The Effectiveness of Coenzyme Q1 and Q10 in Mitigating Myocardial Reperfusion/Ischemia (MI/R) Injury

Myles Ashitey, Jakob Sutton, Joseph Venditto, Kevin Kucharski, Jason Robbie, Daniel Kuo, Robert Barsotti, Lindon Young, Qian Chen
Department of Bio-Medical Sciences, Division of Research, Philadelphia College of Osteopathic Medicine
4170 City Avenue, Philadelphia, PA 19131

Introduction

Acute myocardial infarction (MI) is a major cause of morbidity and mortality worldwide. The goal of therapy is to limit the irreversible cell damage via quick reperfusion. However, the restoration of blood flow to a prolonged ischemic area (MI/R) per se can induce additional cardiac damage [1]. Currently, there are no effective treatments to mitigate this reperfusion induced injury. Oxidative stress, characterized as the rapid production of reactive oxygen species, has been indicated to mediate MI/R injury. Mitochondria may be a principle source of oxidative stress causing MI/R injury. Coenzyme Q10 (CoQ10) is essential for electron transport chain (ETC) in normal mitochondria. It accepts the electron generated from complex I or II to form its reduced form, ubiquinol; then donates the electron to complex III to return its oxidized form, ubiquinone (see figure 1). The bioavailability of CoQ10 is likely reduced during MI/R, which can interrupt the electron transport via ETC, and then free electrons may bind to oxygen to generate superoxide during early reperfusion and attribute to the oxidative stress [2]. CoQ10 also has antioxidant properties and has been used as an adjunctive agent in the treatment of cardiovascular disease, such as congestive heart failure and hypertension [3]. Coenzyme Q1 (CoQ1) is a derivative of CoQ10, but is a more potent antioxidant than CoQ10 due to a shorter isoprene chain (see figure 2) [4]. This study tested the effects of CoQ10 and CoQ1 on postreperfused cardiac function and infarct size in an isolated rat MI/R model.

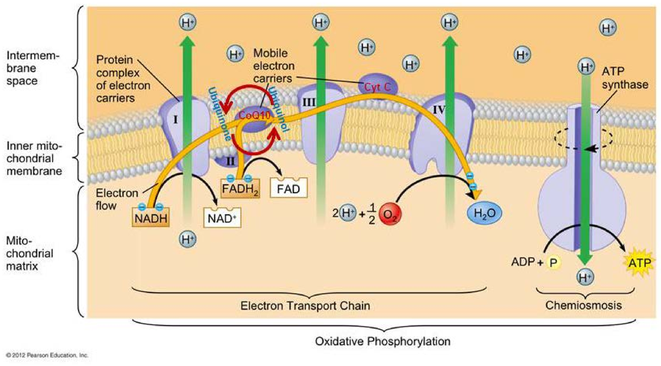


Figure 1. The role of CoQ10 in electron transport chain in mitochondria. CoQ10 will transport electron between the conversion of its oxidized form (e.g., ubiquinone) and reduced form (e.g., ubiquinol). (adapted from 2012 Pearson education, Inc).

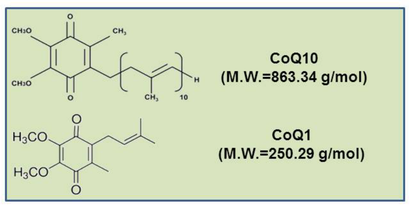


Figure 2. The chemical structure of CoQ10 and CoQ1. CoQ10 has the 1,4-benzoquinone chemical group with 10 isoprenyl subunits in its tail. By contrast, CoQ1 only has 1 isoprenyl subunit in its tail.

Hypothesis

We hypothesized that CoQ10 and CoQ1 would improve post-reperfused cardiac contractile function and reduce infarct size when compared to I/R control with/without drug solvent.

Methods

Isolated Rat Heart MI/R Experiments: Langendorff heart preparation was performed after anesthesia of male Sprague Dawley rats (275-325 g, Charles River, Springfield MA). Hearts were isolated and retrogradely perfused with Krebs' buffer at a constant pressure of 80 mmHg with 37°C and pH of 7.35-7.45 by aerating with 95% O_2/5% CO_2 to get the baseline of cardiac parameters. After 15 min of baseline perfusion, the heart was put through global ischemia by stopping perfusion for 30 min, followed by reperfusion for 45 min. Krebs' buffer alone, 0.2% DMSO alone (0.2% DMSO was used to solubilize CoQ1 and CoQ10), CoQ1 (20 μM), or CoQ10 (20 μM) was infused with 1 ml/min for the first 5 min of reperfusion. The pressure transducer (SPR-524, Millar Instruments, Inc., Houston, TX) was inserted into the left ventricle to record left ventricular end systolic pressure (LVESP), left ventricular end diastolic pressure (LVEDP), maximal rate of left ventricular systolic pressure over time (dP/dt_{max}), minimal rate of left ventricular diastolic pressure over time (dP/dt_{min}) and heart rate. Coronary flow was measured by a flow probe which was placed in line with perfusion line. Data was recorded using a Powerlab Station acquisition system (ADInstruments, Grand Junction, CO) every 5 min during the baseline and reperfusion.

Determination of Infarct size: At the end of the experiments, the left ventricle of the hearts were sectioned into 2 mm thick slices that were subjected to 1% triphenyltetrazolium chloride (TTC) staining to detect infarcted (unstained) and viable (stained brick red) area. Infarct size was expressed as the percentage of infarcted tissue weight to the total tissue weight.

Statistical Analysis: All data in the figures are presented as means ± S.E.M. The data was analyzed by analysis of variance using post hoc analysis with Fisher's PLSD test. $p<0.05$ are considered to be statistically significant.

Results

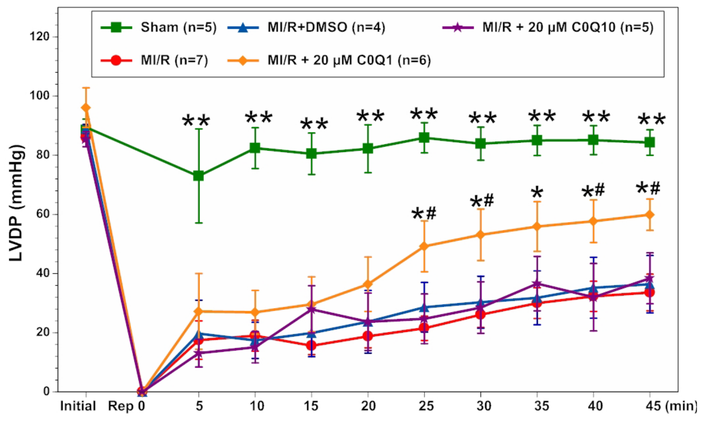


Figure 3. Time course of LVDP for Sham, MI/R, MI/R+ DMSO, MI/R + 20 μM CoQ1, MI/R + 20 μM CoQ10 groups. LVDP is the difference between LVESP and LVEDP. Control MI/R and MI/R + DMSO exhibited significantly lower post-reperfused LVDP compared to the Sham. By contrast, application of 20 μM CoQ1 significantly improved post-reperfused LVDP, which was significantly higher compared to the untreated MI/R controls and the effects of 20 μM CoQ10 treatment. (* p< 0.05, ** p< 0.01 vs. MI/R and MI/R + DMSO; # p< 0.05 vs. MI/R + 20 μM CoQ10)

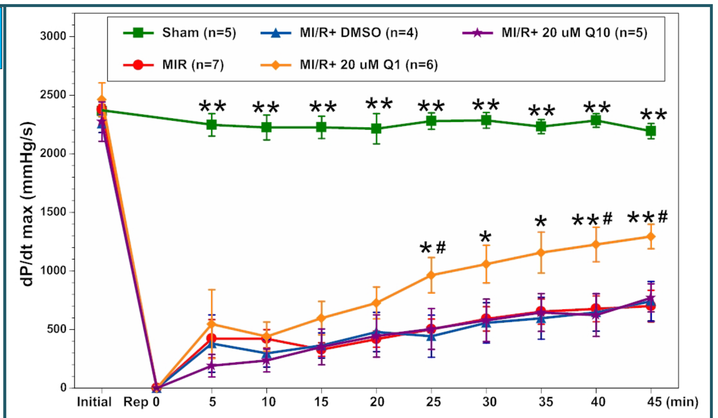
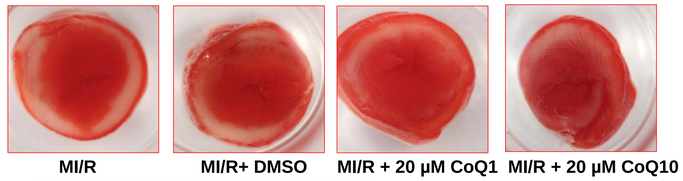


Figure 4. Time course of dP/dt_{max} for Sham, MI/R, MI/R+ DMSO, MI/R + 20 μM CoQ1, MI/R + 20 μM CoQ10 groups. Control MI/R and MI/R + DMSO exhibited significantly lower post-reperfused dP/dt_{max} compared to the Sham. By contrast, application of 20 μM CoQ1 significantly improved post-reperfused dP/dt_{max}, which was significantly higher compared to the untreated MI/R controls and the effects of 20 μM CoQ10 treatment. (* p< 0.05, ** p< 0.01 vs. MI/R and MI/R + DMSO; # p< 0.05 vs. MI/R + 20 μM CoQ10)



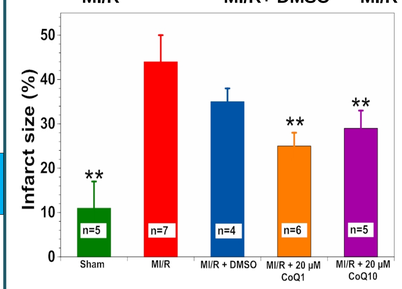


Figure 5. The representative TTC staining pictures and summarized infarct size graph for experimental groups. Sham, CoQ1, and CoQ10 groups exhibited significantly lower infarct size compared to the MI/R group. (** p< 0.01 vs. MI/R)

Conclusions

Our results indicate that CoQ1 was more effective than CoQ10 in restoring post-reperfused cardiac contractile function, but not infarct size during MI/R. These differences may be attributed to CoQ1's stronger antioxidant effects.

References

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Acknowledgements

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