DURING the past decade, the relationship between digitalis drugs and potassium has been extensively investigated. Attention has been given primarily to the effect of potassium upon the digitalized state. It has been shown that administration of potassium abolishes the cardiotoxic manifestations of digitalis. The converse has also been established, namely, that depletion of body potassium stores sensitizes the heart to the toxic action of the digitalis drugs.

While digitalis action is influenced by body electrolyte concentration, it may in turn modify electrolyte distribution. A number of investigators have shown that digitalis reduces the potassium concentration of isolated tissues. Preliminary observations have indicated that the shift in potassium and other ions during digitalization may be of a magnitude readily detected in the blood. Occurrence of these serum-electrolyte changes in the intact organism has not been widely appreciated nor thoroughly investigated either clinically or experimentally. The current study was undertaken to explore the changes in serum concentrations of sodium, potassium, calcium, and hydrogen ions during acute digitalization from the onset of drug action through toxicity and death.

Methods

These studies are based upon 165 discrete digitalizations in 54 mongrel dogs, carried to an end-point of ventricular tachycardia. Thirty-five of the animals were males and 19 females. Weights ranged from 10.0 to 30.0 Kg., with a mean of 16.4 ± 3.58. The animals were anesthetized with sodium pentobarbital in a dose of 30.0 mg./Kg. administered either intravenously or intraperitoneally. In 10 animals, mild narcosis was achieved by use of subcutaneous morphine in a dose of 10 mg./Kg. Digitalization was initiated about one hour after the animals were anesthetized.

During 29 digitalizations, ventilation was artificially maintained by means of a Harvard respiratory pump. Endotracheal intubation was accomplished with a cannula having an inflatable cuff. During 14 of the digitalizations, the animals were ventilated with room air; in 15 digitalizations, 100 per cent oxygen was employed.

Acetyl strophanthidin was the digitalizing drug. This agent is an ultra-rapid-acting synthetic ester of the cardiac aglycone, strophanthidin. In dogs, peak effect is noted in from two to five minutes. Complete dissipation of the effect occurs within two hours. It is, therefore, possible to digitalize animals to an endpoint of ventricular tachycardia as many as six times at two-hour intervals without decrease in dosage or other evidence of cumulation. One of two digitalizing schedules was employed: In the first, 0.25 mg. of acetyl strophanthidin was given intravenously, followed after five minutes by 0.1 mg. given every two minutes until an endpoint of ventricular tachycardia; in the second, the time intervals were the same but the dose was doubled, namely, an initial dose of 0.5 mg. followed by 0.2-mg. increments. The latter dose schedule was employed in animals weighing over 20 Kg. or when an endpoint could not be achieved with the slower digitalization procedure. These schedules were arrived at after much trial and error. It was found that if complete digitalization could be effected within 25 minutes, highly reproducible results could be obtained in successive digitalizations. Ventricular tachycardia, defined as occurrence of four consecutive ventricular ectopic beats, constituted the endpoint.

Blood samples were obtained from the femoral artery by means of a Cournand needle. Sampling was carried out just prior to digitalization, during various stages of the digitalization process, at the time of ventricular tachycardia, and within one to two hours after recovery from the arrhythmia. During 42 digitalizations, arterial and venous samples were obtained simultaneously. The latter were...
Table 1

Arterial Electrolytes, Hematocrit, and pH in Twelve Anesthetized Dogs Not Given Digitalis Drugs

<table>
<thead>
<tr>
<th>Time (hours after anesthesia)</th>
<th>Na (mEq./L.)</th>
<th>K (mEq./L.)</th>
<th>Ca (mEq./L.)</th>
<th>pH</th>
<th>Hematocrit (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>157.0</td>
<td>4.5</td>
<td>5.35</td>
<td>7.24</td>
<td>45.9</td>
</tr>
<tr>
<td>1</td>
<td>157.3</td>
<td>4.7</td>
<td>——</td>
<td>7.25</td>
<td>45.5</td>
</tr>
<tr>
<td>2</td>
<td>156.3</td>
<td>4.6</td>
<td>——</td>
<td>7.31</td>
<td>45.7</td>
</tr>
<tr>
<td>3</td>
<td>156.5</td>
<td>4.3</td>
<td>——</td>
<td>7.34</td>
<td>45.5</td>
</tr>
<tr>
<td>4</td>
<td>156.6</td>
<td>4.2</td>
<td>——</td>
<td>7.34</td>
<td>45.1</td>
</tr>
<tr>
<td>5</td>
<td>156.0</td>
<td>4.1</td>
<td>5.30</td>
<td>7.37</td>
<td>46.0</td>
</tr>
</tbody>
</table>

All values represent mean of determinations in 12 animals.

*Immediately after anesthesia.

drawn from either the upper or lower limbs by means of polyethylene catheters. During 29 digitalizations in which respiration was artificially maintained at a constant rate, arterial blood was analyzed for oxygen, CO₂, and pH.

To determine the stability of electrolytes in anesthetized animals, 12 additional mongrel dogs were anesthetized with sodium pentobarbital; six were artificially ventilated and six were permitted to breathe spontaneously. These dogs were not given digitalis, but hourly for five hours arterial blood was sampled and electrolytes, hematocrit, oxygen saturation, CO₂ content, and pH were determined.

Blood for measurement of oxygen contents and capacities, as well as CO₂ contents, was drawn in heparinized, oiled syringes; determinations were made in duplicate by the technique of Van Slyke and Neill. Blood pH was measured by means of a Beckman model-G pH meter. Readings were made at room temperature and converted to values at body temperature by the Rosenthal correction factor. Sodium and potassium were determined by a lithium internal standard flame photometer. Calcium was determined by the method of Clark and Collip, as well as by a chelation method employing disodium ethylenediaminetetraacetate (Versenate). Conventional statistical equations were employed to calculate standard deviation (S.D.), standard error (S.E.), and correlation coefficient (r). The probability (P) of a correlation coefficient being obtained by chance was evaluated by the t-test.

Results

Arterial Electrolytes in Nondigitalized Animals

Mean electrolyte values in the 12 animals followed hourly for 5 hours are shown in Table 1. Since artificial ventilation did not affect arterial values, all results are pooled. A simple analysis of variance showed that none of the hourly determinations revealed deviations significant at the 5 per cent level. Control and five-hour mean calcium concentrations were not significantly different. Thus, in dogs anesthetized with sodium pentobarbital, arterial electrolytes, pH, and hematocrit remained stable during a five-hour period of observation.

Changes in Arterial Serum Electrolytes During Digitalization

Potassium

Digitalization with acetyl strophanthinid to an endpoint of ventricular tachycardia resulted in an increase in potassium concentration of arterial blood. This occurred in 155, or 94 per cent, of 165 acute digitalizations. In the remaining 10 digitalizations, the potassium decreased in four instances and was unaltered in six. At onset of ventricular tachycardia, serum potassium concentration increased by an average of 0.67 mEq./L., as compared with control values (S.E., ± 0.036; P < 0.01) (tables 2 and 3, fig. 1). The digitalis-induced shift in potassium at times resulted in hyperkalemia. Thus, in 27 digitalizations, the concentration rose from a control mean value of 4.5 mEq./L. to exceed 5.5 mEq./L. at toxicity. In 9 of the 27, it rose above 6 mEq./L., and in 5, above 7 mEq./L. The highest concentration reached was 7.4 mEq./L., representing a 2.2-mEq. change from the control level. In any one animal, similar shifts in potassium occurred upon repeated digitalizations on the same day.

The rise in serum potassium was not due to digitalis toxicity or ventricular arrhythmia.
Shift in arterial sodium and potassium concentrations during acute digitalization with acetyl strophanthidin. The bars represent the mean deviations from the control concentration, each based on a number of digitalizations, as indicated.

This is indicated by the fact that an increase was already evident five minutes after the first dose of acetyl strophanthidin, long before electrocardiographic evidence of toxicity. A statistically significant rise in serum potassium was noted when only 25 per cent of the toxic dose had been injected ($P < 0.02$). The increase was progressive throughout digitalization. In 14 animals, increments of acetyl strophanthidin were administered until emergence of ventricular fibrillation. Just prior to the fatal arrhythmia, arterial potassium concentration had increased by 3.1 mEq./L., as compared with the control value immediately preceding digitalization. The shift in potassium produced by digitalization was transient. Within 12 minutes after recovery from ventricular tachycardia, the average serum potassium had already returned to its control level. Potassium concentration, however, did not remain normal; within 110 minutes after digitalization it fell below the control concentration by 0.2 mEq./L. This reduction was statistically significant ($P = 0.01$). Within two and one-half hours, the potassium had again returned to the control value (fig. 2).

Thus, it can be concluded that increase in arterial potassium concentration is a consistent accompaniment of acute digitalization with acetyl strophanthidin. The increase begins at the very inception of digitalis action and progresses until emergence of ventricular fibrillation.

Sodium

Acute digitalization reduced arterial sodium concentration. Data are available for 159 discrete digitalizations. At onset of ventricular tachycardia, sodium concentration was lowered in 120 digitalizations, or 75.5 per cent, increased in 23 digitalizations, and unaltered in 16. Mean decrease in the arterial sodium level in the 159 digitalizations was 2.6 mEq./L. (S.E., $\pm 0.27$; $P < 0.01$). Sodium concentration was not altered in the early stages of digitalization. While a statistically significant shift in potassium was already noted after administration of 25 per cent of the minimal toxic dose, in the case of sodium about twice as much acetyl strophanthidin was required to produce a significant change in the concentration (tables 2 and 3, and fig. 1). Once the reduction began, it was continuous. In 14 animals digitalized to ventricular fibrillation, the sodium had declined by 11.0 mEq./L. at the time of death.

Unlike the potassium concentration, which was promptly restored to its control level, upon resumption of sinus rhythm, the sodium concentration continued to fall. Maximum
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Table 2
Changes in Arterial Potassium and Sodium During Acute Digitalization to Toxicity

<table>
<thead>
<tr>
<th>Per cent of toxic dose</th>
<th>Sodium</th>
<th>Shift (mEq./L.)*</th>
<th>Potassium</th>
<th>Shift (mEq./L.)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. observ.</td>
<td></td>
<td>No. observ.</td>
<td></td>
</tr>
<tr>
<td>23.0</td>
<td>—</td>
<td>—</td>
<td>14</td>
<td>+ 0.14 ± 0.051</td>
</tr>
<tr>
<td>40.0</td>
<td>53</td>
<td>—</td>
<td>39</td>
<td>+ 0.27 ± 0.04 §</td>
</tr>
<tr>
<td>72.0</td>
<td>43</td>
<td>—</td>
<td>41</td>
<td>+ 0.47 ± 0.05 §</td>
</tr>
<tr>
<td>100.0</td>
<td>159</td>
<td>—</td>
<td>165</td>
<td>+ 0.67 ± 0.04 §</td>
</tr>
</tbody>
</table>

*Compared with control value for each animal; mean and standard error.

†P<0.02.
‡P=0.03.
§P<0.01.

lowering occurred in about 110 minutes after recovery from ventricular tachycardia (fig. 2). At this point the sodium value, based on 49 determinations, was 3.8 mEq./L. (S.E., ± 0.82) less than the predigitalization value. This represented a reduction of 1.18 mEq./L. from the level noted at ventricular tachycardia. Restoration of sodium to its initial concentration was a slow process, requiring several hours. If another digitalization was carried out before full recovery, serum sodium was further reduced. For example, in 14 animals sodium concentration was 5.5 mEq./L. less than the initial control value was at the onset of ventricular tachycardia during a second digitalization carried out two hours after the first. Severe hyponatremia was produced in dogs digitalized to an endpoint of ventricular tachycardia five successive times at two-hour intervals. In these multiple digitalizations, the acetyl strophanthidin requirement remained constant, and the rise in potassium was not cumulative, but nearly identical each time.

Thus, reduction in arterial sodium concentration accompanies acute digitalization to toxicity. The shift in sodium, compared with the concomitant and opposite change in potassium concentration, is of less consistent occurrence, develops later in the process of digitalization, tends to persist longer, and is accentuated by successive digitalizations.

Calcium, pH, Qo, CO2, and Hematocrit

Data are available on changes in serum calcium concentration during 87 digitalizations. Arterial calcium did not alter from its predigitalization value either during or after emergence of ventricular tachycardia (table 3). Similarly, no changes were noted in arterial pH value during digitalization. However, at the time of ventricular tachycardia, a slight but significant increase was observed. The mean increase, based on 29 digitalizations, was 0.05 ± 0.01 (S.E.). In all studies in which the hydrogen ion was determined, ventilation was kept constant by means of a respirator. Arterial oxygen saturation and CO2 content were studied in 19 digitalizations. At toxicity, oxygen saturation was unaltered, while CO2 content decreased by 1.64 volumes per cent (S.E., ± 0.28; P < 0.01). The only other change observed at ventricular tachycardia was a rise in arterial hematocrit. The increase was slight, amounting to 1.2 per cent (S.E., ± 0.54), but nevertheless significant (P = 0.05).

Factors Involved in the Electrolyte Shift

Digitalization was generally completed in less than 15 minutes. Since no other variables were introduced during this brief interval, the very act of digitalization appears to be the cause of the electrolyte changes. It is nevertheless pertinent to examine the possible role of other factors. Sex and body weight bore no relationship to these changes. Age did not appear to be of significance; we have observed similar electrolyte alterations during digitalization of growing puppies. Nearly identical changes occurred in 10 animals anesthetized with morphine instead of pentobarbital. No significant alterations in heart rate or rhythm occurred prior to development.
of ventricular tachycardia. In the spontaneously breathing animal, hyperventilation ensues as digitalis toxicity is approached. It is therefore possible that respiratory alkalosis may have contributed to redistribution of cations within the body. However, electrolyte changes preceded deviation in the ventilatory pattern. Furthermore, no differences were noted in 29 animals ventilated artificially with either air or oxygen, as compared with those breathing spontaneously. Ventricular tachycardia was not responsible for the electrolyte shifts, since changes in potassium and sodium preceded onset of arrhythmia. Changes in potassium and sodium immediately before ventricular tachycardia showed no further increment in potassium and only a slight further decrement in sodium. However, when additional doses of acetyl strophanthidin were given during ventricular tachycardia, the electrolyte changes became even more marked. Small increments of digitalis do not significantly modify blood pressure or cardiac output in the absence of congestive heart failure. One may therefore conclude that the electrolyte shifts were not the consequence of altered cardiac or pulmonary function.

Arterial serum-sodium and potassium concentrations change in opposite directions during digitalization. One might therefore assume that the magnitudes of these shifts are linked. Indeed, as more acetyl strophanthidin is injected in any one animal, the progressive rise in potassium is accompanied by a continuous fall in sodium. However, when the changes in concentration of these two ions occurring at toxicity in 150 digitalizations are plotted against one another, the points are randomly distributed. The correlation between the potassium and sodium shifts at ventricular tachycardia calculated for these digitalizations showed a coefficient of only –0.07. This indicates that, in any one animal, there is no quantitative relationship in deviation of these two cations at the toxic endpoint of digitalization.

Since skeletal muscle constitutes the major depot of exchangeable potassium, its role in the electrolyte shifts was examined. Simultaneous arterial and venous samples were taken from either the fore or hind limb in 42 digitalizations. Potassium concentration was consistently slightly higher in the arterial blood. This difference became statistically significant at ventricular tachycardia (P < 0.01). At this time, arterial potassium con-
centration exceeded the concentration in the simultaneously sampled venous blood by 0.18 mEq./L. During digitalization, no significant alterations occurred in the sodium gradient across skeletal muscle. However, at ventricular tachycardia, the arterial sodium concentration was 1.2 mEq./L less than the venous concentration. This difference is significant at the 4 per cent level.

Relation of Electrolyte Shift to Digitalization Process

The dose of acetyl strophanthidin required to induce ventricular tachycardia bore no relationship to the control potassium or sodium concentration in the arterial blood. The coefficient of correlation was 0.15 in both instances ($P = 0.05$). This indicates that predictability of the required digitalis dose on the basis of the initial electrolyte level is poor, even though the probability figure shows that the small percentage of the variance which can be explained by the initial electrolyte concentration is not likely to be due to chance. Animals requiring the largest amount of drug showed the greatest increases in serum potassium. However, when the 165 digitalizations for which potassium data are available are analyzed, only a weak (but significant) correlation is evident between digitalis dose and resultant potassium rise ($r = 0.29; P < 0.01$). No correlation whatsoever existed between the dose of acetyl strophanthidin and the decrease in sodium concentration. The dose bore no relation to the initial calcium level, arterial pH, or the animal’s sex. A correlation was evident with body weight ($r = 0.43; P < 0.01$).

The amplitude and direction of the T wave in the electrocardiogram are determined in part by the distribution of sodium and potassium. Since acetyl strophanthidin alters the distribution of these cations, electrocardiograms made during 100 digitalizations were examined for changes in T-wave morphology. In 42 per cent of the digitalizations, upright peaking of the late portion of the T wave developed; in 18 per cent, the T wave became increasingly inverted in its late portion; and in the remaining 40 per cent, neither of these changes occurred. Examples of the T-wave changes are illustrated in figure 3. In instances of peaking of the T wave, this change was observed within five minutes after injection of the first dose of acetyl strophanthidin. As more drug was administered, this portion of the T wave increased in amplitude until emergence of ventricular tachycardia. The peaking appeared unrelated to the change in heart rate, for it was noted both when the sinus rate was slowed and when it was accelerated. The magnitude of the T-wave change was unrelated to the amount of drug administered. The mean dose of acetyl strophanthidin required to produce ventricular tachycardia was 0.96 mg. in the 42 digitalizations with upright T-wave peaking and 0.97 mg. in the 40
with no such T-wave alterations (table 4). There was no difference in mean body weight among the groups when animals were classified according to the change in T waves. The shift in sodium was likewise nearly identical in the three groups, but the change in potassium was different. The group exhibiting T-wave peaking sustained twice as great an increase in arterial potassium as the groups without such a change. Thus, the potassium shifts induced by acute digitalization may be responsible for the peaking of the T waves.

Discussion

The earliest consistent change during acute digitalization, preceding even alteration in the electrocardiogram, is increase in arterial potassium concentration. Factors determining extracellular potassium concentration are not as yet precisely defined. It is clear, though, that acid-base balance, depletion or overload of body potassium, and changes in plasma sodium are among the prime factors influencing the concentration of plasma potassium. Numerous observations have confirmed the inverse relationship between plasma potassium level and extracellular pH. However, during acute digitalization, an increase in pH has been noted. In the present study, total body potassium content probably remained constant; furthermore, reduction in sodium, and thus presumably in osmolarity of extracellular fluid, occurred after rise in arterial potassium level. The change induced by digitalization may therefore be reasonably attributed to electrochemical influences which alter the concentration gradient of potassium across the cell membrane.

Schatzmann has clearly demonstrated that cardiac glycosides or their aglycones will prevent uptake of potassium and promote extrusion of sodium by cold-stored red cells. Digitalis effect on distribution of cations is not limited to red cells. Studies of isolated skeletal muscle, heart muscle, and intestine have shown similar alterations in electrolytes. All glycosides so far examined have this action on isolated tissues. It is pertinent to examine whether in the intact animal digitalis drugs other than acetyl strophanthidin have a similar effect upon electrolyte distribution. There are few deliberate studies dealing with this point. Renal excretion of tissue-released potassium should be anticipated in the case of slow-acting digitalis drugs. Deficit in body potassium would therefore occur. Indeed, Aikawa and Rhoades observed a reduction both in total exchangeable potassium and in serum-potassium concentration in rabbits maintained for a week on digoxin. When renal potassium excretion is blocked, even slow-acting glycosides should provoke hyperkalemia. In experiments studying the interaction between quinidine and digitalis drugs, Rodensky, Kathe, and Wasserman noted electrolyte derangements during digitalization of nephrectomized dogs. When digoxin was given intravenously until death, potassium increased preterminally by 2.4 mEq./L., while sodium decreased by 7.7 mEq./L. In view of the rapidity of onset of the cardiac action of ouabain, one would expect a rise in blood potassium during acute digitalization with this drug. Analysis of the data of Page and Real shows that five of six dogs receiving toxic doses of ouabain developed an increase in blood potassium. Average increase for the six animals was 0.4 mEq./L.

It is of interest that, concomitant with the modest electrolyte shift induced by acute digitalization, there occurred peaking of the T waves. Digitalization has been known to depress the S-T segment and invert the first portion of the T wave—the so-called digitalis effect. The change reported here affected the late portion of the T wave and occurred in 60 per cent of digitalizations with acetyl strophanthidin. In 42 per cent, the T wave was upright and increased in amplitude. In 18 per cent, the T wave became more deeply inverted, with downward peaking of its late component. Such peaking of the T wave has also been noted in man. Levine, Angelakos, and Lown have noted that 10 per cent of digitalized patients exhibit prominence of the last portion of the T wave (unpublished observations).

This change in T-wave morphology pro-

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duced by digitalization simulates that which occurs with hyperkalemia. Indeed, the alteration in T wave correlated with the observed increase in the arterial potassium concentration. However, when arterial potassium in dogs is raised, by infusion, to the level achieved by acute digitalization, no such increase in T-wave amplitude is observed. An additional mechanism must therefore be involved. Since there is much evidence that the myocardium loses potassium during digitalization,\textsuperscript{15, 16, 21} it is likely that the T-wave change resulted from an altered potassium gradient across the myocardial cell. Supporting this possibility is our observation that when the serum potassium was maintained constant at a level of about 8 mEq./L while digitalization was carried out, the electrocardiographic changes of increasing potassium intoxication developed. These animals died from cardiac arrest rather than from ventricular fibrillation. In effect, digitalization under these circumstances produced the electrocardiographic pattern of hyperkalemia—the result of a concurrent increase in extracellular and decrease in intramyocardial potassium concentration.

In view of the fact that digitalis drugs may increase extracellular potassium concentration, one might expect some digitalized patients with far-advanced heart failure to exhibit increased reactions to potassium. In one patient, a dose of potassium that was previously well tolerated resulted in severe hyperkalemia and death after the maintenance dose of digitalis was increased.\textsuperscript{22} Rapid infusion of potassium in digitalized patients with atrial fibrillation has been reported to slow the heart rate and favor A-V dissociation.\textsuperscript{23} This has been ascribed to an "additive" effect of potassium upon digitalis action. The phenomenon, however, is not due to digitalis intoxication provoked by potassium, but rather reflects the ready provocation of potassium poisoning in the digitalized patient.

Summary

Studies of the electrolyte alterations in 54 dogs during 165 discrete digitalizations with acetyl strophanthidin to an endpoint of ventricular tachycardia are reported. In 94 per cent of digitalizations, increase in arterial potassium concentration occurred. This was noted as early as five minutes after drug administration. At the time of ventricular tachycardia, the increase was 0.67 mEq./L. When digitalization was carried to ventricular fibrillation, the increase was 3.1 mEq./L. In 75.5 per cent of the digitalizations, arterial sodium concentration decreased; average decrease was 2.6 mEq./L. At ventricular fibrillation, the decrease amounted to 11.0 mEq./L. Arterial calcium concentration and oxygen saturation were not altered. There was a modest decrease in CO\textsubscript{2} content and an increase in arterial pH and hematocrit. Peaking of the late portion of the T wave was common during acute digitalization and correlated with the increase in extracellular potassium concentration. The relationship of the electrolyte changes to the process of digitalization is discussed.

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