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Studies on Digitalis. XVI. Effects on Myocardial Oxygen Consumption *

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The effects of cardiac glycosides on myocardial oxygen consumption (MVo_2) have been investigated extensively, and although the results of these studies have not been entirely uniform, it is now generally considered that these agents are "the only drugs which increase the force of contraction of the myocardium without at the same time increasing oxygen consumption" (1). The finding in previous investigations that digitalis does not increase MVo_2 (2–8) would not appear to be compatible with observations that the glycosides increase the velocity of myocardial fiber shortening (9, 10), since recent studies have suggested that the latter variable is an important determinant of MVo_2 (11, 12). These considerations prompted an examination of the effect of acetylstrophanthidin on MVo_2 in a preparation that allowed control of hemodynamic variables other than contraction velocity that can significantly influence MVo_2.

Methods

Experiments were performed on eight dogs weighing 15.5 to 17.2 kg and anesthetized with morphine, 2.8 mg per kg; chloralose, 96 mg per kg; and urethane, 620 mg per kg. The chest was entered through a sternal splitting incision, and ventilation was maintained with a Harvard respiratory pump, using 100% O_2. Heparin (500 U per kg) was administered. The venae cavae were then cannulated, and the venous return was diverted into a reservoir, from which bypass of the right side of the heart was achieved with an occlusive roller pump, as described in detail previously (12). The pump supplied blood to the pulmonary artery through a cannula inserted via the right ventricular outflow tract; the right ventricle was therefore empty and performing no external work. Fresh blood obtained from donor dogs and exchanged with that of the experimental animal was used to prime the reservoir and circuit. Mean systemic arterial pressure was regulated by a reservoir connected to a compressed air circuit and attached by large bore cannulae to the femoral arteries. The sino-atrial node was crushed, and heart rate was maintained constant by electrical stimulation [1] of the right atrium or ventricle. Stroke volume could therefore be controlled by maintaining the output of the pump constant.

A flow transducer was placed around the ascending aorta, and instantaneous aortic blood flow was measured with a gated-sine wave electromagnetic flowmeter.[2] Left ventricular pressure was measured with a Statham P23Db pressure transducer attached directly to a large-bore metal cannula that was inserted through the the ventricular apex. Central aortic pressure was measured through a similar cannula inserted into the aortic arch through the left subclavian artery. The first derivative (dp/dt) of the left ventricular pressure pulse was determined with an analogue differentiating circuit [3] and was recorded continuously together with pressure, flow, and the electrocardiogram on a direct-writing multichannel oscillograph. Experimental data were also transcribed on FM tape [4] and replayed for analysis of phasic data.

Coronary blood flow was measured during a steady state by timed collection of the right ventricular drainage, this effluent representing total coronary blood flow minus the left ventricular thebesian vein drainage. Arterial and coronary venous blood samples were obtained simultaneously and analyzed in duplicate for O_2 by the method of Van Slyke and Neill. MVo_2 was then calculated as the product of coronary blood flow and the coronary arteriovenous O_2 difference. MVo_2 calculated in this manner represents the contributions both of the functioning left ventricle and of the empty nonworking right ventricle. The latter is undoubtedly very small and has been ignored in this study.

In two hearts the effects of acetylstrophanthidin were studied at high initial left ventricular end-diastolic pressures. Since pulmonary edema and hemorrhage occur at high pressures in the right heart bypass preparation, a disposable bubble oxygenator [5] ventilated with 97% O_2, 3% CO_2 was substituted for the lungs. Blood from the

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[1] American Electronic Laboratories, Colmar, Pa., model 104A.

[2] Biotronex Laboratory, Silver Spring, Md., model BL-310.

[3] Designed by Electronic Gear, Inc., Valley Stream, N. Y., utilizing a Philbrick P65AU operational amplifier.

[4] Model 3900 tape recorder, Sanborn, Cambridge, Mass.

[5] Travenol Laboratories, Morton Grove, Ill.

venae cavae was drained into the oxygenator and then pumped directly into the left atrium through a cannula inserted via a right pulmonary vein. The hila of both lungs and the main pulmonary artery were then ligated.

The experimental design in both preparations was the same. During the control period, i.e., before the administration of acetylstrophanthidin, the relationship between the left ventricular end-diastolic pressure (LVEDP), stroke volume, and stroke work was determined by increasing the output of the pump in a stepwise fashion, with heart rate and mean aortic pressure maintained constant. The output of the pump was then set so that the LVEDP was relatively low in the right heart bypass preparations and relatively high in the other two experiments. Coronary blood flow was measured, and arterial and coronary venous blood samples were obtained in duplicate during a steady state. Then, while pump output, mean aortic pressure, and heart rate were maintained constant, an average of 0.26 cat U per kg (0.19 to 0.40 cat U per kg) acetylstrophanthidin was injected into the reservoir. Ten to 20 minutes later, at the time of the maximal hemodynamic response, $M\dot{V}o_2$ was again determined, and the left ventricular function curve was then repeated.

The diastolic pressure-volume curve of the left ventricle was determined at the end of each experiment by a method described in detail previously (13). In brief, the heart was arrested with 25% KCl, the mitral and aortic valves were occluded, and the cavity was filled with 2-ml increments of fluid. The left ventricular end-diastolic volume was then calculated directly from the resulting pressure-volume curve and the recorded LVEDP.

Stroke work in gram-meters was calculated as [(MAP − LVEDP) (SV) (1.36)]/100, where MAP = mean blood pressure, LVEDP = left ventricular end-diastolic pressure (in millimeters Hg), and SV = stroke volume (in milliliters). Stroke power (in gram-meters per second) was obtained by dividing stroke work by the duration of ejection, and mean ventricular ejection rate (in milliliters per second) was calculated by dividing the stroke volume by the duration of ejection. The maximal rate of left ventricular ejection was determined from the peak deflection of the electromagnetic flowmeter tracing. This value for maximal flow velocity in the ascending aorta does not take into account that very small fraction of blood which enters the coronary circulation during early systole. The tension-time index (TTI) in millimeters Hg per second was determined by planimetric integration of the ventricular pressure pulse during ejection (14). External cardiac efficiency was calculated as the ratio (in per cent) between minute work and the work equivalent of the O_2 consumption per minute (15).

Total tangential wall tension at the internal equator was calculated from the LaPlace relation: $T = P\pi r^2$, where T = wall tension in grams, P = intraventricular pressure in gram-centimeters squared, and r = internal left ventricular radius. r was calculated from the end-diastolic volume and the aortic flow rate by assuming a spherical left ventricular model and solving the equation $V = 4/3\pi r^2$ for r. The tensions calculated from the LaPlace relationship were then plotted at 10-msec intervals, and the area (in gram-seconds) under the tension-time curve from the onset of contraction to peak tension was determined by planimetric integration.

Results

Acetylstrophanthidin exerted a positive inotropic effect in each study. As shown in the representative experiment reproduced in Figure 1, it elevated the relationship between LVEDP and stroke volume (Figure 1A), stroke work (1B), stroke power (1C), mean ejection rate (1D), peak aortic flow rate (1E), and the peak left ventricular dp/dt (1F). The effects of the administration of this drug at a constant stroke volume, aortic pres-

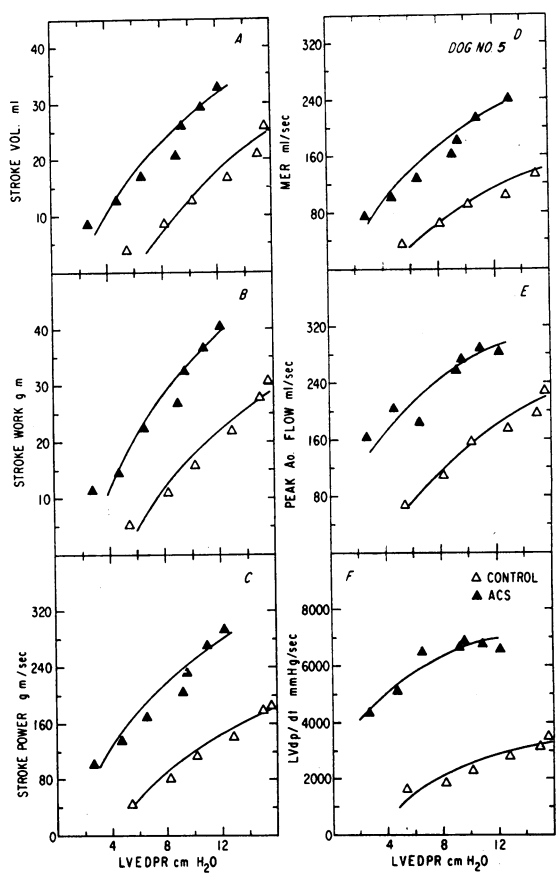

FIG. 1. EFFECTS OF ACETYLSTROPHANTHIDIN (ACS), 0.24 CAT U PER KG, ON MYOCARDIAL PERFORMANCE CURVES IN DOG NO. 5 (HEART WEIGHT = 104 G). Heart rate was maintained at 176 per minute throughout. MER = mean systolic ejection rate; Ao = aortic; LV dp/dt = peak rate of rise of left ventricular pressure. LVEDPR = left ventricular end-diastolic pressure.

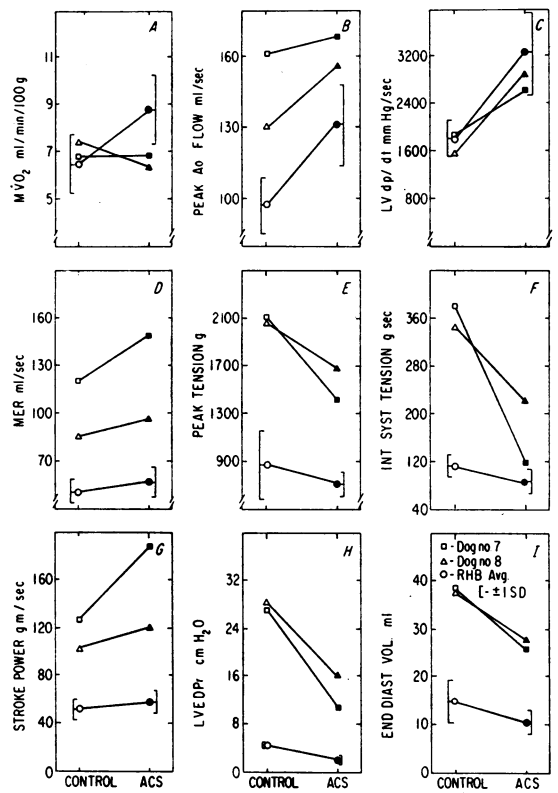

FIG. 2. EFFECTS OF ACETYLSTROPHANTHIDIN. The data shown as circles represent the average values (± 1 SD) in the six right heart bypass (RHB) preparations. The squares and triangles represent the data obtained in experiments no. 7 and 8 in which the LVEDPR was initially high (Table I). MVo_2 = minute myocardial oxygen consumption.

sure, and heart rate are shown in Table I and Figure 2, and representative recordings from both preparations are shown in Figure 3.

The average of duplicate determinations of MVo_2 is shown in Table I; the standard deviation of the differences between duplicate determinations was ± 0.26 ml per minute. In the six experiments with the right heart bypass preparation in which the LVEDP was low, it was observed that MVo_2 rose by an average of 2.56 ml per minute, representing an increase of 34% (Figure 2A). Since mean aortic pressure and stroke volume were maintained constant, left ventricular stroke work also remained essentially unchanged. Accordingly, the ratio of external left ventricular minute work to the work equivalent of the MVo_2, i.e., the external efficiency, decreased in all experiments, by an average of 24.4% of the control value.

TABLE I

*Effects of digitalis on myocardial oxygen consumption**

Exp. no.		HW	ACS dose	MAP	SV	HR	P dp/dt	PAF	CF	MVo_2	LVEDP	LVEDV	SW	SP	MER	TTI	PT	IST
		g	*CU/kg*	*mm Hg*	*ml*		*mm Hg/sec*	*ml/sec*	*ml/min*	*ml O_2/min*	*cm H_2O*	*ml*	*g-m*	*g-m/sec*	*ml/sec*	*mm Hg/sec*	*g*	*g-sec*
1	C	138		70	7.0	138	1,157	99	104	5.85	3.1	10.0	6.4	38	41	13.0	594	66.2
	ACS		0.19	68	7.0	138	1,736	130	130	7.58	2.4	9.3	6.3	41	45	12.0	596	45.4
2	C	133		73	8.9	145	1,277	120	74	7.82	3.3	25.0	8.6	55	57	11.9	1,092	163.7
	ACS		0.25	74	8.3	154	1,724	140	93	8.11	2.0	19.5	8.2	61	62	11.2	966	116.1
3	C	110		80	8.1	179	2,500	111	87	9.79	4.1	14.0	8.7	60	56	12.7	842	80.9
	ACS		0.25	77	8.1	179	4,800	162	140	14.02	1.4	10.0	8.6	59	56	10.4	723	48.2
4	C	106		83	4.2	176	1,640	58	44	6.45	2.7	12.0	4.6	28	25	11.5	826	98.9
	ACS		0.29	80	4.2	176	3,220	81	74	10.71	0.0	6.1	4.6	33	32	10.2	573	51.8
5	C	104		80	7.0	176	1,720	110	64	8.06	7.2	20.0	7.2	49	48	12.3	1,118	167.9
	ACS		0.24	77	7.0	176	4,019	165	77	10.63	1.4	9.8	7.1	63	61	9.8	675	62.7
6	C	126		74	7.3	152	2,440	84	135	7.59	4.1	10.8	7.0	44	46	14.1	750	88.0
	ACS		0.24	75	7.3	152	4,018	111	138	9.83	3.4	9.6	7.2	50	50	14.7	729	70.3
Av.	C	119.5		77	7.1	161	1,789	97	85	7.59	4.1	15.3	7.1	45.7	46.5	12.6	870	110.9
	ACS		0.24	75	7.0	162	3,253	132	109	10.15	1.8	10.7	7.0	51.2	51.0	11.4	710	65.8
7†	C	144		97	23.2	129	1,832	161	127	9.79	27.2	40.5	24.3	122	116	23.1	2,117	379.9
	ACS		0.25	100	23.2	129	2,611	168	135	9.79	10.9	27.6	28.7	185	150	18.1	1,420	116.5
8†	C	107		104	15.8	130	1,550	130	84	7.69	28.6	38.0	17.8	103	85	22.0	2,069	344.4
	ACS		0.40	105	15.8	130	2,900	152	164	6.64	16.3	28.0	20.0	120	96	19.2	1,697	221.4
ACS + preload				105	22.1	130	3,973	200	186	10.60	27.2	37.2	25.5	138	120	23.0	2,172	334.5

* Abbreviations: C = control; ACS = acetylstrophanthidin; HW = heart weight; CU = cat units; MAP = mean aortic pressure; SV = stroke volume; HR = heart rate; P dp/dt = peak first derivative of the left ventricular pressure; PAF = peak aortic flow rate; CF = coronary flow; MVo_2 = minute myocardial oxygen consumption; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; SW = stroke work; SP = stroke power; MER = mean ejection rate; TTI = tension-time index; PT = peak left ventricular tension; IST = integrated systolic tension; ACS + preload = increased SV in experiment no. 8. See text.
† Oxygenator preparation. See text.

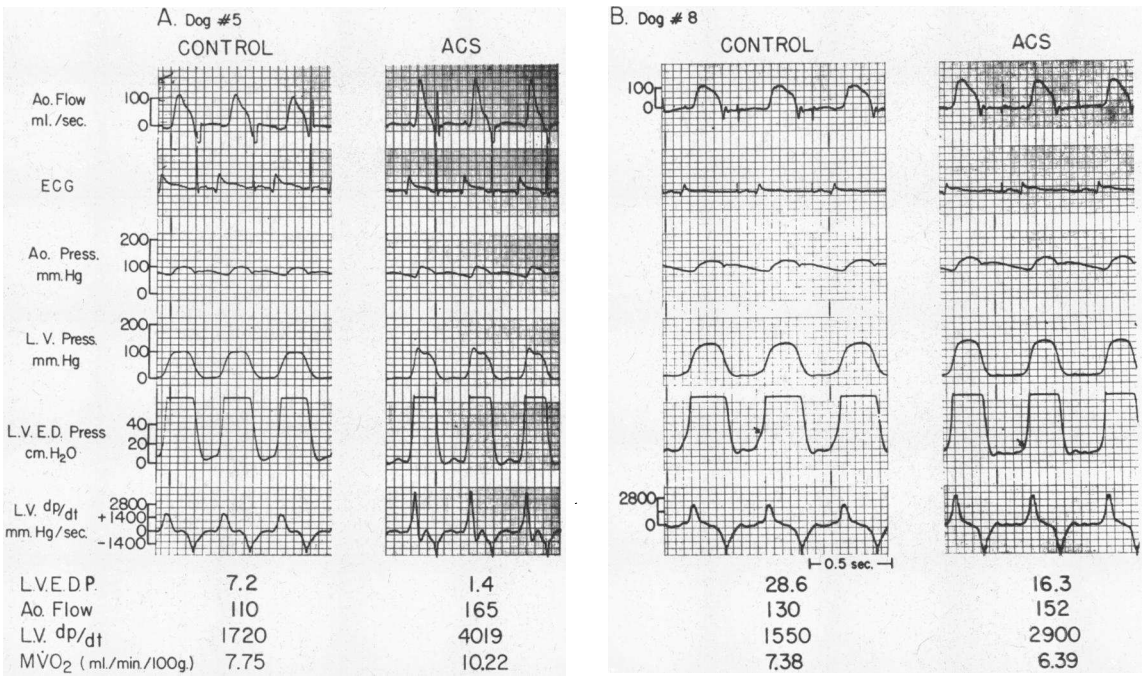

FIG. 3. REPRESENTATIVE TRACINGS OBTAINED FROM TWO EXPERIMENTS.

The peak aortic flow rate, peak rate of rise of left ventricular pressure, mean systolic ejection rate, and stroke power increased significantly, by averages of 36%, 82%, 11%, and 12% of control, respectively (Figure 2B, C, D, G).

The LVEDP was low during the control period (average = 4.1 cm H_2O) and decreased slightly, by an average of 2.3 cm H_2O, after the administration of acetylstrophanthidin (Figure 2H). Similarly, left ventricular end-diastolic volume decreased slightly (Figure 2I). Since aortic pressure was held constant and left ventricular end-diastolic volume declined somewhat, peak left ventricular tension decreased slightly, from an average of 870 g to an average of 710 g (Figure 2E). Since the duration of ejection also tended to decrease, the integrated systolic tension fell somewhat more than the peak tension, from an average of 110.9 g-sec to an average of 65.8 g-sec (Figure 2F).

The results of the two experiments (Table I, no. 7 and 8) in which the control LVEDP and left ventricular end-diastolic volume were markedly elevated differed from those observed in the right heart bypass preparation. Thus, MVo_2 either remained constant after acetylstrophanthidin (no. 7) or declined slightly (no. 8) (Figure 2A). In contrast to the right heart bypass experiments, administration of acetylstrophanthidin now resulted in a marked decrease in LVEDP and left ventricular end-diastolic volume (Figure 2H and I), and as a consequence, peak left ventricular tension and integrated systolic tension declined to a far greater extent than in the right heart bypass preparations (Figure 2E and F). On the other hand, the increases in peak aortic flow, left ventricular dp/dt, and mean systolic ejection rate were comparable to those observed in the six experiments carried out in the right heart bypass preparation.

In experiment no. 8 the administration of acetylstrophanthidin lowered LVEDP from 28.6 to 16.3 cm of H_2O. While the effect of the drug persisted, the LVEDP was re-elevated to 27.2 cm H_2O by increasing stroke volume (Figure 4). This intervention allowed examination of the effects of acetylstrophanthidin on MVo_2 at comparable values of peak and integrated tension. Under these conditions MVo_2 rose significantly above control, from 7.69 to 10.6 ml per minute (Figure 4).

Discussion

Numerous investigators have studied the effects of cardiac glycosides on MVo_2, but the results have been conflicting. In most experiments the

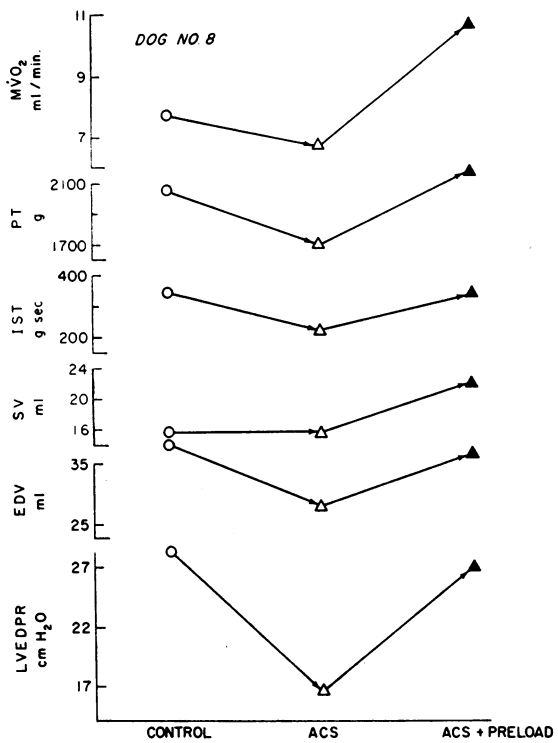

FIG. 4. SUMMARY OF RESULTS IN EXPERIMENT NO. 8. Initially the effects of ACS were determined while the inotropic effect of the drug was permitted to decrease left ventricular end-diastolic pressure and volume (EDV). Then, while the ACS was still acting, ventricular inflow (preload) was increased and LVEDPR and EDV returned close to control levels. PT = peak systolic tension. IST = integrated systolic tension. SV = stroke volume.

O_2 uptake of fresh heart slices and of homogenates of heart muscle and heart muscle mitochondria did not appear to be affected by digitalis substances (16–19). Lee observed in the isometrically contracting, isolated cat papillary muscle that ouabain first increased contractility without affecting $\dot{V}o_2$, but that $\dot{V}o_2$ then rose as the peak inotropic effect was reached and continued to rise as the muscle went into contracture (20, 21). Rohde and Ogawa in 1912 found that strophanthidin increased MVo_2 in the isovolumic cat heart and that this increase was proportional to the augmentation of the product of ventricular pulse pressure and heart rate induced by the drug (22). Peters and Visscher (23) and Moe and Visscher (24) reported that cardiac glycosides tended to increase MVo_2 in the canine heart-lung preparation in which end-diastolic volume was held constant, although in some experiments no change in MVo_2 occurred.

On the other hand, several studies support the contention that digitalis does not affect MVo_2, or even decreases it. Thus, Gremels described a decline in MVo_2 and an increase in efficiency after digitalis administration in the isolated heart-lung preparation (2, 3). Gollwitzer-Meier and Krüger noted no change in MVo_2 in fresh heart-lung preparations and a fall in MVo_2 in grossly failing preparations (4). Olson, Roush, and Liang reported that acetylstrophanthidin did not alter MVo_2 in the failing intact dog heart (5), and Bing and his colleagues (6, 7) observed no alteration in MVo_2 when strophanthidin or lanatoside C was administered to normal subjects or to patients with heart failure. The problem was most recently investigated by Sarnoff and his collaborators in the isolated support canine heart (8). These workers observed that acetylstrophanthidin produced a marked increase in myocardial contractility without a change in either MVo_2 or external efficiency, although they appreciated that the reduction of ventricular end-diastolic volume produced by the drug would be expected to diminish the MVo_2.

Although considerable data indicate that digitalis may exert a positive inotropic effect without increasing MVo_2, our finding of significant augmentation of MVo_2 induced by acetylstrophanthidin contrasts sharply with the results of most of the experiments reviewed above. The present results are in accord, however, with the findings in earlier studies from this laboratory in which the effects of three other inotropic interventions, i.e., paired electrical stimulation, norepinephrine, and calcium were found to augment MVo_2 substantially (11, 12).

This disparity of results may be understood by analyzing the effects of an inotropic intervention on MVo_2, relative to its action on the mechanical factors of contraction that are known to affect the MVo_2. In the right heart bypass preparation, the stroke volume, aortic pressure, and heart rate were all held constant; moreover, since in this nonfailing preparation the LVEDP and left ventricular end-diastolic volume were initially in a low physiological range, these two variables could not decline a great deal after administration of acetylstrophanthidin. Accordingly, both the peak and integrated left ventricular systolic tensions de-

creased relatively little after acetylstrophanthidin had been administered. If the drug had exerted no other hemodynamic effect, then the decline in tension, albeit small, would have been expected to result in a slightly lower MVo_2 (14, 25, 26). However, acetylstrophanthidin also markedly increased the velocity of myocardial fiber shortening as reflected in the augmentation of the peak rate of left ventricular ejection, the peak rate of left ventricular pressure rise, and the mean systolic ejection rate.

Data have previously been presented to support the position that the velocity of myocardial fiber shortening accompanying a basic improvement in contractile state is an important determinant of MVo_2 (11, 12). It would thus appear that the augmentation of MVo_2 observed in the present study is related, at least in part, to this increase in the velocity of myocardial fiber shortening resulting from the increase in the contractile state after acetylstrophanthidin. The digitalis substance also augmented the extent of myocardial shortening. If we assume the left ventricle to have a spherical shape, the left ventricular internal circumference decreased by an average of 2.11 cm, representing 22.9% of the end-diastolic circumference, during each systole in the control period, and by 2.78 cm, representing 33.5% of the end-diastolic circumference during each systole after the acetylstrophanthidin. Therefore, it is possible that this increase in the extent of fiber shortening also played a role in the observed augmentation of MVo_2. Nevertheless, it is clear from this and previous studies (11, 12) that whenever an increase in the contractile state of the heart is induced, as characterized by an augmentation of the intrinsic velocity of muscle shortening, an augmentation of MVo_2 occurs even though there are no changes in external work performance or tension generation.

The major difference between the right heart bypass preparation and the isolated heart or heart-lung preparations employed by earlier investigators who studied the effects of digitalis on MVo_2 therefore appears to lie in the fact that the former preparation was nonfailing whereas the latter were in varying degrees of failure and their LVEDP and left ventricular end-diastolic volumes were of necessity markedly elevated. For example, in the study by Sarnoff and co-workers (8), the control value of LVEDP averaged 19.5 cm of H_2O before the acetylstrophanthidin and was markedly decreased, to an average of 8.6 cm H_2O, after the drug. In contrast, in the present study the control value of LVEDP averaged only 4.1 cm H_2O and declined by only 2.3 cm H_2O. Striking decreases in ventricular end-diastolic volume were also induced by digitalis in the failing hearts studied by Gollwitzer-Meier and Krüger (4). In the face of a constant aortic pressure these striking decreases in ventricular end-diastolic pressure and volume must have been associated with large reductions of ventricular wall tension. Since myocardial wall tension is generally accepted to be an important determinant of MVo_2 (14, 25, 26), the marked decreases in tension occurring in earlier experiments would have been expected to reduce MVo_2 and to oppose the augmentation of MVo_2 resulting from the increased velocity of myocardial fiber shortening and V_{max} (maximal velocity).

The results of several of the earlier investigations are in accord with this hypothesis. As mentioned earlier, digitalis glycosides increased MVo_2 in experiments in which ventricular end-diastolic volume was held constant (22–24). Furthermore, the findings in two of our experiments, in which the level of LVEDP and left ventricular end-diastolic volume before the administration of acetylstrophanthidin were purposely elevated, also support the view that the fall in myocardial tension occurring in the failing heart may mask the increase in MVo_2 produced by digitalis. In these two experiments (Table I, no. 7 and 8) acetylstrophanthidin augmented the peak aortic flow rate, mean ejection rate, and left ventricular dp/dt to about the same extent as in the right heart bypass preparation. However, the absolute reductions in left ventricular tensions, both peak and integrated, were far greater than in the right heart bypass preparation, and MVo_2 failed to rise. Finally, in experiment no. 8, in which LVEDP and left ventricular end-diastolic volume were re-elevated to control levels after the administration of acetylstrophanthidin, thus preventing the decline in left ventricular tension produced by the drug, MVo_2 was observed to rise to values exceeding control (Figure 4).

The results of the present investigation are relevant to a consideration of the effects of digitalis on

MVo_2 in man. Cardiac glycosides have been shown to elevate systemic vascular resistance (27) and arterial pressure (28) and to increase the velocity of myocardial contraction, as reflected in augmentations of the rate of rise of intraventricular pressure (29), mean systolic ejection rate (30), and the rate of movement of radiopaque markers on the ventricles (10). These hemodynamic changes would tend to increase MVo_2 and in the presence of coronary artery disease without heart failure could lead to myocardial ischemia. On the other hand, in the presence of heart failure, the reduction in heart size induced by digitalis would tend to reduce myocardial wall tension and thus prevent the augmentation of MVo_2.

Summary

There has been considerable dispute concerning the effects of digitalis on myocardial O_2 consumption (MVo_2) and efficiency. Analysis of previous data suggested that the interpretation of results was complicated by the changes in circulatory dynamics induced by the drug. Accordingly, the effects of acetylstrophanthidin (average dose = 0.26 cat U per kg) were studied in six nonfailing, canine, right heart bypass preparations in which heart rate, stroke volume, and mean aortic pressure were held constant. MVo_2 increased in all experiments, by an average of 2.56 ml per minute, whereas calculated cardiac efficiency declined by an average of 24.4% of control. Even though mean arterial pressure was held constant, the glycoside reduced the integrated systolic tension by an average of 40%, and the peak systolic tension by an average of 18%, chiefly as a consequence of a small decline in left ventricular end-diastolic volume. However, the velocity of myocardial fiber shortening increased considerably, the peak left ventricular ejection rate rising an average of 36% and the peak ventricular dp/dt increasing by an average of 82%. Acetylstrophanthidin did not alter MVo_2 in two hearts which were studied in an identical manner, but in which left ventricular end-diastolic pressure was initially elevated. However, in those experiments the large fall in end-diastolic volume resulted in a marked fall in systolic tension.

We conclude that digitalis tends to increase MVo_2 but that its strongly positive inotropic effect frequently results in a reduction of ventricular wall tension that tends to oppose and to mask this effect.

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