STUDIES ON DIGITALIS. IV. OBSERVATIONS IN MAN ON THE EFFECTS OF DIGITALIS PREPARATIONS ON THE CONTRACTILITY OF THE NON-FAILING HEART AND ON TOTAL VASCULAR RESISTANCE

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The observations that digitalis exerts a positive inotropic effect on the cat papillary muscle (1) and on the tortoise ventricle (2) led to the view, now generally accepted, that the salutary clinical and hemodynamic effects of this drug in congestive heart failure result primarily from its direct stimulation of myocardial contraction (3). This concept has received support from hemodynamic studies in patients with heart failure, demonstrating that digitalization results in an augmentation of the cardiac output and a lowering of the end-diastolic pressure of the failing ventricle (4–9). Considerable confusion still exists, however, concerning the effects of digitalis on the non-failing human heart, since in the absence of clinical heart failure acute digitalization either depresses the cardiac output slightly or produces no significant change in any hemodynamic parameter (6, 8, 10–14). Such observations have led to the contention that digitalis does not stimulate the non-failing human heart (12, 13, 15, 16).

In the present investigation the direct effects of digitalis preparations on the contractile force of the non-failing human heart were measured with the Walton-Brodie strain gage arch (17). This instrument has been extensively utilized in the study of the effects of drugs on the heart both in the dog (18) and in man (19, 20) and has also been found useful for monitoring myocardial contractile force during cardiac operations (21). In addition, observations were made to ascertain whether or not digitalis preparations have any direct action on the human systemic vascular bed.

METHODS

Digitalization was carried out during cardiovascular operations in 21 patients (Table I). In 18 of these the drug was administered in the course of an open operation during total cardiopulmonary bypass. These 18 patients ranged from 4 to 40 years and averaged 22 years of age. Sixteen of the patients had atrial septal defects and 2 had valvular pulmonic stenosis. None of the patients had a history of congestive heart failure, and although several patients had experienced mild limitation of exercise, in none was this limitation even moderately severe. All were studied by cardiac catheterization before operation, and moderate pulmonary hypertension (systolic pressure greater than 40 mm Hg) was present in 3 of the 16 patients with atrial septal defect. In several of the subjects with this anomaly a small systolic pressure gradient between the right ventricle and the pulmonary artery existed, presumably due to the excessive blood flow across the pulmonic orifice. However, in no patient was the right ventricular end-diastolic pressure elevated above the upper limit of normal (5 mm Hg). Fourteen of the 18 patients who were studied while they were on cardiopulmonary bypass received acetylstrophanthidin, the total dose ranging from 0.5 to 1.5 mg (average 1.15 mg). This dose equaled 0.013 to 0.036 mg per kg and averaged 0.026 mg per kg or 0.155 cat units per kg body weight. In general, smaller doses of acetylstrophanthidin were employed in the early portion of this study. When it became apparent that these doses resulted in no toxic effects they were gradually increased. Three of the other 4 patients digitalized while on cardiopulmonary bypass received 1.2 mg of lanatoside C, while the fourth patient received 0.80 mg of this glycoside. These doses equaled 0.021 to 0.026 mg per kg and averaged 0.022, or 0.088 cat units per kg body weight. It should be noted that the volume of blood circulating in these patients was increased by the volume of the extracorporeal circuit. However, it is not certain that the dilution of the glycosides by this increased circulating volume would modify the uptake of the glycosides by the myocardium.

Three adult patients with rheumatic heart disease received 1.0 to 1.5 mg acetylstrophanthidin immediately after mitral commissurotomy. None of these patients had experienced congestive heart failure and none had an elevated left ventricular end-diastolic pressure before operation, but two had moderate pulmonary hypertension.

For all patients, the pre-anesthetic medications included meperidine (25 to 75 mg), scopolamine (0.1 to 0.4 mg) and promethazine (15 to 50 mg). After intravenous thiopental induction, light general anesthesia was main-

TABLE I

Hemodynamic observations in patients digitalized during operation *

Patient	Age	Weight	Preoperative catheterization data			Dose	Cont. force incr.	Systemic vasc. resist. incr.
			RV press. s/d	PA press. s/d	P/S flow ratio			
	yrs	*kg*	*mm Hg*	*mm Hg*		*mg*	%	%
		Atrial septal defect				Acetylstrophanthidin		
C.R.	8	22	20/0	17/8	1.47	0.7	39	10
G.B.	13	32	25/4	22/7	1.38	1.0	43	13
D.G.	14	49	24/4	24/7	1.64	0.7	16	9
D.R.	18	51	46/5	35/10	1.54	1.0	62	35
E.R.	19	69	34/0	30/10	2.47	1.4	50	29
R.T.	24	65	23/3	20/8	3.03	1.5	117	58
M.T.	28	63	24/0	20/9	2.35	1.5	247	16
A.S.	30	69	32/0	28/10	1.74	1.5	57	29
N.R.	31	60	34/5	26/10	1.96	0.8	UN	10
C.T.	8	23	42/1	40/12	2.24	0.7	36	25
A.T.	27	53	40/2	40/8	2.35	1.5	UN	25
H.L.	28	43	72/2	64/28	1.81	1.4	327	36
		Atrial septal defect				Lanatoside C		
S.W.	11	31	32/0	28/10	2.41	0.8	10	10
J.B.	29	58	26/4	21/6	2.19	1.2	57	10
D.M.	34	58	30/0	26/10	2.04	1.2	UN	34
E.S.	40	57	32/5	30/11	3.91	1.2	26	0
		Pulmonic stenosis				Acetylstrophanthidin		
C.I.	4	17	110/5	11/5	1.0	0.5	30	0
D.A.	29	42	98/5	12/4	1.5	1.5	45	UN
		Mitral stenosis				Acetylstrophanthidin		
R.P.	19	67	48/5	48/22	1.0	1.0	16	
L.R.	30	60	30/4	27/16	1.0	1.25	30	
P.C.	45	69	65/7	65/42	1.0	1.5	25	

* RV press., right ventricular pressure; PA press., pulmonary artery pressure; P/S flow ratio, pulmonic systemic flow ratio; s/d, systolic/diastolic; Cont. force incr., increase in contractile force expressed as per cent above control levels; systemic vasc. resist. incr., increase in systemic vascular resistance expressed as per cent above control levels; UN, recording unsuitable for analysis.

tained with nitrous oxide-oxygen; a muscle relaxant, either succinylcholine or *d*-tubocurarine was also used. Thiopental and meperidine were administered intermittently in small doses.

In the 18 patients who were digitalized while on cardiopulmonary bypass, a median sternotomy was performed, the pericardium was opened and the strain gage arch was sutured to a convenient area on the right ventricle; the segment of myocardium between the two feet of the arch was stretched by about 50 per cent of its diastolic length. Total cardiopulmonary bypass was instituted with a rotating disc oxygenator and a single arm roller pump. Venous blood was drained from the venae cavae by gravity. A square-wave electromagnetic flowmeter (22, 23) in the arterial line was used to permit constant monitoring of the volume of arterial return and insured that the perfusion rate remained constant, ordinarily at 2.2 L per minute per m^2 BSA. The arterialized blood was returned into the cannulated femoral artery; the coronary flow was not interrupted. Arterial blood pressure was measured by means of a Statham pressure transducer through either a polyethylene catheter in the left radial artery or an indwelling needle in the brachial artery. Continuous recordings of the mean arterial and central venous pressures, myocardial contractile force, the electrocardiogram and the perfusion rate were made with a multichannel photographic oscillograph. Approximately 5 minutes after bypass was established and the right atrium or pulmonary artery had been opened, all of the hemodynamic parameters, as well as the myocardial contractile force, had stabilized and at this time the glycoside was administered by rapid injection into the arterial return line of the extracorporeal circuit.

In the 3 patients with rheumatic mitral stenosis who were studied, a left thoracotomy was performed and the strain gage arch sutured to the surface of the left ventricle. In one of these patients a second arch was attached to the surface of the right ventricle. Acetylstrophanthidin was administered intravenously during a five minute period after the commissurotomy had been performed and at a time when both the contractile force and arterial pressure were stable.

The contractile force recorded by the strain gage arch is dependent not only upon the force of contraction of the fibers to which the gage is attached but also the extent to which these fibers have been stretched and the

depth of the sutures which hold the gage to the myocardium (24). Since the electrical output of the arch and, therefore, the resultant deflection in the recording are directly proportional to the contractile force, the alterations in contractile force resulting from the administration of the digitalis preparations were expressed as relative changes from the control level rather than in absolute terms.

RESULTS

Contractile force. Recordings of contractile force were suitable for analysis in 12 of the 14 patients to whom acetylstrophanthidin was administered during cardiopulmonary bypass. The contractile force was increased in every patient, the values at the time of maximal effect ranging from 16 to 327 per cent and averaging 89 per cent greater than the contractile force prior to digitalization (Figures 1 and 2). Contractile force began to increase between 2 and 5 minutes after injection; the maximal change was noted 5 to 20 minutes (average 11.3) following injection. Termination of the intracardiac procedure and the cessation of perfusion prohibited determination of the duration of the inotropic effect. Contractile force recordings satisfactory for analysis were obtained in three of the four patients to whom lanatoside C was given. The maximal contractile force increases were 10, 57 and 26 per cent of the control values (average increase 31 per cent). The peak effect was observed 18, 20 and 27 minutes (average 22) after injection.

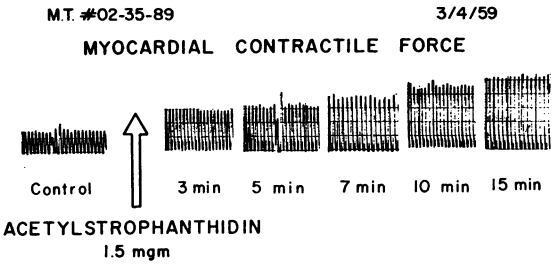

FIG. 1. MYOCARDIAL CONTRACTILE FORCE RECORDINGS IMMEDIATELY PRIOR TO AND AT INTERVALS FOLLOWING THE ADMINISTRATION OF 1.5 MG OF ACETYLSTROPHANTHIDIN TO A 28 YEAR OLD WOMAN WITH ATRIAL SEPTAL DEFECT. Augmentation of contractile force is evident 3 minutes after injection.

The maximal increases in left ventricular contractile force were 16, 30 and 25 per cent (average 24) in the three patients with rheumatic mitral stenosis to whom acetylstrophanthidin was given

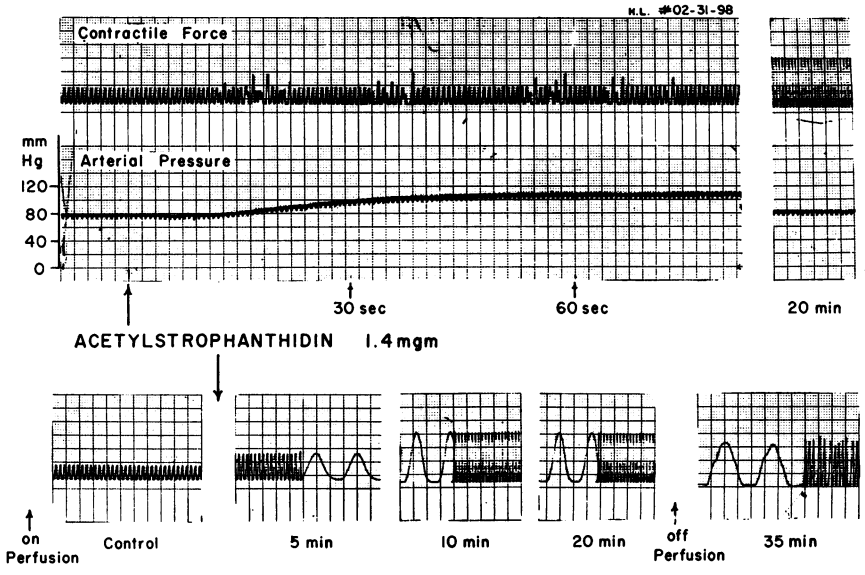

FIG. 2. CONTRACTILE FORCE AND ARTERIAL PRESSURE RECORDINGS IMMEDIATELY AND 20 MINUTES AFTER THE INJECTION OF 1.4 MG OF ACETYLSTROPHANTHIDIN, IN A 28 YEAR OLD WOMAN WITH AN ATRIAL SEPTAL DEFECT, ARE REPRODUCED IN THE UPPER TRACINGS. THE LOWER TRACINGS SHOW CONTRACTILE FORCE RECORDINGS BEFORE INJECTION AND AT INTERVALS AFTER ACETYLSTROPHANTHIDIN. THE FINAL RECORDING WAS OBTAINED AFTER BYPASS HAD BEEN COMPLETED, 35 MINUTES AFTER ADMINISTRATION OF THE DRUG.

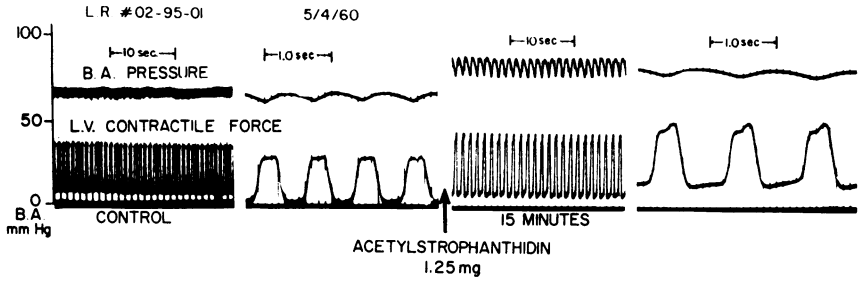

FIG. 3. MEAN BRACHIAL ARTERIAL PRESSURE (B.A.) AND LEFT VENTRICULAR (L.V.) CONTRACTILE FORCE RECORDINGS AT SLOW AND RAPID PAPER SPEEDS IN A 30 YEAR OLD MAN WITH RHEUMATIC MITRAL STENOSIS. The control recordings (left) were obtained just prior to the injection of 1.25 mg of acetylstrophanthidin and the recordings on the right were made 15 minutes after the completion of the injection. The scale on the left refers to the arterial pressure. The baseline of the contractile force recording was not maintained constant. Following acetylstrophanthidin, the elevation of arterial pressure and of contractile force and the slowing of the heart rate are evident.

(Figure 3). In the patient in this group (P.C.) in whom right ventricular contractile force was also recorded, a 33 per cent increase was observed.

No drugs were administered to 12 "control" patients with a variety of congenital cardiovascular anomalies in whom recordings of right ventricular contractile force were carried out during cardiopulmonary bypass. In one patient the contractile force increased by 8 per cent during the course of the perfusion; in five patients this parameter decreased by 5 to 15 per cent of the control value.

Systemic vascular resistance. Since the systemic perfusion rate was held constant during cardiopulmonary bypass, any change in arterial pressure reflects a change in systemic vascular resistance. Mean arterial pressure rose in all but one of the 13 patients who received acetylstrophanthidin while on cardiopulmonary bypass. The changes in systemic vascular resistance ranged from 0 to + 58 per cent and averaged + 23 per cent of the control level (Table I). The arterial pressure rose almost immediately—i.e., within 30 seconds of the injection (Figures 2 and 4). The pressure reached a peak in an average of 3 minutes following injection, and usually gradually declined toward control levels during the remainder of the perfusion.

Arterial pressure rose in three of the four patients who received lanatoside C and it remained unchanged in the fourth patient. The changes in systemic vascular resistance ranged from 0 to + 34 per cent and averaged + 14 per cent of control levels.

No systematic change in arterial pressure occurred during the course of the perfusion in any of the 12 patients to whom no drug was administered.

DISCUSSION

The Walton-Brodie strain gage arch records the isometric tension developed by the fibers to which it has been applied (24) and it is therefore

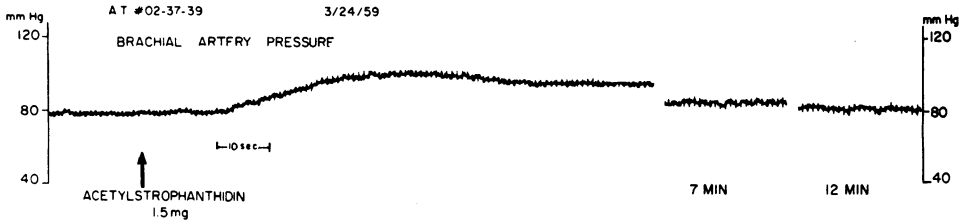

FIG. 4. RECORDING OF BRACHIAL ARTERIAL PRESSURE OBTAINED IN A 27 YEAR OLD WOMAN WHILE HER ATRIAL SEPTAL DEFECT WAS BEING REPAIRED DURING CARDIOPULMONARY BYPASS AT A CONSTANT SYSTEMIC PERFUSION RATE. Arterial pressure begins to rise 20 seconds after the injection. Seven minutes after injection the pressure has already fallen and 12 minutes after injection it is only slightly higher than the control level.

of value in the study of the direct effects of drugs and of other interventions on myocardial contractile force. In the present investigation, as well as in previous ones (19–21), it was found to be as applicable in man as in the experimental animal. Its presence did not interfere with the operation and no complication arose from its use; all of the patients whose data are recorded above survived operation.

Although alterations in the length of the fibers to which the gage is attached modify the contractile force which these fibers develop, such changes in length were minimized by initially stretching the segment of myocardium to which the gage was attached (24). Since the strain gage arch was placed on the right ventricle in most of the patients, other possible effects of changes in peripheral vascular resistance were minimized. In addition, most of the observations reported herein were carried out with the patients on cardiopulmonary bypass, at a constant systemic perfusion rate, and with the right side of the heart open to atmosphere and therefore completely decompressed. These conditions assured that the length of the segment of myocardium to which the gage was attached was constant.

A substantial body of evidence has now been accumulated which supports the contention that digitalis glycosides augment the contractile force of the non-failing dog heart. Wiggers and Stimson (25) and Cotten and Bay (24) found that these drugs shorten the duration of the period of isometric contraction. Walton, Leary and Jones (26), Cotten and Bay (24) and Cotten and Stopp (27) observed that digitalis augments the contractile force of the non-failing heart in experiments on dogs with open chests as well as in unanesthetized dogs with closed chests. Cotten and Stopp (27) showed that digitalis elevates the left ventricular function curve (28).

The experiments reported herein extend these findings to man and demonstrate that two digitalis preparations, acetylstrophanthidin, and lanatoside C, produce a substantial augmentation of the force of ventricular contraction when they are administered to patients who are not in heart failure. However, the patients with atrial septal defect and those with pulmonic stenosis undoubtedly had right ventricular dilatation and/or hypertrophy. In order to determine the actions of the digitalis preparations on myocardium which had not been subjected to an abnormal hemodynamic burden for a prolonged period of time, the effects of acetylstrophanthidin on left ventricular contractile force were recorded in three patients immediately following mitral valvulotomy; the drug elevated left ventricular contractile force in each instance. The relative increments in contractile force were somewhat smaller in these three studies than in the patients digitalized during cardiopulmonary bypass. The significance of this difference is difficult to interpret because: *1*) there was a wide scatter of the contractile force responses in both groups of patients; *2*) the conditions under which the drug was given differed appreciably in the two groups; and *3*) in the patients studied during cardiopulmonary bypass the strain gage arch was attached to the *right* ventricle, while in the patients with mitral stenosis, it was placed on the *left* ventricle.

Although digitalization was found to augment the force of contraction in chronically stressed nonfailing hearts, the possibility that the stimulating effects are of different intensity in failing hearts or in entirely normal hearts has not been excluded. The concept that digitalis glycosides either have no effect on the non-failing heart or actually depress its contractility arose from the observations which showed that these drugs do not either modify or decrease the cardiac output, both in the dog (29, 30) and in man (6, 8, 10–14). This view received support from the experiments of Wedd and Blair who noted that, although digitalis did not stimulate contractions of strips of turtle ventricle, an augmentation of contraction did occur when digitalis was applied after the contractility of the muscle had been depressed by a variety of chemicals or by reduction of the pH (31). Furthermore, Olson recently reported that when the administration of digitoxin to dogs in experimental congestive heart failure resulted in clinical improvement, the abnormally elevated intrinsic viscosity of myosin which occurs in experimental heart failure was restored to normal; however, digitoxin did not alter the viscosity of the myosin of the non-failing heart (32). On the other hand, Kako and Bing found that digoxin and ionic calcium augmented the contractility of

actomyosin threads obtained from normal hearts as well as those from the hearts of patients with congestive heart failure (33).

The observation that digitalis profoundly augments the contractile force of the non-failing heart, without elevating its output, serves to re-emphasize the view that alterations of cardiac output are of little value in predicting changes in myocardial contractility (28). The effects of norepinephrine on the human heart are somewhat analogous, since this drug increases myocardial contractile force (20) without raising cardiac output (34). In the case of digitalis, it is possible that the actions of the drug on the peripheral circulation may be responsible for the discrepancy between the changes in cardiac output and in myocardial contractile force. In other studies in dogs carried out in this laboratory (35), digitalization resulted in an augmentation of intravascular blood volume and a decline in the venous return to the extracorporeal circuit. Similarly, Cotten and Stopp (27) observed in dogs that the decline in cardiac output following digitalization was associated with a fall in left atrial pressure. However, when the left atrial pressure was held constant by means of blood infusion, digitalis resulted in an elevation of cardiac output. It would appear likely that, in the dog, digitalis results in constriction of the hepatic venous sphincter with trapping of blood in the splanchnic bed and elevation of portal venous pressure. The resultant decline in ventricular filling pressure prevents the increased contractility from expressing itself as an increased cardiac output. It is possible that a similar mechanism operates in the human subject without heart failure and accounts for the dissociation between myocardial contractile force and cardiac output. Indeed, the studies of Baschieri, Ricci, Mazzuoli and Vassalle (36) have shown that, in man, digitalis elevates hepatic vein wedge pressure and lowers splanchnic blood flow, thus producing a substantial augmentation of hepatic vascular resistance.

In view of the positive inotropic effect of digitalis on the non-failing heart, the fear of cardiac depression when these drugs are used "prophylactically" (15, 16, 37) would not seem to be warranted. Thus, the exhibition of cardiac glycosides does not appear to be contraindicated in patients without overt heart failure in whom the development of heart failure is feared because of the superimposition of an excessive hemodynamic burden resulting from an acute infection or surgical procedure. Indeed, the demonstration in the present study of the substantial augmentation of contractile force provided by digitalis has led to the establishment of a policy at the National Heart Institute to digitalize all patients prior to intracardiac surgery.

The administration of a drug to a patient on cardiopulmonary bypass makes it possible to determine its direct effects on the systemic vascular resistance. The hemodynamic dissociation of the heart from the peripheral circulation facilitates study of the latter, since any changes in arterial pressure which occur while the systemic perfusion rate is held constant reflect changes in the systemic vascular resistance. Although it has long been suspected that digitalis produces systemic vasoconstriction (38, 39) the powerful cardiac effects of this drug made it difficult to interpret precisely the changes in arterial blood pressure. In an earlier study carried out on dogs on cardiopulmonary bypass, it was demonstrated that digitalis glycosides have a direct pressor effect (40). In the present investigation these observations were extended to and confirmed in man.

SUMMARY

The direct effects of two digitalis preparations on the contractile force of the heart were studied by means of the Walton-Brodie strain gage arch in 21 patients who had never experienced congestive heart failure. Fourteen patients with either atrial septal defect or pulmonic stenosis, studied during cardiopulmonary bypass, were given 0.5 to 1.5 mg of acetylstrophanthidin, a dose which averaged 0.026 mg per kg body weight. This resulted in an increase in contractile force which ranged from 16 to 327 per cent and averaged 89 per cent of the contractile force measurement prior to digitalization. In three patients who received an average dose of 0.022 mg per kg of lanatoside C during cardiopulmonary bypass, the right ventricular contractile force increased by an average of 31 per cent of control levels. In an attempt to study the response of a ventricle which had not been subjected to an abnormal hemodynamic burden for a prolonged period of time, left ventricular

contractile force was recorded immediately after mitral valvulotomy in three patients. Acetylstrophanthidin increased contractile force an average of 24 per cent of the control levels. The administration of the digitalis preparations to patients on cardiopulmonary bypass at a constant perfusion rate permitted study of the direct effects of these drugs on systemic vascular resistance. Acetylstrophanthidin resulted in a brief increase in systemic vascular resistance which averaged 23 per cent and lanatoside C resulted in an average increase of 14 per cent of the control levels. It is concluded that these digitalis preparations augment the contractile force of the non-failing human heart and constrict the systemic vascular bed.

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