Efficacy of Coenzyme Q₁₀ Administration in Experimentally Created Aortic Stenosis and Pacemaker Induced Tachycardia

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INTRODUCTION

Coenzyme Q₁₀ (CoQ₁₀) is said to be concerned with succinic dehydrogenase, NADH dehydrogenase, cytochromes and the electronic conduction system in intracellular mitochondria and thereby to activate cell respiration.

In order to investigate the effect of CoQ₁₀ under conditions which increase the demand for oxygen of the myocardium, that is, a rise in the left ventricular pressure or tachycardia, we had arterial stenosis created experimentally, had tachycardia induced by...
atrial pacing in mongrel dogs, administered CoQ₁₀ under these conditions and measured the oxygen consumption rate and lactic acid consumption rate of the myocardium to study this aspect of myocardial metabolism.

**SUBJECTS AND METHODS**

The subjects were seven mongrel dogs weighing 14–24 kg.

The animals were anesthetized by intravenous injection of pentobarbital 30 mg/kg. After intratracheal intubation, a ventilator was used to maintain arterial pH and PaO₂ at the normal level.

Fixing the animals in the supine position, the thorax was open with a median incision. The pericardium was cut from the base to the apex.

With a catheter introduced via femoral artery, the left ventricular pressure (P₅₇), left ventricular enddiastolic pressure (Pᵥₑₑ₃) and aortic pressure (P₃₉) were measured with a Statham P₂₃Db transducer.

Using an electromagnetic flow meter placed at the starting point of the aorta and anterior descending branch of the left coronary artery, the aortic blood flow (ABF) and the coronary blood flow (CBF) were measured and recorded simultaneously with electrocardiograms.

A balloon catheter was inserted via the carotid artery and held in position at the lower part of the aortic valve as shown in Fig. 1. Physiological saline solution was

![Fig. 1. A balloon catheter was inserted via the carotid artery and held in position at the lower part of the aortic valve.](image)

![Fig. 2. Tachycardia was induced with a pacing catheter inserted via the femoral vein into the right atrium.](image)
poured into the balloon to inflate it and cause aortic stenosis. Care was then taken so that no arrhythmia occurred. The pressure gradient between PLV and PAO was set at about 30 mmHg or less. The duration of stenosis was five minutes.

On the other hand, tachycardia was induced with a pacing catheter inserted via the femoral vein into the right atrium as shown in Fig. 2 and the pacing frequency was 1.5 or 2 times the basic heart rate.

However, the pacing frequency 1.5 times the heart rate was used in most cases because the Wenckebach phenomenon appeared before the frequency reached a level 2 times the heart rate.

The intensity of pacing was 2 times the threshold for the sensitivity and the duration was set as 2 msec.

The duration of pacing was 5 minutes.

Under such a setting, a control study was first conducted and aortic blood and coronary venous blood via the jugular vein were sampled simultaneously immediately before completion of aortic stenosis and tachycardia.

CoQ₁₀ 5mg/kg was injected slowly via the intravenous route. After about 10 minutes, aortic stenosis and tachycardia were likewise induced and blood was sampled and the oxygen concentrations and lactic acid concentrations in the myocardium were determined.

The oxygen uptake of myocardium was calculated as (oxygen concentration of aortic blood - oxygen concentration of coronary venous blood)/oxygen concentration of aortic blood. Lactate was measured by UV method.

All values were expressed as mean ±1 standard deviation.

RESULTS

A) Aortic stenosis

Fig. 3 illustrates the simultaneous recording of ECG, ABF, PLV and PAO. On the left is shown the control. At the arrow on the right, the balloon was inflated to create aortic stenosis.

PLV rose, while PAO rose transiently but returned to the original level shortly, and there occurred the pressure gradient between PLV and PAO.

ABF decreased slightly, but CBF remained almost unchanged. Even with Plved of high sensitivity, changes were hardly observed. The heart rate (HR) on the electrocardiograms remained almost unchanged.

(1) Oxygen extraction

In the control study, the oxygen extraction was measured five minutes after creation of aortic stenosis and comparison was made of the values at each pressure gradient with the values in the control study as the standard. Results are shown in Fig. 4. On the left is the no CoQ₁₀-administration group and on the right the administration group.

The oxygen extraction increased in either group until the pressure gradient between
PLY and P\textsubscript{AO} reached about 30mmHg, but there was no significant difference between the two groups.

(2) Lactate uptake

Comparison was made of the lactate uptake at the pressure gradient between P\textsubscript{LV} and P\textsubscript{AO} as in the case of the oxygen extraction. Results are illustrated in Fig. 5. The

\textbf{Fig. 3.} On the left is shown the control. At the arrow on the right, the balloon was inflated to create aortic stenosis.

ECG: electrocardiogram \quad ABF: aortic blood flow

CBF: coronary blood flow \quad P\textsubscript{LV}: left ventricular pressure

P\textsubscript{AO}: aortic pressure

\textbf{Oxygen extraction}

\textbf{Fig. 4.} On the left is the no CoQ\textsubscript{10} administration group, on the right the administration group.
lactate uptake showed a slight rise and fall compared with the control in either group. There was no significant difference arising from whether or not CoQ₁₀ was administered.

B) Tachycardia

Tachycardia was induced by atrial pacing. The simultaneous recording of tachycardia thus induced is shown in Fig. 6. On the left are the results in the control study and on the right are those in tachycardia.

In tachycardia the pulse pressure of P₂AO became slightly narrow and CBF increased slightly.

P₁LV and P₁LVED remained almost unchanged.

![Lactate uptake](image)

**Fig. 5.** Comparison was made of the lactate uptake at the pressure gradient between P₁LV and P₂AO as in the case of the oxygen extraction.

![ECG](image)

![ABF](image)

![CBF](image)

![P₂AO](image)

![P₁LV](image)

**Fig. 6.** On the left are the results in the control study and on the right are those in tachycardia.
(1) **Oxygen extraction** (Fig. 7)
The rate of rise in the oxygen extraction became slightly slow at the time of tachycardia in the CoQ₁₀ administration group compared with the no-administration group, but there was no statistically significant difference between the two.

(2) **Lactate uptake** (Fig. 8)
The lactate uptake showed a decrease at the time of tachycardia in 2 out 7 cases of the no CoQ₁₀-administration group.
DISCUSSION

Usually, the oxygen supply and the oxygen demand are well balanced or at least the oxygen supply is enough in the myocardium. It is therefore presumed that the metabolism becomes aerobic in case of the oxygen supply exceeding the oxygen demand and that the metabolism becomes anaerobic in case of the oxygen demand exceeding the oxygen supply.

Theoretically, the relation may be expressed as oxygen supply $\approx (A-V)$ oxygen dissociation $\times$ CBF$^{1}$

As a method for meaning $(A-V)$ oxygen dissociation as a relative change, mention is made of the oxygen extraction. It is expressed as $(A-V)$ oxygen dissociation/ aortic oxygen $(O_2/AO_2)^{2}$

On the other hand, the relation may be expressed as oxygen demand $= PLV \times HR \times LVEDV$.

LVEDV (left ventricular end diastolic volume) may be substituted by PVED to some extent$^{3}$

The lactate uptake is calculated from $L/aL$ (arterio-venous lactic acid concentration/ lactic acid concentration in arterial blood ), which enables one to learn indirectly the oxidated state of the NAD system$^{4}$

That is, a rise in the lactate uptake means the aerobic metabolism under way. If the aerobic metabolism is normal, the lactate uptake does not diminish.

A fall in the lactate uptake may be taken to mean that the anaerobic metabolism is under way. Going by the theory mentioned earlier, it is when there are a rise in the left ventricular pressure and tachycardia that the oxygen demand of the myocardium is increased. If the oxygen supply is not sufficient under these conditions, the progress of the reaction of the TCA cycle will be suppressed and the aerobic energy production will fall off to produce anaerobic energy. So, aortic stenosis was first created for this study.

In this case, a maximum rise in PLV is desirable, but there is a limit for PLV to be kept at the same level for 5 minutes without causing arrhythmia experimentally.

In the present study the PLV–PAO pressure gradient was set at about 30 mmHg or less.

I$^{5}$ have already reported that there is a good correlation between PLV (PLV stenosis−PLV control)/PLV control and PLV–PAO pressure gradient, e.g., PLV% control (PLV stenosis/PLV control $\times 100$) being about 120 when the PLV–PAO pressure gradient is about 30 mmHg.

Accordingly, it follows that PLV increases with an increase in the PLV–PAO pressure gradient.

With the PLV–PAO pressure gradient being about 30 mmHg, CBF remains almost unchanged.

Fig. 4 shows a slight rise in the oxygen extraction irrespective of whether or not
CoQ_{10} is administered.

In Fig. 5 is shown the lactate uptake examined at the time. With an increase in the PLV–PAO pressure gradient, the lactate intake rose or fell slightly in some cases. This is not due to the influence of CoQ_{10} administration but rather suggests that aortic stenosis or the rise in PLV of that magnitude needs no effect of CoQ_{10} and that the oxygen supply to the myocardium does not fall short of the oxygen demand.

As the reason, mention is made of the fact that there is no marked fall in the lactate uptake despite a rise in PLV. Findings above suggest that with stenosis, in other words, the PLV–PAO pressure gradient of that magnitude, the oxygen supply to the myocardium exceeds the demand.

Under such conditions, there appears to be not much room for the action of CoQ_{10}. The question is what the influence of CoQ_{10} will be in case the PLV–PAO pressure gradient is increased more to elevate PLV further.

Next, the effect of CoQ_{10} administration as the time of tachycardia was examined. As shown in Fig. 6, CBF is increased slightly. As seen from Fig. 7, the oxygen extraction is increased with tachycardia and the degree of increase has nothing to do with whether or not CoQ_{10} is administered. From this finding it is surmised that the oxygen supply is increased at the time of tachycardia.

On the other hand, the pacing rate is 1.5 times the basic heart rate. So, the oxygen demand ought to be 1.5 times that in the study group.

However, this does not necessarily mean that the demand exceeds the oxygen supply in each case because the question of the individual difference is involved. In this experiment too, the lactate uptake rose slightly in 5 out of 7 cases of the no CoQ_{10}–administration group and fell off sharply in 2 out of 7 cases.

This suggests that the myocardium was inclined toward the anaerobic metabolism in these 2 cases that showed a sharp fall in the lactate uptake.

By contrast, the fall in the lactate uptake was not observed at the time of tachycardia in the CoQ_{10} administration group. That is probably because CoQ_{10} confirmed the oxygen consumption of the myocardium, suppressed the anaerobic production of energy and improved the energy metabolism.

**CONCLUSION**

For the purpose of studying how CoQ_{10} exerts effect in case of the oxygen demand being increased, we opened the chests of 7 mongrel dogs after anesthesia, made a simultaneous recording of PLV, PAO, PLVED, CBF, ABF and ECG, created aortic stenosis experimentally, had tachycardia induced by atrial pacing and studied the oxygen extraction and lactate uptake at the time.

In aortic stenosis, it was suggested that the aerobic metabolism would be under way with the PLV–PAO pressure gradient of about 30 mmHg.
In tachycardia 1.5 times the basic heart beat, meanwhile, a distinct fall in the lactate uptake was seen in 2 out of 7 cases, and this fall diminished after administration of CoQ₁₀.

Thus it was suggested that CoQ₁₀ would suppress the anaerobic production of energy and improve the energy metabolism.

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