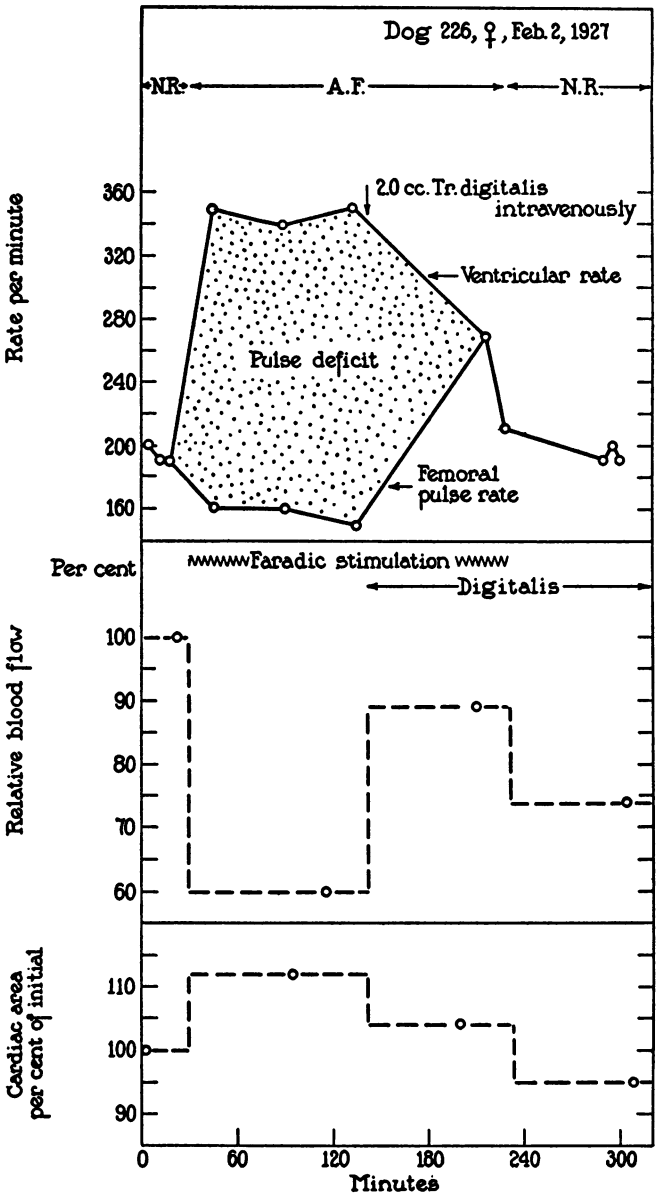

FIG. 4. IN THIS FIGURE IS SHOWN THE EFFECT OF GIVING DIGITALIS ON THE RELATIVE BLOOD FLOW, CARDIAC SIZE, VENTRICULAR AND FEMORAL PULSE RATES PER MINUTE IN DOG 226 DURING ARTIFICIAL AURICULAR FIBRILLATION.

In four untrained dogs similar observations were made (Table 2). The arteriovenous oxygen difference was measured representing, as it does, the oxygen consumed by the tissues per liter of blood, and from this the relative blood flow [2] (6) has been calculated, the control period being placed at 100; the results in all these measurements are similar to those in which the cardiac output was measured. Dog 226 (Table 2, Figure 4) may serve to illustrate the course of events. There was decrease in relative blood flow and increase in cardiac size when the cardiac mechanism was that of auricular fibrillation; increase in output and decrease in size when digitalis was given during this rhythm and finally, decrease in output and decrease in cardiac size with the return of the normal rhythm. The results in the three other dogs are similar.

A note on the effect of giving digitalis to a dog in the presence of edema artificially induced

In dog 265, edema of the extremities occurred as a result of taking sodium bromide [3] (18, 19, 20, 21). The fluid intake was uniform, being 1500 cc. a day. The diet consisted of milk and eggs given by stomach tube at the same time each evening. The output of urine was measured. The dog was trained in the use of the spirometer for measuring oxygen consumption. All measurements were made when the dog was in a basal metabolic state. On November 27, 1928, when edema appeared, the cardiac output measured 1550 cc. per minute and the area of the heart 48.3 sq. cm.; the left and right ventricular excursions measured in moving x-ray films (1) 2.8 mm. and 3.4 mm. respectively (Table 3, Figure 5). Tincture of digitalis (Upsher Smith) 2.7 cc. was given intravenously to this dog after these measurements had been made. The output of urine increased, the dog lost weight, and became free of edema on November 30. Twenty-four hours after the administration of digitalis, cardiac output *increased* to 2100 cc. (136 per cent of the initial output), cardiac size decreased to 47.5 sq. cm. (89 per cent) and the left and right ventricular excursions both increased (4.8 mm. and 4.8 mm. respectively). Two days later still, when edema had quite disappeared, the cardiac output *increased* still further to 2550 cc. (173 per cent), cardiac size dimin-

[2] "Relative blood flow" is a ratio between some state of flow and another, for example, between the arteriovenous oxygen difference per liter of blood in a normal cardiac mechanism and an abnormal one, the metabolism, that is to say, the oxygen consumption, remaining constant.

[3] This dog was given by stomach tube sodium chloride 15.0 grams (10 per cent solution) a day for 5 days. She was then given, in the same manner, sodium bromide 15.0 grams (10 per cent solution) a day for 5 days, when she became drowsy. Four days later (November 27, 1928) edema of the extremities was observed. Water was given in the morning with sodium chloride or sodium bromide, and milk and eggs in the evening to bring the total daily intake of fluid up to 1500 cc. The caloric value of the food intake was constant.

TABLE 3

The effect of giving digitalis on the cardiac output, cardiac size and extent of ventricular excursions in dog 265 (♀) subject to edema after taking sodium bromide

Date	Time with reference to administration of digitalis	Weight	O_2 content		Arteriovenous oxygen difference	O_2 consumption	Cardiac output	Cardiac output per cent of initial	Cardiac area *	Cardiac area per cent of initial	O_2 capacity	Ventricular excursions **		Presence of edema	Digitalis ***
			Arterial blood	Mixed venous blood								Left	Right		
1928		*kgm.*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc. per minute*	*cc. per minute*	*per cent*	*sq. cm.*	*per cent*	*per cent*	*mm.*	*mm.*		*cc.*
November 27	Before	14.0	18.86	11.47	7.39	115	1550	100	48.3	100	21.09	2.8	3.4	Yes	2.7
November 28	24 hours after	13.4	15.45	10.50	4.95	105	2100	136	47.5	98	19.03	4.8	4.8	Yes	
November 30	72 hours after	12.8	15.85	11.57	4.28	110	2550	173	42.4	88	18.41	5.2	5.6	No	

* These x-ray photographs were taken at a distance of 34 inches.

** Measured from tracings made of the x-ray moving films (Cohn and Stewart (1)).

*** Tincture of digitalis (Upsher Smith) given intravenously.

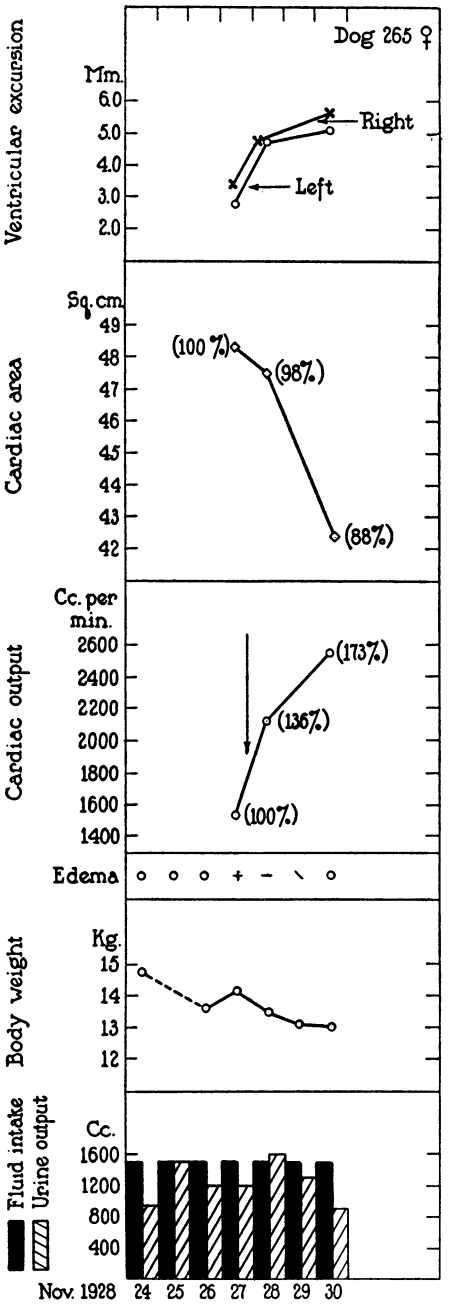

FIG. 5. IN THIS FIGURE IS SHOWN THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND EXTENT OF VENTRICULAR EXCURSIONS IN DOG 265, SUBJECT TO EDEMA, THE RESULT OF ORAL INGESTION OF SODIUM BROMIDE.

In interpreting the symbols relating to the presence of edema, 0 = absent, + = present, − = unchanged, and \ = decreasing.

ished further to 42.4 sq. cm. (88.0 per cent), and the ventricular excursions increased to 5.2 mm. (left) and 5.6 mm. (right).

Summary: When digitalis was given to a dog, the subject of edema artificially induced, cardiac output increased, cardiac size diminished and the extent of ventricular excursions increased. The dog lost weight and became free of edema.

DISCUSSION

That the effect of giving digitalis to intact normal dogs is to decrease cardiac output and cardiac size and to increase ventricular excursions appears to be a fact (1, 17). Its effect in dogs in which the hearts were enlarged, but in which there was no evidence of heart failure has also been studied. In this situation, as in the normal one, the effect was to decrease cardiac output and cardiac size and to increase the extent of ventricular excursions (2). The effect of giving digitalis has been studied therefore under the following circumstances. First, in normal dogs the hearts of which were normal in size; second, in dogs the subject of muscular hypertrophy following the creation of artificial valvular lesions. In both these, the result is decrease in output. And now there is a case in which information was still lacking, namely, in intact, unanesthetized dogs in which the cardiac output is diminished and the heart dilated due to the action of auricular fibrillation artifically induced. The result is *increase* in cardiac output and *decrease* in cardiac size. Insufficient hearts become smaller, it seems, and, unlike normal hearts in which it decreases, increase their output as the result of a change dependent on the heart itself, and obviously independent of changes in a peripheral mechanism, such as that of the throttle action of the hepatic veins. The outstanding point is this, that at a time when the basic mechanism of the heart beat remained unchanged, the action of digitalis resulted in increase in output, though the rate decreased; occasionally it increased the output still more when the normal rhythm was restored, though the normal did not attain the fibrillatory rate.

In these observations and in the ones published in the third paper (22) parallel phenomena have been studied in dogs and in human beings, namely, the effect of giving digitalis to normal animals and to normal human beings on the one hand; on the other, the effect in dogs in which the cardiac output is diminished and dilatation is present, and in patients the subjects of heart failure, whose hearts are enlarged and their output diminished. The output, both in normal dogs and in normal men, as well as the size, decrease; in diseased human beings and in abnormal dogs during heart failure, increase in output and decrease in size take place. Discussion of these results will be found in a third report (22). It is sufficient to state now that digitalis seems to exert the same essential effects both

in normal and diseased hearts; it decreases cardiac size, its effect on tone, and it increases the extent of ventricular contraction, its effect on contraction (1, 2).

Edema which results in dogs from the oral administration of large doses of sodium bromide is probably not analogous to edema occurring in heart failure. The mechanism of its occurrence is not clearly known. It is presumably the result of shifting of ions in the blood, so that bromide ions are substituted for chloride ions; in consequence of this process, water is retained in the tissues. The course of events following the administration of digitalis in this condition resembles that in heart failure in human beings, namely, the cardiac output increases, the cardiac size decreases and the extent of ventricular excursion increases.

SUMMARY AND CONCLUSIONS

1. During auricular fibrillation when the ventricular rate is rapid the cardiac output per minute is less than it is during the normal, slower sinus rhythm (3). In consequence of this abnormal rhythm in intact unanesthetized trained dogs the heart increases in size. This conclusion is based on a larger number of observations than was possible in an earlier paper (4).

2. When the cardiac output is diminished and the heart is dilated due to artificial auricular fibrillation, the administration of digitalis results in increase in cardiac output and decrease in cardiac size.

3. When the normal rhythm returns, the heart being, of course, still under the influence of digitalis, the output either increases, the size remaining unchanged (from that in the fibrillatory state), or both output and size decrease.

4. The observations show, as do the ones next to be reported, that digitalis has the same action in normal and in pathological hearts; it decreases cardiac size (an effect on tone). The amount of the cardiac output which results from this action depends upon the initial size of the heart; it decreases in normal hearts, and increases in dilated ones.

5. In a dog, the subject of edema due to taking sodium bromide, the administration of digitalis increased cardiac output, decreased cardiac size and increased the extent of ventricular excursions.

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