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The effect of coenzyme Q10 on endothelial function in a young population

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Objective: Coenzyme (CoQ10) is an enzymatic co factor used in normal cellular metabolism. Recent evidence shows that in people with heart disease it can reverse endothelial cell damage in the blood vessels. It is also a potent antioxidant.
Design: One group pretest-posttest design.
Methods: In the present study, endothelial function was evaluated using the response to occlusion and heat before and 2 weeks after administration of CoQ10, 300 mg/day. Thirty Eight subjects, who are physical therapy students, participated in a series of experiments to see if taking 300 mg of CoQ10 daily for 2 weeks would impact resting blood flow in the forearm skin and the blood flow response to 4 minutes of vascular occlusion and the response to local heat (42°C) for 6 minutes.
Results: The results showed that, for this population, there was no difference in the response to heat. However, the response to occlusion was improved after administration of CoQ10.
Conclusions: It would appear that in a young population CoQ10 has no effect on the nitric oxide vasodilator pathway in skin but does influence other vasodilator pathways.

Key Words: Blood flow, Circulation, Flow mediated dilation, Q10, Vitamins

Introduction

The importance of neutralizing free radicals for health has been the subject of numerous papers in the last 30 years. Free radicals are commonly produced and neutralized in the body [1]. Some free radicals are produced and used for cellular communication, and others are produced as a natural product of cellular metabolism [2-5]. For example, nitric oxide is released from mitochondria and vascular endothelial cells to increase circulation in the tissue [4].

Older adults have lower levels of antioxidant enzymes [6] and are therefore more susceptible to injury from pro-oxidant challenges [7]. Thus, especially in older individuals, the production of free radicals at rest and during exercise can cause significant damage to tissue leading to an inflammatory response to exercise [1,7,8].

When free radicals reach a critical level, rather than increasing blood flow, they biodegrade nitric oxide and prostacyclin into inactive forms. In the presence of free radicals such as hydrogen peroxide, nitric oxide is reduced to peroxynitrite (ONOO) afree radical with no influence on circulation [9]. Bioconversion of nitric oxide to peroxynitrite is believed to be one of the mechanisms associated with the reduction in circulation at rest and during stress in older people and people with diabetes [9].

The first paper suggesting that high free radicals may damage tissue appeared in 1978 [10,11]. From this time, in parallel with papers quantifying damage to tissue by free radicals, the hunt was underway to find dietary supplements that may prevent this damage [12]. A number of studies have

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been conducted on antioxidants that might reduce free radicals and hence be protective of blood flow in the myocardium and other organs in the body [13,14]. Coenzyme Q10 (CoQ10) supplementation reduces free radicals in the blood as assessed by superoxide dismutase and malondialdehyde (MDA) [13]. Since free radicals are strongly associated with cardiovascular disease and diabetes [15-17], natural foods or vitamins might reduce free radicals [15-17]. In addition to disease, later papers have shown that free radicals may also impair exercise performance [18]. Many different vitamins and additives have been investigated to reduce free radicals in the blood [12,19,20]. Recently there has been great interest in CoQ10. CoQ10 is an electron acceptor that allows pyruvic acid to enter the mitochondria. It is also the first hydrogen acceptor in oxidative phosphorylation. Pharmaceuticals like Lipitor deplete Q10 and cause atrophy of muscle and muscle cramps and weakness [21]. But recent evidence shows that it is also a potent anti-inflammatory which can reduce inflammation and endothelial damage after a heart attack and may even reduce inflammation from exercise [12]. Some reviews feel that it is an ergogenic agent that prevents the loss of muscle strength during exercise and increases endurance by absorbing free radicals in muscle during exercise [12,22].

One source of free radicals, as cited above, is the ingestion of dietary fat [23-25]. Previous studies in this lab have shown that even the ingestion of a single high fat meal can, in some races, impair blood vessel (endothelial) function [26-28]. Endothelial function was measured in previous studies in 2 ways. A classic way is the response to vascular occlusion [9]. This involves placing an occlusion cuff over the arm for 4 minutes at the axilla and then, after pressure is removed, noting the blood flow response for a period of 2 minutes. It is the gold standard for assessing endothelial function. Another measure of endothelial function is the skin response to local heat [9,29-32]. When heat is applied to the skin, there is an increase in blood flow mediated by two different mechanisms. Initially, tactile neurons in the skin release substance P and calcitonin gene related peptide when the skin is exposed to local heat [33,34]. This causes an increase in potassium permeability in vascular smooth muscle surrounding the endothelial cell [22,33,35]. Relaxation of vascular smooth muscle then increases blood flow. But this response only lasts a few minutes. The sustained response to increasing temperature in the skin is mediated by transient receptor potential vanilloid type-4 (TRPV-4) voltage gated calcium channels in the vascular endothelial cells [36-39]. Above a temperature of 35^{o}C, these cells cause an exponential increase in calcium influx into the endothelial cell from the interstitial space. Calcium activates the enzyme nitric oxide synthase producing endothelial nitric oxide [40]. Nitric oxide, a potent vasodilator, diffuses into the surrounding smooth muscle activating cyclic guanosine monophosphate which in turn increases potassium permeability and relaxes vascular smooth muscle [22,33,41-43]. In a previous study, we have shown that both responses are increased in young people with intake of a mixture of antioxidants for 2 weeks. In the present investigation, we expanded these studies. A single antioxidant was tested-CoQ10. It was administered for 2 weeks and then the effect of endothelial function was assessed.

Methods

Subjects

Thirty eight subjects participated in the experiments. Subjects were of similar age, not taking alpha blockers, beta blockers, alpha agonists or antagonists, or any other medication that would affect peripheral blood flow. They were not taking calcium channel blockers or any pain medications. All subjects were vitamin naïve for at least a month prior to the beginning of this study. No subjects were smokers. All subjects were physical therapy students at Azusa Pacific University with similar levels of activity. All methods and procedures were approved by the Institutional Review Board of Azusa Pacific University. All subjects signed a statement of informed consent. The demographics of the subjects are shown in Table 1.

Methods

Measurement of skin temperature

Skin temperature was measured with a thermistor (SKT RX 202A) manufactured by BioPac systems (BioPac Inc., Goleta, CA, USA). The thermistor output was sensed by an SKT 100 thermistor amplifier (BioPac Inc.). The output, which was a voltage between 0 and 10 volts, was then sam-

Table 1. Demographics of the subjects (N=38)

	Age (yr)	Height (cm)	Weight (kg)	BMI
Mean (SD)	24.2 (2.6)	170.4 (9.0)	67.3 (13.1)	23.0 (2.7)

BMI: Body Mass Index.

pled with an analog to digital converter at a frequency of a 1,000 samples per second with a resolution of 24 bits with a BioPac MP150 analog to digital converter. The converted data was then stored on a desk top computer using Acknowledge 4.1 software for future analysis. Data analysis was done over a 5 second period for mean temperature. The temperature was calibrated at the beginning of each day by placing the thermistors used in the study in a controlled temperature water bath which will be calibrated against a standard thermometer.

Measurement of skin blood flow

Skin blood flow was measured with a Moor Laser Doppler flow meter (VMS LDF20, Devon, UK). The imager uses a red laser beam (632.8 nm) to measure skin blood flow using the Doppler effect. After warming the laser for 15 to 30 minutes prior to use, the laser was applied to the skin through a fiber optic probe placed above the forearm (Figure 1). The probe was a VP12B. The Moor Laser Doppler flow meter measures blood flow through most of the dermal layer of the skin but does penetrate the entire dermal layer. Blood flow is then calculated in a unit called Flux based on the red cell concentration in red cell velocity with a stated accuracy of ±10%. The tissue thickness sampled is typically 1 mm in depth.

Control of skin temperature

Skin temperature was controlled by a Moor temperature controller (SHO2) with an SHO2-SHP1 skin temperature module which integrated with the blood flow fiber optic probe also shown in Figure 1. This is a closed loop electric warmer (thermode) where temperature is controlled to 0.1 degrees C.

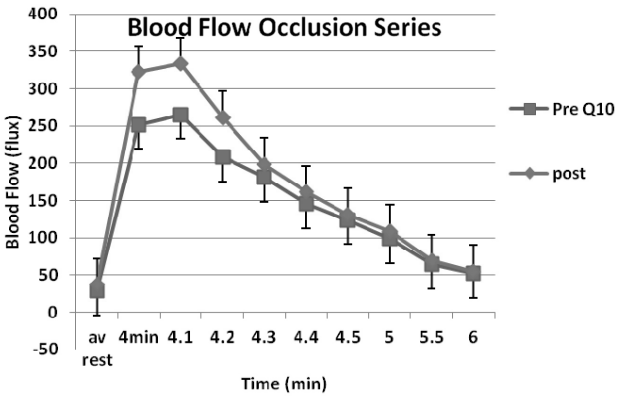

Figure 1. Illustrated here is the blood flow response of the skin at rest and for 2 minutes after vascular occlusion. Data represents the mean of 38 subjects before and after 2 week administration of Q10 ± the standard deviation.

Measurement of endothelial function

Endothelial function was measured by arterial occlusion. The blood flow to the arm was occluded for 4 minutes by placing a pneumatic occlusion cuff on the upper arm under the axilla and inflating the cuff for 4 minutes. After the pressure was released, forearm blood flow was measured for 2 minutes to assess the reactivity of the blood vessels to occlusion and anoxia.

Measurement of the response to heat

The response of the skin to heat was measured by applying the heated probe to the skin for 6 minutes. The thermode was set at a temperature of 44 degrees centigrade. This warmed the skin and blood flow was then recorded.

Procedures

Subjects were interviewed for inclusion and exclusion criteria. Those subjects that were eligible were placed into the studyand read and signed a statement of informed consent. Next, subjects rested for 15 minutes while height and weight were taken. Baseline skin blood flow was recorded for 1 minute over the forearm. After this period of time, the thermode was applied upon the arm above the brachioradialis muscle to warm the skin to 44^{o}C. The thermode was left on for 6 minutes. On another day, occlusion was applied by a blood pressure occlusion cuff inflated to 200 mmHg for 4 minutes followed by 2 minutes of additional blood flow recording. Skin temperature at this site was measured throughout the experimental period. Each experiment took approximately 10 minutes and was performed on 2 separate days. The experiments were repeated but after subjects had administered 300 mg/day of CoQ10 for 2 weeks.

Statistical analysis

Data was summarized as Means and standard deviations. Baseline characteristics of Caucasians and Asians were compared using ANOVA. A mixed factorial ANOVA was conducted to compare the blood flow response to 4 minutes of vascular occlusion and 6 minutes of local heat before and after two different meals with or without vitamins in Koreans and Caucasians. Also, a paired t-test was conducted

to compare the MDA concentration before versus after the meals with or without vitamins. The level of significance was set at p=0.05.

Results

Figure 1 shows the results of the measurement of skin blood flow after 4 minutes of vascular occlusion in the subjects. As seen here, for all subjects, there was a rapid increase in skin blood flow after the occlusion cuff was released. Blood flow peaked about 10 seconds after the occlusion was released and then fell exponentially during the 2 minutes post occlusion time period that blood flow was measured. There was a difference in the subjects between the pre and post Q10 administration. Before the group had Q10 administered, the peak blood flow was lower than after the administration of Q10 as shown in Figure 1. While the blood flow was only higher in the first half minute after the occlusion was released, these data were significantly higher in the post Q10 group compared to the pre Q10 subjects ($p < 0.05$). For the last 1.5 minutes post occlusion, there was no difference between the groups. However, the total impact of the administration of Q10 is best seen in the excess blood flow post occlusion. Excess blood flow is the total blood flow in excess of rest during the 2 minutes post occlusion [44,45]. The total blood flow after occlusion pre Q10 was 143±62 ml whereas after administration of Q10 it was 173±45 ml. This amounted to an increase of 20.3%. This increase was significant ($p < 0.01$).

The response to heat was different. There was no difference in the rate of rise of skin temperature (Figure 2) or the blood flow response to heat (Figure 3) before and after administration of Q10.

Discussion

Anti-oxidants have been under investigation for a number of years in terms of their ability to work as ergogenic agents to improve exercise performance and to reverse and prevent cardiovascular diseases and endothelial dysfunction. For heart patients, Q10 has shown great promise in older individuals with cardiovascular disease [26,46]. Other studies have shown that it may be an ergogenic agent to increase exercise performance since free radicals may reduce muscle strength and endurance [12,47]. In older individuals where free radicals normal increase with the ageing process, Q10 has been shown to increase blood flow and improve the cardiovascular system as well as increase basil metabolism [14,48,49]. Q10 has been shown to reverse endothelial dysfunction in diabetic patients, especially those taking statins [50,51]. However, little has been done on a younger population with no pathologies.

In the present investigation, we examined the blood flow in the skin during 2 stressors, the response to occlusion, the gold standard for evaluating endothelial function [34], and the response to heat [34]. Resting blood flow was unaffected by Q10 for 2 weeks. Data presented here support the hypothesis that the response to occlusion is increased after Q10 administration. However, the response to heat was not altered, at least in this population of young subjects.

The response to heat is mediated largely by nitric oxide re-

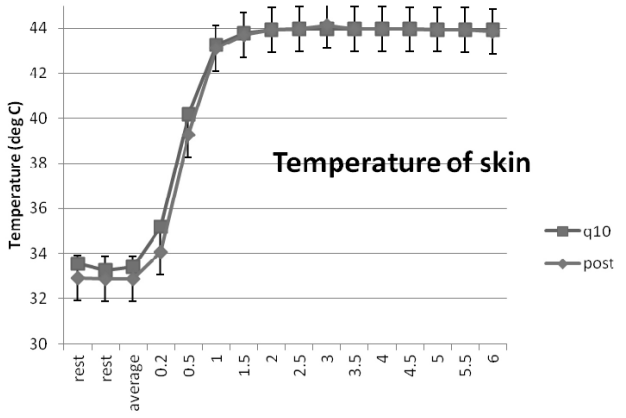

Figure 2. Illustrated here is the temperature response of the skin at rest and for 6 minutes after exposure to a 44 degree C thermode. Data represents the mean of 38 subjects before and after 2 week administration of Q10 ± the standard deviation.

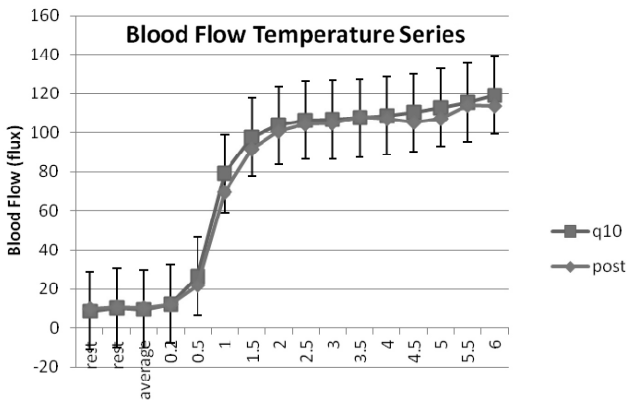

Figure 3. Illustrated here is the blood flow response of the skin at rest and for 6 minutes after skin heating with a 44 degree C thermode. Data represents the mean of 38 subjects before and after 2 week administration of Q10 ± the standard deviation.

leased form vascular endothelial cells [14,34,41,49]. The enzyme, nitric oxide synthetase is activated by intracellular calcium that moves from the extracellular compartment through TRPV-4 temperature sensitive voltage gated calcium channels [52]. In this population, this mechanism does not seem to be altered by Q10. Since this pathway is sensitive to the concentration in free radicals in the cell, it does seem that Q10 did not alter this pathway in a significant way [14]. This may be due to low concentrations of free radicals in young healthy people. In older people, Q10 may have a strong effect on blood flow. However, this is not the case for the response to occlusion.

The response to vascular occlusion was increased significantly after the administration of Q10 for only 2 weeks. This blood flow increase after occlusion is not mediated entirely via the nitric oxide pathway [53]. Other pathways are involved such as prostacyclin [53]. For large arteries, blood flow increases are mediated by shear receptors that use a prostaglandin intermediate to increase activity of nitric oxide synthetase and is linked to the activation of PI3K [52,53]. For smaller arteries, nitric oxide plays a smaller role and the flow mediated response, as seen here, is due also to the release of prostacyclin and endothelial derived relaxation factors [54].

Q10 has been shown to be useful in reducing cardiovascular disease [46]. It has been shown to increase resistance to low density lipids and reduce lipid peroxidation in cells [55]. In a recent study, Q10 has been shown to reduce neuronal cell death by activating the PI3K pathway in neurons [52]. PI3K is one of the main intracellular factors responsible for the transmission of signals in the cell and used in multiple pathways. It is also a key step in oxidative phosphorylation in the inner mitochondrial membrane. Defects in oxidative phosphorylation have been linked to neurological disease [7,9,49]. The PI3K pathway mediates the movement of glucose into the cell and is also activated by insulin [56]. It is possible that the increased response to occlusion in the subjects after Q10 administration is linked to activation of the PI3K signaling pathway which directly increase tissue blood flow. The effects of Q10 on vascular function, while established, are usually investigated in relation to pathology such as reduced vascular response following administration of statins [50,57]. In younger individuals, short term administration of Q10 has little effect on exercise performance [57]. In the present investigation, we did see a change in blood flow after Q10 administration for the response to occlusion. However, to our knowledge, this is the first study showing short term administration effects on the response to vascular occlusion. Further investigation is needed.

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