

## Studies on Digitalis. XIII. A Comparison of the Effects of Potassium on the Inotropic and Arrhythmia-producing Actions of Ouabain \*

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Although it is generally recognized that digitalis-induced arrhythmias can be suppressed by the administration of potassium (1-3), it is not clear whether the potassium ion also influences the positive inotropic effect exerted by the glycosides on the intact mammalian heart. Clarification of this problem is important in the understanding of the interrelationships between the actions of glycosides and potassium, and is clinically significant in view of the frequency with which potassium is administered to patients who are or have been receiving digitalis. Accordingly, the present investigation was undertaken to determine the manner in which potassium suppression of ouabain-induced arrhythmias affects the augmentation of ventricular contractile force produced by the administration of the glycoside.

### Methods

Ten mongrel dogs, weighing between 10 and 25 kg, were anesthetized with intravenous sodium pentobarbital (35 mg per kg) and ventilated with a positive displacement pump that was supplied with a mixture of room air and 100% O<sub>2</sub>. The right ventricle was exposed through a median sternotomy, a Walton-Brodie strain gauge arch (4) was sutured to the right ventricle, and the muscle segment beneath the gauge was stretched approximately 50% beyond its initial length. This maneuver allows recording of the changes in contractile force of the segment of myocardium between the points of attachment of the gauge despite some changes in right ventricular dimensions (5). Heparin, 5 mg per kg, was administered intravenously. With a compressed air-blood reservoir that was connected to a femoral artery through a large bore cannula, mean arterial pressure was maintained constant despite any changes in blood volume that might have occurred as a consequence of bleeding or blood withdrawal for plasma K concentration. Body tempera-

ture was monitored with a thermistor probe placed in the superior vena cava and was maintained constant with heating pads. Femoral arterial pressure was measured with a Statham P23D strain gauge transducer, and arterial blood was withdrawn at intervals for determinations of plasma K by flame photometry. Right ventricular contractile force, arterial pressure, and a limb lead of the electrocardiogram were recorded continuously on a direct-writing oscillograph. In two of the ten animals the sinoatrial node was crushed and heart rate maintained constant by stimulating the right atrium at a rate just above the spontaneous rate. Two animals had undergone bilateral adrenalectomy 1 week before the experiment and were then maintained on steroid replacement therapy.

After control measurements, an intravenous dose of ouabain, 30  $\mu$ g per kg, was administered over a 5-minute period. Ten to 15 minutes later a constant infusion of ouabain, 30  $\mu$ g per kg per hour, was begun and was continued for the remainder of the experiment. Ouabain intoxication became evident after approximately 40 minutes of the infusion, and it was manifested by ventricular tachycardia (seven animals), ventricular bigeminal rhythm (one animal), nodal tachycardia (one animal), and electrical alternans (one animal). With the onset of the arrhythmia, KCl infusion was begun at a rate of 2 mEq per kg per hour and was continued (along with the ouabain) until sinus rhythm had been restored. The KCl infusion was then decreased to a rate of 1 mEq per kg per hour, and it was continued at this level (together with the ouabain) until toxicity recurred, at which time the experiment was terminated. Arterial blood was withdrawn for plasma K determinations at 15-minute intervals before the commencement of the KCl infusion and at 5-minute intervals thereafter.

In two control animals in which myocardial contractile force was also measured continuously, ouabain was replaced by its diluent, isotonic saline, which was infused at comparable rates. Eighty minutes after the saline was begun, an infusion of KCl, 2 mEq per kg per hour, was also started. After 3 minutes, the rate of KCl infusion was reduced to 1 mEq per kg per hour and continued at this level for an additional 40 minutes.

### Results

The values for right ventricular contractile force and plasma potassium concentration in each

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TABLE I

*The effect of ouabain on contractile force before and after suppression of toxic arrhythmias with potassium*

Dog*	Control	After loading dose, preinfusion	At one-half infusion time	Just before initial toxicity, before K‡	Just before recurrent toxicity, after K
1†					
% inc. CF		57	72	108	122
Plasma K (mEq/L)	3.4	3.9	4.1	3.8	4.9
Cum. dose ouabain (µg/kg)		30.0	41.7	53.5	68.5
2					
% inc. CF		33	19	33	86
Plasma K	3.5	4.2	4.6	4.8	5.6
Cum. dose ouabain		30.0	37.5	45.0	59.5
3‡					
% inc. CF		21	23	38	54
Plasma K	2.8	3.5	3.3	4.2	5.5
Cum. dose ouabain		30.0	40.3	50.5	62.0
4					
% inc. CF		55	66	72	83
Plasma K	3.4	4.7	4.4	4.4	5.8
Cum. dose ouabain		30.0	44.0	58.0	73.0
5					
% inc. CF		20	23	45	53
Plasma K	3.5	3.8	3.8	3.7	5.1
Cum. dose ouabain		30.0	42.5	55.0	72.5
6					
% inc. CF		36	36	21	40
Plasma K	3.3	3.0	3.2	3.4	4.2
Cum. dose ouabain		30.0	40.3	50.5	74.5
7					
% inc. CF		13	28	45	53
Plasma K	3.4	3.6	3.8	5.1	7.8
Cum. dose ouabain		30.0	35.0	40.0	58.5
8‡					
% inc. CF		28	37	55	79
Plasma K	3.3	3.7	3.6	3.6	7.5
Cum. dose ouabain		30.0	36.3	42.5	55.0
9					
% inc. CF		42	59	88	85
Plasma K	3.0	3.1	3.6	3.9	5.4
Cum. dose ouabain		30.0	40.0	50.0	60.0
10†					
% inc. CF		122	118	140	183
Plasma K	2.6	3.4	4.1	3.6	5.2
Cum. dose ouabain		30.0	45.5	61.0	77.5

\* Abbreviations: % inc. CF = per cent increase in contractile force above control; cum. dose ouabain = cumulative dose of ouabain.

† Adrenalectomized animals.

‡ Animals in which heart rate was kept constant.

§ Initial toxicity was characterized by ventricular tachycardia in animals 1 to 7, nodal tachycardia in animal 8, ventricular bigeminal rhythm in animal 9, and electrical alternans in animal 10.

animal at various times during the experiments are given in Table I, whereas the average changes in these variables are illustrated in Figure 1. Typical illustrations of the recordings of ventricular contractile force and the corresponding plasma potassium concentrations in two animals at these

various time intervals are reproduced in Figures 2 and 3. The initial injection of ouabain always produced a rapid increase in contractile force, and at the onset of the continuous infusion this variable had risen by an average of  $43 \pm 10\%$  (SE) of control, whereas the plasma K had risen from 3.2

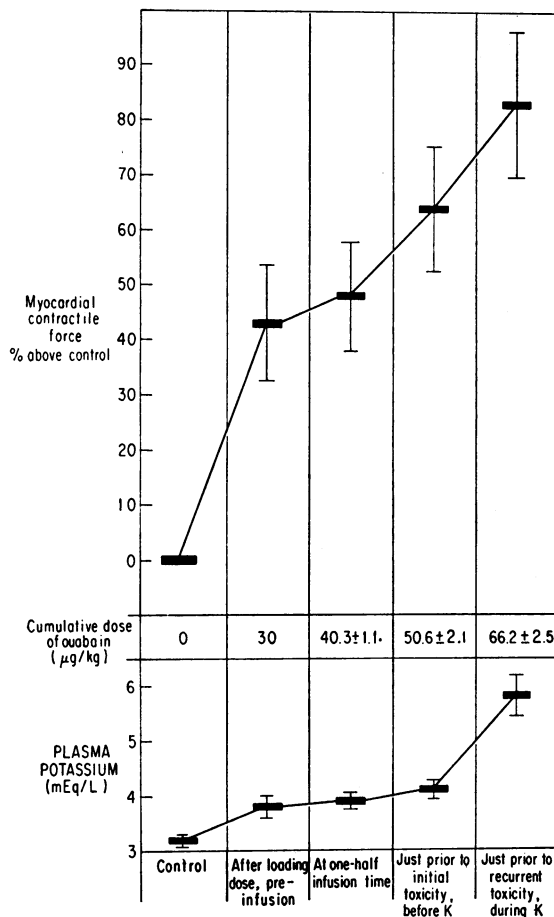


FIG. 1. THE AVERAGE CHANGES IN RIGHT VENTRICULAR CONTRACTILE FORCE AND PLASMA POTASSIUM CONCENTRATIONS  $\pm$  STANDARD ERROR DETERMINED AT VARIOUS INTERVALS DURING THE EXPERIMENT.

$\pm 0.1$  to  $3.8 \pm 0.2$  mEq per L. During the constant infusion of ouabain, contractile force continued to increase, but at a slower rate. Arrhythmias became apparent initially after the ouabain infusion had been in progress for an average of 41.2 minutes, at which time a total of  $50.6 \pm 2.1 \mu\text{g}$  per kg ouabain had been administered. The increase in contractile force just before initial toxicity averaged  $65 \pm 12\%$  of control, and the plasma K was  $4.1 \pm 0.2$  mEq per L. In nine of the ten dogs contractile force did not plateau before initial toxicity but increased progressively.

The level of contractile force could not be determined with accuracy in the presence of toxic arrhythmias because of the irregularity of the rhythm (Figures 2 and 3). However, sinus rhythm was always restored with the KCl infusion within 3 minutes, at which time plasma K averaged  $5.6 \pm 0.5$  mEq per L. With the continuing infusion of both ouabain and KCl it was possible to maintain sinus rhythm for an additional  $31 \pm 3.7$  minutes before toxicity recurred. Thereafter, as sinus rhythm was maintained and an additional  $15.6 \pm 1.3 \mu\text{g}$  per kg of ouabain was administered, contractile force showed a further progressive increase in nine of the ten animals. With all ten animals included, this increase averaged  $19 \pm 6\%$ , a value that is statistically significant ( $p < 0.01$ ). This additional increase produced a total average increase in contractile force for the entire study of  $84 \pm 13\%$ . The plasma K just before recurrent toxicity averaged  $5.8 \pm 0.4$  mEq per L.

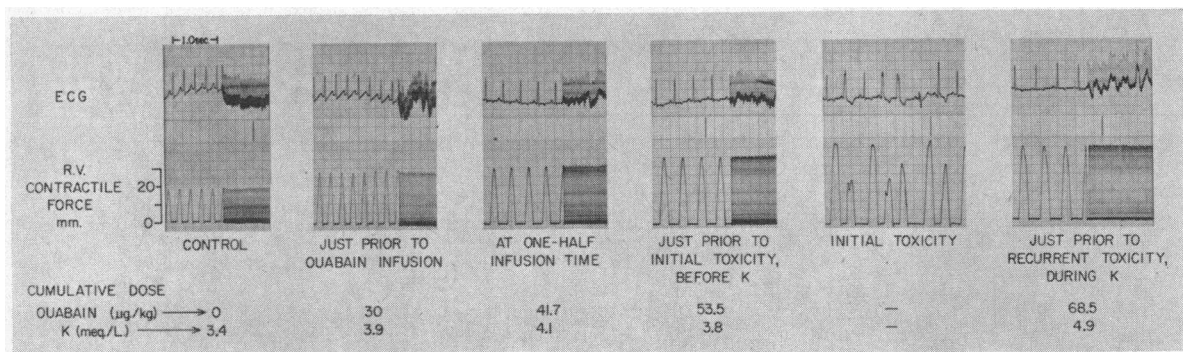


FIG. 2. AN ILLUSTRATION OF THE CHANGES IN RIGHT VENTRICULAR CONTRACTILE FORCE OCCURRING AT VARIOUS INTERVALS DURING THE INFUSION OF OUABAIN INTO DOG 1. The cumulative dose of ouabain administered and the plasma potassium concentration existing at the time each recording of contractile force was made are given at the bottom of the Figure. ECG = electrocardiogram.

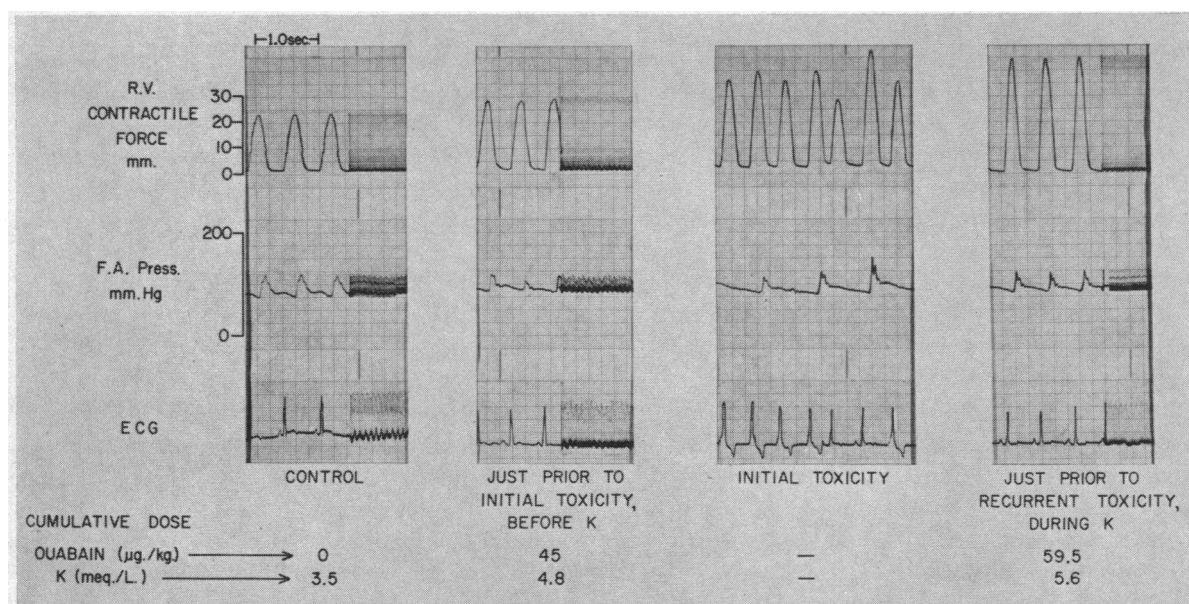


FIG. 3. AN ILLUSTRATION OF THE CHANGES IN RIGHT VENTRICULAR CONTRACTILE FORCE OCCURRING DURING THE INFUSION OF OUABAIN INTO DOG 2. F.A. press. = femoral arterial pressure.

In contrast to the arrhythmias occurring at the time of initial toxicity, those occurring with recurrent toxicity were characterized by varying degrees of impaired atrioventricular and intraventricular conduction and eventual ventricular asystole.

The heart rates of the eight unpaced animals generally fell before initial toxicity and thereafter remained relatively constant during the remainder of the experiment, averaging  $169 \pm 19$  beats per minute before the administration of ouabain,  $144 \pm 7$  per minute just before initial toxicity, and  $144 \pm 9$  per minute before recurrent toxicity.

The alterations of contractile force in the two dogs in which heart rate was controlled and in the two adrenalectomized animals were similar to those observed in the other six dogs, both before and during potassium infusion (Table I). In the two control animals that received no ouabain, contractile force varied by less than 10% during the initial 80 minutes of saline administration and during the 40 minutes of KCl infusion. In these animals, plasma K rose from control values of 3.5 and 4.7 mEq per L to 5.4 and 6.5 mEq per L, respectively, during the KCl infusion.

### Discussion

In the present investigation it was possible to antagonize the arrhythmia-producing effect of a

digitalis glycoside with potassium without apparently altering the positive inotropic action of the drug. Not only did the administration of KCl allow additional ouabain to be infused, but before arrhythmias recurred, contractile force was elevated above the peak level that had been observed just before initial toxicity. The elevation of plasma K required for this apparent dissociation between the arrhythmia-producing and inotropic effects of ouabain was not excessive.

A number of experimental precautions were taken to ensure that the augmentation of myocardial contractile force that was observed both before and after initial toxicity was in fact produced by ouabain. Systemic arterial pressure was maintained constant to reduce possible changes in contractile force due to reflex-induced variations in autonomic stimulation of the myocardium. An initial loading dose of ouabain was given to shorten the experimental period and thereby minimize any fluctuations of contractile force due to reduction in the depth of anesthesia. Although an elevation of pulmonary arterial pressure may cause an increase in right ventricular contractile force as measured with the strain gauge arch, this appears to occur only with marked elevations in pressure (5). Whereas pulmonary arterial pressure was not measured during this study, precautions were taken to prevent conditions known to produce such

pressure elevations, i.e., complete arterial saturation was maintained and gross pulmonary atelectasis was prevented in each animal during the experiment. Also, it is not likely that the administration of ouabain increased the pressure in the lesser circulation since the glycosides have been shown to have little effect on the pulmonary arterial and right ventricular systolic pressures in the normal heart (6-8).

Whereas it is recognized that both ventricular tachycardia (9) and potassium (10) may, under certain circumstances, induce catecholamine release, this factor could not have accounted for the additional increase in contractile force observed after suppression of initial toxicity, since this increase developed gradually during the 20 to 30 minutes after restoration of sinus rhythm, was not prevented by adrenalectomy, and was not observed in the control animals. Changes in heart rate could not have been responsible for the positive inotropic effect that was observed, since heart rate generally fell before the appearance of initial toxicity and remained relatively constant during the second period of sinus rhythm. In addition, increases in force were noted in the two animals in which rate was kept constant by right atrial stimulation. Changes in contractile force induced by alterations in body temperature were also precluded. There is no reason to believe that the addition of K itself augmented contractility, since numerous studies both *in vivo* and *in vitro* have shown that this ion either does not alter the contractile state of the heart or, when given in large doses, actually reduces it (11-17). Furthermore, in the control dogs the infusion of KCl did not materially alter contractile force.

It has been shown that digitalis modifies a number of the electrical properties of cardiac cells (18-22) and can inhibit active cation transport across the myocardial cell membrane (23, 24). Although the mechanism by which K suppresses digitalis toxicity has not been defined, it has been demonstrated that K can reverse digitalis-induced changes in transmembrane potentials in Purkinje fibers (25). It has also been speculated (26), and there is evidence to support the contention (27), that K may displace digitalis from carrier sites on the cell membrane, thereby reducing the effects of digitalis on this structure. Although there is no unanimity of opinion concerning the mechanism

responsible for the inotropic action of glycosides, there are considerable data that suggest that it is not causally related to the inhibition of active monovalent cation transport (28-36). Whereas the present study was not designed to elucidate the specific mechanisms responsible for the arrhythmia-producing and inotropic actions of the glycosides, the dissociation of these effects by the administration of K suggests that they are not produced by identical actions of the glycoside on the heart.

Although previous investigations have not been concerned with a comparison of the effects of K on the inotropic and arrhythmia-producing actions of a digitalis glycoside, the results of the present study are in agreement with those studies in which quantitatively similar inotropic responses to ouabain or acetylstrophanthidin were observed among cardiac preparations exposed to different concentrations of extracellular potassium. Garb and Venturi observed similar inotropic responses to ouabain in isolated cat papillary muscles bathed in fluid in which the K concentration varied from 3.5 to 8.5 mmoles per L (37). Leonard and Hajdu found both in isolated amphibian and mammalian tissues that the usual alteration of the force-frequency relationship produced by strophanthidin was not affected by twice normal K concentrations in the bath (38). Similarly, Leight, Roush, Rafi, and McGaff observed that normal dogs, K-depleted, and hyperkalemic animals all showed quantitatively similar inotropic responses to acetylstrophanthidin (15).

Whereas the hazards in applying observations made in normal animals to clinical heart failure with its attendant changes in serum electrolyte concentrations and pH must be recognized, the observations of the present study may nonetheless be of relevance to the clinical use of digitalis glycosides. It is current practice to treat many digitalis-induced arrhythmias by discontinuing the glycoside and administering K. Whereas this approach is usually effective in abolishing the arrhythmia, the maximal possible inotropic effect that the glycoside can produce may not be achieved. This circumstance may be of the greatest clinical significance in patients who are depleted of K, and who therefore have a lower threshold for digitalis-induced toxicity (3), and in patients with intractable congestive heart fail-

ure, in whom the greatest possible improvement in myocardial contractility must be achieved. It is possible that under appropriate clinical conditions it may be advisable not to discontinue digitalis if the arrhythmia can be controlled with K. It must be appreciated, however, that the elevation of serum K necessary to suppress the toxic arrhythmias may be difficult to attain continuously. It must also be recognized that the administration of K may produce a more rapid and potentially dangerous elevation in the plasma level of this ion in the presence of digitalis than in its absence (39-41).

The findings in this study are also pertinent to the widely accepted notion that as the quantity of digitalis administered approaches that which produces toxicity, the inotropic effects of the additional increments of the drug become progressively less (42, 43). When 40.3  $\mu\text{g}$  per kg ouabain (80% of the dose required to produce initial toxicity) has been administered, myocardial contractile force has increased by 48% of control. The administration of the additional 10.3  $\mu\text{g}$  per kg, which had to be infused before initial toxicity occurred, was associated with a further increment in contractile force to 65% above control. A still greater increase of contractile force, to a level averaging 84% above control, occurred when toxicity was suppressed and an additional 15.6  $\mu\text{g}$  per kg ouabain was administered. Thus, these observations do not support the view (42, 43) that the inotropic effects of additional glycoside are minimal as the toxic dose is approached.

### Summary

The present investigation was directed toward determining the relative effects of potassium on the arrhythmia-producing and inotropic actions exerted by digitalis glycosides on the intact heart. Ten anesthetized dogs were given ouabain (30  $\mu\text{g}$  per kg, followed by 30  $\mu\text{g}$  per kg per hour) while right ventricular contractile force was measured with a Walton-Brodie strain gauge arch. Arterial pressure and body temperature were kept constant. When toxic arrhythmias occurred, sinus rhythm was restored with an infusion of KCl, and the administration of both KCl and ouabain was continued until toxicity recurred. Plasma K increased from an average control value of 3.2 mEq per L to 4.1 mEq per L at initial toxicity and was 5.7 mEq per L when toxicity recurred. Contractile

force increased by an average of 65% of control before initial toxicity developed. After restoration of sinus rhythm, there was a further increase in force averaging 19% of control before toxicity recurred. These results were not modified by adrenalectomy or by maintaining heart rate constant with right atrial stimulation, and KCl infusion without ouabain did not affect contractile force. It is concluded that the suppression of ouabain-induced arrhythmias by KCl does not depress the positive inotropic effect of the glycoside and permits the administration of additional amounts of the glycoside, which actually produce a further increase in contractile force.

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