Coenzyme $Q_{10}$ Attenuates the Progression of Cardiomyopathy in Hamsters

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SUMMARY

Coenzyme $Q_{10}$ (10 mg/kg/day) or digoxin (2 µg/kg/day) was given orally to cardiomyopathic hamsters (BIO 14.6) for 8 weeks from 12 weeks of age. The left ventricular weight per gram of body weight (mg/g) was lower ($p<0.01$) in the coenzyme $Q_{10}$ group (3.09±0.13) than in the digoxin (3.32±0.20) and control (3.44±0.14) groups. Left ventricular function was evaluated in isovolumically beating hearts. Left ventricular developed pressure (63±5 vs. 54±10 mmHg, $p<0.05$), $+dP/dt$ (1385±100 vs. 1211±136 mmHg/sec, $p<0.05$), and $-dP/dt$ (1068±126 vs. 896±141 mmHg/sec, $p<0.05$) were greater in the coenzyme $Q_{10}$ than in the control group. The time constant of left ventricular relaxation was shorter in the coenzyme $Q_{10}$ group than in the control group (25±3 vs. 28±3 msec, $p<0.05$). By contrast, in the digoxin group, the indices of left ventricular function did not differ from the control group. These results suggest that coenzyme $Q_{10}$, but not digoxin, attenuated disease progression and preserved left ventricular function in cardiomyopathic hamsters.

Additional Indexing Words:
Cardiomyopathy  Digoxin  Ventricular function  Cardiac hypertrophy  Isolated heart

CARDIOMYOPATHIC hamsters are known to develop pathological changes which mimic human cardiomyopathy. Since this animal model develops myocardial necrosis, fibrosis and hypertrophy, it has been used both to elucidate the mechanisms of cardiomyopathy and to examine the effects of a variety of therapeutic interventions.

Coenzyme $Q_{10}$ is a drug that is used clinically for the treatment of cardiomyopathy. Although the drug attenuates ischemic injury in animal models, the effects of coenzyme $Q_{10}$ on cardiomyopathy have been poorly documented in experimental models. By contrast, the effects of digoxin in...
Congestive heart failure have been well-established in animal experiments. The present study was conducted to characterize the mechanical properties of the left ventricle in the cardiomyopathic hamster and to investigate the effects of coenzyme Q10 and digoxin on left ventricular function in this animal model.

**Materials and Methods**

*Materials:*

Male cardiomyopathic Syrian hamsters (BIO 14.6) and golden hamsters were used at 20 weeks of age.

*Drug administration protocols:*

Myopathic hamsters were divided into 3 groups, a control group, a coenzyme Q10-treated group and a digoxin-treated group. The coenzyme Q10 group received 10 mg/kg/day of coenzyme Q10 orally for 8 weeks from 12 weeks of age. The digoxin group received 2 µg/kg/day of digoxin orally for the same time period. The golden hamsters did not receive drug treatment. Immediately after the completion of drug administration in these 2 groups, left ventricular function was evaluated using the isovolumically beating perfused heart preparation setup.

*Isovolumically beating perfused heart preparation:*

Hamsters were sacrificed and their hearts were excised rapidly. The aorta of each heart was then cannulated with a plastic tube and retrograde perfusion was initiated with oxygenated Krebs-Henseleit buffer (118 mM NaCl, 25 mM NaHCO3, 4.7 mM KCl, 1.2 mM KH2PO4, 1.2 mM MgSO4, 2.0 mM CaCl2, 0.4 mM Na2EDTA, 5.5 mM D-glucose and 1.0 mM lactate) at 37°C. The perfusion rate of the buffer was adjusted using a peristaltic pump to maintain coronary perfusion pressure at 90 mmHg. A latex balloon was inserted into the left ventricle from the left atrial appendage, and left ventricular pressure was monitored with a Statham P23 ID transducer via a plastic tube connected to the balloon. Left ventricular end-diastolic pressure was set at 10 mmHg by infusing water into the balloon. The left ventricular pressure was recorded on both a chart recorder and magnetic tape.

*Assessment of left ventricular systolic and diastolic function:*

From the left ventricular pressure record on magnetic tape, the following indices were calculated with the use of a personal computer and an
A-D converter: left ventricular developed pressure (left ventricular peak systolic pressure-left ventricular end-diastolic pressure), peak positive dP/dt (+dP/dt), peak negative dP/dt (-dP/dt) and the time constant (T) of left ventricular isovolumic relaxation. The time constant was calculated by the monoexponential method (T_L) as well as by the best fit method (T_BF),\textsuperscript{7} where left ventricular pressure is assumed to decay exponentially towards an asymptote (P_B). Left ventricular systolic and diastolic pressure-volume plots were obtained by stepwise changes of the left ventricular balloon volume.

Statistical analysis:
Indices of left ventricular function and heart weight were compared among the different groups using Student’s t-test. Data are shown as the mean±SD, and p values less than 0.05 were regarded as significant.

Results

Heart weights of control and cardiomyopathic hamsters:
Figure 1 shows the heart weight and left ventricular weight normalized by body weight in the 3 groups of cardiomyopathic hamsters and in normal golden hamsters. In the control group of cardiomyopathic hamsters, both heart weight and left ventricular weight were higher than in the golden hamsters. In the coenzyme Q\textsubscript{10} group, the normalized heart weight and left ventricular weight were both lower than in the control group. However, in the digoxin group neither of these indices differed from the control group values.

Left ventricular function in control and cardiomyopathic hamsters:
Indices of left ventricular function are shown in Table I. Data regarding the left ventricular function of golden hamsters at the same age are also shown. In the cardiomyopathic hamsters without drug treatment (control group), left ventricular developed pressure, +dP/dt and the −dP/dt were lower than in the golden hamsters. The time constant (T) of left ventricular isovolumic relaxation measured by the monoexponential method (T_L) was longer in cardiomyopathic hamsters than that in golden hamsters, indicating impairment of ventricular relaxation in the cardiomyopathic hamsters. The time constant measured by the best fit method (T_BF) was similar in cardiomyopathic hamsters and golden hamsters, but the asymptote of left ventricular relaxation was higher in cardiomyopathic hamsters.
Fig. 1. Heart weight (HW) and left ventricular weight (LVW) in relation to body weight (BW) in cardiomyopathic hamsters and golden hamsters. C=control group; DG=digoxin group; CQ10=coenzyme Q$_{10}$ group; G=golden hamsters. **p<0.01 vs. C.

Table I. Indices of Left Ventricular Function

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<th>BIO 14.6</th>
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<th>Golden hamsters</th>
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<tr>
<td></td>
<td>Control</td>
<td>CQ</td>
<td>DG</td>
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<tr>
<td>DP (mmHg)</td>
<td>54.0±10.1</td>
<td>63.4±4.6*</td>
<td>50.2±12.1</td>
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<tr>
<td>+dP/dt (mmHg/sec)</td>
<td>1211±136</td>
<td>1385±100*</td>
<td>1126±242</td>
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<tr>
<td>-dP/dt (mmHg/sec)</td>
<td>896±141</td>
<td>1068±126*</td>
<td>867±206</td>
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<tr>
<td>T_L (msec)</td>
<td>38.3±6.8</td>
<td>36.8±5.2</td>
<td>38.8±9.5</td>
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<tr>
<td>T_BF (msec)</td>
<td>28.1±2.7</td>
<td>25.2±2.6*</td>
<td>24.9±1.9*</td>
</tr>
<tr>
<td>P_B (mmHg)</td>
<td>3.9±2.7</td>
<td>5.0±1.7</td>
<td>4.9±1.9</td>
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* p<0.05, ** p<0.01 vs. Control. CQ=coenzyme Q$_{10}$ group; DG=digoxin group; DP=developed pressure; T_L=time constant of left ventricular pressure fall calculated by the mono-exponential method; T_BF=time constant calculated by the best fit method; P_B=asymptote of left ventricular pressure decay.

Left ventricular function in the 3 groups of cardiomyopathic hamsters:

As shown in Table I, the left ventricular developed pressure, +dP/dt and -dP/dt were higher in the coenzyme Q$_{10}$ group than in the control
The time constant $T_{BF}$ was slightly shorter in the coenzyme $Q_{10}$ and digoxin groups than in the control group, although $T_{L}$ did not differ among the 3 groups. The asymptote of left ventricular relaxation ($P_B$) did not differ among the 3 groups.

*Left ventricular systolic pressure-volume relations* (Table II):

Left ventricular systolic pressure-volume relations from the 3 cardio-

<table>
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<th>Table II. Left Ventricular Systolic Pressure-Volume Relation</th>
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<tr>
<td>Golden (n=4)</td>
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<td>BIO 14.6</td>
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<tr>
<td>Control (n=8)</td>
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<td>CQ (n=8)</td>
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P=left ventricular peak systolic pressure; V=left ventricular volume; V/W=normalized left ventricular volume (left ventricular volume divided by left ventricular weight); Golden=golden hamsters; CQ=coenzyme $Q_{10}$ group; DG=digoxin group.

Fig. 2. Systolic left ventricular pressure (LVP)-volume (LVV) relations in the 3 groups of cardiomyopathic hamsters and in golden hamsters. C=control group; DG=digoxin group; CQ=coenzyme $Q_{10}$ group; G=golden hamsters.
myopathy groups and healthy golden hamsters are shown in Fig. 2. These relationships were shifted to the right for the 3 groups of hamsters with cardiomyopathy, indicating depressed systolic function. The plots for the coenzyme Q_{10} group lay between those for the golden hamsters and the control group. Slopes of the plots and x-intercepts were not significantly different among the 4 groups. Left ventricular systolic pressure was plotted against the normalized left ventricular volume (i.e., volume divided by left ventricular weight) in Fig. 3. Again the slopes and x-intercepts of the 4 groups did not differ significantly.

Left ventricular diastolic pressure-volume relations:

Left ventricular diastolic pressure-volume relations in the 3 cardiomyopathy groups are shown in Fig. 4. Left ventricular end-diastolic volume was significantly smaller in the coenzyme Q_{10} group than in the control group at each level of left ventricular end-diastolic pressure (upper panel of Fig. 4). However, when the normalized left ventricular volume was used, the left
ventricular end-diastolic pressure-volume relation was not significantly different between the groups (lower panel of Fig. 4).

**DISCUSSION**

*BIO 14.6 as a model of cardiomyopathy:*

The BIO 14.6 strain of Syrian hamsters is known to develop myocardial lesions, including myocardial necrosis, calcification and fibrosis. Thus, it has been intensively studied as a model of human cardiomyopathy. Forman et al have studied the myocardial function of cardiomyopathic hamsters using papillary muscle preparations. They demonstrated that developed force and the maximum rate of force development (corrected by cross-sectional area) were depressed from 60 to 320 days of age. However, those experiments were not performed under physiological conditions. More recently, Wikman-Coffelt et al showed that left ventricular systolic pressure and dP/dt in the isolated working heart were depressed at 250 days of age.
in another strain of cardiomyopathic hamsters. Thus, there is now little doubt that left ventricular function is depressed in cardiomyopathic hamsters.

Despite the utility of this animal model, detailed data on the left ventricular systolic and diastolic function of cardiomyopathic hamsters have not been reported. This lack of information can probably be attributed to the technical difficulties in evaluating left ventricular function in small animals. In the present study, we demonstrated that both left ventricular relaxation and systolic function are impaired in the cardiomyopathic hamster. However, the diastolic pressure-volume relations indicated that left ventricular distensibility or diastolic stiffness may not be altered significantly at 20 weeks of age.

**Myocardial disease process in cardiomyopathic hamsters:**

The biochemical changes shown to accompany mechanical dysfunction in cardiomyopathy are depletion of myocardial high energy phosphate\(^{10,11}\) and carnitine.\(^{12}\) In addition, the calcium transport properties of the sarcoplasmic reticulum may be impaired.\(^{13}\) However, the etiology of these mechanical and biochemical changes in cardiomyopathic hamsters is still unclear. Calcium overload may play an important role in the development of myocardial necrosis.\(^{14,15}\) According to Factor et al.,\(^{16}\) microvascular spasms are prominent in these animals. Therefore, reperfusion following coronary microvascular spasms could also contribute to myocardial injury.

**Previous trials of drug therapy in the cardiomyopathic hamster:**

A variety of drugs, including calcium antagonists,\(^{17,18}\) \(\beta\)-blockers,\(^{17}\) \(\alpha\)-blockers\(^{17,19}\) and carnitine,\(^{20}\) have been tried to prevent disease progression in the cardiomyopathic hamster. However, the effects of coenzyme Q\(_{10}\) on the disease process in this animal model have not been reported.

**Effects of coenzyme Q\(_{10}\) on cardiomyopathy in the Syrian hamster:**

The present study demonstrated that coenzyme Q\(_{10}\) could reduce left ventricular hypertrophy and preserve left ventricular function in the cardiomyopathic hamster. Coenzyme Q\(_{10}\) is known to attenuate reperfusion injury probably through its free radical scavenging action.\(^{41-61}\) A protective effect of coenzyme Q\(_{10}\) has also been reported in adriamycin-induced myocardial damage,\(^{21}\) and in diabetic rat hearts.\(^{22}\) In the cardiomyopathic hamster model, coenzyme Q\(_{10}\) may retard the progression of the disease process and preserve ventricular function by preventing myocardial reperfusion injury following coronary microvasospasm.

It is interesting that digoxin failed to reduce cardiac hypertrophy and
preserve ventricular function. These results indicate that digoxin may not be able to prevent the progression of cardiomyopathy in this hamster model. Digoxin may even accelerate the progression of myocardial necrosis by increasing the calcium overload.

Clinical implications:

The cause of dilated (congestive) cardiomyopathy in humans is still unclear and may well be multifactorial. Coronary microvascular spasms have been suggested to be one of the causes of myocardial necrosis and subsequent heart failure in patients with dilated cardiomyopathy. McMurtry et al recently demonstrated that malondialdehyde, a marker of lipid peroxidation, showed increased levels in patients with chronic congestive heart failure due to ischemic heart disease. Although direct evidence supporting the role of reperfusion injury and free radicals in cardiomyopathy is yet to be demonstrated, coenzyme Q10 may be effective against human cardiomyopathy by attenuating reperfusion injury due to coronary microvasospasm.

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