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Myocardial Responses to Acetylstrophanthidin During Veratrum Alkaloid Refractoriness (39131)[1]

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The veratrum alkaloids have been used clinically to reduce blood pressure. Although the neural effects of these drugs probably predominate when administered to the intact animal, the cellular effects remain as obscure as those of the cardiac glycosides. The field has been reviewed by Krayer and Acheson (1) and Benforado (2, 3). However, only a few studies have dealt specifically with the effects of the veratrum alkaloids on the relation between myocardial potassium balance and performance. Using the isolated, perfused, hypodynamic guinea pig preparation, Vick and Kahn (4) concluded that while the cardiac glycosides inhibit the myocardial uptake of potassium the structurally related veratrum alkaloids increase potassium efflux concomitant with a positive inotropic effect. Morales and Acheson (5) did not observe a consistent change in myocardial potassium balance associated with the positive inotropic effect of veratridine in the dog heart–lung preparation. However, their method for detecting gains or losses of potassium was rather insensitive and their preparation exhibited severe disturbances of cardiac rhythm.

The experiments to be described were undertaken in an attempt to quantify the relationship between the positive inotropic and potassium losing effects of the veratrum alkaloids and to compare these to the same responses to a cardiac glycoside. Early in the experiments we observed that myocardial refractoriness to the veratrum alkaloids developed in terms of both performance and potassium balance while the cardiac glycosides still elicited a myocardial effect. Therefore, we undertook a series of experiments to document this finding further and to determine if myocardial refractoriness to the veratrum alkaloids substantially altered the positive inotropic and potassium-losing effects of cardiac glycosides.

Materials and Methods. Mongrel dogs of varying weight and of both sexes anesthetized with intravenously administered pentobarbital sodium (25–30 mg/kg) were used in the experiments. A Langendorff blood perfused dog heart similar to that described previously (6) was prepared in the following manner: while maintained on positive pressure ventilation, a transverse thoracotomy was done through the fifth intercostal space and the heart was isolated by ligating the inferior and superior vena cavae, azygos vein, lung roots, brachiocephalic artery, left subclavian artery, and the aortic arch immediately below the left subclavian artery. The left subclavian artery was cannulated and connected to the femoral arteries of an intact anesthetized dog, thereby providing coronary artery inflow. Total coronary outflow (less left Thesbesian) was diverted from the right ventricle through a low resistance rotameter (7) and then to a reservoir connected to the jugular veins of the intact dog. Left ventricular Thesbesian drainage was obtained through a catheter inserted through the apical dimple. Heart rate was maintained constant in each experiment using electrodes sewn either to the right atrium or to both the right atrium and right ventricle. The stimulus was delivered using a Grass S-8 stimulator.

Changes in ventricular performance were monitored using a strain gauge arch (8) applied to the left ventricular wall and set to approximately 130% of the resting fiber length. Coronary arterio-venous oxygen difference was monitored continuously using a Guyton oxygen analyzer (9), which was

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calibrated during the experiment by manometric analysis.

Myocardial oxygen consumption was calculated as the product of total coronary blood flow and coronary arterio-venous oxygen difference. Coronary arterial and venous whole blood potassium concentration was monitored continuously using on-line automated flame photometry (10). This technique is particularly suited to analysis of dog blood since the dog erythrocyte has a low potassium content compared to the human erythrocyte. Changes in myocardial potassium balance were calculated as the product of the coronary arterio-venous blood potassium difference integrated over the period of change and total coronary blood flow.

After establishing a steady state as indicated by the constancy of the continuously recorded parameters, 50 μg of acetylstrophanthidin[2] were injected into the coronary artery of the isolated heart. After the response to this first injection of acetylstrophanthidin had terminated, 200 μg of cryptenamine acetates (Unitensin) were injected into the coronary artery. When the response to this injection of cryptenamine acetates terminated, a second injection of 200 μg of cryptenamine acetates was given. The heart was usually refractory to this second injection. If not, a third injection of 200 μg of cryptenamine acetates was given to which the heart was invariably refractory. Finally, a second 50-μg injection of acetylstrophanthidin was administered into the coronary artery. Statistical analysis of the data was done employing the Wilcoxon signed rank for paired data.

Results. The experimental protocol and drug sequence described above were carried out in each of six isolated dog hearts. The results from one experiment are shown in Figs. 1a through 1d. The first injection of acetylstrophanthidin (Fig. 1a) produced an increase in left ventricular force and its first derivative, a 224-μEq loss of potassium, no change in coronary blood flow and a modest increase in myocardial oxygen consumption. Similar results were observed following the first injection of the cryptenamine acetates (Fig. 1b) while the second injection (Fig. 1c) had little or no effect. However, the second injection of acetylstrophanthidin (Fig. 1d) produced a 1139-μEq loss of myocardial potassium and an increase in ventricular force, its first derivative, coronary blood flow and myocardial oxygen consumption.

Table I presents the data from all the experiments. Before the hearts became refractory to the cryptenamine acetates, acetylstrophanthidin produced a mean loss of 172 μEq of potassium and during refractoriness a mean loss of 465 μEq, the difference being significant ($P < 0.05$). Refractoriness to the cryptenamine acetates had no significant effect on the response of the other parameters to acetylstrophanthidin.

Discussion. The experiments described above show clearly that (a) the myocardial refractoriness which develops to the administration of the cryptenamine acetates occurs in terms of both its mechanical and potassium losing effects, (b) during myocardial refractoriness to the cryptenamine acetates the mechanical and potassium losing effect of acetylstrophanthidin still persists; in fact, the myocardial potassium losing effect of acetylstrophanthidin is potentiated significantly while its effect on myocardial performance is not.

The most widely accepted hypothesis concerning the mechanism of action of the cardiac glycosides on the heart appears to be that they inhibit the sodium pump leading to an increase in intracellular sodium which "in some manner" makes more calcium available to the contractile machinery. According to this hypothesis the loss of potassium is a secondary effect of the glycoside (11). It is of interest that those who subscribe to this position ignore a number of studies in which the mechanical effects of the glycosides can be temporally dissociated from their effects on sodium–potassium adenosine-triphosphatase (12–14) which is considered to be the so-called sodium pump.

The most relevant paper concerning the mechanism (or) mechanisms of the myocardial effects of the veratrum alkaloids is that of Horackova and Vassort (15). They ob-

[2] Provided through the courtesy of Eli Lilly and Company, Indianapolis, Indiana.

TABLE I. EFFECT OF ACETYLSTROPHANDTHIDIN ON POTASSIUM BALANCE, AND MYOCARDIAL PERFORMANCE AND OXYGEN CONSUMPTION BEFORE (B) AND DURING (D) REFRACTORINESS TO CRYPTENAMINE ACETATES

Experiment	Net K[a] loss (Eq)		Increase in ventricular force (g)		Increase in ventricular (df/dt g/sec)		Changes in MVO_2[b] (ml/min)	
	B	D	B	D	B	D	B	D
1	260	354	25	40	383	383	0	1.7
2	78	166	46	38	259	129	−1.0	−0.5
3	108	106	24	12	548	109	−1.6	0
4	193	546	25	38	690	1035	2.3	3.3
5	169	480	240	60	2720	769	0.9	2.9
6	224	1139	35	10	370	212	0.9	1.9
Mean	172.0	465.2	65.8	33.0	828.3	439.5	0.25	1.55
±SD	69.0	371.9	85.8	19.0	939.0	380.5	1.42	1.53
P	<.05		>0.10		>0.10		>0.10	

[a] K = potassium.
[b] MVO_2 = myocardial oxygen consumption.

served that the potentiation of contraction of the frog heart caused by veratrine was associated with a prolongation of the action potential and an increase in the fast inward current and that all of the responses to veratrine were prevented by the administration of tetrodotoxin. They concluded that "the positive inotropic action of veratrine alkaloids depends on a greater influx of sodium ions, whose increased intracellular concentration probably governs the amount of Ca ions available for the tension enhancement."

The similarity between the conclusion of Horackova and Vassort (15) regarding the mechanism of action of the veratrine alkaloids and that for the cardiac glycosides (11) discussed above is of interest. The effect of both drugs is attributed to an increase in intracellular sodium although in the one instance the increase is presumed to be due to an inhibition of sodium efflux (inhibition of sodium–potassium adenosinetriphosphatase), while in the other it is presumed to be due to an increase in sodium influx.

At the same time, the consistent association between the increase in myocardial contractility and loss of myocardial potassium in response to both drugs cannot be ignored. The experiments of Horackova and Vassort (15) do not preclude the possibility that the potentiation of contraction caused by the veratrum alkaloids (and the cardiac glycosides) requires an associated decrease in intracellular potassium.

The finding that the potassium losing effect of the cardiac glycosides is potentiated during veratrum alkaloid refractoriness suggests a relationship between the two observations with which the following hypothesis would be consistent. As shown by Horackova and Vassort (15), the initial dose of veratrum opens the sodium channels causing a rapid influx of this ion, which in some way leads to an increase in myocardial contractility. The channels then remain open for some period of time due to binding of the alkaloid to the myocardial cell membrane. As a result of the increase in intracellular sodium, the sodium–potassium pump is stimulated (16) so that, even though sodium conductance continues to be high, sodium is rapidly extruded thereby returning intracellular sodium towards its original concentration. Since the activity of the sodium pump is now increased, inhibition by a cardiac glycoside then causes a greater gain of sodium and, as found in the present experiments, a greater loss of potassium than before veratrum refractoriness.

Summary. Studies were undertaken in the isolated blood perfused dog heart to determine the nature of the myocardial refractoriness induced by veratrum alkaloids. The initial intracoronary injection of cryptenamine acetates (Unitensin) was always associated with an increase in myocardial contractility and a loss of myocardial potassium. Subsequent doses produced refractoriness with respect to both the contractile

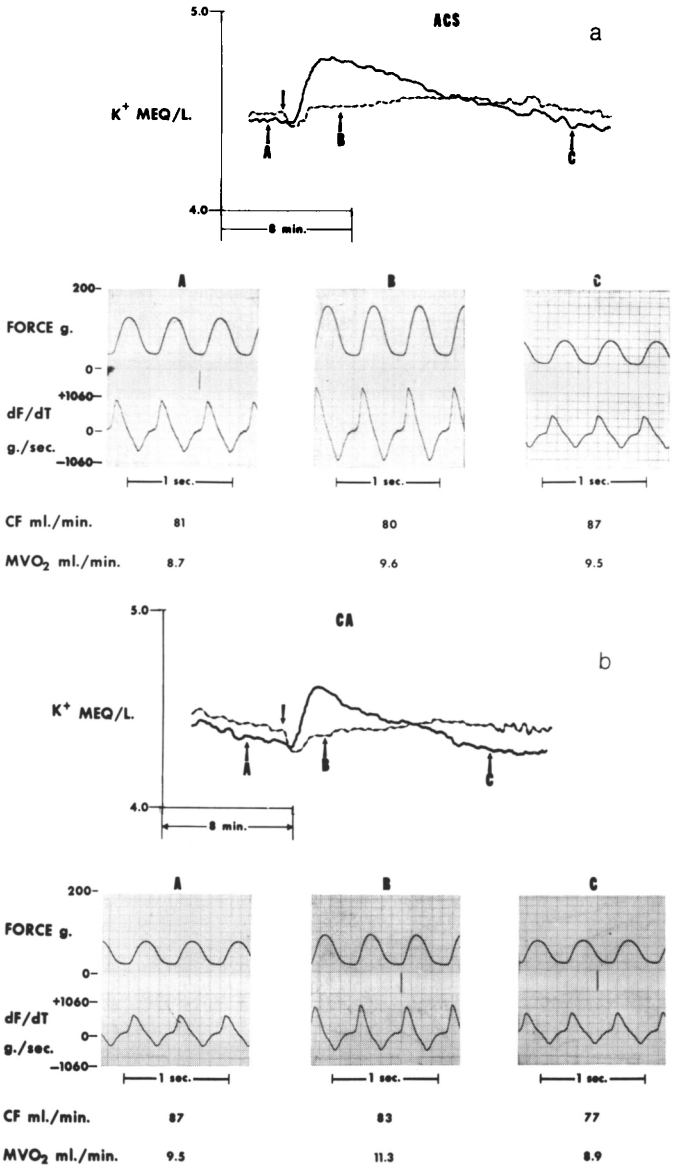

FIG. 1a. The influence of acetylstrophanthidin on myocardial potassium balance, performance, coronary blood flow, and oxygen consumption. The upper panel is a tracing of the coronary arterial (broken line) and coronary venous (solid line) blood potassium concentration. The downward arrow on the potassium tracing indicates the time that 50 μg of acetylstrophanthidin were injected into the coronary artery inflow line. The transient decrease in the coronary artery blood potassium concentration is a dilution artifact since the arterial sampling for the potassium analysis was done downstream from the injection site. Panel A of the hemodynamic tracings was obtained in the control state prior to the injection of the acetylstrophanthidin; panel B was obtained during the elevation of the coronary venous blood potassium concentration as indicated in the potassium tracing; and panel C represents that obtained at the time indicated in the K tracing. For further description of figure, see text.

FIG. 1b. The influence of cryptenamine acetates on myocardial potassium balance, performance and blood flow and oxygen consumption. The abbreviations and description of figure are the same as those for Fig. 1a. Experiment is from same heart as shown in Fig. 1a. For further description of figure, see text.

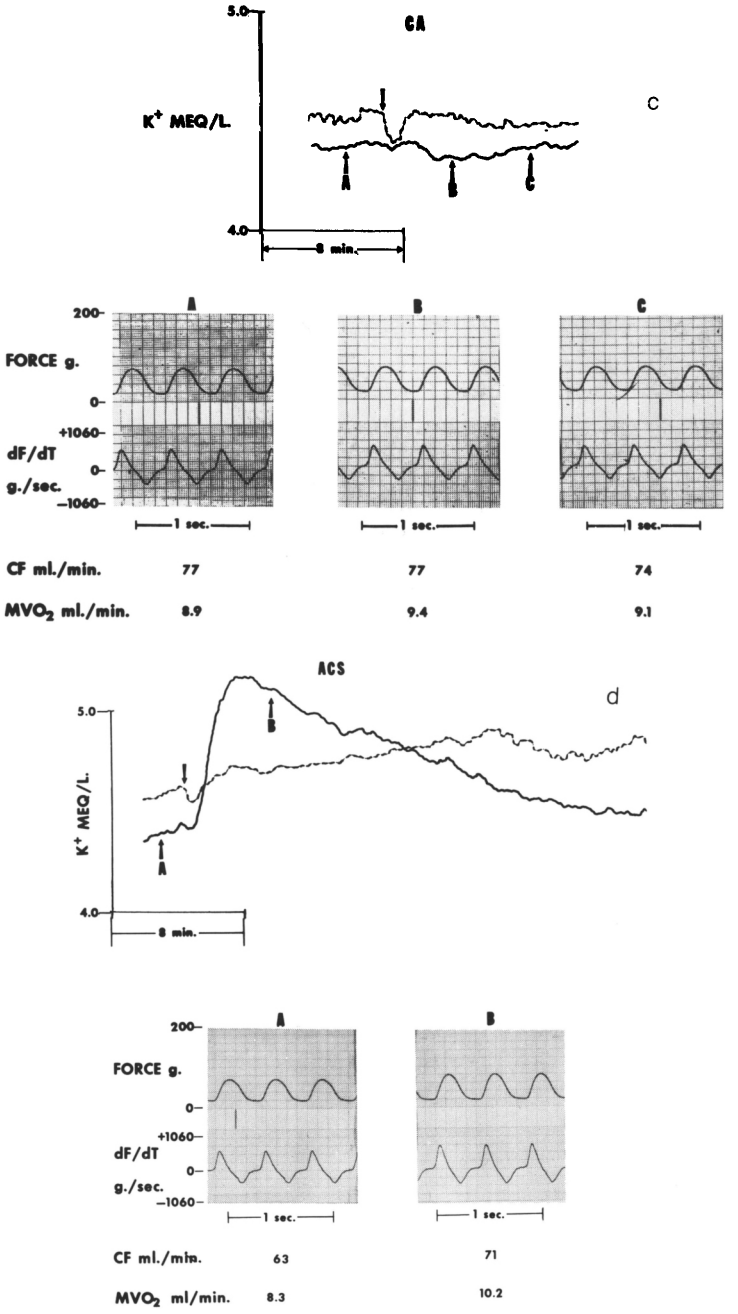

FIG. 1c. The influence of a second dose of 200 μg of cryptenamine acetates to the same heart shown in Fig. 1b. At this time the 200-μg injection had no effect on either myocardial potassium balance or myocardial performance. Experiment is from the same heart as shown in Fig. 1b. For further description of figure, see text.

FIG. 1d. The influence of acetylstrophanthidin (50 μg) on myocardial potassium balance and performance during veratrum alkaloid refractoriness. Legends and abbreviations the same as in the previous three figures. This experiment was obtained from the same heart as shown in the previous three figures. For further description of figure, see text.

and potassium responses. Acetylstrophanthidin still produced an inotropic and potassium losing effect during veratrum refractoriness; however, the potassium losing effect of the glycoside was potentiated whereas the contractile response was not.

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