Experimental Study of Cardiomyopathy Induced by Glucocorticoids

TAKASHI ITO,* MIZUHO MURATA* and AKIMITSU KAMIYAMA**

Abnormal ECG changes were found in some patients who were treated glucocorticoid during long term. In experimental animals, chronic administration of glucocorticoid resulted abnormal ST and T changes of ECG, increased duration of action potential and induced electron microscopical changes of mitochondria. No significant changes were found in serum and myocardial potassium content.

STEROID induced myopathy, so called steroid-myopathy has been well known in skeletal muscle, but not likely in cardiac muscle. However, we have observed abnormal electrocardiographic changes in some patients treated with glucocorticoids for long terms, such as reversible ST and T changes (Fig. 1). The present studies were carried out to elucidate the effects of glucocorticoids on cardiac muscle.

MATERIALS AND METHODS

As mentioned in previous report5 dogs, rabbits and rats were experimented. Twenty rabbits were injected 0.5 mg/day of dexamethasone for 3 to 10 months. Fifteen rabbits were fed with low potassium diet for 6 weeks. ECG of rabbits were followed during the course of the experiment. Potassium values were determined in serum and myocardial tissue of the rabbits. Action potentials of cardiac cell were recorded by using routine microelectrode technique. Morphological studies were carried out light and electron microscopically and also histochemically. In addition to these studies, hemodynamic parameters were measured.

RESULTS

As shown in Table I, each group of rabbits showed no significant difference in heart weight. Serum potassium level was significantly low in low potassium diet group, but potassium content of myocardium did not show any difference among three groups. As for hemodynamic studies, there were no differences in left ventricular pressure and dp/dt, but the values of Vmax decreased in steroid treated group.

Electrocardiographic findings: The ECG taken during treatment with dexamethasone (Dex) showed depression of ST segment and inversion of T wave. These changes appeared about one month after daily injection of Dex, and continued after interruption of injection (Fig. 2, 3). Rabbits with low potassium diet

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TABLE 1  MEAN BODY WEIGHT, HEART WEIGHT, SERUM AND CARDIAC MUSCLE POTAS-
SIUM CONTENT, AND $V_{\text{MAX}}$ OF THE LEFT VENTRICLE OF RABBITS

<table>
<thead>
<tr>
<th></th>
<th>Normal control</th>
<th>Steroid hormone treated</th>
<th>Low-potassium diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 6$</td>
<td>$n = 6$</td>
<td>$n = 7$</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>2,460</td>
<td>2,470</td>
<td>2,470</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>5.4</td>
<td>6.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Heart wt. (%)</td>
<td>0.22</td>
<td>0.25</td>
<td>0.21</td>
</tr>
<tr>
<td>Serum $K^+$ (mEq)</td>
<td>3.3</td>
<td>3.1</td>
<td>2.7**</td>
</tr>
<tr>
<td>$K^+$ content in</td>
<td>76.2</td>
<td>74.6</td>
<td>79.9</td>
</tr>
<tr>
<td>cardiac muscle (mEq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{\text{Max}}$ ($K = 28$)</td>
<td>5.6</td>
<td>5.0*</td>
<td>5.4</td>
</tr>
</tbody>
</table>

*P < 0.05  **P < 0.01

Rabbit 7B-06

before  → Dex $5 \text{mg/day} \rightarrow 2 \text{M} \rightarrow  \rightarrow  10 \text{M}

I

II

Fig.2. Changes of ECG, it continued after interruption of injection of glucocorticoid.

Rabbit 7B-04

Dec $5 \text{mg/day} \rightarrow  \rightarrow  \rightarrow  \rightarrow  10 \text{M}

I

II

Fig.3. ECG change of another rabbit, it seemed to be accelerated by re-injection of Dex.

showed only flattening of T wave.

Electrophysiological studies: Table II shows the effects of glucocorticoids on transmembrane action potentials of cardiac cell. Those were recorded from epicardial and endocardial layer. Duration of action potential of the rabbits chronically injected increased particularly in subepicardial layer. Furthermore, deeper resting potentials were observed in subendocardial layer of treated rabbits. These discrepancies of action potentials between layers might be likely to explain the changes of ECG during glucocorticoid treatment. Table III shows action potentials of rats. Duration of action potential increased on clinically treated group.

Morphological studies: There could not be found any significant changes in light microscopical and histochemical observation. However, electron microscopic studies disclosed cardiac muscle changes following glucocorticoid treatment. Arrangement of myofibril was almost normal but apparent changes were found in mitochondria, cristae were irregular and swollen (Fig. 4). These changes were found diffusely and especially in subepicardial layer. More severe changes consisted of vacuolization of mitochondria and disarrays of myofilaments (Fig. 5). Widening of intercalated disc was also observed (Fig. 6).

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TABLE II  TRANSMEMBRANE ACTION POTENTIALS OF RABBITS

![Graph showing transmembrane action potentials]

<table>
<thead>
<tr>
<th>Epicardium</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>113.0</td>
<td>86.7</td>
<td>152.0</td>
<td>127.8</td>
<td>5.1</td>
<td>259.0</td>
</tr>
<tr>
<td>SH treated</td>
<td>121.4</td>
<td>90.4</td>
<td>186.3</td>
<td>150.6</td>
<td>5.7</td>
<td>210.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endocardium</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>116.3</td>
<td>85.8</td>
<td>201.8</td>
<td>152.0</td>
<td>3.8</td>
<td>245.0</td>
</tr>
<tr>
<td>SH treated</td>
<td>131.8</td>
<td>100.8</td>
<td>216.7</td>
<td>180.5</td>
<td>3.8</td>
<td>273.0</td>
</tr>
</tbody>
</table>

TABLE III  TRANSMEMBRANE ACTION POTENTIALS OF LV PAPILLARY MUSCLE OF RATS INJECTED WITH 33 MCG/DAY FOR 3 WEEKS

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C*</th>
<th>D**</th>
<th>E**</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>83.46</td>
<td>72.14</td>
<td>18.36</td>
<td>28.54</td>
<td>47.19</td>
</tr>
<tr>
<td>SH</td>
<td>86.32</td>
<td>72.86</td>
<td>23.08</td>
<td>34.65</td>
<td>55.70</td>
</tr>
</tbody>
</table>

C : control  SH : steroid treated  *P < 0.1  **P < 0.05

A : total ampl (mV)  B : resting pot (mV)  C : 25%  D : 50% duration (msec)  E : 75%

Fig.4. Electron microscopical changes of mitochondria, myofibril was found normal, irregularity and swelling of crista were observed diffusely in the glucocorticoid treated rabbits. (Calibration bar on the photo shows 1 mccm)
Changes. As for adrenalectomized animal, changes of mitochondria and intact myofilament were reported, but transmembrane potassium gradient decreased.\textsuperscript{12,13} Electrophysiologically, in adrenalectomized and saline-maintained rat, no significant changes were observed in duration and resting membrane potential.\textsuperscript{14} In our observation duration of action potential increased in chronically treated rats.

Therefore, steroid-induced changes on cardiac muscle may be attributed to effects mediated by some metabolic actions of glucocorticoids, and they also may produce some fine structural changes. However in order to prove these speculation about mechanisms of glucocorticoids on cardiac muscle, further studies will be necessary.

REFERENCES


\textbf{DISCUSSION}

In previous studies, mineralocorticoid-induced changes of cardiac muscle have been well observed.\textsuperscript{9,10} However, there are only few reports on glucocorticoid-induced changes of cardiac muscle.\textsuperscript{9,10} In these reports, changes of mitochondria and any electrophysiological changes had not been described. It is not likely, the results in present article were caused by potassium imbalance, because any significant changes in serum or tissue potassium levels were not observed. And their ECG changes were not similar to that of low potassium diet group. According to previous reports on morphological changes, low potassium is induces some derangements of myofilaments on early stage\textsuperscript{11} and it disagree from our observation. It may be possible that adrenal insufficiency induced by chronic glucocorticoid treatment may act some part on these

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