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Research Article

THE HEMODYNAMIC RESPONSE TO LANATOSIDE C OF DOGS WITH EXPERIMENTAL AORTIC-CAVAL FISTULAS

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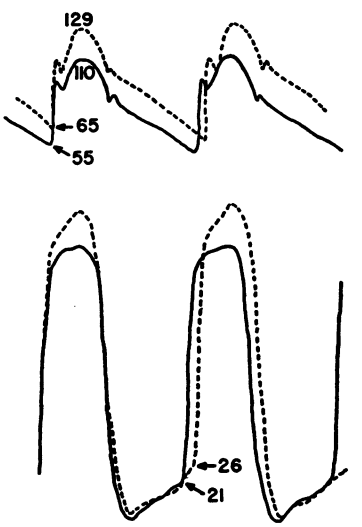
Previous work has demonstrated that a severe burden is placed on the circulatory system of the dog by the surgical production of a long-sustained aortic-caval fistula (1). Circulatory distress is manifested by ascites, edema of all extremities and the lungs, together with a marked rise in left ventricular end-diastolic pressure, cardiac output, cardiac work, heart rate, and a depression of total peripheral resistance. The heart is at or near a state of cardiac decompensation, as indicated by the level of cardiac work and the response of the circulatory system to the infusion of whole blood or saline (1). Such infusions generally cause the cardiac output and cardiac work to decline and the left ventricular end-diastolic pressure to rise further, while the maximum level of cardiac work attained before infusion approximates that in the normal dog with massive infusion (1). To obtain further information on the physiological state of these dogs their response to rapid digitalization has been determined. This has been compared with the response of dogs without aortic-caval fistulas. The results of this study form the basis for this report.

METHODS AND PROCEDURES

A van Leersum carotid loop and cardiopexy were constructed first to aid in determining the arterial pressure, left ventricular end-diastolic pressure, and cardiac output (2). Later an anastomosis approximately 10 mm. in length was made between the aorta and inferior vena cava below the renal vessels (1). Weeks to months later measurements were made of the effect of Lanatoside C on the cardiac output, carotid blood pressure, heart rate, and left ventricular end-diastolic pressure. Pressures were recorded either by membrane manometers or by strain gauges connected to needles inserted into the left ventricular cavity and carotid loop. Figure 1 shows the character of the pressure curves obtained from the carotid loop and left ventricular cavity before and after digitalization of the anesthetized dog with an aortic-caval fistula. Cardiac output was calculated from the arterial dilution curve of Evans blue dye as modified for the recording cuvette densitometer (3). The dye was injected into the right atrium through a catheter inserted via the external jugular vein, and arterial blood was sampled from the carotid artery. Experiments were performed on the unanesthetized and anesthetized animal. The unanesthetized dogs had been trained previously to lie quietly on a table. In the anesthetized dogs anesthesia



CONTROL — LANATOSIDE C ----

FIG. 1. SUPERIMPOSED TRACINGS OF CAROTID (UPPER) AND LEFT VENTRICULAR (LOWER) PRESSURE CURVES TAKEN BEFORE (SOLID LINE) AND 45 MINUTES AFTER (BROKEN LINE) DIGITALIZATION OF ANESTHETIZED DOG WITH AN AORTIC-CAVAL FISTULA

Numbers refer to carotid systolic and diastolic pressures and to left ventricular end-diastolic pressure in mm. Hg.

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TABLE I

Physical status of dogs with chronic aortic-caval fistulas

Dog No.	Weight (*Kg.*) Before	After	Fistula duration (*days*)	Remarks
1	13.1	12.6	37	No edema, ascites or evidence of circulatory stress
2	12.6	13.0	30	Hind leg edema. No ascites or evidence of congestive heart failure
3	15.5	21.4	55	Much edema of all extremities and ascites; tissue loss
4	11.8	11.2	49	Slight ascites and leg swelling
5	12.3	11.1	23	No ascites, edema or evidence of circulatory stress
6	10.0	13.8	40	Stormy history with marked ascites, edema of all extremities
7	17.3	15.4	385	Mild ascites and edema of front and hind extremities
		17.8	425	Marked ascites and edema of all legs with considerable recent weight gain
8	17.3	16.8	69	No ascites, slight edema
9	13.6	21.8	69	Considerable ascites and edema of front and hind legs. Pulmonary edema at death on 153rd day
10	14.6	14.1	70	Considerable edema of all legs
11	18.2	17.2	70	Pulmonary edema
12	17.3	20.9	150	Marked ascites, peripheral edema

was accomplished by premedication with 3 mgm. per Kg. of morphine sulfate, followed by 0.25 cc. per Kg. of a 1:1 mixture of Dial-urethane and pentobarbital. Arterial oxygen saturation was maintained by a demand valve apparatus connected to an oxygen tank; phasic intrapleural pressure was recorded with an optical segment capsule connected to a trocar in the left intrapleural space near the heart, and these pressures were used to correct the simultaneously recorded left ventricular end-diastolic pressure. Procaine amide (200 mgm. in 50 cc. saline) was given to abolish sinus arrhythmia in some of the animals (noted in Table II). The methods used to analyze the data were as follows: 1) Stroke volume index in cc. per M^2 (stroke volume/surface area M^2); 2) stroke work index in gm.M per M^2 (stroke volume index × (mean arterial pressure − left ventricular end-diastolic pressure) × 13.6); 3) cardiac work index in gm.M per M^2 per min. (cardiac index × (mean arterial pressure − left ventricular end-diastolic pressure) × 13.6); and 4) total peripheral resistance (mean arterial pressure × 100/ cardiac output in cc.).

After control observations of cardiac output and pressures had been completed, either 0.045 or 0.025 mgm. per Kg. of Lanatoside C was given intravenously as a single dose and at the end of 30 to 60 minutes the observations were repeated. The larger amount of the drug is at

TABLE II

Effect of Lanatoside C in dogs with aortic-caval fistulas †

Dog No.	L.V.E.D.P. B	A	C.I. B	A	C.W.I. B	A	S.V.I. B	A	S.W.I. B	A	M.A.P. B	A	T.P.R. B	A	H.R. B	A
1	32	35	6.5	6.8	4,150	6,080	62	60	40	54	79	101	2.1	2.5	104	113
2	15	12	4.3	4.7	3,390	5,000	59	55	45	59	71	90	2.8	3.3	74	85
3	19	17	4.3	5.1	4,250	5,960	34	39	33	45	91	103	2.7	2.6	129	132
4	22	26	8.1	7.2	6,640	6,250	66	68	54	59	82	90	1.8	2.2	122	106
5	19	13	10.5	7.9	8,430	7,070	69	53	55	47	78	79	1.4	1.9	152	150
6	37	37	9.6	8.8	2,814	3,638	58	56	17	24	58	67	1.0	1.3	167	157
7	26	22	11.0	7.6	10,580	9,040	76	77	73	91	97	109	1.4	2.2	145	99
7′	29	30	6.7	6.1	6,710	7,503	69	63	69	77	103	120	2.2	2.7	97	97
8	13	15	10.1	9.6	15,444	13,474	94	90	143	124	125	117	1.8	1.8	108	108
9*	28	26	7.6	7.7	5,374	6,180	55	59	40	48	80	85	1.3	0.9	138	130
10*	14	14	6.9	5.8	6,832	4,318	86	71	86	54	87	70	2.0	3.1	80	80
11*	28	29	6.7	6.5	6,370	6,365	39	44	38	42	98	102	1.7	2.2	170	150
12	26	17	6.9	8.3	5,161	5,983	50	69	37	49	81	70	1.4	1.0	138	120
Aver.	24	23	7.6	7.1	6,620	6,682	63	62	56	60	87	93	1.8	2.1	125	117

† Measured and calculated parameters *before* (B) and 30 to 60 minutes *after* (A) the injection of Lanatoside C. Left ventricular end-diastolic pressure, mm. Hg (L.V.E.D.P.); cardiac index (C.I.); cardiac work index (C.W.I.); stroke volume index (S.V.I.); stroke work index (S.W.I.); mean arterial pressure, mm. Hg (M.A.P.); total peripheral resistance (T.P.R.); and heart rate (H.R.). The data under 7 and 7′ were obtained from the same animal on the 385th and 425th post-operative day. The asterisk indicates those dogs receiving 0.025 mgm. per Kg. of Lanatoside C; all others received 0.045 mgm. per Kg. Animals 1 to 7 were studied under Dial-urethane pentobarbital anesthesia and received procaine-amide to abolish sinus arrhythmia. Animals 8 to 12 were trained and determinations were made using local procaine (1 per cent) subcutaneously at the site of needle puncture.

TABLE III

Effect of maintenance digitalization in dogs with aortic-caval fistulas *

Dog No.	Weight (Kg.)		L.V.E.D.P.		C.I.		C.W.I.		S.V.I.		S.W.I.		M.A.P.		T.P.R.		H.R.	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
8	16.8	16.8	13	4	10.1	6.7	15,444	7,470	94	61	143	68	125	86	1.8	1.8	108	110
9	21.8	19.5	29	21	7.6	7.1	5,374	8,015	55	44	40	50	80	104	1.3	1.8	138	160
10	14.1	13.6	14	9	6.9	4.5	6,832	4,957	86	45	86	49	87	89	2.0	3.5	80	100
11	17.2	17.2	28	32	6.7	6.3	6,370	4,660	39	45	38	34	98	86	1.7	1.9	170	140
12	20.9	20.9	26	33	6.9	7.9	5,161	3,700	50	66	37	31	80	68	1.4	0.9	138	120
Aver.	18.2	17.6	22	20	7.6	6.5	7,836	5,760	65	52	69	46	94	87	1.6	2.0	127	126

* Animals 8, 9, 10, and 11 maintained on Digitoxin for four days after initial digitalization with Lanatoside C; studies made before and on fourth day after digitalization. Animal 12 studied before and one day after digitalization. Abbreviations as in Table II.

least 30 per cent of the lethal dose reported for some other cardiac glycosides (4), and is about twice the dose used per kilogram of body weight in the studies by Stead, Warren, and Brannon (5) on human subjects in congestive heart failure. This amount of the drug is an effective dose, as indicated by the work of Li and Van Dyke (6). In one unanesthetized animal, the observations were repeated the next day and in four others, they were repeated after four days of digitalization. The four animals received daily maintenance doses of digitoxin, administered intramuscularly in amounts equivalent to one-tenth of the original digitalizing dose of Lanatoside C (Table III).

RESULTS

In the group of dogs with fistulas hemodynamic studies were made 23 to 425 days after creation of the aortic-caval fistula. The condition of the dogs and their hemodynamic status varied considerably (Table I). Some gained a considerable amount of weight with ascites and edema of all extremities while others gave no external evidence of circulatory stress or insufficiency. Table II presents the data obtained in the group with fistulas, both anesthetized (1–7) and unanesthetized (8–12), before and 30 to 60 minutes after the intravenous administration of Lanatoside C. It can be seen that before digitalization the average work load of these hearts was quite high. The left ventricle maintained an average cardiac index of 7.6 liters per minute, a cardiac work index of 6,620 gm. meters, and a stroke volume index of 63 cc. The carotid pulse pressure averaged 60 mm. Hg (data not shown), despite a heart rate of 125 per minute and a high left ventricular end-diastolic pressure of 24 mm. Hg. In some dogs previous measurements indicated that the extent of cardiac work response, after reaching a high level, was maintained. In others, maximum cardiac performance had been passed at the time of these studies. For example, in dog 7 after induction of the fistula the cardiac index dropped from 11 liters on the 385th day to 6.7 liters on the 425th day. During the interim the dog developed massive edema of the extremities, ascites, dyspnea, and increased body weight.

Although following digitalization, the dogs with fistulas varied somewhat in their response, the average changes show a slight decrease in the cardiac index, cardiac work index, and heart rate, with slight increases in mean arterial pressure and total peripheral resistance. The effect of the Lanatoside C in these animals does not correlate with the loads under which the heart was working, or with the height of the end-diastolic pressure in the left ventricle. For example, following Lanatoside C, the cardiac work index of dog 2 increased even though the cardiac work index was initially only 3,390 gm.M per M^2 per min. with a left ventricular end-diastolic pressure of 15 mm. Hg, while in dog 7, the cardiac work index fell after the drug even though this dog had a high cardiac work level (10,580 gm.M per M^2 per min.) and a high left ventricular end-diastolic pressure (26 mm. Hg). The effect of the drug on these dogs appears independent of the hemodynamic state of the circulation or of the work load on the heart.

Table III presents the data from five dogs with fistulas that were maintained on digitoxin from 1 to 4 days after initial digitalization with Lanatoside C. Their hemodynamic status was not improved.

TABLE IV

Effect of Lanatoside C in normal dogs *

Dog No.	L.V.E.D.P.		C.I.		C.W.I.		S.V.I.		S.W.I.		M.A.P.		T.P.R.		H.R.	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	9	9	1.8	1.6	1,870	2,000	36	34	36	44	86	103	8.0	11.0	49	46
2	8	8	1.9	2.4	2,500	3,890	29	29	37	47	103	128	9.3	9.3	68	83
3	17	11	2.9	2.1	3,290	2,370	52	48	59	55	100	95	6.4	8.6	56	43
4	7	5	1.7	1.4	1,735	1,440	29	27	29	27	81	79	9.2	10.9	59	53
5	12	12	3.0	2.8	3,080	3,890	40	48	42	65	88	114	5.1	7.0	74	59
6	15	12	2.6	2.0	2,370	1,970	26	24	24	24	83	86	6.2	8.4	101	81
7a	7	7	2.6	2.4	3,610	2,860	43	45	60	53	109	95	8.2	7.5	60	54
b		7		2.4		3,650		40		61		119		9.7		60
Aver.	10	9	2.4	2.1	2,640	2,760	37	37	41	47	93	102	7.5	9.0	67	60

* Animals 1, 2, 3, 4, 5, and 6 anesthetized. Animal 7 trained, unanesthetized; 7a and b data obtained 30 and 60 minutes, respectively, after digitalization. Abbreviations as in Table II.

Actually, four of the dogs showed a considerable reduction in cardiac work.

The influence of Lanatoside C upon the circulation was assessed in seven dogs without aortic-caval fistulas (Table IV). Six were anesthetized and one was trained and unanesthetized. The data in Table IV indicate that the performance of the left ventricle was not greatly altered by Lanatoside C. The average changes following rapid digitalization are very similar to those seen in the animals with fistulas. A slight decrease in cardiac index and heart rate with an increase in mean arterial pressure and peripheral resistance was noted.

DISCUSSION

The results of this study are in agreement with previous reports in the literature which indicate that in the normal heart digitalis, when effective, generally decreases cardiac output and heart rate and increases mean arterial pressure (7, 8).

In the animals with fistulas it is difficult to be certain that heart failure was always present since the direct effects of the fistula would be to produce hind-limb edema, increase venous pressure, and perhaps cause ascites as well. However, there were other physical signs and physiological measurements which indicated that these animals were at or beyond their maximum cardiac work level. Some animals developed edema of the fore-limbs as well as the hind-limbs, and a number of the dogs died of pulmonary edema which is highly indicative of cardiac failure under these circumstances. The maximum cardiac work levels in these preparations were similar to those obtained in normal dogs with massive infusion of blood or saline (1). The left ventricular end-diastolic pressure was consistently elevated in the fistula group, the lowest value being 13 mm. Hg with an average value of 24 mm. Hg; whereas, the corresponding value for the normal animals was 10.7 mm. Hg. Furthermore, the infusion of whole blood or saline into these animals led to an additional large increase in left ventricular end-diastolic pressure, and an early decline in cardiac work and output (1). This evidence indicates that these dogs were working at or very near the limit of their cardiac performance.

Acute digitalization with Lanatoside C failed to improve the cardiac work response in animals with aortic-caval fistulas. The cardiac index did increase in four of the twelve dogs, but the increase was only minimal and one of the animals had shown a similar increase following digitalization before the aortic-caval fistula had been constructed. Four of the animals were maintained on digitalis with no improvement, confirmatory evidence that digitalization did not improve cardiac performance. These data do not explain the lack of response to digitalis in these animals, but they do indicate that there is an undefined difference between these animals and, for example, animals with cardiac failure produced by pulmonary artery constriction (9).

SUMMARY

Dogs were prepared with a chronic aortic-caval fistula. At the time of study, performance of the left ventricle was characterized by a high level of

left ventricular end-diastolic pressure, cardiac output, stroke volume, and stroke work, and in most instances with one or more evidences indicative of cardiac failure such as pulmonary edema, edema of the extremities, and ascites. After a period varying from one to 14 months, the dogs were digitalized rapidly with Lanatoside C and the hemodynamic effects were observed during the next hour and in some animals after four days of maintenance dosage on digitoxin. Measurements of various cardio-dynamic parameters indicated that digitoxin did not alter measurably the cardiac performance.

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