Effect of Potassium and of Desoxycorticosterone Acetate in Acute Heart Injury in the Rat

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The rat myocardium was injured by means of a hot probe applied to the exposed surface of the left ventricle and the sequence of electrocardiographic changes was studied. Administered potassium as potassium chloride aggravated the electrocardiographic changes, while the administration of DCA improved the cardiographic picture. It is suggested that the beneficial action of DCA may be due to its plasma potassium lowering effect.

In recent years, a considerable volume of information has accumulated regarding the cardiac effects of alterations in the extracellular potassium concentration. As the potassium concentration rises there is a sequence of electrocardiographic changes characterized by an increase in the height of the T wave, a disappearance of the P wave, a broadening of the QRS complex and finally, cardiac arrest in diastole. In contrast, a diminution in the potassium concentration is reflected mainly in a flattening of the T wave.

While the marked effects of variation in potassium concentration on cardiac function seem to be well established, there is no settled opinion as to the fate of cardiac potassium in heart disease. It has been shown that in some types of chronic heart disease the myocardial tissue loses potassium, but whether this is an additional handicap is not definitely known. Evidence has also been sought regarding changes in potassium concentration or distribution in acute myocardial infarction, but thus far the data are inconclusive.

It seemed to us of some importance to obtain further evidence regarding the role of potassium in acute focal cardiac damage. Presumably, necrosis of cardiac muscle, like that of skeletal muscle releases considerable amounts of potassium. While this would be of little importance in the necrotic area itself, the potassium might well accumulate in the adjacent partially damaged area and interfere with the action potentials developed in this area. Thus, the potassium liberated from the necrotic zone might further impair the function of a comparatively large segment of heart muscle. Furthermore, it has been shown by Selye that in the alarm phase of the general adaptation syndrome there is a tendency towards an accumulation of serum potassium. The acute development of an area of cardiac necrosis might certainly be expected to act as an alarming stimulus. Consequently, it might be argued that there is not only a local accumulation of potassium adjacent to the necrotic area, but also a general accumulation of this ion as a result of the nonspecific effects of sudden damage.

It seemed to us that such a disturbance in potassium as here postulated could be studied indirectly. Thus, the electrocardiographic response of animals with acute myocardial damage might be expected to become aggravated in the presence of administered potassium, while improvement might follow treatment aimed at accelerating the removal of potassium.

Methods

Albino rats were used throughout and methods were accordingly adapted to this species.

The electrocardiograph. A string galvanometer with the modifications described by Rappaport and Rappaport was used. With this equipment, Lead I is sometimes very small, owing to the vertical position of the rat heart, and rotation of the animal to right or left changes the amplitude of the complexes in this lead. To overcome these drawbacks a tilt-board was designed. The skin web between digits was pierced by a sharp surgical needle attached to the center of each silvered electrode plate, and jelly was also applied. This method of contact reduced electrical interference to a minimum. The animal's incisors were hooked under a metal arc at the head of the board and the tail drawn through a hole at the base and transfixed. This ensured rigidity of the animal's
posture, especially since the line of the spine was
maintained by a ridge along the center of the board.
The whole board was then tilted to the left and sup-
ported at an angle of 70 degrees. This maneuver
throws the heart into a more horizontal position and
Lead I yields a readable, fairly constant configuration
approximating that of man.

In order to avoid the variable effects of the
animal struggling on the board, Evipal sodium was
selected as anesthetic. Evipal is fast in action, short-
lived and, in the doses used (10 mg. per 100 Gm. in-
traperitoneally in the male, 9 mg. in the female) is
apparently without effect on the heart, as deter-
mined by the uniformity of repeated tracings on
different occasions.

Myocardial damage. Local damage to the myo-
cardium was produced by a hot probe. With the
animal under Evipal anesthesia, an incision was
made through the shaved skin 1 cm. to the left of the
sternum. Pectoral muscles were separated and the
ribs exposed. The left chest wall was then incised
and opened. Care was taken in spreading the in-
cision open not to tear through the fine pleuroperi-
cardial membrane separating the right from the left
pleural cavity.

A round probe with a flat tip 1 mm. in diameter
was then rapidly heated to red in an open flame and
applied to the left ventricle near the tip. The wound
was then closed rapidly and the pleural cavity aspir-
ated. With this technic, the chest was never open
longer than one and one-half minutes and the mor-
tality in 65 operations was only 3 per cent.

Experiments

The range of normal variation in the electro-
cardiogram. The range of variation in the
electrocardiographic tracing in 21 representa-
tive animals was first studied. There was some
slight respiratory variation in the amplitude of the
deflections particularly in S3. Left axis
deviation was not seen, the T wave was never
inverted or depressed, and only occasionally
was a small Q wave seen. The rhythm was
always regular.

Repeat tracings obtained in these animals
during a one month period showed only minor
variations in the amplitude of the different
deflections.

Some chest leads were also taken on these
animals by the use of a small manual electrode
with a contact plate 4 mm. in diameter con-
ected directly to the left arm plate. For this
lead, the left forelimb of the animal was not
connected and the amplifier connections of
left arm and left leg were switched. The explor-
ing electrode was applied with jelly to the
shaved chest. The electrode placed about 1
cm. to the left of the xiphisternum yielded a
highly variable pattern. This was to be ex-
pected in view of the relative size of electrode
and heart. In this study of myocardial injury,
however, it became important to use "Lead IV"
to reinforce the findings in the standard first
lead, especially since sharp inversion of the T
wave in Lead IV never occurred spontaneously
in the normal animal, although the S-T
segment and T wave in this lead were some-
times slurred below the line.

Experiment 1

This experiment was designed as a pre-
liminary study of the effect of thoracotomy and
of myocardial damage on the electrocardi-
ogram and on the plasma potassium con-
centration.

Twenty-six male albino rats of an inbred
Wistar strain, weighing approximately 250
grams each, were divided into three groups.
Group I, consisting of 10 animals, served as
untreated control. The 8 animals of Group II
were subjected to a sham thoracotomy oper-
tation. The 8 animals of Group III were sub-
jected to myocardial injury according to the
method described. All animals received Purina
Fox Chow and water ad libum.

Electrocardiographic tracings were obtained
in all animals on the day preceding operation
and again on the first, second, and third post-
operative days. By the second or third post-
operative day electrocardiographic evidence of
myocardial injury was maximal. Blood was
taken on the third day by heart puncture for
the determination of plasma potassium ac-
cording to the method of Polley.18 The animals
were then killed and the gross appearance of
the heart noted before fixation. Sections of
heart were then stained with hematoxylin and
eosin and examined microscopically.

Electrocardiograms. No change was observed
in the tracings obtained in Group I, the con-
trol animals, which were examined on four
occasions in the experiment. Similarly, Group
II, subjected to a sham operation, showed no
abnormalities except in 2 cases. Autopsy of
these 2 animals showed that the heart had been
caught in suturing the thoracotomy wound.
Electrocardiographic evidence of injury was clearly apparent in the tracings of Group III. The changes observed could be divided into two categories, those which were definite or marked and those which were slight or suggestive. It seemed to us that a distinct and constant inversion of the T wave in Lead I (and often T₂ as well) represented a marked change (fig. 1), while minor changes in Lead I with supporting changes in Lead IV could be considered as slight or suggestive.

Four of the 8 animals in Group III of this experiment showed definite changes, while 3 showed suggestive changes. The eighth animal in this group showed no electrocardiographic evidence of the damage inflicted.

Pathologic examination. At autopsy, all animals showed about the same degree of epicardial injury. There was a white spot about 1.5 mm. in diameter surrounded by zones of purplish or reddish discoloration. Microscopically, there was a fairly deep arc of necrotic muscle surrounded by a reactive zone. There was a variable degree of pericarditis present which may have contributed to the electrocardiographic pattern.

Plasma potassium. Analysis of plasma samples obtained on the third postoperative day revealed no difference in the plasma potassium levels of the three groups.

Experiment 2

As a result of the first experiment it became feasible to study the effect of administered potassium and of measures tending to reduce the plasma potassium concentration in animals with a myocardial injury.

Thirty female albino rats of the Sherman strain, weighing approximately 120 grams, were divided into four groups. Group I, consisting of 7 animals, served as untreated control, while the 7 animals of Group II were subjected to myocardial injury as described above. Group III consisted of 8 animals subjected to myocardial injury and given added potassium, while the 8 animals of Group IV received desoxycorticosterone acetate (DCA) as treatment following the injury.

In preliminary experiments in animals of this weight it had been determined that the intraperitoneal administration of 1.2 per cent potassium chloride (approximately isotonic) temporarily elevated the plasma potassium concentration by 3 to 4 mEq., an elevation which itself did not cause marked electrocardiographic changes. Similarly, it had been determined that the administration of 3.1 per cent potassium citrate for twelve days as drinking water to such animals elevated the plasma potassium level about 1.5 mEq. without electrocardiographic changes. In view of these findings, the animals of Group III received additional potassium by the intraperitoneal injection of 3 cc. of 1.2 per cent potassium chloride three times a day postoperatively at six hour intervals, while 3.1 per cent potassium citrate was substituted for their drinking water.

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Fig. 1.—Definite electrocardiographic changes after injury. (a) Control. (b) Second post-operative day. Note Q waves and inversion of the T wave in Leads I, II, and IV.
Among its many other effects, DCA is known to lower the plasma potassium concentration. For this reason it was administered to the animals of Group IV. Three one-third portions of a 75 mg. Cortate pellet were separately implanted subcutaneously in each animal at the time of operation.

An electrocardiographic tracing was taken each day for three days postoperatively in all animals. Blood samples were taken by heart puncture on the third postoperative day, about six hours after the last potassium chloride injection, following which the animals were killed.

Table 1 presents the essential findings. Electrocardiographic changes are denoted as definite or suggestive, according to the criteria stated for the preceding experiment. For convenience in assessing results the pathologic changes were graded plus 1 to plus 4.

The untreated control group showed neither electrocardiographic abnormality nor cardiac pathologic.

Four of the 7 untreated injured animals of Group II developed electrocardiographic evidence of injury. In contrast, 7 of the 8 animals in Group III, given added potassium, developed changes. On the other hand, only 2 of the 8 animals in Group IV, given DCA, showed cardiographic evidence of damage. The degree of injury and pericarditis in the three groups was closely comparable.

The plasma potassium concentration was altered only in the group treated with DCA. Here the treatment was quite effective in lowering the plasma potassium within the threeday period. It should be pointed out that despite the lack of an altered plasma potassium level in Group III, these animals were probably subjected to transient elevations in the quantity of circulating potassium.

One animal in Group III and one in Group IV succumbed as a result of gross infection. This factor was controlled in the third experiment of the series by the administration of penicillin.

Taken as a whole, this experiment suggests that a high potassium intake adversely affects the injured myocardium as measured by the electrocardiogram. In the potassium-treated group, not only did more animals develop electrocardiographic changes (7 out of 8) in contrast with the control injured group, but also more showed a marked change (6 out of 8) even when the injury and pericarditis were not especially severe. This finding is in agreement with the observation of Sharpey-Shafer that in man the administration of potassium exaggerated the pattern of infarction and increased the inversion of the T wave. These results contrast with the observation that only 2 of the 8 DCA-treated animals in which the potassium level was lowered developed an altered electrocardiographic pattern.

**Experiment 3**

This experiment was designed to enlarge upon the effect of DCA treatment on the damaged heart by using a larger series of animals. Penicillin was used to control the variable of infection, and an attempt was made to produce a more severe injury so that a beneficial effect of DCA might be more easily observed.

Thirty-eight male albino rats of an inbred Wistar strain, weighing approximately 100
grams each, were divided into three groups. Group I, consisting of 6 animals, served as untreated control. The remaining 32 animals were subjected to myocardial injury, half of these (Group II) receiving no treatment and half (Group III) receiving DCA treatment postoperatively as described in the previous experiment. In applying the hot probe to the region of the apex of the heart an effort was made to secure a greater degree of injury than previously by holding the probe against the heart for a longer period.

In the week previous to operation, 4-lead electrocardiograms were taken on all 38 animals. Three hours before operation all these animals received subcutaneously 6000 units of procaine penicillin in 2 per cent aluminum monostearate diluted in sesame oil.

Following operation, 4-lead tracings were obtained from all injured animals on the first, second, third, fourth, and sixth postoperative days. Table 2 presents the findings, using the criteria previously described.

Two animals in Group II, the untreated injured group, died during the course of the experiment. In one, the only ascertained cause of death was the myocardial injury. The second animal succumbed some time after an Evipal injection, although the dose used had previously been well tolerated.

### Table 2. Electrocardiographic Findings in Control Rats, Injured Untreated Rats, and Injured Rats given DCA

<table>
<thead>
<tr>
<th>Group Treatment</th>
<th>Control</th>
<th>Injured</th>
<th>Injured + DCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of animals</td>
<td>6</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>No. with ECG changes:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2nd &amp; 3rd post-operative days</td>
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<td></td>
<td></td>
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<td>0</td>
<td>14</td>
<td>10</td>
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<tr>
<td>suggestive</td>
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<td>2</td>
<td>4</td>
</tr>
<tr>
<td>none</td>
<td>6</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>4th post-op. day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dead</td>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>definite</td>
<td></td>
<td>4</td>
<td>3</td>
</tr>
<tr>
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<td>9</td>
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</tr>
<tr>
<td>none</td>
<td></td>
<td>1</td>
<td>8</td>
</tr>
<tr>
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<tr>
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</tbody>
</table>

Electrocardiograms. No changes were observed in the control group.

In Group II, injured and without subsequent treatment, all 16 animals showed electrocardiographic evidence of damage. Of these, 14 showed the marked type of change.

Of the 16 animals receiving DCA, Group III, 14 showed electrocardiographic changes. Ten of these were of the marked type. Again, the degree of injury and pericarditis in the two injured groups was closely parallel.

In this experiment the animals were followed for six days so that it was possible to observe their progress which, in many cases, tended toward electrocardiographic recovery. Since changes in the T wave in Lead I and the S-T segment in Lead I afforded the best electrocardiographic evidence of damage, it was felt that a tracing could not be considered normal until these segments were within the normal range. Although T1 was often small and to some extent variable it was never found below the isoelectric line in the normal. A tracing was therefore considered to have become normal when the affected T1 segment became perfectly isoelectric. Figure 2 illustrates a typical tracing, showing progression from a definitely changed pattern back to normal. Similarly, partial recovery was considered to have occurred when the abnormal pattern
was obviously regressing but the T segment was still below the isoelectric line.

Table 2 includes the electrocardiographic progress of the treated and untreated injured animals. It is apparent that the animals treated with DCA recovered a normal pattern more quickly than the untreated group. Thus, of the 14 animals in Group III (DCA-treated) which showed electrocardiographic changes, 6 had recovered by the fourth day (42.5 per cent). In contrast, of the 16 untreated animals (Group II) which showed electrocardiographic changes, only one (6.2 per cent) had recovered by the fourth day. By the sixth day, 11 of the 14 animals (78 per cent) in the treated group had completely recovered as judged by the electrocardiogram, while the remaining 3 had partially recovered. In contrast, at this time only 5 of the 16 untreated animals (31.2 per cent) had recovered, 7 showed partial recovery, and 2 were still grossly abnormal.

**Discussion**

As a working hypothesis, it was postulated that the release of potassium from a necrotic area of heart muscle might affect the electrical potentials developed in the surrounding zone. On this premise, the electrocardiogram in rats with a myocardial injury was studied in order to ascertain whether the administration of potassium or, conversely, its lowering, would alter the course of electrocardiographic events. Under the specified experimental conditions used here it was observed that added potassium exerted a deleterious effect on the electrocardiograph, while the administration of DCA, possibly acting through a lowered potassium, appeared beneficial. While these results support the original hypothesis, they do not, of course, preclude other explanations.

From the practical standpoint, these results should be considered in relation to myocardial infarction in man. Although the acute pro-
procedure used here for the production of cardiac injury does not bear any similarity to events in the human episode, presumably the potassium changes postulated might obtain regardless of how cardiac necrosis occurred. It seems to us, however, that extending these observations from the rat to man directly is not without hazard. These data regarding the beneficial effect of DCA on the electrocardiographic pattern of rats damaged by a myocardial burn are presented in the hope that the suggestive results obtained may receive amplification and the suggested hypothesis be confirmed or refuted.

SUMMARY

1. Myocardial injury was produced in rats by searing a small area of the epicardial surface. The evolution of electrocardiographic changes was followed.

2. The administration of added potassium parenterally and in the drinking water increased the severity of electrocardiographic changes, while treatment with DCA had an apparently beneficial effect.

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