Effect of Alcohol on Thiamine Deficient Cardiac Lesions

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SUMMARY
Experiments were carried out to study whether thiamine deficiency is connected with alcoholic heart disease or not.

Thiamine deficient rats were orally given shōchū, whisky and 40% ethanol either until the last stage or for 10 weeks through a stomach tube. General symptoms, electrocardiographic abnormalities, and cardiac histological and electron microscopical changes in the alcohol administered groups were less severe than those in the non-administered group. That is the alcohol lessened thiamine deficient cardiac lesions.

From the above, it is assumed that alcoholic heart disease is of essentially different nature from thiamine deficient cardiac lesions. And discussions were given on the mechanism.

Additional Indexing Words:
Alcoholic heart disease Thiamine deficiency

In the previous paper,1) the effect of alcohol on normal rat's heart has been reported. The present paper is a report on the effect of alcohol on thiamine deficient rat's heart.

MATERIALS AND METHODS

1) Feedings and general procedure:
Wistar strain male rats 4 weeks old (body weight about 50 Gm.) were at first given a normal diet and tap water ad libitum. A week later they were divided into 2 groups; normal group and thiamine deficient group.1)

Thiamine deficient group was divided into non-administered group (control group) and into 35%* shōchū, 39% whisky and 40% ethanol administered group at 1 week of thiamine deficiency. The alcohol administered groups were given 15 ml./Kg. of alcohol through a stomach tube accurately into stomach every morning before feeding. Concerning their thiamine deficient progress, food intake, general condition and body weight were examined every day and electrocardiograms were at first recorded twice a week but daily at the last stage. At the last stage of

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* per cent by volume
thiamine deficiency or at the 10th week when they did not come into this stage, their blood and organs were collected. The organ weight, contents of lactic and pyruvic acids in blood and heart muscle, and histological and electron microscopical findings of the heart were examined and compared with the clinical and electrocardiographic findings.

2) Electrocardiographic examination:
Several min. after the rat became quiet, standard limb lead and unipolar limb lead were recorded.11

3) Biochemical examination:
The contents of lactic and pyruvic acids were determined by enzymatic method using LDH (to be reported later).

4) Histological examination:
The cervical blood vessel of the rat was incised with one stroke with surgical scissors under non-anesthetic condition, bleeding blood was collected at once into a test tube and the heart was excised right away. A slice of the apical ventricular wall was cut off quickly, fixed in iced 2% osmic acid solution buffered with veronal-acetate at pH 7.4 for 1 hour, dehydrated in a graded series of ethanol and embedded in epoxy resin. Ultrathin sections were made with LKB ultramicrotome, doubly stained with uranyl acetate and lead citrate, and examined with NEC type 7A electron microscope.

Another slice of the same ventricular wall was fixed in 10% formalin, embedded in paraffin, cut into thin sections, stained with hematoxylin and eosin (H.E), and examined with light-microscope.

The organ weight was weighed by torsion balance immediately after collection.

RESULTS

Progress of body weight:
In control group, body weight began to decrease from 12 to 14 days of thiamine deficiency and at 35 to 45 days of thiamine deficiency, body weight decreased to almost the same level as before the start and all cases showed agonal symptoms.

In alcohol administered groups, body weight decrease was slow in all and contrarily body weight increase cases were observed in quite a number (Fig. 1).

General symptoms:
In control group, food intake began to decrease from 2 weeks of thiamine deficiency and the debility, electrocardiographic changes, and paralysis appeared with the progress.

In alcohol administered groups, similar symptoms appeared in about half of them but in the other half, no symptoms were observed (Table I).
Table I. Findings of Alcohol Administered

<table>
<thead>
<tr>
<th>No.</th>
<th>Thiamine Deficient Days</th>
<th>Kinds of Alcohol</th>
<th>General Symptoms</th>
<th>Body Weight</th>
<th>Heart Weight</th>
<th>Pyruvic Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mg.</td>
<td>mg./100Gm.</td>
<td>mg./100ml.</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td></td>
<td>Severe paralysis, emaciation</td>
<td>73</td>
<td>324</td>
<td>444</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
<td></td>
<td>Light paralysis, light emaciation</td>
<td>73</td>
<td>355</td>
<td>486</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>Control</td>
<td>Light emaciation</td>
<td>84</td>
<td>414</td>
<td>493</td>
</tr>
<tr>
<td>17</td>
<td>49</td>
<td></td>
<td>Emaciation</td>
<td>75</td>
<td>345</td>
<td>460</td>
</tr>
<tr>
<td>E19</td>
<td>49</td>
<td>Emaciation, moribund condition</td>
<td>60</td>
<td>280</td>
<td>467</td>
<td>1.31</td>
</tr>
<tr>
<td>E11</td>
<td>55</td>
<td></td>
<td>Light paralysis, emaciation</td>
<td>102</td>
<td>531</td>
<td>521</td>
</tr>
<tr>
<td>12</td>
<td>61</td>
<td>35%</td>
<td>Emaciation</td>
<td>87</td>
<td>401</td>
<td>461</td>
</tr>
<tr>
<td>13</td>
<td>65</td>
<td>Shōchū</td>
<td>Healthy</td>
<td>218</td>
<td>1,431</td>
<td>656</td>
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<tr>
<td>15</td>
<td>68</td>
<td></td>
<td>Healthy</td>
<td>193</td>
<td>815</td>
<td>424</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td></td>
<td>Prostration, moribund condition</td>
<td>101</td>
<td>425</td>
<td>421</td>
</tr>
<tr>
<td>E3</td>
<td>62</td>
<td></td>
<td>Paralysis, emaciation</td>
<td>94</td>
<td>434</td>
<td>464</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>39%</td>
<td>Healthy</td>
<td>227</td>
<td>935</td>
<td>412</td>
</tr>
<tr>
<td>1</td>
<td>68</td>
<td>Whisky</td>
<td>Healthy</td>
<td>158</td>
<td>607</td>
<td>384</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td></td>
<td>Severe paralysis, prostration</td>
<td>161</td>
<td>748</td>
<td>465</td>
</tr>
<tr>
<td>E6</td>
<td>35</td>
<td></td>
<td>Severe paralysis</td>
<td>85</td>
<td>466</td>
<td>548</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>40%</td>
<td>Healthy</td>
<td>172</td>
<td>707</td>
<td>411</td>
</tr>
<tr>
<td>E10</td>
<td>68</td>
<td>Ethanol</td>
<td>Healthy</td>
<td>198</td>
<td>1,038</td>
<td>534</td>
</tr>
</tbody>
</table>

* Rats struggled violently when samples were taken.
Thiamine Deficient Rats

<table>
<thead>
<tr>
<th>Acid</th>
<th>Lactic Acid</th>
<th>Electrocardiographic Findings</th>
<th>Myocardial Histological Findings (H.E. Stain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart mg./100Gm.</td>
<td>Blood mg./100ml.</td>
<td>Heart mg./100Gm.</td>
<td>Heart rate 200-166/min., supraventricular premature beat, normal axis, T wave slight elevation</td>
</tr>
<tr>
<td>1.24</td>
<td>7.4</td>
<td>84.2</td>
<td>Myocardial cell partial atrophy, interstitial cell increase, cross-striation clear</td>
</tr>
<tr>
<td>0.90</td>
<td>13.8</td>
<td>86.9</td>
<td>Similar to above</td>
</tr>
<tr>
<td>0.83</td>
<td>21.2</td>
<td>82.5</td>
<td>Similar to above</td>
</tr>
<tr>
<td>1.49</td>
<td>53.7</td>
<td>72.6</td>
<td>Similar to above</td>
</tr>
<tr>
<td>1.19</td>
<td>17.8</td>
<td>46.1</td>
<td>Myocardial cell marked atrophy, fat increase, cross-striation clear</td>
</tr>
<tr>
<td>1.76</td>
<td>23.8</td>
<td>46.9</td>
<td>Myocardial cell partial atrophy, interstitial cell increase, cross-striation clear</td>
</tr>
<tr>
<td>0.92</td>
<td>8.8</td>
<td>21.1</td>
<td>No change</td>
</tr>
<tr>
<td>0.85*</td>
<td>33.0*</td>
<td>120.8*</td>
<td>No change</td>
</tr>
<tr>
<td>0.66*</td>
<td>17.9*</td>
<td>87.9*</td>
<td>No change</td>
</tr>
<tr>
<td>0.68</td>
<td>22.8</td>
<td>54.3</td>
<td>Myocardial cell slight atrophy, interstitial cell increase</td>
</tr>
<tr>
<td>0.89</td>
<td>18.9</td>
<td>43.8</td>
<td>Heart rate 200-140/min., supraventricular premature beat, normal axis, T wave slight elevation</td>
</tr>
<tr>
<td>0.86*</td>
<td>13.5*</td>
<td>76.8*</td>
<td>No change</td>
</tr>
<tr>
<td>0.83*</td>
<td>36.0*</td>
<td>113.5*</td>
<td>No change</td>
</tr>
<tr>
<td>0.96</td>
<td>56.9</td>
<td>121.7</td>
<td>No change</td>
</tr>
<tr>
<td>0.98</td>
<td>21.2</td>
<td>97.4</td>
<td>Heart rate 360/min., right axis, T wave flat</td>
</tr>
<tr>
<td>0.74*</td>
<td>31.7*</td>
<td>139.6*</td>
<td>No change</td>
</tr>
<tr>
<td>0.70*</td>
<td>14.1*</td>
<td>109.7*</td>
<td>Myocardial cell atrophy, interstitial cell increase</td>
</tr>
</tbody>
</table>

E: Electron microscopic examination cases
Examination findings:

Because only the left over after excision for histological examination (excision about 50–100 mg.) was weighed, accurate comparison could not be had but heart weight was heavier in 40% ethanol and shōchū groups. Concerning cardiac histological findings (H.E stain), changes were observed in all control groups but in alcohol administered groups, changes were generally few and there were more cases with no changes (Table I).

As there were variations in contents of lactic and pyruvic acids, definite conclusion could not be drawn from these data alone. Together with the data obtained in other experiments, the correlations between keto acids and
Electrocardiographic changes will be reported in my next paper.

**Electrocardiographic findings:**

In control group, abnormalities were observed in all. But, in alcohol administered groups, changes were generally few and there were quite a number of cases with no changes at all (Table I).

Following figures show typical cases with the most severe changes in each group: Fig. 2 is 40% ethanol group showing slight bradycardia and flattening

![Electrocardiogram](image1)

**Fig. 2.** No. 6 rat: 40% Ethanol administered case, thiamine deficient 35 days, 89 Gm., severe paralysis, heart rate 360/min.

![Electrocardiogram](image2)

**Fig. 3.** No. 11 rat: Shōchū administered case, thiamine deficient 55 days, 102 Gm., emaciation, light paralysis, heart rate 200–186/min.
Fig. 4. No. 3 rat: Whisky administered case, thiamine deficient 62 days, 94 Gm., emaciation, severe paralysis, heart rate 200-140/min.

Fig. 5. No. 19 rat: Thiamine deficient 49 days, 60 Gm., severe emaciation, heart rate 140/min.
of T waves. Fig. 3 is shōchū group showing bradycardia and supraventricular premature beat. Fig. 4 is whisky group showing bradycardia and supraventricular premature beat. Fig. 5 is non-administered group (control group) showing the most severe changes of a-v rhythm, extreme bradycardia, and flattening and inversion of T waves.

**Electron microscopic findings:**

Typical cases with the most severe changes in each group were examined. In thiamine deficient group (control group), extreme swelling, deformation, loss of electron density of matrices and vacuolation of mitochondria, and fragmentation, destruction and disappearance of cristae were the most conspicuous. In between swollen mitochondria, deformed mitochondria that can be considered deformed by pressing of swollen mitochondria and condensed mitochondria were occasionally observed. The sarcoplasmic reticulum was slightly enlarged but in myofibrils, almost no changes were observed (Fig. 6, 7).

In ethanol administered group, slight swelling of mitochondria, slight decrease of electron density of matrices and deformation of cristae were observed, but changes were less in comparison to control group (Fig. 8).

In shōchū and whisky groups, only slight swelling of mitochondria and
Fig. 7. The same case as shown in Fig. 6. Extremely swollen mitochondrion is observable. A mitochondrion that can be considered deformed by pressing of swollen mitochondria exist also. ×7,000

Fig. 8. No. 6 rat: 40% Ethanol administered case, thiamine deficient 35 days, 89 Gm., severe paralysis. Light swelling and light decrease of electron density of mitochondria and deformation of cristae are observable. Fig. 2 is an electrocardiogram of this case. ×7,000
Fig. 9. No. 11 rat: Shōchū administered case, thiamine deficient 55 days, 102 Gm., emaciation, light paralysis. Light swelling of mitochondria and disarrangement of cristae are observable. Fig. 3 is an electrocardiogram of this case. ×13,000

Fig. 10. No. 3 rat: Whisky administered case, thiamine deficient 62 days, 94 Gm. emaciation, severe paralysis. Light swelling of mitochondria and disarrangement of cristae are observable. Fig. 4 is an electrocardiogram of this case. ×20,000
disarrangement of cristae were observed and therefore, changes were much less (Fig. 9, 10).

**Discussion**

The relationship between alcoholic heart disease and thiamine deficiency has been a problem for a long time but there have been very few experiments of alcohol loading combined with thiamine deficiency.

As findings such as anorexia, body weight decrease, neuroparalysis, myocardial histological changes and electrocardiographic changes observed in thiamine deficient group (control group) have already been stated, discussion on them are omitted here.

On the electron microscopic findings of myocardium in thiamine deficiency, there are very few reports. Meesen has stated that a significant increase of the mass of the mitochondria was observed in vitamin B deficiency. Suzuki has reported the decrease in electron density of mitochondrial matrix, swelling and rupture of mitochondria, reduction and derangement of cristae, mitochondrial degeneration, enlargement and destruction of cisternae of sarcoplasmic reticulum, appearance of large vacuoles, and disappearance of cross striation in the myofibril on thiamine deficient rats. Miwa also has reported similar changes of mitochondria and cristae. Bözner and co-workers have observed the marked increase, enlargement and deformation of mitochondria, disappearance of granules, and rapid recovery by thiamine administration.

In the author's experiments also, extreme swelling, deformation, loss of matrix and vacuolation of mitochondria, and fragmentation, destruction and disappearance of cristae have been most conspicuous. The distinctive feature of electron microscopic findings of myocardium in thiamine deficiency are considered to be mitocondrial changes.

On the other hand, as to electron microscopic findings of alcoholic heart disease, the degeneration of myofibrils, swelling, damage and vacuolation of mitochondria, alterations of cristae, dilatation of sarcoplasmic reticulum, lysosome-like bodies, and increase of lipid and glycogen are generally well known. Recently Schmalbruch and Dume also reported similar findings on the myocardium in the heart of a clinically healthy man with severe alcoholism.

Experimentally, besides the reports of Bishop and co-workers, and Szanto and co-workers, there are reports by Suzuki, Ito and co-workers, and Lacerda and co-workers. Although there are differences in degree of changes, similar findings to those in humans i.e. swelling of mitochondria,
enlargement of sarcoplasmic reticulum, fragmentation and destruction of cristae, fragmentation of myofibrils, and appearance of vacuole have been observed.

As to electrocardiographic changes of alcoholic heart disease, following the reports of Eliaser and Giansiracusa,23, 24) Brigden25) and Robinson,26) and Evans,27) 29) there are many reports and various changes have been observed.

As noted from the above, it is obvious that cardiac lesions can occur clinically and experimentally either by thiamine deficiency or by alcohol intake. In case thiamine deficiency was one of the causative factors of alcoholic heart disease, it can be assumed that under the condition of alcohol loading plus thiamine deficiency, a more severe cardiac lesions would naturally occur. The present experiments were carried out assuming such results but unexpectedly the results were entirely contrary i.e. not only was the effect doubled by alcohol loading to thiamine deficiency but thiamine deficient cardiac lesions were lessened by alcohol. At the present stage, the results are difficult to explain but if alcoholic heart disease and thiamine deficient cardiac lesions were assumed to be of entirely different nature, it can be understood to a certain extent.

On the author's above findings there are similar reports—the appearance of deficiency symptoms in thiamine deficient rats delayed by alcohol administration, 30) the onset of polyneuropathy in thiamine deficient rats delayed by ethanol or whisky,21) the onset of opisthotonus and death in thiamine deficient pigeons delayed by alcohol,32) and thiamine deficient rats that took alcohol prolonged their lives.33) On the mechanism, clear explanations were not stated, but the following were considered as the cause i.e. alcohol does not increase thiamine requirements,31, 32) alcohol metabolism requires less thiamine than glucose or fat metabolism and so alcohol has thiamine-sparing action when it is used as calorie source,30, 33, 35) and metabolic rate of alcohol does not decrease in thiamine deficient conditions and blood pyruvic acid of thiamine deficient dogs falls sharply with alcohol administration.34)

When thiamine is deficient, oxidation of pyruvic acid is disturbed, pyruvic acid accumulates in tissue and blood, reductive reaction of pyruvic acid to lactic acid is accelerated, and at this stage, the NADH (coenzyme) is oxidized into NAD. On the other hand, when alcohol is metabolized, NAD is utilized and converted into NADH, and it is said that metabolic rate of alcohol is limited by the reoxidation rate of this NADH.36) 38) The acceleration of alcohol metabolism by pyruvic acid loading is considered as caused by the coupled oxidation-reduction reaction centered around NAD and NADH36) 38) (Fig. 11).

In case a part of thiamine deficient cardiac lesions was caused by abnormal
accumulation of pyruvic acid (mitochondrial changes observed in electron micrograph have been recently considered as caused by pyruvic acid accumulation), removal of pyruvic acid by alcohol administration naturally lessens the deficiency symptoms and at the same time, the calorie liberated by the decomposition of alcohol is most likely used beneficially in maintenance of cell functions.

Under these considerations, the fact that thiamine deficient cardiac lesions have become less severe by alcohol administration can be explained reasonably. Further experiments will be carried out on this.

**REFERENCES**