STUDIES IN CONGESTIVE HEART FAILURE

IX. The Effect of Digitalis on the Potassium Content of the Cardiac Muscle of Dogs

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Previous investigations (1, 2) have shown that the potassium content of the cardiac muscle is decreased in patients dying of congestive heart failure. This diminution was found only in dilated hearts and appeared to be related to overwork and the attendant fatigue. As digitalis is the sovereign remedy in the treatment of cardiac fatigue it was thought that knowledge of its effect on the potassium content of the heart was desirable.

The drug was given subcutaneously as Digifolin (Ciba) to dogs in doses of varying size. The plan of administration consisted in giving the equivalent of a full therapeutic dose in man, i.e., 0.2 to 0.3 cc. per kilogram of body weight in twenty-four to forty-eight hours and then giving larger or smaller daily "maintenance" doses, according to whether "toxic" or "therapeutic" effects were desired. At intervals varying from one to thirty-seven days after the administration of the drug had been started the animals were killed, and their hearts were analyzed for potassium according to the technique which has been described in our previous studies. Daily pulse counts and electrocardiograms were made in some of the animals.

Twenty-seven animals were used in the course of the experiment and they were divided into four groups on the basis of the amount of digifolin given them. The "control" group which numbered ten, received no digitalis; three of these were healthy normal dogs which were killed by bleeding; the other seven animals had been utilized for various types of experimental studies which did not include the administration of digitalis. The second group comprised ten animals to whom digifolin was given in "therapeutic" doses—by which is

meant in amounts insufficient to produce toxic symptoms. The most characteristic toxic symptom in dogs being vomiting, no animal who vomited or who appeared very ill whether or not there was actual vomiting, was put in this group. Seven animals received digifolin in "toxic" doses; four of these were killed and three given sufficient digifolin to cause death (i.e., "fatal" doses). It will be noted that some of the animals in the toxic group received less of the drug than did many in the "therapeutic" group, but they usually received more

TABLE 1

The solids and potassium content of the cardiac muscle of dogs not receiving digitalis

Animal number	Right ventricle			Left ventricle			Remarks
	Solids	Potassium in dry tissue	Potassium in wet tissue	Solids	Potassium in dry tissue	Potassium in wet tissue	
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	
N_1	22.9	1.50	0.345	23.0	1.33	0.314	Normal
N_2	21.5	1.76	0.378	22.3	1.48	0.330	Normal
N_3	22.8	1.51	0.365	22.8	1.40	0.320	Normal
E. B. 22	20.3	1.50	0.305	21.4	1.70	0.364	Barbital spinocaine
E. B. 23	20.7	1.29	0.266	20.9	1.30	0.272	Barbital spinocaine
E. B. 24	21.0	1.86	0.390	20.8	1.65	0.342	Barbital spinocaine
E. B. 25	21.8	1.44	0.313	22.0	1.39	0.306	Barbital spinocaine
E. B. 26	21.4	1.60	0.343	22.0	1.45	0.320	Barbital spinocaine
A. B. 2				22.4	1.37	0.307	Traumatic shock
A. B. 3				21.9	1.35	0.296	Traumatic shock

in proportion to the length of time the drug was administered. Vomiting was considered the criterion of toxicity. The three animals in the "fatal" group received large amounts (4.8 to 11.0 cc. per kilo) of digifolin and death was due to the action of the drug.

RESULTS

The changes in the clinical states, pulse rates and electrocardiograms were the same as are usually found in dogs to which digitalis has been given. These have been considered in detail by other authors and need not be discussed here.

The values for the solids and the potassium content of the hearts

TABLE 2

The total solids and potassium content of the cardiac muscle of dogs receiving digitalis

Animal number	Duration of experiment	Total amount digifolin given	Right ventricle			Left ventricle			Vomiting	Remarks	
			Solids	Potassium in dry tissue	Potassium in wet tissue	Solids	Potassium in dry tissue	Potassium in wet tissue			
	days	*cc. per kilo*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*			
D_7	1	0.25		1.24		21.8	1.28	0.280	0	Killed	
D_8	1	0.25	20.9	1.34	0.280	21.3	1.40	0.298	0	Killed	
D_9	2	0.60	21.7	1.71	0.370	22.0	1.45	0.319	0	Killed	
D_{10}	2	0.60	20.9	1.69	0.353	20.2	1.73	0.349	0	Killed	
D_{11}	1	0.55	22.1	1.06	0.234	23.0	1.46	0.337	0	Killed	"Therapeutic doses"
D_5	4	1.4	22.0	1.17	0.258	22.6	1.45	0.327	0	Killed	
D_6	4	1.4	22.6	1.29	0.290	23.0	1.49	0.342	0	Killed	
D_{17}	30	1.31	18.1	1.21	0.218	18.7	1.00	0.187	0	Killed	
D_{16}	37	1.52	20.3	1.56	0.317	21.2	1.42	0.301	0	Killed	
D_{15}	36	1.57	20.9	1.55	0.324	22.4	1.30	0.291	0	Killed	
D_{12}	7	0.75	22.0	0.99	0.217	21.3	1.14	0.243	++	Killed	Toxic doses
D_{13}	14	0.95	20.1	1.15	0.231	20.3	1.09	0.221	+	Killed	
D_{14}	21	1.10	20.9	0.99	0.208	21.9	1.00	0.219	+	Killed	
D_4	11	5.0	20.8	1.16	0.240	21.1	0.90	0.190	+++	Killed	
D_1	8	4.8	20.2	0.85	0.172	22.2	1.02	0.228	+++	Died	Fatal doses
D_2	8	5.7	20.6	0.98	0.201	20.5	1.07	0.217	+++	Died	
D_3	17	11.0	27.5	0.83	0.227	21.2	1.10	0.243	+++	Died	

TABLE 3

Average values for the solids and potassium content of the cardiac muscle of dogs, arranged according to the amount of digitalis administered

Amount of digitalis received	Number of animals	Right ventricle			Left ventricle		
		Solids	Potassium in dry tissue	Potassium in wet tissue	Solids	Potassium in dry tissue	Potassium in wet tissue
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
None	10	21.5	1.56	0.338	21.9	1.44	0.317
"Therapeutic"	10	21.1	1.38	0.294	21.6	1.40	0.303
Toxic	4	20.9	1.07	0.224	21.1	1.03	0.218
Fatal	3	22.8	0.89	0.200	21.3	1.06	0.229

of the control animals are shown in table 1, and the findings in the dogs which received digitalis are given in table 2. For the sake of clarity average values for the four groups of animals are given in table 3. The percentage of solids was practically the same in the dogs which received digitalis as in the controls. The potassium content of the cardiac muscle was markedly decreased in those animals which received toxic or fatal doses of digitalis. The animals which received "therapeutic" doses of digitalis had on the average about fifteen per cent less potassium in their right ventricles than did the controls. However, the left ventricles contained only about three per cent less.

TABLE 4

The effect of digitalis on the potassium content of skeletal muscle

	Animal number	Solids	Potassium in dry tissue	Potassium in wet tissue	Remarks
		per cent	*per cent*	*per cent*	
Controls	N_1	24.9	1.22	0.304	No digitalis
	N_2	23.6	1.43	0.338	
	N_3	25.9	1.31	0.339	
Dogs receiving digitalis	D_1	25.7	1.22	0.313	Received digitalis for eight days. Death from digitalis intoxication
	D_2	24.8	1.24	0.306	

In order to determine whether or not the effect of the drug in regard to potassium was specific for cardiac muscle the skeletal muscle was analyzed in two animals which were given fatal doses of digitalis. In both of these animals the potassium content of the heart was markedly diminished (table 2, dogs D_1 and D_2) but their skeletal muscles contained normal amounts (table 4). These observations suggest that the action of digitalis on potassium distribution may be specific for cardiac muscle.

DISCUSSION

From these data it seems clear that digitalis in toxic dosage causes a diminution in the potassium content of the cardiac muscle of dogs but not of their skeletal muscles, while in amounts corresponding to

therapeutic doses in man this effect is either absent or very slight. Since the majority of the animals which exhibited diminution in the potassium content of heart muscle vomited more or less copiously, the question arises as to whether this diminution might not have been due to the vomiting *per se* rather than to a more direct action of the drug. This appears unlikely because if loss of potassium from the body due to vomiting occurred, one would expect the skeletal as well as the cardiac muscle to be affected. Such was not the case.

It was shown in previous papers (1, 2) that the potassium contents of the cardiac muscle of patients dying of congestive cardiac failure were decreased. Since all of these subjects had received digitalis one might be inclined to think that the drug rather than the disease was the cause of the loss of the potassium. However, doses corresponding to those given the patients caused little or no decrease in the potassium content of the dog's hearts. Furthermore, it was shown that, in patients who received no digitalis, dilatation of the right ventricle due to massive collapse of the lung or to pneumonia was associated with an abnormally low potassium content of that ventricle only, whereas, in dogs digitalis affects the potassium content of both ventricles simultaneously. For these reasons it appears that dilatation rather than digitalis was the chief cause of the changes previously reported in human subjects.

At the present time we are not in a position to understand the significance of the fact that even in therapeutic doses there seems to be a slight tendency for digitalis to diminish the potassium content of the heart muscle. The close relation of calcium to digitalis action is well known (3) (4) and it is conceivable that digitalis may act in such a way as to readjust the ionic balance, even at the expense of loss of base from the muscle. A study of calcium in the cardiac muscle is now being instituted.

SUMMARY

The potassium content of the cardiac muscle was markedly less in a series of dogs receiving toxic doses of digitalis than in a group of control animals. Dogs which were given doses corresponding to those used therapeutically in man had a little less potassium in their hearts than did the controls but the difference was slight. The potassium

content of skeletal muscle was not less in dogs receiving digitalis than in control animals.

BIBLIOGRAPHY

1. Harrison, T. R., Pilcher, C. and Ewing, G., J. Clin. Invest., 1930, viii, 325. Studies in Congestive Heart Failure. IV. The Potassium Content of Skeletal and Cardiac Muscle.
2. Calhoun, J. A., Cullen, G. E., Clarke, G. and Harrison, T. R., J. Clin. Invest., 1930, ix, 393. Studies in Congestive Heart Failure. VI. The Effect of Overwork and Other Factors on the Potassium Content of the Cardiac Muscle.
3. Burridge, W., Quart. J. Med., 1916, ix, 271. Researches on the Perfused Heart.
4. Billigheimer, E., Ztschr. f. klin. Med., 1924, c, 411. Vergleichende Untersuchungen über die Wirkung und Wirkungsweise des Calciums und der Digitalis.