THE ELECTROCARDIOGRAPHIC APPEARANCES OF MYOCARDIAL INFARCTION IN THE RAT

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This report is concerned with electrocardiographic investigations made on rats subjected to procedures designed to produce myocardial infarction by dietary means (Thomas and Hartroft, 1959) or by injections of isoproterenol (Rona, Chappel, Balazs and Gaudry, 1959). Such electrocardiograms provide early evidence of infarction in the living animal.

An attempt has also been made to define the normal electrocardiogram of the rat.

METHODS

Electrocardiograms.—Unanaesthetized rats were secured in a clamp (Fig. 1) described by Drury, Harris and Maudsley (1930), care being taken to avoid pressure on the neck. Electrodes, which consisted of small hypodermic (BD20) needles, were inserted under the skin of the left and right forelimbs and the left hindlimb. The leads were connected to a Matthew's portable electrocardiograph of the moving mirror type manufactured by the Clifton Instrument Co. Cambridge. Standard leads were taken in the conventional manner. When taking a precordial lead, the leads from the limbs were each connected through a 5000 ohm resistance ; the precordial electrode was inserted under the skin at points on the thorax to correspond to the conventional positions in man (V_{1-6}) and connected to the instrument with the switch set to the standard lead 1 position.

A few electrocardiograms were taken for comparison using a direct writing instrument (" Electrite model ", Cambridge Instrument Company, Cambridge).

Diets.—Laboratory bred piebald rats were fed a stock diet after weaning and used as normal controls. After reaching 100 g. body weight, 25 male rats were also fed a diet known to produce myocardial infarction (Thomas and Hartroft, 1959) consisting of cholesterol 50g., thiouracil 3 g., cholic acid 20 g., butter 400 g., sucrose 169 g., casein 200 g., choline chloride 10 g., salts 40 g., cellulose powder 100 g., magnesium oxide 5 g., inositol 2 g., thiamine 16 mg., riboflavin 16 mg., pyridoxine HCl 16 mg., folic acid 10 mg., calcium pantothenate 40 mg., biotin 0·6 mg., B_{12} 0·05 mg., nicotinamide 0·2 g.; a weekly supplement comprising 1000 i.u. vitamin A and 40 i.u. vitamin D supplied as one drop of halibut liver oil, 2 mg. α-tocopheryl acetate in 2 drops arachis oil and 0·05 mg. 2-methyl-1 : 4 naphthoquinone in one drop arachis oil.

Injections of isoproterenol.—Isoproterenol (1-[3,4 dihydroxyphenyl]-2 isopropylamino ethanol) was injected as the sulphate (Abbott's Laboratories Ltd.) or hydrochloride (supplied by Dr. G. Rona, Research Laboratories, Ayerst, McKenna and Harrison, Ltd., Montreal) in doses ranging from 5–80 mg. free base/kg. body weight. They were given subcutaneously and intraperitoneally to normal rats of both sexes ranging from 100–300 g. body weight. The minimum period of injection was 2 consecutive days but some animals were injected daily for several weeks.

Animals fed a diet known to produce myocardial infarction survived for an average period of 100 days. Necropsy was carried out as soon as possible after death. Rats injected with isoproterenol and normal controls survived and were killed by ether anaesthesia. Specimens were taken of the heart, thoracic and abdominal aorta and fixed in neutral buffered formal saline. Frozen sections were stained by Oil red O and paraffin sections by a variety of conventional methods.

RESULTS

Normal animals

The normal rat electrocardiogram showed P, Q, R, S and T waves as in man. Of the 3 standard limb leads, lead 2 appeared to show the individual waves best. Precordial leads V_1 and V_2 (and sometimes V_4) were recorded.

A conspicuous feature was elevation of the S-T segment in all leads examined (Fig. 2*a* and 2*b*) : this was an almost invariable finding and made the normal rat electrocardiogram bear a superficial resemblance to that of myocardial infarction or pericarditis in man. Lombard (1952) noted the lack of an iso-electric S-T segment in the rat and other small mammals, with the exception of the guinea pig.

Q waves, when they could be distinguished, were always small ; S waves were found infrequently. An N wave has been described in the rat electrocardiogram by Heise and Kimbel (1955). We could find no clear evidence of this positive deflection between QRS and T, either with photographic or direct writing electrocardiogram methods, but occasionally the T wave showed a double peak.

Precordial leads showed upright P waves followed by ventricular complexes with upright T waves. There was little change in the electrocardiogram as the chest lead position was moved across the precordium ; the main deflection was the R wave, which was closely followed by T, with a shallow trough of S–T segment between. The voltage of Rv_1 was usually lower than that of Rv_2–v_4. In lead V_1, T was as tall as, or taller than R. In leads V_2 and V_4, T was nearly always lower than R. S waves were seen rarely, and only in lead V_1.

The heart rate usually lay between 380–480/min. and abnormal rhythms were not seen. The important observation was made that pressure on the neck by the neck clamp could cause a marked reduction in heart rate : in one case from 450/min. to 150/min., with the appearance of sinus arrhythmia (Fig. 3*a* and 3*b*). Another animal, which had a normal heart at necropsy responded with a prolonged P–R interval, ectopic and dropped beats (Fig. 4). In man, A–V block of this degree indicates organic heart disease.

The heart rate was often so fast that P waves were partly superimposed on antecedent T waves, preventing accurate measurement of the P–R and Q–T intervals. Where they could be measured the normal range was found to be P–R 0·04–0·06 sec. and Q–T 0·08–0·10 sec. Where an S wave was present the QRS interval was found to be in the region of 0·02 sec.

Electrocardiograms were carried out over a period of 4 months in 10 normal rats to look for the effects of increasing age. During this interval there was a fall in heart rate associated with lowering of the T wave, the peak tending to become rounded or slurred. T wave inversion was not seen. The average height of R in lead V_1 fell from 4·5 mm. to 1·7 mm.

Animals on " infarct " producing diet

Serial electrocardiograms of the 25 animals in this group were examined before the results of necropsy were known, and 5 animals were thought to show clearly abnormal tracings. Reference to the histological reports revealed that 4 of these 5 had myocardial infarction ; the mechanism of infarction is discussed elsewhere (Gresham and Howard, 1960). The animal which did not show cardiac infarction at necropsy nevertheless had a ball thrombus in the aorta which may have partially occluded the coronary ostia (Fig. 5).

One animal with histological evidence of an infarct had normal electrocardiograms, the last tracing having been taken 12 days before death. The histological appearances in the heart were those of recent infarction ; probably not more than a week old.

One animal developed a prominent Q wave in lead V_1 (Fig. 6) with upright T in lead V_1 and normal leads 2 and V_2. It died 21 days later and had a transmural infarct.

Two animals developed inverted T waves, and were found at necropsy to have subendocardial infarction. The abnormalities appeared first at 39 and 15 days before death. One of these animals had inverted T waves in leads 2 and V_2 ; in the other one the inverted T was limited to lead V_1. These abnormalities persisted in all later electrocardiograms being seen in one animal's tracings over 34 days. In these 2 animals, T inversion was complete, negative T waves (Fig. 7 ; Fig. 8) following R with little to indicate an S–T segment between them. However one of them showed partial, or terminal, T inversion in V_2 at first (Fig. 9) ; complete T inversion appeared later and was associated with a fall in R amplitude from 3 to 1 mm.

One animal developed sinus bradycardia of 100/min. and terminal inversion of T in lead V_1 only. It died next day and was found to have an apical infarct.

None of the 21 animals on the diet which had normal hearts at necropsy showed T wave inversion of either kind.

The only arrhythmia seen was caused by two probable premature ventricular contractions, in an animal with massive infarction and inverted T waves. (Fig. 10.)

Animals injected with isoproterenol

Electrocardiograms were taken of 8 animals being given isoproterenol. Two animals, given 80 and 40 mg. free base/kg. body weight by daily injection, showed sinus tachycardia of 450—500/min. in tracings taken just after injection on the second day ; both had partial T wave inversion in V_2 and V_4.

Two other animals, given 20 mg. free base/kg. by daily injection showed tachycardia of the same order 24 hr. after the second injection ; one had partial T wave inversion in V_2 only, the other lowering and slurring of T in V_2 without inversion in any lead.

Electrocardiograms of 4 further animals were taken on the day they were killed, 24 hr. after the last injection (25 mg. free base/kg.). The heart rate was 330–370/min. and only one animal had T inversion—partial inversion in V_2 associated with a rate of 370/min. The other 3 animals had varying degrees of T wave slurring.

At necropsy, although the hearts were macroscopically normal, all of the animals had small foci of subendocardial necrosis, mainly in the left ventricle. The coronary arteries were normal.

DISCUSSION

The normal electrocardiograms were similar to those described by Lombard (1952), Irmak and Aykut (1955) and Heise and Kimbel (1955), but the N wave described by the latter workers was not detected using both direct writing and photographic methods. Heise and Kimbel worked with anaesthetised animals, which reduced tachycardia, and used a faster paper speed (80 mm./sec. as compared with 30 mm./sec.), factors which may account for the difference.

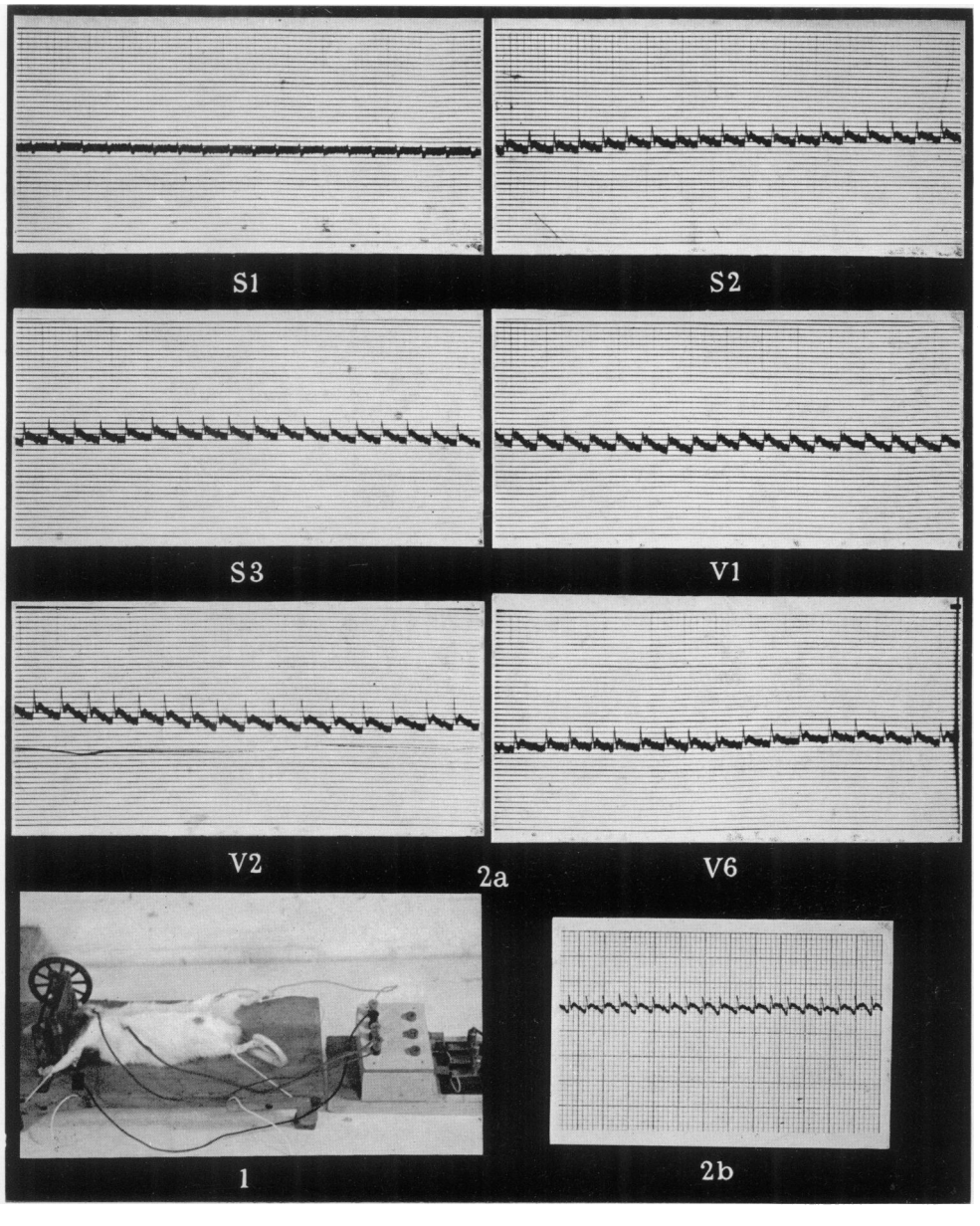
Elevation of the S–T segment, which was found constantly in the precordial leads, was a normal feature. Lombard (1952) has observed this in the rat and other small mammals. The reason for this difference from the normal electrocardiogram in man is not known. Lowering of the T wave, with rounding or slurring of the peak, was found in normal animals with increasing age, but T inversion was not found in lead 2 or in the precordial leads.

In the animals fed on infarct producing diet, T wave inversion was associated with myocardial infarction in all but one animal, and this animal died with a ball thrombus in the aorta. Its electrocardiograms showed constant T wave inversion over 17 days and then reverted to normal on the day before death. It is likely that the thrombus partially or intermittently occluded the coronary ostia, resulting in myocardial ischaemia. Our findings suggested that T inversion indicated myocardial ischaemia, and that ischaemia usually led to subendocardial infarction without further change in the electrocardiogram. Certainly in man the transient ECG changes of myocardial ischaemia are indistinguishable from those of subendocardial infarction (Goldberger, 1953). Although S–T depression is characteristic of these conditions in man, no depression was seen in the rat ; it might however have been masked by the normal elevation of S–T. No evidence was found of abnormal S–T elevation comparable with that seen in man after coronary occlusion. One animal with transmural infarction showed a prominent Q wave in V_1 21 days before death. This may be comparable with the abnormal Q wave of human transmural infarction, but other animals were found with RS patterns in lead V_1 and it is possible that a small initial R wave would have shown on a longer run.

The lesions produced by isoproterenol were much smaller than those produced by the diet, so it is perhaps not surprising that the injected animals produced less pronounced T wave inversion. The injections caused a striking tachycardia and it has been found the drug also lowers blood pressure while increasing the oxygen needs of heart muscle by direct action (Rona *et al.* 1959). It is likely that myocardial ischaemia is the result, repeated injections leading to patchy sub-

EXPLANATION OF PLATE.

FIG. 1.—A rat secured in the clamp with the electrodes inserted.
FIG. 2*a*.—ECGs of a normal rat using the photographic method. Leads S1, 2 and 3, V1, 2, 3, 4 and 6.
FIG. 2*b*.—ECG of a normal rat using the direct writing method.
FIG. 3*a*.—ECG of normal rat before pressure on neck. Lead V2.
FIG. 3*b*.—ECG of same rat after pressure on neck showing bradycardia. Lead V2.
FIG. 4.—ECG of normal rat after pressure on neck showing an ectopic beat, a dropped beat and a prolonged PR interval. Lead V2.
FIG. 5.—Ball thrombus in the aorta of a rat fed "infarct producing" diet.
FIG. 6*a*.—ECG showing normal pattern. Lead V1.
FIG. 6*b*.—ECG of same rat with infarct showing prominent Q waves. Lead V1.
FIG. 7*a*.—ECG showing normal pattern. Lead V2.
FIG. 7*b*.—ECG of same rat with infarct showing inversion of T wave. Lead V2.
FIG. 8*a*.—ECG showing normal pattern. Lead V2.
FIG. 8*b*.—ECG of same rat with infarct showing giant inverted T waves. Lead V2.
FIG. 9*a*.—ECG showing normal pattern. Lead V2.
FIG. 9*b*.—ECG of same rat with infarct showing terminal inversion of T wave. Lead V2.
FIG. 10.—ECG of rat with infarct showing two premature ventricular contractions and inverted T waves. Lead V2.



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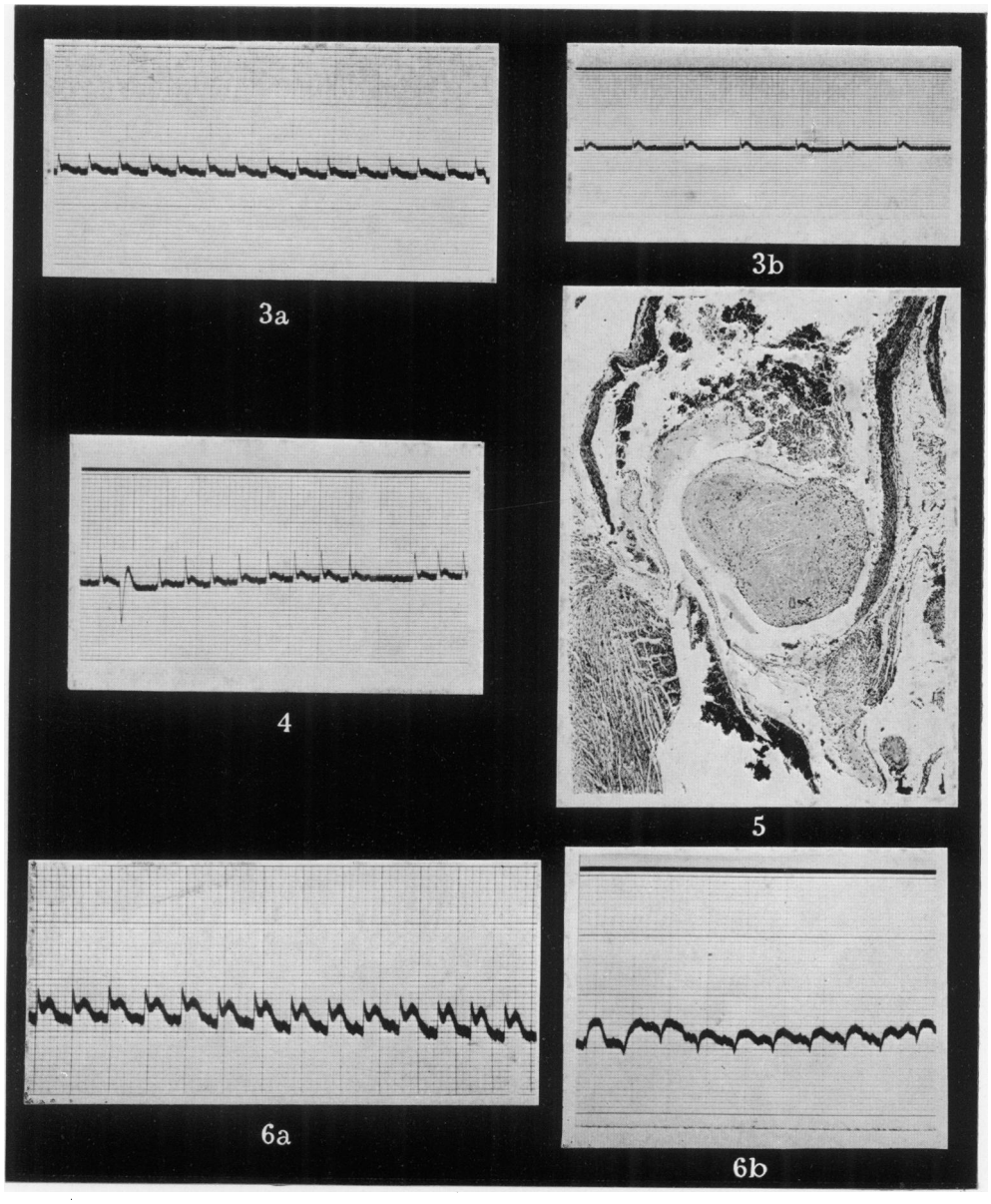


3a

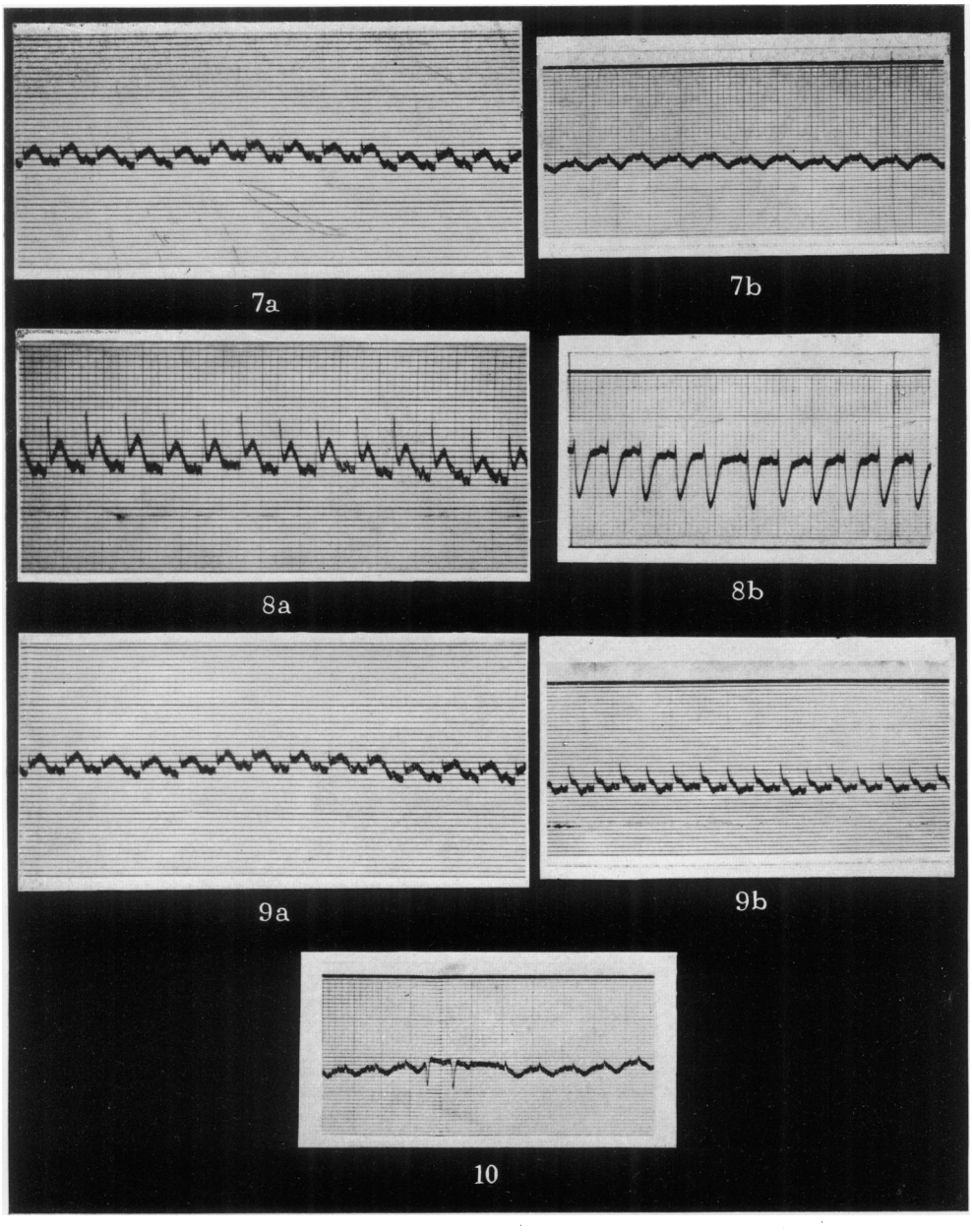
3b

4

5

6a

6b



7a

7b

8a

8b

9a

9b

10

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endocardial infarction. Our ECG findings in a small number of animals treated in this way are in keeping with such a course of events.

SUMMARY

Electrocardiograms were taken of rats which were normal or subjected to treatments which produce myocardial infarction, either by feeding a diet containing 40 per cent butter, 5 per cent cholesterol, 2 per cent cholic acid and 0·3 per cent thiouracil, or by injecting isoproterenol.

In normal rats, elevation of the S–T segment was a constant feature. No evidence was obtained for the existence of the N wave claimed by Heise and Kimbel (1955).

Using the dietary method, 5 out of 25 rats had myocardial infarction. All, except one with recent infarction, had abnormal electro-cardiograms consisting chiefly of T wave inversion which appeared from 15–40 days before death.

Rats injected with isoproterenol had small foci of sub-endocardial necrosis and showed electrocardiograms with inverted T waves.

It was concluded that electrocardiography can provide early evidence of infarction in the living rat.

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