ELECTROCARDIOGRAM OF THE RABBIT FOLLOWING INJURY TO THE MYOCARDIUM AND TREATMENT WITH VARIOUS SUBSTANCES

N. A. Muzlaeva

A. N. Severtsov Institute of Animal Morphology (Director, Corresponding Member AN SSSR G. K. Khrushchov), AN SSSR, Moscow
(Presented by Academician N. N. Anichkov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 51, No. 6, pp. 37-42, June, 1961
Original article submitted March 30, 1960

It is known that after damage, heart muscle does not regenerate, and the damaged area is replaced by a scar of connective tissue [1]. The electrocardiogram then indicates the presence of a scar [6]. Our group has shown [4] that in rats the myocardium may regenerate after electrodiathermal coagulation, and that regeneration may be stimulated by means of a hydrolyzate of cardiac muscle. The electrocardiogram became normal during the time when the formation of new muscle could be observed in the center of the damage area. Then the newly formed muscle fibers were absorbed as the scar developed in a dense ridge around the damaged area. The electrocardiogram then once more showed the characteristic form associated with a scar.

The aim of the present investigation was to determine the changes in the rabbit electrocardiogram induced by the following measures: damage to the myocardium (control experiment), damage and stimulation of the regenerating myocardium, myocardial damage and prevention of the development of a scar, infliction of myocardial damage, and stimulation of regeneration to prevent the development of a scar. A hydrolyzate prepared from rabbit heart [4] was used to stimulate regeneration, and trypsin [14] was used to prevent cicatrization.

METHOD

The principal experiment was made in March and April of 1958 on 60 adult male chinchilla rabbits weighing 2·5–3·5 kg. In October, 1958, operations were made on a further 13 rabbits of the same strain and weight, and certain seasonal effects were disclosed. The control group consisted of 12 animals, and in each of these three experiments 20 rabbits were used. Before operation, the electrocardiogram was recorded without anesthesia; the electrocardiograph was an EKP-4m instrument, and three standard leads were used and connected with needle electrodes. The writing speed was 50 mm per second, and the sensitivity was 20 mm per mv.

Under urethane anesthesia and aseptic conditions, an incision was made precisely in the midline of the thorax, the heart was exposed, and the pericardium opened. Damage was then inflicted on the anterior wall of the left ventricle by diathermal coagulation. At the site of the damage, a white conical region developed having a depth of 5–6 mm, the apex of the cone being directed inward. The wound was sewn up in layers. Immediately after the operation, and subsequently after 1,3,5,8,12,17,24,32,45 and 64 days a record was made of the electrocardiogram. In all the experiments, the time at which the hearts were taken for fixation and the times at which the electrocardiograms were recorded were the same. In the four experiments, a total of 1149 ECG curves were taken from the three leads, and of them 766 records obtained from leads II and III were measured and studied.

After the operation, rabbits of the experimental group were treated with hydrolyzate, trypsin, and with a combination of hydrolyzate and trypsin. The hydrolyzate was prepared by our previous method [4], and 1 ml containing 40 mg of the dry substance was injected subcutaneously on the first day after the operation, and subsequently six times at intervals of 1 day. The trypsin was injected intraperitoneally on the first day after the operation, and then daily for ten days. Each dose contained 40 mg of the dry substance in 1 ml of phosphate buffer. When both substances were given, the hydrolyzate was given first, and seven days after the operation both the hydrolyzate and trypsin were given together in the same dose and at the same time as in the other two experiments.

RESULTS

The normal rabbit electrocardiogram (Fig. 1 a) has been studied in considerable detail [3, 9–12]. The frequency of the heart beat varies between 160 and 320 strokes per minute, and usually lies between 200 and 240 beats per minute. Unlike the rat electrocardiogram, the RST segment as a rule lies on the baseline, although the latter is not always well shown. The height of the R wave in the rabbit in lead II may vary between 0.07 and 0.25 mv, and usually lies between 0.1 and 0.15 mv; in lead III it varies from 0.08 to 0.35 mv, and usually lies between 0.15 and 0.20 mv.

Normally in rabbits the amplitude of the T wave is very large, particularly in lead II, and it is frequently twice as high as the QRS complex. It is rare for the T wave to be flattened so as to lie on the baseline, or to be poorly shown.

The S wave in lead II is found more frequently than it is in lead III; in 63 cases, it was well shown 19 times in lead II (30.1%), while in lead III it was found in 10 (16%) of the rabbits.

The Q wave occurs still more rarely: in lead II, out of the same 63 rabbits it occurred three times (4.8%), while in lead III it was found four times (6.3%). In these leads, the P wave was always positive, and varied within normal limits.

The published reports on the electrocardiogram in myocardial damage concern chiefly myocardial infarct induced by a ligature applied to a branch of the coronary arteries [2,3]. Some work has been done [8] on the morphological changes resulting from diathermal coagulation of the rabbit myocardium. However, no observations were made on the regeneration of muscle in the damaged zone. In [5,13], a description is given of the recovery of the electrocardiogram of animals in which the heart was damaged by resection of the ventricular wall, or by transplanting various tissues into it. In these cases recovery was quite rapid. The point where the myocardium had been cut and sutured was filled by scar tissue. Recovery of the electrocardiogram to normal also occurs in people after a penetrating myocardial wound has been sewn up [7].

Diathermal coagulation causes a marked change in the electrocardiogram which in its acute stage is very typical. The heart beat is increased on average by 9.5%. The QRS complex is greatly changed, the RST segment is displaced downward, forming an arc with a greatly deepened S wave. Similar changes take place in leads II and III. The curve has the appearance of a succession of monophasic loops. This is the acute phase (Fig. 1 b), which in rabbits lasts for a period from a few hours to 2 days after the operation.

During this time the animals were in very bad condition, they did not eat, they drank scarcely anything, and a large percentage died. In the following days, the heart beat remained high, or else very slightly slowed. The QRS complex was abnormal, in some cases the R voltage was reduced, and then, when the electrocardiogram was of an abnormal type, there was sometimes no R wave at all. The segment RST gradually returned toward the baseline; in many cases of abnormal electrocardiogram, it continued without any clear demarcation into the smooth T wave. All these changes are characteristic of the subacute phase (Fig. 1 c).

By the eighth day after the operation, the heart beat had returned to normal; subsequently there was either a small decrease or increase depending probably on the condition of the animal at the time the electrocardiogram was recorded. There then began the stage of cicatrization (Fig. 1 d), which in the electrocardiogram is shown by the return of the RST segment to the baseline; the T wave changed from the flat condition of the subacute phase to become slightly negative, and in the following days recovered until it was once more well shown. We never observed a "coronary" T wave when recording from the standard leads. The height of the R wave in the cicatricial phase is either unchanged or else reduced, though insignificantly. The cicatricial phase lasted until the end of the experiment, i.e., until the 64th day. We never observed any return, even temporary, of the electrocardiogram to normal. The electrocardiogram of another group of rabbits taken in autumn differed from that of the spring animals, which showed a smaller change of a different type; the baseline was particularly straight, and all the waves, particularly the T wave, were of smaller amplitude.

In the experiment in which the hydrolyzate was given, the electrocardiogram and the duration and sequence of the changes were similar to those in the control series. However, in the three of the nine animals which survived until this time, the electrocardiogram became normal between the 9th and 12th days, and it did not do so in the control series. There was a complete return of all the indices to their original value: the heart rate was 220–245 beats per minute, the height of the R wave in lead II was 0.1–0.18 mv, and in lead III, 0.14–0.22 mv; the ST segment was at the normal level, usually at the baseline; the T wave was no longer flattened or slightly negative as it was in

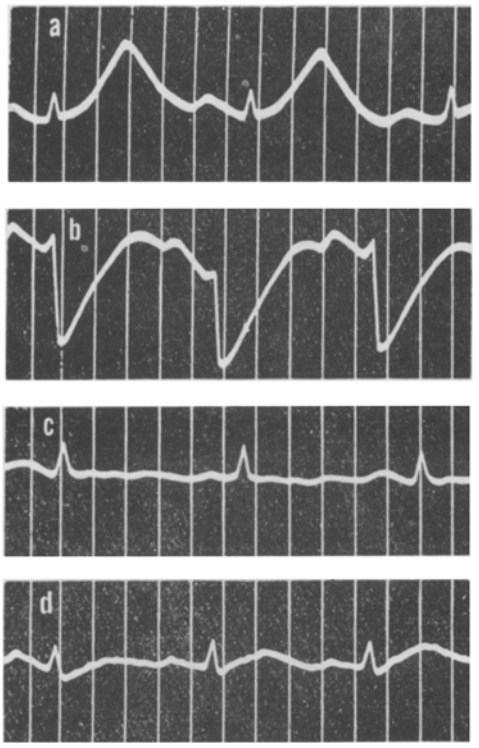

Fig. 1. Changes of the electrocardiogram of a rabbit following myocardial damage. A) Normal animal (before operation); b) immediately after operation (acute stage); c) four days after operation (subacute stage); d) 20 days after operation (cicatricial stage).

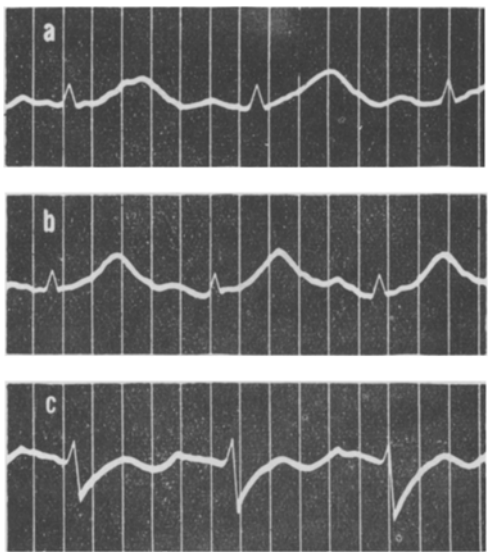

Fig. 2. Recovery of the electrocardiogram during regeneration of the myocardium. A) Normal; b) acute stage; c) 24 days after operation.

the subacute and cicatricial stages, but was well shown. However, we never observed a precise repetition of the curve exactly as it had been recorded before the operation.

It must be pointed out that, during normalization of the electrocardiogram in rats in which the myocardium had been damaged, we observed a complete repetition of the curve as recorded before damage to the heart, a result which was never obtained in rabbits. This difference in degree of recovery between rabbits and rats must be attributed to the less fixed position of the rabbit heart in the thoracic cavity, which leads to a change in the direction of the axis and so affects the electrocardiogram. In rabbits of this group, indications of a return toward normal of the electrocardiogram were maintained until the 30th-33rd day after the operation. Later, deviations from the normal occurred.

Both in these experiments on rabbits, and in our previous experiments on rats [4], where regeneration of the damaged myocardium was stimulated by hydrolyzate, the same effect occurred, and the electrocardiogram returned to normal. This effect took place in 33% of the rabbits between the 9th and 12th day after the operation. When rabbits with a damaged myocardium were treated with trypsin, again the electrocardiogram showed no pecularities which distinguished it from that of the control group, but the recovery showed constant features: it began on the 17th day after the operation and was maintained until the end of the experiment, i. e., until the 64th day after the operation, and occurred in five of the seven rabbits (71%) remaining alive at this time. The common feature of the action of trypsin on the damaged heart of both rabbits and rats is a comparatively late recovery of the electrocardiogram; in rabbits it begins on the 17th day, and in rats on the 20th. In both the electrocardiogram remains normal until the end of the experiment, i.e., in rabbits until the 64th day, and in rats until the 76th day. The percentage of rabbits in which the electrocardiogram recovered with trypsin was considerably higher than it was in rats.

In rabbits, the best result was obtained by combined treatment with hydrolyzate and trypsin. In this experiment the heart beat, the amplitude and sign of the principal waves, the position of the RST segment, and other features of the ECG, were precisely the same as they were in the controls. The duration and the sequence of the physiological stages remained normal, though the recovery period extended from the 12–18th to the 32nd-45th day after operation (Fig. 2, a, b, c).

In our previous experiments on rats with damaged hearts, when first given, the combined treatment with trypsin and vitamin B_{12} caused a 2–2 $\frac{1}{2}$-fold increase in the ECG above normal. Subsequently, the amplitude of the R wave fell to the original value, and the ECG returned to normal in all cases.

We are now in a position to compare the effects of identical substances on rabbits and rats. The hydrolyzate stimulated regeneration in rats. In 50% of the animals the ECG then became normal from the 12th day onward. In rabbits, in 33% of the cases recovery has occurred by the 9–12th day. Treatment of either rabbits or rats with trypsin caused a stable recovery lasting from the 17–20th day until the end of the experiment. However, in rats the percentage

recovering was very small, while in rabbits it was high. The combined action of treatment with a stimulant to regeneration (which in rabbits was hydrolyzate, and in our previous experiments on rats was vitamin B_{12}) led to a more marked recovery of the functional condition of the damaged myocardium than when hydrolyzate or trypsin were used separately, and in all cases the ECG returned to normal.

SUMMARY

A study was made of the ECG in normal rabbits in which diathermal injury had been inflicted on the myocardium, which was then treated with certain preparations which assisted recovery. In 33% of the cases treatment with hydrolyzate brought about recovery of the ECG between the 9–12th and 30th postoperative days. With trypsin, in 71% of the cases the ECG returned to normal between the 17th and 64th days. The combined treatment with hydrolyzate and trypsin was effective in 100% of the cases, when the ECG became normal after the 12–18th day.

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