Electrocardiographic Findings in Experimental Murine Myocarditis — Arrhythmias in the Chronic Stage —

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We studied serial electrocardiographic changes in murine myocarditis due to encephalomyocarditis (EMC) virus. After taking control electrocardiograms using standard extremity and 2 precordial leads, 86 mice were intraperitoneally inoculated with a 0.1 ml of the M variant of EMC virus suspension containing 100 TCID$_{50}$. Electrocardiograms were recorded everyday from the 2nd to the 14th day, and thereafter once every 3–5 days until the 35th day.

The cumulative incidence of myocarditis was 90% (77 out of 86). The control electrocardiogram showed a heart rate of 528 ± 87 beats/min (mean ± SD) and PR intervals of 0.03–0.05 sec, and significant rhythm or conduction disturbances were not found. Various electrocardiographic abnormalities, such as atrial (10%) and ventricular (21%) premature contractions, were noticed on the 4th to the 14th day. After 15–35 days arrhythmias still remained in 3 mice.

The presence of arrhythmias in the chronic stage of myocarditis suggests that arrhythmias in some patients with no other clinical manifestations may be a sequel of the previous viral myocarditis.

Thus, this study may contribute clinically to the clarification of the electrocardiographic characteristics in viral myocarditis.

CLINICAL manifestations of viral myocarditis generally consist of electrocardiographic abnormalities, enzymatic disorders, and the occurrence of congestive heart failure and even of sudden death.$^1$–$^3$ However, there have been only a few reports on the electrocardiographic characteristics in viral myocarditis.$^4$–$^6$

In our previous studies, we showed that in mice encephalomyocarditis (EMC) virus could produce significant myocarditis, which was followed by congestive heart failure.$^7$–$^{10}$

The present report describes the electrocardiographic findings in experimental murine myocarditis based on long-term observations of up to 35 days after the inoculation with EMC virus.

MATERIALS AND METHODS

The M variant of EMC virus was used. The virus stock was prepared in cultures of FL cells in Eagle’s minimum essential medium. The virus was stored at −70°C until used. Inbred strains of BALB/c, C$_3$H/He and DBA/2 mice were obtained from Charles River, Japan. These strains have been maintained continuously through brother-sister matings. At 4–6 weeks old, 86 mice (BALB/c, 20; C$_3$H/He, 20; DBA/2, 46) were inoculated intraperitoneally with 0.1 ml of virus

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Fig. 1. A normal electrocardiogram of a mouse. Note the high take-off of the T waves.

Fig. 2. Electrocardiograms of a mouse with myocarditis due to encephalomyocarditis virus. Arrows indicate the occurrence of atrial premature contractions.

Fig. 3. Electrocardiograms of a mouse with myocarditis due to encephalomyocarditis virus. Arrow-heads indicate ventricular premature contractions.

Fig. 4. Light microscopical picture of the left atrium of the mouse shown in Fig. 2. Note the presence of the degeneration of the myocardial cells and mononuclear cell infiltrations. Hematoxylin and eosin stain, x 180, BALB/c mouse.

suspension, containing 100 TCID_{50} (50% tissue culture infective dose) per 0.1 ml.

For the recording of the electrocardiograms, the mice were anesthetized by an intraperitoneal administration of pentobarbital only before viral inoculation and on the 2nd day after inoculation, and thereafter no anesthetics were used. The dose for the anesthetic threshold was 0.045–0.060 mg per gram of body weight according to the method of Pilgrim and De Ome. The recovery time of the mice was short. The animals were placed in a supine position. Electrocardiograms were taken using a direct inking-writing 3-channel Mingograph. Leads I, II, III, aVR, aVL, aVF, V_{1} and V_{6} electrocardiograms were recorded at a paper speed of 100 mm/sec with a sensitivity of 1.0 mV/1.0 cm (V_{1} and V_{6})
RESULTS

Gross Pathology

Yellowish-white patches were found on the surface of the right and the left ventricle of the heart from the 4th through the 35th day after inoculation with the virus.

Electrocardiograms

Electrocardiograms of the control mice were

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Fig. 5. Light microscopical picture of the interventricular septum of the mouse shown in Fig. 3.

There are calcifications of the necrotic myocardial fibers. Hematoxylin and eosin stain, x 180, DBA/2 mouse.

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Fig. 6. Serial electrocardiograms of a mouse in the chronic stage of myocarditis.

Arrows and arrow-heads indicate the occurrence of ventricular premature contractions.
of 7 mice (43%) (Fig. 6). The pathologic study in this stage revealed marked dilatation of both ventricles and massive myocardial fibrosis with calcification (Fig. 7).

**Incidence of Myocarditis**

The cumulative incidence of myocardial lesions in the infected mice was 90% (77 of 86 mice).

**DISCUSSION**

In our previous studies, we have found the occurrence of severe myocarditis in DBA/2 mice inoculated with the M variant of EMC virus.\(^7\)\(^-\)\(^10\)

In these studies myocardial lesions appeared earlier and more extensively than those which we had observed in coxsackievirus myocarditis\(^12\)\(^-\)\(^17\) and pathologic lesions were noticed not only in the right and the left ventricle (including the interventricular septum) but also in the atria. This animal model is considered to be excellent for studying the pathogenesis and the natural course of viral myocarditis. In addition, EMC virus myocarditis in the later stage may show lesions similar to those in dilated (congestive) cardiomyopathy.\(^7\)\(^-\)\(^10\)

In the present study, various electrocardiographic abnormalities corresponding to the pathologic lesions were observed after 4 days. There have been no previous reports on the correlation between the electrocardiographic abnormalities and the myocardial lesions in viral myocarditis, except for that of Monath et al.\(^8\) However, they did not study the findings in the chronic stage. Thus, in the present study the relationship between the electrocardiographic abnormalities and the cardiac pathology was made clear experimentally for the first time.

Furthermore, the presence of arrhythmias in the chronic stage of myocarditis suggests that arrhythmias in some patients with no other clinical manifestations may be a sequela of previous viral myocarditis. Thus, the present study may contribute clinically to the clarification of the electrocardiographic characteristics in viral myocarditis.

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