Effect of Digitalis Glycosides on the Myocardial Sodium and Potassium Balance

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The effect of nontoxic and of toxic doses of digitalis glycosides on the sodium and potassium balance of the myocardium continues to be disputed despite the development of new techniques of investigation. Since 1930, the majority of investigators have found that potassium is liberated from cardiac muscle following digitalis administration. Boyer and Poindexter found an increase in intracellular potassium in the heart muscle after digitalization. Other investigators, however, noted no change in the myocardial potassium and/or sodium concentration after the administration of digitalis.

In the past several years, the technique of coronary sinus catheterization has been used to study the effects of digitalis glycosides in the anesthetized intact dog and in man. The A-V difference of sodium and potassium has been used as a measure of the myocardial exchange. Since the magnitude of the coronary arteriovenous potassium difference depends on (1) the coronary flow per unit of time, (2) the speed with which potassium is released from the heart muscle, and (3) the total potassium lost from the heart, the A-V difference alone may give misleading information about the potassium balance. The conflict of the results of such studies may arise in part from the failure to measure the total amount of potassium lost from the heart.

The purposes of the present study are: (1) to determine the effects of nontoxic and toxic doses of digitalis glycosides on the sodium and potassium balance of the dog heart, (2) to relate the magnitude of the shift and of the cumulative debt of potassium to the onset of cardiac arrhythmias, and (3) to determine the effects of altering the serum potassium level by glucose and insulin and by potassium chloride prior to or following digitalization.

Methods

The experiments were performed on 18 mongrel dogs weighing 15 to 26 Kg. They were anesthetized with intravenously administered sodium pentobarbital (30 mg./Kg.). The chest was opened at the fourth left intercostal space, and respiration was maintained artificially. Heparin (5 mg./Kg.) was injected intravenously to prevent clotting. The aorta was cannulated via the right carotid artery, and phasic aortic pressure was recorded by a modified Gregg manometer. A modified Morawitz cannula was placed in the coronary sinus through an incision in the right atrial appendage. Coronary sinus blood flow was measured by the method described by Levy and Frankel. A Sanborn direct writing apparatus was used to record electrocardiograms (lead II) during the control and experimental periods. Blood samples were drawn at 1, 3, 5, and 10 minute intervals from the coronary sinus and from an indwelling cannula in the femoral artery for determination of plasma sodium and potassium levels. An Internal Lithium Standard Flame Photometer was used to analyze plasma samples in duplicate.

Aortic pressure, heart rate, coronary sinus blood flow, electrocardiograms, and samples of femoral arterial and coronary sinus blood for determining plasma sodium and potassium were obtained during the control and experimental periods.

The effects of digitalis glycosides, glucose and insulin, and potassium chloride on the above parameters were measured. The cardiac glycosides used were Acetyl Strophanthinidin (Lilly),• 0.5 mg./cc, 4 cat units, and K-Strophosid (Sandoz), 0.5 mg./cc, 3 cat units. The nontoxic dose used was 0.05 mg./Kg., and the toxic dose used with both drugs was 0.1 mg./Kg., given in a single injection or multiple smaller injections. In certain experiments 50 ml. of 50 per cent glucose in water and 15 units of crystalline insulin were administered prior to, together with, or after the digitalis.

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Supported in part by grants from the Cleveland Area Heart Society.

Received for publication May 3, 1960.

*We are indebted to the Eli Lilly Company for the generous supply of Acetyl Strophanthinidin.
Table 1
Effects of a Single Toxic Dose of Acetyl Stropho-
thidin on Average Coronary A-V Difference of Sodium and Potassium of Four Dogs (discussed in text)

<table>
<thead>
<tr>
<th></th>
<th>Sodium A-V Difference</th>
<th>Potassium A-V Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S. D.</td>
<td>S. D.</td>
</tr>
<tr>
<td>Control</td>
<td>-4.5 ±2.04</td>
<td>-0.139 ±0.021</td>
</tr>
</tbody>
</table>
| After single toxic dose of digitalis glycoside-Acetyl Stropho-
thidin, 0.1 mg./Kg. |            |                          |
| 1 minute   | -5.7 ±1.70            | -0.66 ±0.042             |
| 3 minutes  | -3.5 ±1.80            | -1.42 ±0.145             |
| 5 minutes  | -2.8 ±1.92            | -1.13 ±0.173             |
| Average for first 5 minutes | -4.1 ±1.86 | -1.10 ±0.095 |

glycosides. Varying amounts of a potassium chloride solution (2 mEq./ml.) were given in one series of experiments. All drugs were given via the intravenous route.

In Part I, 9 dogs (nos. 1-9) were given digitalis glycosides and studied until death or the end of the experimental period. In Part II, glucose and insulin were administered to 9 dogs (nos. 6-14) prior to, simultaneously with, or after digitalization. In Part III, 4 dogs (nos. 15-18) were given potassium chloride in varying amounts (60 to 120 mEq.) 40 to 60 minutes prior to digitalization.

Results
Part I: Electrolyte, Hemodynamic, and Electrocardiographic Changes following the Administration of Digitalis

Nine dogs were given a digitalis glycoside at variable times and in variable doses and were observed until death or the end of the experimental period. Five dogs (nos. 1-5) were studied during periods of 70 to 110 minutes, and 4 dogs (nos. 6-9) were studied during periods of 21 to 40 minutes prior to the administration of glucose and insulin. The entire former group and dog no. 9 received Acetyl Stropho-
thidin while the remainder of the latter group received K-Strophosid. Four dogs (nos. 1, 3, 4, 5) were given single toxic doses; 5 dogs (nos. 2, 6, 7, 8, 9) received multiple nontoxic doses. Four of the first 5 dogs survived the total experimental period which ranged from 70 to 110 minutes with an average of 84 minutes. One dog developed ventricular fibrillation at 70 minutes. The survival times and fates of dogs nos. 6-9 are discussed in Part II.

A biphasic change in potassium levels was observed in all 8 animals followed for more than 35 minutes (fig. 1C). Following intravenous injection of Acetyl Stropho-
thidin the coronary sinus potassium levels showed an initial sharp rise with a subsequent fall but never returned to control levels. The femoral arterial potassium levels increased gradually, reaching constant levels near the end of the experimental period. There was a significant and consistent negative A-V difference of potassium during the first 25 minutes of the experiments, at the end of which time a positive A-V difference of potassium occurred and continued to the conclusion of the experiments. The peak potassium A-V differences in the 4 dogs given single toxic doses of digitalis occurred in the first 5 minutes (table 1). They averaged 1.10 mEq./liter and ranged from 0.93 to 2.13 mEq./liter. The peak A-V differences in the 5 dogs given nontoxic doses of digitalis also occurred in the first 5 minutes but were of a smaller magnitude, ranging from 0.11 mEq./liter to 0.79 mEq./liter with an average of 0.42 mEq./liter. The average control levels of potassium were 3.0 mEq./liter in both the femoral artery and coronary sinus. The average potassium level at the junction of the femoral arterial and coronary sinus potassium concentration curves was 4.8 mEq./liter. The product of coronary blood flow (CBF) and the A-V difference of potassium also demonstrated the initial negative and later positive myocardial potassium (fig. 1D) balance. There was no consistent or significant alteration in either femoral arterial or coronary sinus sodium levels in the above dogs (table 1).

Following the administration of digitalis there was an initial increase in systemic blood pressure and coronary blood flow lasting 10 to 20 minutes, after which they fell to control or below control values (fig. 1A and B.). The changes in heart rate were more variable. In the majority of the dogs after the adminis-
tration of digitalis, the heart rate decreased during the first 3 minutes and increased or remained the same subsequently.

Cumulative Myocardial Potassium Debt and Electrocardiographic Changes

In 8 of 9 dogs the myocardium went into potassium debt for the entire test period. In the one exception (dog no. 1), the potassium debt was repaid, and a small positive balance occurred. The magnitude of the debt was greatest at the 20 to 25 minute period, and became progressively less as the experiment proceeded. An example is shown in figure 1E. The electrocardiographic changes occurring at various times throughout the experiment are shown in figure 2. The letters in figure 1E showing the time sequence and potassium status of the myocardium correspond to the lettering of the electrocardiograms in figure 2.

In this series of experiments the electrocardiographic changes following digitalis administration were typical of digitalis intoxication. The early minor changes, such as slowing of the rate, peaking the T waves, ST-T depression, first degree A-V block, progressed to later and more complex arrhythmias terminating in ventricular asystole and/or fibrillation. The progressive deterioration of the electrocardiograms occurred while the potassium debt was being repaid, and fatal arrhythmias occurred when the debt was almost repaid in toto. Examples are shown in figures 1E and 2.

Part II: Effects of Decreasing Serum Potassium with Insulin and Glucose on Digitalis Effects

In this series of experiments, 9 dogs (nos. 6-14) were given glucose and insulin prior to, simultaneously with, or after digitalis administration. Dogs nos. 6, 7, and 8 were given K-Strophosid, and dogs nos. 9, 10, 11, 12, 13, and 14 were given Acetyl Strophanthidin. All animals were observed until death occurred or to the end of the experimental period.

Glucose and Insulin Prior to Digitalis

Dogs nos. 12, 13, and 14 were given glucose and insulin 30 to 40 minutes prior to the administration of digitalis. These 3 dogs died of ventricular fibrillation 25, 23, and 19 minutes, respectively, after the administration of digitalis. Their control potassium levels were lower than in normal animals treated with digitalis alone. In dog no. 12 the control potassium value in the coronary sinus was 1.94 mEq./liter, in the femoral artery 2.21 mEq./liter; in dog no. 13 control value in the coronary sinus was 1.48 mEq./liter and the femoral artery 1.49 mEq./liter; and in dog no. 14 the control coronary sinus and femoral arterial samples were identical, 1.74 mEq./liter.

Following digitalization, there was no significant A-V potassium difference although in both the coronary sinus and the femoral artery, the potassium rose sharply in the first 5 minutes (fig. 3C).

The circulatory hemodynamics changed markedly. The heart rate increased immediately and remained elevated until death. The blood pressure rose initially but at the end of 10 minutes was below control levels. Coronary blood flow increased 3- to 4-fold and began to decrease at the 15 minute interval but never below control values until death occurred. Figure 3A and B is illustrative of the changes in these 3 animals. The myocardium, which was in positive potassium balance before the digitalis was administered, remained in positive potassium balance in this series of experiments, although fluctuations in the A-V differences occurred after digitalis. The product of the A-V potassium difference times the coronary blood flow showed an initial positive balance followed by a small negative balance with a final positive balance (fig. 3D). The electrocardiographic changes in this series of animals were similar to those in Part I except for the more rapid deterioration of the electrical events terminating in ventricular fibrillation. Figure 4 serves as an example.

Glucose and Insulin Simultaneously with and Following Digitalis Administration

The duration of this experiment was brief, from 3 to 15 minutes. All 6 dogs died of ventricular fibrillation before the end of the experimental period. Dogs nos. 10 and 11 received the drugs simultaneously and died of ventricular fibrillation in 10 and 16 min-
Effects of Acetyl Strophanthidin on the myocardial potassium balance of a dog. In A, vertical bars represent blood pressure and joined dots, heart rate; B, coronary blood flow; C, plasma potassium, in coronary sinus, dots joined by solid lines, and in femoral artery, dots joined by dashes; D, myocardial potassium shift; E, cumulative potassium debt. Arrow indicates intravenous administration of 1.6 mg. of Acetyl Strophanthidin. Note biphasic shift in myocardial potassium, negative for the first 25 minutes and positive thereafter. The cumulative myocardial potassium debt was greatest at 20 minutes and decreased progressively thereafter. Progressive deterioration of the electrocardiogram occurred (see fig. 2) as the debt was reduced, and ventricular fibrillation occurred when positive myocardial balance was attained (discussed in text).
MYOCARDIAL SODIUM AND POTASSIUM

Figure 2

Same dog as figure 1. A shows the control record, lead II; B shows a slowing of the rate, first degree A-V block, and minor S-T depression; C and D show incomplete and complete bundle branch block, respectively; E shows bundle branch block and S-T segment depression; F shows heterotopic activity with periods of bigeminy; G and H show runs of ventricular ectopic beats and complete A-V dissociation; I and J show heterotopic activity with slower rate of the S-A node; K and L show runs of ventricular tachycardia which terminate in ventricular fibrillation (discussed in text).

sinus of 4 animals was 7.92 mEq./liter. The range in the coronary sinus was 6.9 to 9.4 mEq./liter, and in the femoral artery 8.64 to 10.50 mEq./liter. After the administration of a digitalis glycoside a biphasic change in potassium levels in the coronary sinus and femoral arterial samples was evident even though the levels of potassium decreased in both the coronary sinus and femoral artery as a result of discontinuing the potassium chloride infusion. There was an initial negative A-V potassium balance followed by a small positive A-V potassium balance (fig. 5C).

The heart rate, blood pressure, and coronary blood flow in this series of animals showed the same initial increments after digitalis as in the other experiments. However, the pulse rate remained stable and did not parallel the changes in the levels of the coronary sinus potassium. The blood pressure did not fall much below control levels, and the coronary blood flow returned approximately to control levels. An example of these changes is shown in figure 5A and B.

A marked cumulative potassium debt occurred, and, unlike the other experiments, was not repaid (fig. 5E).

In 3 dogs, minimal electrocardiographic changes occurred. In the control period, the T waves were peaked, reflecting the effect of increased potassium. After the administration of the digitalis glycoside, transient ST-T changes of digitalis effect appeared. No arrhythmias occurred (fig. 6). As mentioned before, dog no. 15 which had shown similar electrocardiographic changes after digitalis, developed ventricular fibrillation 3 minutes after a second dose of digitalis.

Sodium Changes

There were no significant or consistent changes in sodium balance following the administration of the digitalis glycosides (table...
Discussion

It is now well established that nontoxic and, especially, toxic amounts of cardiac glycosides influence the electrolyte balance of the heart, but the relation of alterations of myocardial and extracellular potassium to the chronotropic (arrhythmic) action of digitalis has not yet been clarified. Following the administration of a rapidly acting digitalis glycoside, such as Acetyl Strophanthidin, the heart soon develops a negative potassium balance. In the present study, the biphasic shift of potassium of the myocardium, negative for approximately 25 minutes, and then positive, is similar to that also reported in dogs by Hellem and associates. In our experiments, this biphasic response was more marked after toxic doses of digitalis glycosides than either after smaller doses or in the potassium pre-treatment experiments. When the loss of potassium from the myocardium is extensive and rapid, the coronary arteriovenous difference is great, and myocardial potassium balance is more readily determined. Thus the failure of other investigators to confirm this negative myocardial balance in a similar type of experiments in dog or in man may be due to the use of other digitalis glycosides, K-Strophosid and Cedilanid, respectively, which produce a slower rate of loss of potassium from the myocardium.

The shifts of potassium produced by digitalis are related to changes produced in the membrane of the myocardial fibers. Since there was no consistent relationship between the potassium balance and heart rate in our experiments, it is probable that digitalis produced the imbalance in some other way, either by blocking the re-entry of K⁺ during dias-
tole or by exaggerating the release of $K^+$ with each systole.

In addition to its action on the myocardium, digitalis glycoside liberates sufficient potassium from extracardiac tissues, such as liver, skeletal muscle, and red blood cells to produce a rise in arterial potassium. In the present and other reports the early rise in coronary sinus potassium is greater than that of the femoral artery, suggesting that the negative balance of the myocardium occurs more rapidly than the mean negative balance of noncardiac tissues. During the subsequent positive balance of the myocardium, the level of the arterial potassium continues to rise, representing continuation of a negative balance of extracardiac tissues.

The disturbance of potassium balance produced by nontoxic doses of digitalis glycosides subsided within an hour, and the myocardial potassium returned to control levels in our study. This finding is in agreement with earlier studies that therapeutic doses did not influence the concentration of potassium in the heart muscle.

The severity of the electrocardiographic changes did not correlate with the magnitude of the cumulative potassium debt, as determined from the coronary arteriovenous difference and coronary blood flow per unit of time. The most serious arrhythmias developed when the myocardial potassium debt had been substantially reduced, and ventricular fibrillation occurred when a positive myocardial potassium balance was attained or was being approached.

The explanation of the above phenomenon is not known, but according to current views should be related to the ionic balances, particularly of potassium between the inside and the outside of the myocardial fibers. The precipitation of fatal ventricular arrhythmias at the time that the potassium balance is being restored suggests the possibilities (1) that the intracellular potassium has not been restored to its predigitalis state but is bound or not readily available for transmembrane release because of the influence of subcellular structures upon the kinetics of potassium within the myocardial fiber, or (2) that the returning potassium is actually situated in the interstitial spaces, and that a potassium balance has not been attained. A more direct approach involving chemical analysis of the myocardium will be required to explain the above finding.

The increased digitalis sensitivity following or accompanying insulin and glucose likewise may be related to a "modified state" of intracellular potassium as well as to low serum potassium. It has been amply demonstrated that several inorganic substances including potassium participate in carbohydrate metab-
Effects of Acetyl Strophanthidin on myocardial potassium balance of dog pretreated with potassium chloride. Legends as before. Sixty mEq. of potassium chloride were administered intravenously during 35 minutes prior to the administration of 1.75 mg. of Acetyl Strophanthidin, indicated by arrow. Note biphasic shift in myocardial potassium balance, negative for 20 minutes, and positive later. Although the cumulative myocardial potassium debt increased, no arrhythmias occurred (see fig. 6; discussed in text).

Figure 5

Same dog as figure 5. Both A (control lead II electrocardiogram before Acetyl Strophanthidin) and B, at 1 minute, show peaked T waves of hyperkalemia; C, D, and E, at 3, 5, and 15 minutes, respectively, show lower P waves and S-T segment depression, first degree A-V block, and decrease in amplitude of the T wave; F, G, and H, at 20, 40, and 60 minutes, respectively, again show peaked P waves and T waves as seen in control records; the first degree A-V block and S-T segment depression have disappeared (discussed in text).

Figure 6

Circulation Research, Volume VIII, September 1960

olism. In the presence of tissue, glucose and insulin potassium is incorporated into a potassium hexosephosphate complex. Further support of the concept that the myocardial potassium may not be "readily available" may be derived from the observations of the insulin and glucose pretreated animals. In these experiments the rises of potassium in the coronary sinus and femoral arterial samples after digitalis were nearly equal, that is, the A-V difference was insignificant, indicat-
ing either that the potassium was liberated primarily from extracardiac tissues, or that the usual potassium efflux produced by digi-
talis was approximately equal to an influx secondary to the effects of insulin on the myo-
cardial membrane. 20

The development of early death in the insu-
lin and glucose pretreated animals is even more difficult to explain, since ventricular fibrillation occurred when the potassium lev-
els in the coronary (femoral) arterial and venous circulation (Ko+) were restored to normal or above normal, that is, the predigi-
talis hypokalemia had subsided, and the myocardium was in positive potassium bal-
ance. This differs from the digitalsis sensitivity in patients following carbohydrate adminis-
tration or during dialysis which is related predominantly to the low extracellular potas-
sium levels. 21, 22 The lethal effect of a combination of digitalsis, insulin and glucose, the relationship between the electrocardiographic changes and carbohydrate meals in digital-
ized 21 and nondigitalized 23 patients, and the hypokalemia in insulin-induced hypoglyce-
emia 24 have obvious clinical importance.

The protective action of potassium salts against digitalsis intoxication first noted by Samson and Anderson in 1930 25 has been confirmed by the present data and by other investigators. 26 In our experiments, pretreatment with potassium undoubtedly increased both the intracellular and extracellular concentra-
tion of potassium ions and protected the heart from the toxic effects of digitalsis gly-
cosides. The increase of extracellular potassium ions has an effect opposite to those of decreasing extracellular potassium (see above). The animals pretreated with potassium showed effects opposite from the insulin and glucose pretreated group, namely, in the former the serum potassium was elevated, and T waves were peaked; and after the adminis-
tration of digitalsis despite a biphasic myocardial potassium shift, only minor electro-
cardiographic changes occurred. These disappeared before the termination of the experiment in contrast to the fatal and rapid progression of the insulin and glucose experi-
ments. It is possible that in the insulin and glucose pretreated dogs Ko+ did not rise suffi-
ciently to reverse the toxic actions of digi-
talis.

In the present study, as in that of others, 5, 7 no consistent or significant changes in the concentration of sodium were detected. Hel-
lems and associates, however, did report a sodium shift and a change in pH. 8

In our study, changes in coronary blood flow correlated with the systemic blood pressure.
Both increased immediately after digitaliza-
tion and decreased when arrhythmias ap-
peared. These changes are probably a function of cardiac output and may suggest that some degree of occult cardiac failure was present in our preparations. Other investigators have found that doses comparable to those used clinically produce variable effects on blood pressure and either no significant change or a small decrease in coronary blood flow. 27

Summary

Nontoxic and toxic doses of digitalsis glyco-
side produced a rapid release of potassium from the myocardium and from extracardiac tissues of the dog. For approximately 25 min-
utes after the administration of a digitalsis glycoside the myocardium was in negative potassium balance and within an hour re-
turned to positive balance. The most serious electrocardiographic changes transpired when the myocardium approached or attained potas-
sium balance. Pretreatment with potassium chloride protected the heart against arrhyth-
mas by increasing Ko+. Pretreatment with glucose and insulin enhanced the arrhythmic action of the digitalsis glycosides presumably by producing a low serum potassium (Ko+) and possibly by modifying the state of intra-
cellular potassium (Ki+).

Acknowledgment

We are indebted to Dr. Nick Sperelakis, Depart-
ment of Physiology, School of Medicine, Western Reserve University, for helpful comments and criticism.

Summario in Interlingua

Doses toxic e nontoxic de glycosido de digitalis producen un rapido liberation de kalium ab le myo-
cardio e ab tissus extracardiac del can. Durante
alterationes electrocardiographs occurreva quando le myocardio approchava o attingeva le stato de balanza negative de kalium. Preretoramento con chloruro de kalium le lv + extra le fibras myocardial. Pretratamento con niyocardio npprochava o attingeva le stato de balanza. Intra un hora illo glucosa e insulina promoveva le effecto arrhythmic del glucoside de digitalis, presumitamente per producere un basso nivello de kalium in le sero e possibilemente per modificar le stato de kalium intracellular.

References
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JOHN R. BLACKMON, HÉRMAN K. HELLERSTEIN, LOUIS GILLESPIE, JR. and ROBERT M. BERNE

Circ Res. 1960;8:1003-1012
doi: 10.1161/01.RES.8.5.1003

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