Electrocardiogram in the Normal Rat and Its Alteration with Experimental Coronary Occlusion

By Sigurd J. Normann, B.S., Robert E. Priest, M.D., and Earl P. Benditt, M.D.

STUDY OF myocardial necrosis and infarction induced experimentally in rats would be aided by a reliable technique for recording the associated electrocardiographic changes. While electrocardiograms on rats have been made, the resolving power of the equipment has not been entirely satisfactory. Furthermore, the suitability of the leads for detecting myocardial necrosis, the stability of electrodes, and the constancy of the electrocardiographic pattern invited further study.

The electrophysiology of very rapid heart rates necessitates recording equipment with frequency response and paper speeds sufficient to resolve without distortion the P, QRS, and T components. Direct penwriting equipment with these characteristics has now been developed. When combined with subdermal electrodes—which allow easy placement, standardized contact surface, and the development of precordial leads—such a recording system affords reliable reproduction in serial tracings and resolution of QRS potentials as well as rapidity in handling the animals.

To our knowledge, electrocardiographic alterations with myocardial infarction in the rat have not previously been described. When applied to animals having myocardial necrosis associated with coronary ligation, this system of electrocardiography easily detected the electrical changes. The following describes the technique, its application, and its validation.

Methods

Electrocardiograms were recorded on normal male Sprague-Dawley rats under light ether anesthesia in the prone position. Electrodes consisted of 26-gauge needles placed subcutaneously for 1 cm. Standard limb leads were constructed from electrodes placed at the right and left forepaws and the tail, and in addition unipolar leads were located at the midstream anteriorly (V ant.) and at the anterior axillary line lateral to the xiphoid process (V lnt.).

The potentials were recorded with a Tektronix preamplifier and an Offner direct-writing ink recorder with frequency response of full amplitude to 200 c.p.s. and paper speed up to 250 mm. per second. Sensitivity was adjusted so that 1 millivolt was equal to a 30-mm. deflection. Tracings thus obtained have been compared with oscillograph recordings, and all components seen on the latter were resolved by the former.

Infarction was produced in 10 rats after the technique of Johns and Olson. A clean, but not aseptic, left thoracotomy incision was made with the animal under positive-pressure ether anesthesia administered by face mask. Atraumatic 0000 silk suture was used to ligate the left coronary artery distal to the branching of the circumflex artery and at the border of the left atrial appendage. Immediate blanching of the anterior left ventricle could be observed and the chest was closed with 0000 chromic suture and the skin with stainless steel clips. Of the animals operated upon, 10 survived the immediate postoperative period and are the subject of the study on myocardial infarction. For control purposes several animals were subjected to thoracotomy without coronary ligation.

Electrocardiograms were taken before and after operation at two hours, eight hours, one day, two days, four days, and seven days. The animals were sacrificed at seven days, and microsections of the heart, liver, and lungs were prepared and stained with hematoxylin and eosin, phosphotungstic acid hematoxylin, and Van Gieson's iron hematoxylin.
Table 1
Amplitude and Duration of the Components of the Normal Rat Electrocardiogram Obtained on Forty-four Sprague-Dawley Rats

<table>
<thead>
<tr>
<th>Component</th>
<th>Weight (Gm.)</th>
<th>Rate (1 min.)</th>
<th>Electrical axis (degrees)</th>
<th>P-R (msec.)</th>
<th>Q-T (msec.)</th>
<th>P1 (mv.)</th>
<th>P2 (mv.)</th>
<th>P3 (mv.)</th>
<th>P4 (mv.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>253.7</td>
<td>388.3</td>
<td>52.2</td>
<td>50.97</td>
<td>53.6</td>
<td>0.028</td>
<td>0.030</td>
<td>0.005</td>
<td>0.041</td>
</tr>
<tr>
<td>Range</td>
<td>174</td>
<td>340</td>
<td>30</td>
<td>48</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>292</td>
<td>504</td>
<td>80</td>
<td>70</td>
<td>70</td>
<td>0.083</td>
<td>0.083</td>
<td>0.033</td>
<td>0.066</td>
</tr>
</tbody>
</table>

*Amplitude is expressed in millivolts (mv.), duration in milliseconds (msec.).

Results

Normal Controls

The recording technique afforded good resolution of the QRS components in leads I, II, V3ant., and V4lat., but lead III tended to be isoelectric or indefinitely defined. Electrocardiograms were recorded on 10 normal animals serially on three successive days, and the tracings were found to be reproducible. Table 1 summarizes the comparative average, range, and standard deviation for the amplitude and duration of the different components of the normal electrocardiogram obtained from 44 Sprague-Dawley rats.

The values for the components of the normal electrocardiogram of the rat obtained by this technique serve to confirm those already on record, and differ mainly in that the voltages recorded here are less; however, the range and standard deviations are also smaller. It should be emphasized that the T wave is partially superimposed upon the termination of the QRS complex so that there is no lead with a discernible S-T segment and accurate measurement of duration of the QRS is not possible. One animal in this series had an inverted T wave in lead I. Initial Q waves were not found.

Experimental Infarction

Following ligation of the left coronary artery in the rat, massive left ventricular necrosis is regularly produced and sometimes includes the interventricular septum and occasionally the right ventricle. In only two animals included in the series—those surviving the immediate postoperative period—was transmural infarction of the left ventricular wall not produced. In these instances small focal areas of necrosis were observed in the epicardium on the left ventricle near the site of the ligature and may have resulted from trauma rather than coronary occlusion (fig. 1 upper).

When examined seven days following injury, the infarcted areas were readily apparent; they were pale, soft, and flabby, and bulged a little. In one heart a ventricular aneurysm was noted. Ventricular rupture did not occur despite extensive infarction, and indeed all animals surviving the immediate postoperative period survived the next seven days.

Microscopically, the infarcts showed organization with vascularization and fibroblastic proliferation. Neither elastic fibers nor fibrin could be demonstrated, but small bundles of collagen were present between fibroblasts in the areas of organization. The area of infarct was sharply delineated, and the lesions which were transmural showed pronounced loss of striated muscle cells, so that the normally thick left ventricular wall was much thinner (fig. 2 upper). With extensive...
Infarction three zones were usually evident: an epicardial layer in which necrotic muscle was replaced by organization, a central layer of coagulative necrosis, and an endocardial layer of organizing necrotic muscle with a narrow band of subendocardial muscle fibers which retained striations. These presumably viable muscle fibers were not present in all areas, and for descriptive purposes the infarcts were considered to be transmural. There was no evidence of intraventricular mural thrombosis. Acute passive congestion of the liver was not observed and the lungs showed only patchy alveolar edema and atelectasis. In several animals focal subacute pneumonitis was present.

Serial electrocardiographic tracings were obtained on eight animals with transmural infarctions of the left ventricle and on two with epicardial lesions located near the site of the ligature. In the eight tracings obtained on animals with transmural infarction, a characteristic pattern emerged consisting of...
the presence of a Q wave with inversion of
the T wave which, when present in more than
one lead and evident on serial tracings, was
considered to be diagnostic of myocardial in-
farction (fig. 2 lower). Changes in the S-T
segment are not helpful in the diagnosis of
myocardial infarction in the rat as the T
wave follows immediately or is partially
superimposed upon the QRS.
Although the presence of a Q wave was
not observed in normal animals, it tended
to appear early and persist through serial
tracings of anterior or apical infarction and
was particularly prominent in leads I, II, V_{anterior},
and V_{lateral}. No Q wave was observed in lead
III. In two tracings of lead I made during
the placement of the ligature, a Q wave
associated with inversion of the T wave was
immediately present upon ligation, but was
transitory, lasting less than two minutes.

Figure 2
(Upper) Transmural infarction of the left ventricular wall following ligation of the
left coronary artery. Hematoxylin and eosin, × 7. Electrocardiogram from this animal
is shown in the lower section of this figure. (Lower) Electrocardiographic alterations
with transmural infarction of the left ventricle; 1 mv. equals 30 mm.; paper speed was
100 mm/sec.
with return to the preocclusive pattern. By two hours after operation the Q wave was again prominent and persistent, suggesting an initial injury-potential followed by rapid evolution of the infarction pattern.

Increased amplitude of the R wave was noted to occur with infarction, but the change was not persistent, often appearing in leads I, V₉₅, and V₁₀, by two hours, but returning to the value of the preoperative tracing or below by seven days. S waves were prominent in lead III and were occasionally noted in leads I and II.

Inversion of the T wave was consistently observed in the presence of a Q wave occurring in leads I, II, V₉₅, and V₁₀, but not in lead III. It should be recalled that a negative T wave in lead I may be normal.

Disturbances of rate were not noted in any of the animals despite extensive infarction. Heart rate, amplitude of P wave, and the P-R interval remained constant. On the other hand, a consistent prolongation of the Q-T interval was noted, from an average of 53.6 to 82.0 msec. at 24 hours.

In the two cases of small epicardial lesions near the border of the atrial appendage, tracings diagnostic of infarction were not obtained. The tracings were considered abnormal, however, for, although Q waves and inverted T waves were not observed, the Q-T interval was prolonged, amplitude of the R wave was increased, and the S wave was prominent (fig. 1 lower). Animals with thoracotomy alone showed no significant electrocardiographic changes from preoperative tracings.

Discussion

For ease of manipulation of animals and to standardize the contact surface, needle electrodes have been employed in this study in preference to saline conduction media. With reduction of contact surface, however, the amplitudes recorded by needle electrodes are of lesser magnitude than those previously reported for saline, paste, or wire. The advantages of this electrode system coupled with direct-writing recording equipment are in the accurate and distinct resolution of the electrical forces, the ability to reproduce serial tracings, and the ease and rapidity with which animals may be recorded. The electrocardiograms obtained from normal rats in this way are similar to those previously reported with respect to configuration and time constants.

Component voltages are less than previously reported, but also show less variability in serial tracings and less deviation from animal to animal.

Anterior and apical transmural infarctions reliably produced alterations in the electrocardiogram consisting of Q-wave deformity, increased amplitude of the R wave, lengthening of the Q-T interval, and inversion of the T wave. The presence of a QR or Q-S configuration was considered the most reliable indication of infarction and usually appeared from two to eight hours following coronary ligation. The early appearance of a Q wave with the QR configuration becoming a Q-S pattern suggests progressive myocardial necrosis, which is consistent with the histology of the infarcts at seven days.

Small epicardial lesions failed to produce a Q-wave deformity in any lead, although augmentation of the R wave and Q-T prolongation was observed. Such lesions histologically did not involve the inner 80 per cent of the myocardium thought to be productive of Q-wave deformity.

Although extensive transmural infarction of the left ventricular wall and interventricular septum was produced, arrhythmias were not obtained, and there was no instance of mural intraventricular thrombosis. Arrhythmias are frequently encountered following coronary ligation in dogs. Mural thrombi have been observed in the atria of aged rats and following infarction in rats on high-fat diets. In the presence of extensive necrosis of the left ventricular wall, it is not clear why mural thrombi did not occur.

Summary

A reliable and reproducible method of recording rat electrocardiograms is described, including the use of precordial electrodes.
This system was utilized in studying 44 normal animals and in recording the electrical abnormalities associated with the ligation of the left coronary artery in 10 rats. The characteristics of the normal electrocardiogram of the rat are described. Following apical and anterior infarction, Q waves in association with transitory R-wave augmentation appeared, with prolongation of the Q-T interval, electrical axis deviation, and inversion of the T wave. No abnormal conduction patterns were noted. The pathological lesions are described, and attention is called to the absence of mural intraventricular thrombosis despite transmural infarction.

References
Electrocardiogram in the Normal Rat and Its Alteration with Experimental Coronary Occlusion

SIGURD J. NORMANN, ROBERT E. PRIEST and EARL P. BENDITT

doi: 10.1161/01.RES.9.2.282

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1961 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/9/2/282