MYOCARDIAL RESPONSE TO ACETYL STROPHANTHIDIN IN CONGESTIVE HEART FAILURE: A STUDY OF ELECTROLYTES AND CARBOHYDRATE SUBSTRATES *

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The concept of a defect in the conversion of chemical energy to work as the cause of low output heart failure has been based on the finding of normal myocardial extraction of substrate and oxygen in this clinical state (1, 2). However, the alternative view, that there is failure in transformation of the energy of substrate oxidations to a biologically useful form, cannot be excluded (3). Of particular interest, as regards the former theory, is the problem of evaluating those physical-chemical factors which initiate or contribute to the alteration of myocardial protein in heart failure.

A consideration of the role of changes in intracellular ionic content in the regulation of cardiac performance has been stimulated by finding an intimate relation between these parameters in the staircase phenomenon (4). Other isolated muscle work has shown that changes in electrolyte concentration at the superficial level of the cell can affect contractile strength of muscle before the ion penetrates the interior of the muscle (5, 6).

Although there is at present no adequate methodology for precise study of these phenomena in the human heart *in vivo*, it was considered of importance to seek information concerning the myocardial transfer of ions in the limited circumstance

of drug-induced recovery from cardiac failure. In a prior report (7), data were presented which indicated the facility with which acetyl strophanthidin mobilized electrolytes in the myocardium of the intact dog, its abrupt course of action enabling detection of these changes.

METHODS

The design of this study was such as to rely on the assumption that the coronary arteriovenous differences of electrolytes and metabolites could be validly accepted as a measure of their net uptake by, or release from, the myocardium. Although the transcappillary exchange rates of an ion, such as potassium, are blood flow dependent (8), an estimation of the effects of altered blood flow *per se* upon measured arteriovenous differences appeared in order. In the intact human, two procedures which usually increase coronary blood flow, exercise (9) and hypoxia (10), were chosen to study coronary arteriovenous differences of potassium. Five minutes of exercise produced no significant change in six patients. The mean of the planimeted A-V difference areas for potassium was $+0.01 \pm 0.08$ square inches in the control and $+0.06 \pm 0.20$ in the experimental period. Similar results were obtained with hypoxia, induced by 10 per cent oxygen inhalation for 25 minutes in five patients. The mean control value was $+0.06 \pm 0.25$ square inch and the hypoxia value, $+0.27 \pm 0.23$. These findings are in agreement with those of Driscoll and Berne (11), in which coronary blood in the dog was increased up to 100 per cent by varied procedures without significant change in the potassium arteriovenous differences.

The effects of digitalis preparations on coronary blood flow in the human have not been elaborated except for strophanthus, which produced no change (12). If one assumes that acetyl strophanthidin behaves similarly or increases coronary flow within the limits of the above experiments, then inferences may be drawn in regard to net movement of ions. An unexpected decrease in coronary blood flow should reveal increases in extraction of oxygen and cation, events which, as detailed below, did not occur.

Eighteen patients were chosen from the emergency room service, who presented themselves with the usual

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TABLE I

Sequential hemodynamic response to acetyl strophanthidin, 1.1 mg., in five patients with low output heart failure

Patient Age, race, sex Diagnosis B.S.A. in M. ²	Time	Pulse	Mean arterial pressure	Oxygen consump- tion	Systemic A-V oxygen differ- ence	Cardiac output	Stroke output	Stroke work	Mean pressures	
									Pulmo- nary capillary	Pulmo- nary artery
	<i>min.</i>		<i>mm. Hg</i>	<i>ml./min.</i>	<i>ml./L.</i>	<i>L./min.</i>	<i>ml./beat</i>	<i>Gm./M.</i>	<i>mm. Hg</i>	
W. D.	0	120	130	275	85.4	3.22	26.8	34.8	28	44
66, W. M.	5	90		335	84.9	3.95	43.8		40	50
HCVD	15	70	142	265	63.6	4.17	59.7	84.8	37	45
1.78	25	78	120	270	68.3	3.95	50.6	60.7	30	38
M. B.	0	92	176	255	91.5	2.46	26.7	47.0	30	57
38, N. F.	5	92	170	343	81.8	4.19	45.5	77.4		64
HCVD	15	91	182	340	69.1	4.92	54.1	98.5		62
1.95	25	94	170	267	57.3	4.66	49.5	94.2		55
J. B.	0	91	116	303	93.0	3.26	35.8	41.5	28	49
47, N. M.	5	85	132	303	101.3	3.96	45.4	60.0	31	56
ASHD	15	86	122	303	76.6	3.96	46.0	56.1	40	53
2.14	25	86	106	293	73.4	3.99	46.4	49.3	33	54
E. S.	0	115	164	281	104.3	2.69	23.4	38.4	37	68
39, N. F.	5	115	202	360	124.2	2.90	25.2	50.9		70
HCVD	15	103	200	306	93.4	3.28	31.8	63.6		70
1.83	25	102	180	307	85.5	3.59	35.2	63.4		66
J. B.	0	71	123	212	62.7	3.38	47.6	58.5	25	32
49, N. M.	5	68	137	230	55.5	4.14	60.9	83.4		31
ASHD	15	67	111	220	53.6	4.10	61.2	67.9		21
1.77	25	68	100	227	55.7	4.08	60.0	60.0	16	24
Mean values	0	98	141	265	87.4	3.00	32.06	44.0		50
	5	90	160	315	89.5	3.83	44.16	67.9		54
	15	83	151	286	71.3	4.09	50.56	74.2		50
	25	86	135	272	68.0	4.05	48.34	65.5		47

symptoms and evidence of left-sided or left- and right-sided heart failure. X-ray evidence of pulmonary congestion and cardiac enlargement was present in all. There was no evidence of primary valvular heart disease. The clinical types included hypertensive, arteriosclerotic and unknown etiologies. No patient had received digitalis therapy in the preceding three weeks, nor diuretics for the preceding four days. Oxygen, in the semi-Fowler position, was the only therapy received prior to the period of study, which was performed within 18 hours after admission. Nembutal®, 1.5 gr. intramuscularly, was administered about two hours before the collection of the first samples. With catheters in the coronary sinus and right atrium, and a Cournand needle in the brachial artery, simultaneous blood sampling was performed.

Acetyl strophanthidin,¹ 1.1 mg., was injected into the right atrium over a period of one and one-half minutes. The mid-point of injection was considered zero time. Since the hemodynamic response to this drug, in a group of five patients in which serial Fick cardiac outputs were obtained, reached maximum by 15 minutes (Table I), the cardiac output was determined in the experimental group at this time. The control determination was five

minutes before infusion, and, at the same time, simultaneous sampling of arterial and coronary sinus blood for control A-V difference of oxygen, carbon dioxide, glucose, lactate and pyruvate was performed. Sampling for these substances was repeated at 5 to 7 minutes and at 15 minutes after injection of strophanthidin. Paired samples for electrolyte determinations were drawn from the brachial artery and coronary sinus at about 14 and 4 minutes before giving the drug, and approximately at 2, 4, 7, 10, 14, 20 and 25 minutes afterward.

Phasic and mean arterial pressures were obtained at 5 minute intervals with a Sanborn electromanometer and recorded on the Sanborn polyviso. Stroke work against pressure was calculated as the product of the mean femoral artery pressure and stroke output, and expressed in gram-meters (13). The electrocardiogram (Lead V₆ or V₇) was recorded on the polyviso just prior to giving the drug and at 1 minute intervals for 15 minutes; thereafter, at 5 minute intervals.

Oxygen consumption was determined by analysis of expired air and room air for oxygen, on a Pauling oxygen analyzer. The blood gas analyses were carried out in duplicate by the method of Van Slyke and Neil. Determinations of glucose, lactic acid and pyruvic acid, performed in 11 patients of the group, were done by the methods of Somogyi (14), Barker and Summerson (15), and Friedemann and Haugen (16), respectively. Sodium

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TABLE II
Findings before and after 1.1 mg. of acetyl strophanthidin in 18 patients with low output heart failure

Patient Age, race, sex Diagnosis	Time	Stroke output	Stroke work	O ₂ BA-CS	CO ₂ (CS-BA)	Hematocrit		Electrocardiogram				
						BA	CS	Heart rate	QT	ST	T wave	Rhythm
	min.	ml./beat	Gm./M.	ml./100 ml.	ml./100 ml.							
J. B.	0	61.9	66.9	11.73	5.75	40	41	78	0.43	ISO†	Upright	N‡
70, N. M.	5					40	41	82	0.40	S§	S	S
ASHD*	15	96.1	113.4	11.39	9.03	39	40	80	0.40	S	S	S
M. P.	0	41.9	53.6	13.29	9.78	38	39	76	0.38	ISO	Inverted	Few PVC
56, W. M.	5					38	39	70	0.38	S	S	S
HCVD	15	75.5	99.7	12.45	17.73	37	38	66	0.38	S	S	S
W. C.	0	80.9	88.2	12.95	9.75	43	44	80	0.37	ISO	ISO	N
48, N. M.	5			13.01	10.58	44	44	72	0.38	S	S	S
ASHD	15	111.5	131.6	12.90	7.30	43	44	74	0.38	S	S	S
D. M.	0	72.1	77.9					83	0.39	ISO	Inverted	N
42, W. M.	5							82	0.38	S	S	S
HCVD	15	86.9	117.3					80	0.38	S	S	S
B. L.	0	75.6	128.5	7.39	5.43	26	26	91	0.42	ISO	Upright	N
39, W. F.	5					26	26	90	0.41	S	S	S
HCVD/An.	15	87.4	162.6	6.75	4.72	26	26	86	0.41	S	S	S
J. S.	0	37.3	49.2	12.25	8.36			72	0.38	ISO	Upright	N
64, W. M.	5			11.41				63	0.36	Shortened	S	S
HCVD	15	54.8	72.3	11.48	9.38			78	0.38	Shortened	S	S
J. T.	0	25.7	25.2	15.62	13.81	50	50	90	0.32	ISO	Upright	Few PVC¶
45, N. M.	5					50	50	106	0.26	Shortened	Diphasic	N
Idiopathic	15	38.9	43.5	15.97	10.80	49	49	72	0.28	Shortened	Diphasic	N
G. A.	0	25.8	30.2	13.16	15.15	46	46	96	0.34	ISO	Upright	N
38, N. M.	5					45	46	94	0.32	S	S	N
HCVD	15	33.3	44.6	15.4	15.71	45	46	92	0.32	S	S	N
J. T.	0	61.5	96	11.92	10.60	45	45	86	0.38	ISO	Inverted	N
50, W. M.	5					44	45	83	0.39	S	S	N
HCVD	15	66	112	13.01	9.36	45	45	73	0.38	S	S	N
W. C.	0	40.4	32.3	12.00	8.83	40	41	98	0.34	ISO	ISO	N
41, N. M.	5					40	40	72	0.36	S	S	N
Idiopathic	15	46.7	43.9	11.39	9.94	39	40	90	0.34	S	S	N
E. L.	0	28.3	47.0	14.81	11.76	46	46	115	0.33	ISO	Inverted	N
70, W. M.	5					45	45	111	0.30	S	Deeper	Few PVC
HCVD	15	33.2	56.4	13.60	11.16	44	44	120	0.31	S	Deeper	N
E. R.	0	63.8	81.7	12.39	8.27	41	42	77	0.42	ISO	Upright	N
56, N. M.	5			12.30		41	41	72	0.38	S	Diminish.	N
HCVD	15	68.0	87.0	12.36	8.24	41	42	77	0.38	S	Diminish.	N
P. T.	0	57.2	74.4	11.26		46	46	83	0.42	ISO	Diphasic	N
39, N. M.	5					46	46	86	0.41	S	S	N
Myocard.	15	69.1	71.9	11.36		46	46	79	0.41	S	S	N
H. M.	0	58.2	60.5	12.85	9.62	50	50	100	0.34	ISO	Upright	N
40, N. M.	5					50	50	92	0.32	S	S	N
Idiopathic	15	54.9	68.1	10.97	4.11	50	50	100	0.32	S	S	N
H. W.	0	47	69.6	12.04	11.13	47	48	83	0.34	ISO	Inverted	N
39, N. M.	5			13.37	10.32	48	47	81	0.32	S	S	N
HCVD	15	55.5	60.5	12.46	8.84	47	47	83	0.32	S	S	N

* ASHD, arteriosclerotic heart disease.

† ISO, isoelectric.

‡ N, normal.

§ S, same as control period.

|| HCVD, hypertensive cardiovascular disease.

¶ PVC, premature ventricular contractions.

TABLE II—Continued

Patient Age, race, sex Diagnosis	Time	Stroke output	Stroke work	O ₂ BA-CS	CO ₂ (CS-BA)	Hematocrit		Electrocardiogram				
						BA	CS	Heart rate	QT	ST	T wave	Rhythm
	min.	ml./beat	Gm./M.	ml./100 ml.	ml./100 ml.							
L. B.	0	59.1	68.6	10.66	7.39	37	37	84	0.38	ISO	Diphasic	N
50, N. M.	5					36	37	66	0.36	S	S	N
ASHD	15	62.3	52.3	10.49	7.38	36	37	75	0.37	S	S	N
E. L.	0	106.4	173.4	8.80	6.30	30	30	75	0.44	ISO	Upright	Few PVC
51, W. M.	5			8.83	6.07	30	30	71	0.40	S	Diphasic	S
HCVD/An.	15	81.2	139.7	8.25	6.64	29	29	76	0.42	S	Upright	S
D. H.	0	98.6	138.0	7.78	5.38	48	48	86	0.40	ISO	Upright	N
63, W. M.	5					47	47	84	0.40	S	S	N
Idiopathic	15	65.8	55.0	11.91	9.94	47	46	84	0.40	S	S	N
Mean	0			11.82	9.21			86				
values	5							82				
	15			11.89	9.39			83				

and potassium determinations were done in duplicate, with less than 2 per cent error on a Beckman flame photometer, using samples which showed no visible hemolysis. Calcium analysis was done in seven patients by the versene titration method of Zak, Hindman and Fisher (17), with an error of determination less than 3 per cent.

Since the plotting of electrolyte concentrations on linear graph paper would seem to give a more complete picture of the changes occurring than just a comparison of maximum change in arteriovenous differences, identical time periods have been planimeted for comparison (Figure 1). The nadir of the relatively rapid fall in coronary sinus potassium concentration following the maximum response was chosen as the end of an arbitrary period (Period II) during which the maximum response to the drug occurred. The area under the curve was planimeted from the first minute to the end of this period at 10 to 13 minutes. An identical time (Period I) prior to drug injection was measured for comparison in each case, and the same duration was used for Period III, when the maximum hemodynamic response had been attained or was waning. Standard methods were used in applying the test for statistical significance of the observed changes (18).

RESULTS

The general hemodynamic response to 1.1 mg. of intravenous acetyl strophanthidin in five patients is tabulated in Table I. As judged by the per cent increase in stroke work, the major effect had been attained by 5 minutes, and, in two instances, this was the maximum effect observed. The rapid changes during the time of the drug's action make the Fick method less accurate, but the close approximation of the oxygen consumption and pulse rate in two successive determinations, at 5 and 15 minutes for M.B. and J.B., and 15 and 25 minutes

for W.D., E.S. and J.B., indicate sufficient reliability for hemodynamic interpretations. The use of the 15 minute mark to qualitatively assess the inotropic response in the group studied for myocardial metabolism seems warranted by these data. The transient paradoxical rise in pulmonary arterial pressures while the cardiac output is rising probably resulted from a rapid displacement of blood from the periphery at this time.

The patients in Table II have been arranged in decreasing order of stroke output and work response. The fact that 8 of 18 failed to react in a therapeutic way may represent a compounding of several factors: the brief period of action of this

FIG. 1. A REPRESENTATIVE ELECTROLYTE RESPONSE TO ACETYL STROPHANTHIDIN

The equal time periods delimit the time-concentration areas which were planimeted for comparisons. These areas are considered positive when the arterial concentration exceeds the venous, and negative when the venous exceeds the arterial.

TABLE III
Arterial levels and myocardial extraction of carbohydrate substrates

	Lactate				Pyruvate				Glucose									
	Control		7 minutes		15 minutes		Control		7 minutes		15 minutes							
	B.A.	A-V	B.A.	A-V	B.A.	A-V	B.A.	A-V	B.A.	A-V	B.A.	A-V						
M. P.	8.43	+2.40	13.32	+3.10	8.64	+1.51	1.15	+0.30	0.95	+0.29	0.98	+0.24	74.0	+1.5	74.0	+1.5	68.5	-16.0
J. S.	5.37	+2.07	5.46	+2.01	5.34	+0.12	1.19	+0.14	1.02	+0.06	1.09	+0.11	81.0	-0.5	81.0	-0.5	78.5	+ 0.5
J. T.	15.80	+1.80			13.90	+0.60	1.57	+0.16			1.37	+0.15	90.5	+9.0	90.5	+9.0	89.0	+ 0.5
J. T.	14.00	+2.40			11.00	-2.20	1.63	+0.06			1.44	+0.17	84.1	+1.2	84.1	+1.2	85.0	+ 4.9
W. C.	12.60	+3.97	9.66	+3.36	9.87	+4.07	1.73	+0.62	1.36	+0.54	1.34	+0.30	117.0	+1.0	117.0	+1.0	99.0	+ 8.0
E. L.	10.77	+2.34	11.73	+1.32	10.71	+0.42	1.52	+0.13	1.80	+0.56	1.43	+0.33	102.0	+5.5	102.0	+5.5	100.0	+ 7.5
H. M.	6.72	+2.34	6.00	+2.55	4.41	+1.59	1.24	+0.41	1.03	+0.43	1.36	+0.10	91.0	+3.0	91.0	+3.0	93.0	+ 8.0
H. W.	9.98	+4.10	8.19	+3.75	5.37	+1.01	1.27	+0.34	1.03	+0.43	0.96	+0.29	96.0	-1.5	96.0	-1.5	98.0	+ 3.0
L. B.	7.86	+2.28	7.80	+2.22	8.04	+3.75	1.24	+0.34	0.91	+0.28	0.96	+0.29	85.0	+6.0	85.0	+6.0	81.0	+ 5.5
E. L.	4.83	+2.37	3.36	+2.46	2.52	-0.78	0.71	+0.17	0.63	+0.28	0.58	+0.18	101.0	0.0	101.0	0.0	106.5	+ 5.5
E. L.	4.05	+0.12	3.10	+1.05	4.17	+1.27	1.62	+0.10	1.55	+0.08	1.60	+0.19	76.5	+4.0	76.5	+4.0	75.5	- 0.5
E. R.																		
Mean	9.05	+2.38	7.85	+2.42	7.63	+0.84	1.33	+0.223	1.21	+0.31	1.21	+0.24	92.3	+2.9	92.0	+2.1	89.8	+2.16
S. D.	±3.89		±3.09		±3.52		±0.31				±0.30							
S. E.	±1.17		±1.03		±1.06		±0.09				±0.09							
p					<0.02*		<0.05*				<0.01*							

* Comparison with control.

digitalis preparation, the degree of myocardial disease, and the blood loss necessitated by the sampling procedures.

The myocardial extraction of oxygen was not significantly changed by strophanthidin from the mean control level of 11.82 ml. per 100 ml., a value slightly higher than the 10.3 ml. per 100 ml. in normals for this laboratory (19), which becomes more elevated if the anemic patients are excluded. The carbon dioxide production response showed wide variation with no significant pattern for the group. Likewise, there were no gross changes in myocardial water transfer as measured by the rough index of hematocrit. While the chronotropic response was small but definite in most instances, the electrocardiographic response was not indicative of digitalization except in three instances, M.P., J.S. and J.T., where minimal ST segment changes occurred. In only one patient, a 70 year old male, was there evidence of a toxic effect from strophanthidin, with unifocal premature ventricular beats, lasting, transiently, for two minutes.

The mean arterial levels of the three carbohydrate substrates measured were all elevated during the period of untreated heart failure (Table III), but only lactate and pyruvate declined significantly toward the normal levels after treatment (19). The extraction of these substances appeared to be maintained normally by the failing heart, although this was probably dependent upon the elevated arterial levels.

The extraction of pyruvate and glucose was not altered after strophanthidin, but lactate extraction, although unchanged at 7 minutes, was substantially diminished at 15 minutes. The p value for this change was slightly higher than 0.02 but less than 0.05, thus bearing a fair probability of significance.

As representatively depicted in Figure 1, acetyl strophanthidin precipitated a rapid movement of potassium from the heart. This was true for all but one of the group of 18 (Table IV), a patient with the clinical criteria of myocarditis who did not respond to strophanthidin therapeutically and who was poorly manageable on a clinical basis.

The maximum negative potassium A-V difference usually occurred at four minutes after infusion, and measurement of Period II, as designated

TABLE IV
Myocardial arteriovenous differences of potassium and sodium before and after acetyl strophanthidin

Patient	Potassium (mEq./L.)									Planimetered area in sq. in.		
	Control			Maximum			Recovery*			I	II	III
	B.A.	C.S.	Diff.	B.A.	C.S.	Diff.	B.A.	C.S.	Diff.			
J. B.	3.94	4.42	-0.48	4.78	6.22†	-1.44	4.65	4.85	-0.20	-0.77	-3.10	-1.1
M. P.	3.76	3.42	+0.34	4.06	4.48†	-0.42	3.79	3.66	+0.13	+0.50	-0.34	+0.16
W. C.	4.26	4.23	+0.03	4.64	4.98†	-0.34	Still-A-V at 25 min.			+0.04	-0.75	-0.77
D. M.	4.20	4.30	-0.10	4.90	5.70†	-0.80	5.00	4.90	+0.10	-0.60	-1.64	-0.12
B. L.	4.64	4.37	+0.27	4.66	5.04†	-0.38	Still-A-V at 25 min.			+0.36	-0.33	-0.38
J. S.	5.37	5.31	+0.06	6.09	6.51†	-0.39	5.79	5.56	+0.23	+0.06	-0.58	+1.3
J. T.	4.56	4.65	-0.09	5.19	5.76†	-0.57	5.20	5.42	-0.22	+1.17	-0.94	
G. A.	4.39	4.42	-0.03	4.91	5.88†	-0.97	4.72	4.78	-0.06	-0.23	-1.66	-0.10
J. T.	3.79	3.20	+0.59	4.32	4.80†	-0.48	3.60	3.60	0.00	+1.12	+0.16	-0.10
W. C.	4.85	4.81	+0.04	4.79	5.41†	-0.62	Still-A-V at 25 min.			-0.02	-1.0	-2.31
E. L.	3.89	3.65	+0.25	3.75	4.70†	-0.95	4.05	3.98	+0.07	+0.51	-1.19	-0.56
E. R.	4.34	4.51	-0.17	4.51	5.68†	-1.17	4.75	4.71	+0.04	-0.40	-0.98	+0.00
P. T.	4.25	4.50	-0.25	4.75	4.76†	-0.01	4.78	4.79	-0.01	-0.08	+0.12	+0.44
H. M.	5.24	5.34	-0.10	5.60	6.50†	-0.91	5.89	5.92	-0.03	-0.25	-1.15	+0.60
H. W.	4.58	4.47	+0.11	4.95	5.58†	-0.63	4.54	4.41	+0.13	+0.10	-1.33	-1.38
L. B.	4.65	4.40	+0.25	4.97	5.29†	-0.59	4.66	4.74	-0.08	+0.30	-0.46	+0.36
E. L.	3.85	3.83	+0.02	4.04	4.52†	-0.48	4.01	4.16	-0.15	-0.09	-1.09	-0.48
D. H.	4.68	4.59	+0.08	5.09	5.30†	-0.21	4.99	4.75	+0.24	+0.03	-0.24	-0.33
Mean	4.40		+0.05	4.77		-0.63	4.69		+0.01	+0.097	-0.94	-0.45
S. D.	±0.49			±0.768			±0.666			±0.51	±0.74	±0.76
S. E.	±0.12			±0.181			±0.178			±0.12	±0.17	±0.18
t				5.07							7.2	2.5
p				<0.001							<0.001	<0.05%

Patient	Sodium (mEq./L.)									Planimetered area in sq. in.		
	Control			Maximum			Recovery*			I	II	III
	B.A.	C.S.	Diff.	B.A.	C.S.	Diff.	B.A.	C.S.	Diff.			
J. B.	154	151	+3.0	152	151†	+1.0	154	152	+2.0	+1.10	+0.91	-0.80
M. P.	134	135	-1.0	137	133§	+4.0	135	135	0.0	-0.03	+0.64	-0.45
W. C.	152	151	+1.0	152	146†	+6.0	150	151	-1.0	-0.09	+0.35	-0.97
D. M.												
B. L.	131	134	-3.0	131	131†	0.0	127	131	-4.0	-0.9	-0.9	-1.60
J. S.												
J. T.	152	150	+2.0	147	153†	-6.0	Still-A-V at 15 min.			-1.0	-1.31	
G. A.	137	140	-3.0	137	138†	-1.0	139	139	0.0	-1.4	+0.20	-0.10
J. T.	153	153	0.0	158	153§	+5.0	154	152	+2.0	0.0	+0.81	-0.51
W. C.	157	158	-1.0	157	149†	+8.0	154	153	+1.0	-0.01	+0.77	-0.80
E. L.	134	134	0.0	133	131†	+2.0	131	131	0.0	-0.08	+0.09	-0.02
E. R.	152	151	+1.0	149	151†	-2.0	153	148	+5.0	-0.08	+0.06	+0.21
P. T.	138	139	-1.0	137	135†	+2.0	136	135	+1.0	-0.24	+0.31	+0.27
H. M.	152	157	-5.0	155	156§	-1.0	160	154	+6.0	-1.13	-0.93	+1.18
H. W.	157	152	+5.0	154	147†	+7.0	149	148	+1.0	+0.92	+0.90	-1.66
L. B.	151	152	-1.0	150	150†	0.0	153	151	+2.0	-0.50	+0.21	+0.30
E. L.	160	153	+7.0	151	157§	-6.0	152	152	0.0	+1.49	-0.64	-0.12
D. H.	160	157	+3.0	163	167§	-4.0	Still-A-V at 25 min.			+0.11	-0.93	-1.3
Mean	148.4		+0.5	147.7		+1.0	146.2		+1.0	-0.12	+0.07	-0.43
S. D.	±9.94			±9.7			±10.4			±0.79	±0.84	±1.3
S. E.	±2.57			±2.51			±2.9			±0.20	±0.21	±0.35
t											0.35	1.23
p											>0.70	>0.20

* Fourteen to 17 minutes.

† Four minutes.

‡ Two minutes.

§ Seven minutes.

|| Change from control value.

TABLE V
Myocardial arteriovenous differences of calcium before and after acetyl strophanthidin

Patient	Calcium (mEq./L.)									Planimetered area in sq. in.		
	Control			Maximum*			Recovery†					
	B.A.	C.S.	Diff.	B.A.	C.S.	Diff.	B.A.	C.S.	Diff.	I	II	III
M. P.	4.51	4.44	+0.07	4.57	4.18	+0.39	4.13	4.17	-0.04	+0.22	+0.51	+0.26
D. M.	4.39	4.46	-0.07	4.42	4.10	+0.32	4.17	4.17	0.0	-0.21	+0.30	-0.14
J. S.	4.12	4.05	+0.07	4.12	4.03	+0.09				-0.26	+0.09	
J. T.	4.33	4.42	-0.09	4.28	4.61	-0.33	4.60	4.85	-0.25	-0.28	-1.11	-0.90
J. T.	4.30	4.25	+0.05	4.35	4.47	-0.12	4.16	4.07	+0.09	-0.32	-0.25	+0.10
E. L.	4.96	5.05	-0.09	4.97	4.73	+0.24	5.03	4.88	+0.15	-0.50	+0.53	+0.33
E. R.	4.71	4.66	+0.05	4.65	4.87	-0.27	5.00	4.78	+0.22	+0.10	-0.52	+0.20
Mean	4.47		-0.01	4.48		+0.05	4.51		+0.02	-0.18	+0.12	-0.03
S. D.											±0.52	
S. E.											±0.20	
p											>0.20	

* Values at 4 to 7 minutes.

† Values at 14 to 17 minutes.

in Figure 1, shows a substantial negative phase of potassium transfer with the planimeted area of -0.94 square inch, representing a change of real significance (p less than 0.001). The subsequent period revealed a persistence of this negative phase through the 25 minute point that was probably significant. The actual cellular loss of potassium during Period II is not subject here to exact calculation, but, assuming a plasma flow of 50 ml. per 100 Gm. per minute and a cellular potassium content of the heart in failure at 6.3 mEq. per 100 Gm. (20), the decrement would range from 3 up to 7 per cent. There was no correlation between the potassium loss and the hemodynamic response to the drug ($r = 0.41$). In addition, there was no evident contrast in ionic change between those with and those without significant slowing of heart rate, in agreement with studies in the dog, in which prevention of rate changes failed to modify the strophanthidin potassium effect (21).

The simultaneous early rise in arterial potassium was too high to be derived solely from cardiac tissue, and probably represents mobilization from skeletal muscle (22). In two additional patients, sampling of the hepatic vein after strophanthidin revealed a slightly positive A-V difference of potassium, so that the liver is unlikely as a source area.

The simultaneous sodium determinations showed considerable variability in response, and the slight change in mean values for the group were of no statistical importance. In Table V, the calcium

data on seven patients treated with strophanthidin are enumerated. The mean arterial levels were not significantly altered, nor were the planimeted areas for periods of the drug's activity significantly different from the control. The possibility remains of a larger group showing significant uptake of calcium, since this was the direction of ion movement in five of the seven patients.

DISCUSSION

The question of dosage and duration of administration must inevitably be considered in trying to assess the approximation of a digitalis preparation to toxicity. While a fixed dosage-electrocardiographic response may be predictable in normal animals, this, as noted by Friedberg (23), is often not the case in the clinical situation. In view of the fact that ventricular premature beats in a brief episode were seen in but 1 of the total of 23 patients after 1.1 mg. of strophanthidin, and that, in general, there was no specific digitalis effect on the electrocardiogram, this arbitrarily chosen dosage could be fairly adjudged as nontoxic. However, one cannot be certain that effects induced at a rapid rate of administration necessarily occur at slower rates. Conn's finding (24) of a qualitatively similar ionic alteration with chronic administration of digitoxin indicates that such a change is not limited to the particular circumstances of this experiment. It is presumed, then, that this telescoping of the events which usually

occur with digitalization enable the detection of changes in plasma concentration arising out of myocardial processes. The failure to demonstrate myocardial ionic exchange after cedilanid (25) can reasonably be ascribed to a less rapid mobilization of potassium.

The nonfeasibility of acquiring data in a given patient at progressive dosage levels makes reliance on animal studies necessary for the correlation of potassium change and hemodynamic activity over a range of dosage values. Vick and Kahn (26), using different concentrations of ouabain, were able to detect potassium losses whenever a positive inotropic effect was produced in the isolated guinea pig heart, losses which were small until excess of 50 per cent positive inotropic effect was produced. It is of interest that in two patients not included in this report 0.55 mg. of acetyl strophanthidin, one-half of the dosage chosen for this study, induced no detectable potassium change. Another patient receiving 0.9 mg. showed a potassium loss quite comparable to that following 1.1 mg.

The significance of the reduction in potassium content of the human heart in failure, as determined by the postmortem tissue analysis of Harrison, Pilcher and Ewing (22), is not clear, especially since other body tissues also participate in the negative potassium balance. It remains to be shown whether this altered potassium level influences contractility of the failing heart. The fact that the initial improvement in cardiac performance is associated with substantial egress of this ion, raises the question whether the maintenance of this new functional status is accompanied by a new equilibrium state with a diminished potassium gradient. The persistently negative phase of potassium net balance, after the peak therapeutic response has been attained, would indicate so. Even though the total exchangeable potassium content of the body tended to recover toward normal in the isotopic study of Aikawa and Fitz (27), the lowered myocardial content in autopsy specimens of digitalized patients (20) supports the above view.

Although the experiments with strophanthidin in the dog indicated that ventricular arrhythmias were associated with larger potassium outflow (7), there appeared in this study to be no difference based upon therapeutic response. Whereas the human heart undergoing a positive inotropic response always exhibited a potassium loss, the

degree of change in mechanical function was not quantitatively related. A more direct measure of cardiac contractility than cardiac stroke work might lend added assurance to this conclusion. Moreover, even if the potassium changes were related to the functional response, the state of the basic contractile unit would be of prime importance amongst the determinants of cardiac response. Studies of a canine failing heart preparation have indicated substantial deviations from normal in the protein complex (1, 28). It would seem highly probable that in these patients there was variation in the myocardial protein of unknown extent, perhaps dependent upon the degree of destruction, dilatation, hypertrophy and cardiac decompensation among other factors.

Another interesting negative correlation was the general lack of characteristic repolarization changes on the precordial electrocardiogram despite the presence of substantial ionic shifts. As this manner of recording the process of electrical recovery correlates well with the direct cellular recording microelectrode (29), the manifestation of an altered recovery phase may require a more sustained ion effect.

The maintenance of a net loss of potassium despite the abruptly elevated arterial levels points to a potent effect on potassium transfer out of the heart. Whether inward flux is modified in any way by strophanthidin directly, or by the increased perfusing concentrations under the conditions of this experiment, is not known. But it is of note that this phenomenon did not appear to inhibit the positive inotropic response. Although the rise was a limited one, this finding would tend to support work on isolated heart (30), in which increasing concentrations of potassium in the perfusate were found to have no effect on the therapeutic actions of ouabain despite an effective antagonism in the presence of toxic dosages.

Despite the fact that a unitary theory of myocardial contraction based on ionic changes is not justified, it is worth noting that both digitalis and veratrum (26) preparations precipitate potassium egress from the heart simultaneous with the positive inotropic effect. These instances, at least, fulfill the requirements of the reduced internal ionic content theory (4). The converse ionic movement found with adrenalin (31) and nor-adrenalin (32) would appear to rule out a uni-

versal application of the simple relationship postulated by this theory. Since Gruhzt and Farah (33) were able to block the glycoside inotropic effect with dinitrophenol, but not the inotropic effect of adrenalin, separate mechanisms of action for these agents are probable. Nevertheless, the obligatory participation of the ionic transfers in their therapeutic effect is unproven.

Although no simultaneous movement of sodium was found in these patients, the fact that a small change might be obscured by the high plasma levels of this ion is an important consideration, and would make cellular analysis desirable to settle the question whether electroneutrality is maintained by an equivalent exchange of monovalent cation. Failure to find such evidence would lead to a search for anion moving with potassium; one intriguing possibility is suggested by the finding of amino acid reduction in digitalis induced contraction (34).

The failure, in the seven patients studied, to find evidence that the transfer of calcium ion in the heart is altered in a consistent fashion during the course of strophanthidin's activity does not necessarily detract from Loewi's concept of the role of extracellular calcium acting on the cell membrane to facilitate contraction in this circumstance (35), providing one assumes that the calcium, so acting, does not alter the concentration equilibrium between interstitial fluid and capillary. If its specific effect is to modify permeability to potassium, the perfusion concentration of calcium might be expected to relate quantitatively to the egress of potassium. Within limits of the levels observed in these patients, no such parallelism was found. Further clarification of the status of net calcium transfer in this situation may be attainable through measuring arteriovenous concentration differences of ultrafiltrable calcium. Whereas large changes in this biologically active moiety should be reflected in assays of total concentration, a minute change may remain undetected.

The finding of a significantly increased concentration of arterial lactate and pyruvate suggests a reduced ability of some tissues, at least, to store or utilize these substances for energy production in the course of untreated cardiac failure. The extraction of glucose, lactate and pyruvate by the heart was maintained normally although at a higher perfusion level. Strophanthidin appears to modify

carbohydrate metabolism of extracellular tissue, whether or not increased peripheral blood flow occurs, since an appreciable fall in arterial lactate and pyruvate took place. While the myocardial extraction of both was normal at 7 minutes after infusion, that of lactate was reduced at 15 minutes to a probably significant degree ($p < 0.05 > 0.02$), and may indicate among other alternatives an accelerated production by glycolytic pathways during this time. A clarification of this interpretation from various experiments on isolated tissue is not obtainable, particularly since, as Olson has indicated (1), the conditions of these studies, notably the stimulatory effect upon tissue respiration, preclude comparison with *in vivo* experiments.

The association of potassium loss and glycogenolysis in liver metabolism, the latter process reaching a peak after the ionic change in epinephrine studies (36), bears a resemblance to these findings with strophanthidin. Although the potassium movement has been dissociated from the hepatic glycogenolytic process through the use of adrenergic blockade (37), their mutual independence in the heart has not been established.

SUMMARY

Preliminary to an examination of the myocardial metabolic changes induced by acetyl strophanthidin, the hemodynamic effect of 1.1 mg. intravenously was studied in five patients with low output heart failure. A substantial stroke work increase occurred within five minutes, becoming maximal at nearly twice the control level by 15 minutes and declining in 25 minutes.

The same rapid mode of administration was employed in 18 patients with cardiac decompensation in whom myocardial extractions of electrolytes and carbohydrate substrate were determined by paired arterial and coronary sinus sampling. The significantly greater increment in coronary sinus potassium, usually maximal within four minutes, indicated a net myocardial loss of this ion which was not counteracted by a directional reversal of this ionic movement during the observation period. This phenomenon was not quantitatively related to the stroke work response and was not, with one exception, associated with toxic electrocardiographic manifestations. Likewise, with few ex-

ceptions, evidence of an altered repolarization phase on the precordial electrocardiogram was lacking. No significant changes were observed in the extractions of sodium and calcium.

Despite elevated arterial concentrations of glucose, lactate and pyruvate, the myocardial extraction of these substances was within normal limits prior to therapy. Following strophanthidin the arterial levels of lactate and pyruvate diminished, a change which was apparently not dependent on total blood flow increase. Extractions were not significantly altered until 15 minutes, when a reduction in the arteriovenous difference of lactate was noted. The possible relationship of this finding to potassium egress from the heart was considered.

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ANNOUNCEMENTS OF MEETINGS

The Fifty-First Annual Meeting of THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION will be held in Atlantic City, N. J., on Monday, May 4, 1959, at 9:00 A.M. at the Casino Theater on the Steel Pier.

The Sixteenth Annual Meeting of THE AMERICAN FEDERATION FOR CLINICAL RESEARCH will be held in Atlantic City, N. J., at the Casino Theater on the Steel Pier on Sunday, May 3, 1959, at 9:00 A.M.

THE ASSOCIATION OF AMERICAN PHYSICIANS will hold its Seventy-Second Annual Meeting in Atlantic City, N. J., at the Casino Theater on the Steel Pier on Tuesday, May 5, 1959, at 9:30 A.M. and in the Vernon Room, Chalfonte-Haddon Hall, on Wednesday, May 6, 1959, at 9:30 A.M.