Myocarditis Induced by Sympathomimetic Amines (1)

MOTOSHI NODA*, OSAMU KAWANO, OSAYUKI UCHIDA, TAKASHI SAWABE, GENICHI SAITO, AND KAZUNAGA FUKAWA**

Production of myocardial lesions with sympathomimetic amines was studied in rats. Subcutaneous administration of isoproterenol at the daily doses of 1.2 mg and 0.7 mg per kg for 14 days caused a marked diffuse myocarditis. The myocardial lesions were detected by electrocardiogram 1 week after the beginning of the administration. Norepinephrine, nor-fenefrine and phenylephrine did not show any pathologic change in the myocardium. The significance of the toxic effects of these amines was studied.

Many types of sympathomimetic amines are widely used in therapeutics because of their potent cardiovascular and bronchodilator actions. On the other hand, some of these compounds show injurious effect on the cardiovascular system itself. In 1909, Fleisher et al. described experimental myocarditis caused by epinephrine. Since then, there have been many reports of cardiac lesions induced by epinephrine, norepinephrine, and several other sympathomimetic amines. Previously, the authors found slight lymphocytic cell clumps in the myocardium of rats treated with norfenefrine as well as rats which were untreated. The present study was devised to examine myocarditis resulting from the toxicity of representative sympathomimetic amines including norfenefrine.

Materials and Methods

Sprague-Dawley male rats of 9 weeks weighing 280–320 g were used. The drugs tested were norepinephrine, isoproterenol, norfenefrine and phenylephrine. Preliminary studies were carried out to establish the effects of these drugs on the blood pressure and heart rate using 25 rats. After carotid artery cannulation under intraperitoneal urethane anesthesia, blood pressure and electrocardiogram were recorded at frequent intervals by "polygraph" – multichannel ink writing oscillograph (San-ei instrument Co., Ltd.).

Forty five rats were divided into 9 groups and each group received subcutaneous administration of the drugs at 24 hour intervals for 13 days in accordance with the injection schedule described below.

Group I control; 1 ml/kg of physiological salt solution
Group II norepinephrine 1.0 mg/kg
Group III norepinephrine 0.6 mg/kg
Group IV isoproterenol 1.2 mg/kg
Group V isoproterenol 0.7 mg/kg
Group VI norfenefrine 9.0 mg/kg
Group VII norfenefrine 5.8 mg/kg
Group VIII phenylephrine 9.7 mg/kg
Group IX phenylephrine 6.2 mg/kg

Electrocardiograms were recorded before administration of the drugs and 7 days after commencement of administration under intraperitoneal pentobarbital anesthesia by limb leads. Histologic examination was done after sacrificing the animals on the 14th day of the experiment approximately 24 hours after the last injection.

Results

Blood pressure: The effects of the amines on the mean blood pressure are showed in Fig. 1. Norepinephrine distinctly elevated the blood pressure between 20–30 mmHg (mean: 23 mm-

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Fig. 1. Blood pressure and heart rate of the rats treated with sympathomimetic amines

Hg) for approximately 10 minutes after administration. Isoproterenol constantly depressed the blood pressure between 20-50 mmHg (mean: 42.3 mmHg) for two or three hours. Noradrenaline and phenylephrine showed a slight pressor activity ranging between 7-25 mmHg (mean: 10 mmHg) and 7-27 mmHg (mean: 15 mmHg), respectively. The dose and response relationship was not definitive for each amine at the doses used in this experiment.

Heart rate: Significant changes in the heart rate were induced by 1.2 mg and 0.7 mg per kg of isoproterenol. The heart rate was raised by 30-40 beats per minute in each case. No marked change was observed with norepinephrine, noradrenaline and phenylephrine (Fig. 1).

Electrocardiogram: The same electrocardiogram recordings were obtained through the careful fixation of the animals so as to avoid any change in the electrical axis. One of the characteristic findings of the electrocardiogram of rats was the elevation of the ST and the T which began from the mid-portion of the QRS segment. In Fig. 2 such findings in a normal rat are shown. Norepinephrine, noradrenaline and phenylephrine did not produce any remarkable change except for occasional tachycardia. In isoproterenol treated rats, significant depression of the ST segment to 0.1 mV and the Q wave to 0.06 mV was frequently observed, as well as the inverted T in leads I and II. These findings were considered to be signs of widespread myocardial lesion. All ani-

Fig. 2. Electrocardiograms of a rat treated with isoproterenol 1.2 mg/kg.

leads

I

II

III

before


after 7 days

0.1sec 500μV

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TABLE I  Electrocardiogram findings

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>PR (msec)</th>
<th>QRS (msec)</th>
<th>QT (msec)</th>
<th>ST-T depression</th>
<th>inverted T</th>
<th>deep Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>36.7–46.7</td>
<td>16.7–22.0</td>
<td>52.0–70.0</td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>41.6–43.4</td>
<td>16.7–20.0</td>
<td>55.0–66.7</td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>0.6 mg/kg</td>
<td>40.0–45.0</td>
<td>16.7–18.3</td>
<td>60.0–66.7</td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2 mg/kg</td>
<td>40.0–46.7</td>
<td>16.7–18.3</td>
<td>58.3–91.6</td>
<td>5/5</td>
<td>5/5</td>
<td>4/5</td>
</tr>
<tr>
<td>0.7 mg/kg</td>
<td>41.6–50.0</td>
<td>18.3–20.0</td>
<td>50.0–78.3</td>
<td>4/5</td>
<td>5/5</td>
<td>5/5</td>
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<tr>
<td>Norfenefrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.0 mg/kg</td>
<td>41.6–45.0</td>
<td>16.7–20.0</td>
<td>58.3–76.0</td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>5.8 mg/kg</td>
<td>40.0–45.0</td>
<td>16.7–18.5</td>
<td>58.3–76.0</td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
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<tr>
<td>9.7 mg/kg</td>
<td>41.7–50.0</td>
<td>16.7–18.3</td>
<td>51.6–75.0</td>
<td>0/4</td>
<td>0/4</td>
<td>0/4</td>
</tr>
<tr>
<td>6.2 mg/kg</td>
<td>40.0–45.0</td>
<td>16.7–18.3</td>
<td>61.6–75.0</td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
</tbody>
</table>

TABLE II  Pathologic findings

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>Heart weight/100 g Body weight</th>
<th>Histologic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.36 ± 0.05</td>
<td>n.p. (minute lymphocytic infiltrate; 2/5)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>0.38 ± 0.03</td>
<td>n.p. (minute lymphocytic infiltrate; 2/5)</td>
</tr>
<tr>
<td>0.6 mg/kg</td>
<td>0.37 ± 0.04</td>
<td>n.p. (minute lymphocytic infiltrate; 2/5)</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2 mg/kg</td>
<td>0.47 ± 0.05*</td>
<td>marked myocarditis; 5/5</td>
</tr>
<tr>
<td>0.7 mg/kg</td>
<td>0.44 ± 0.02*</td>
<td>marked myocarditis; 5/5</td>
</tr>
<tr>
<td>Norfenefrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.0 mg/kg</td>
<td>0.39 ± 0.07</td>
<td>n.p. (minute lymphocytic infiltrate; 2/5)</td>
</tr>
<tr>
<td>5.8 mg/kg</td>
<td>0.35 ± 0.01</td>
<td>n.p. (minute lymphocytic infiltrate; 2/5)</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.7 mg/kg</td>
<td>0.39 ± 0.05</td>
<td>n.p. (minute lymphocytic infiltrate; 1/4)</td>
</tr>
<tr>
<td>6.2 mg/kg</td>
<td>0.40 ± 0.02</td>
<td>n.p. (minute lymphocytic infiltrate; 2/5)</td>
</tr>
</tbody>
</table>

* Statistically significantly different from control (p < 0.05)  n.p. : not particular

Mals of group IV and V showed such signs of myocardial lesions on the electrocardiogram. Results of an analytical study of the electrocardiograms are shown in Table I.

Pathologic change: Marked response of the heart to isoproterenol was noticed. The heart was enlarged in all animals of groups IV and V. Heart weight was 0.47 ± 0.05 g per 100 g body weight in group IV and 0.44 ± 0.02 g per 100 g body weight in group V, in contrast to 0.36 ± 0.05 g per 100 g body weight in the control group. In other groups treated with norepinephrine, norfenefrine and phenylephrine no cardiac enlargement was observed (Table II).

Microscopically, the myocardium of the isoproterenol treated groups showed remarkable diffuse or focal myocarditis (Fig. 3). A large and patchy foci of myocarditis showing organization with fibroblast proliferation and lymphocytic infiltrate were observed. No distinct polymorphonuclear leucocytic infiltration, hemorrhage or infarct-like lesions was present. In general, these myocardial lesions were concentrated in the sub-endocardial region of the left ventricle and near the apex. In case of severe lesion, the right ventricle near the apex was sometimes involved. The coronary artery and its branches were intact. All of the ten cases in groups IV and V treated with isoproterenol at the doses of 1.2 mg and 0.7 mg per kg, respectively, showed the severe myocardi-
tis described above.

Animals treated with norepinephrine, norfene-
frine and phenylephrine were free from myocard-
dial lesions. No involvement of muscle fibers was
revealed by photomicroscopic observations in the
groups treated with these amines. However, very
small clumps of lymphocytes in interstitial spaces
were noticed in many groups, including the con-
trol group. There was no significant difference in
the frequency of such lymphocytic clumps be-
tween the control and other groups. The results
of the pathologic findings are summarized in
Table II. No specific findings were detected in the
lung, liver, kidney, adrenal, spleen, pancreas,
stomach, intestine, colon, bone marrow, thymus
and brain.

**Discussion**

From the present study, it is evident that isoproterenol possesses a distinct property to pro-
duce myocardial lesions in rats at the doses of
our experiment, while norepinephrine, norfene-

![Fig. 3. Photomicrographs of a heart treated with isoproterenol 1.2mg/kg. Note the marked proliferation of perimysial cells and fibroblasts with lymphocytic infiltration. a. ×40 b. ×100](image-url)
frine and phenylephrine have less active cardio-
toxicity.

The production of cardiac lesions with isopro-	erenol was first reported by RONA and CHAPPEL
(1959).11,12 In their reports, isoproterenol in-
jection was considered to be a reliable method for
producing experimental myocardial infarct-like
lesions. Among the many types of sympathomi-
metic compounds, isoproterenol is known to be
one of the most potent cardiotoxic amines.11,12
It is reported that myocardial necrosis can be
produced by a dose of 0.118 μmoles (0.02 mg)
per kg.9 Recently, KIMURA et al13 proposed a
diagnostic method for detecting latent coronary
insufficiency through the infusion of isoprotere-
nol. When coronary insufficiency is present, the
occurrence of angina-like precordial pain and ST
depression are frequently present. They reported
that they used 70–100 μg intramuscularly or 8–
60 μg by intravenous infusion of isoproterenol
for this purpose. There are other reports on the
side effects of isoproterenol in clinical therapeu-
tics. Tachycardia and precordial discomfort have
reportedly been occasionally observed.14–17 Al-
though the toxic dose has been established phar-
macologically, it is still not known whether this
dose is the same for cases with pathological heart
conditions. The authors feel that greater care
should be paid in the administration of isopro-
terenol.

There have been different opinions about the
mechanism of the action of such sympathomimetic
amines on the myocardium. One is that the
lesions are a direct effect of isoproterenol on the
myocardial cells as WARTMAN18 has postulated.
Some hold that these injuries are caused by the
cardiovascular actions of the amine such as de-
pressed blood pressure, increased heart rate, in-
creased contractile force and left ventricle work,
etc.9,11 There are other investigators who consider
that the metabolic effects of the amine are also
important.9,19

In our experiment, the character of the car-
diac lesions closely resembles myocarditis rather
than myocardial infarction. Marked proliferation
of perimysial cells and fibroblasts, abundant lym-
phocytic infiltrate and absence of neutrophiles
are noticed, whereas fresh infarct-like changes or
foci of degenerative muscle bundles were not pre-
sent. From these findings it is debatable whether
the primary cellular response to isoproterenol is
the direct degeneration of myocardial cells or an
interstitial inflammatory response without car-
diac necrosis. There are several reports in which the
cardiac lesions have been described as necrosis of
the myocardium. At present the authors postulate
that smaller dosages cause minimal degenerative
changes in the myocardium and evident con-
secutive response in interstitial cells, while larger doses
tend to induce massive myocardial necrosis.

Cardiac lesions with other sympathomimetic
amines have been known experimentally6,8,9 as
well as clinically.20 Cardiac impairment with epine-
phrine has been established since JOSUE (1904)21 in
experiments. ROSENBLOM8 who investigat-
ed the cardiotoxicity of 15 sympathomimetic
amines, reported isoproterenol and phenyle-
ephrine to show injurious effects from doses of
0.118 μmoles (0.02 mg) per kg, norepinephrine
from 1.18 μmoles (0.20 mg) per kg and epine-
phrine, noradren and methoxamine from 11.8
μmoles (2.16 mg, 2.59 mg and 2.91 mg, respec-
tively) per kg. In therapeutics, SZAKACS and
CANNON19 described "norepinephrine myocardi-
tis" in man following prolonged infusion of this
amine. In our experiment no remarkable change
was found with norepinephrine, norfenefrine and
phenylephrine. We consider that these differences
can be explained on the basis of doses, strain of
animals and other conditions. Slight patchy lym-
phocytic infiltrates in the control group and some
of the other groups treated with norepinephrine,
norfenefrine and phenylephrine must be con-
sidered incidental findings which is occasionally
found in experimental animals.10

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