Effect of Vitamin E on Cardiac Dysfunction Induced by Short-Term Starvation

Protocol of thesis
Submitted in partial fulfillment of Master Degree
In
Basic Medical Science (Physiology)

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Introduction:

Adult humans often undertake acute fasts for cosmetic, religious and medical reasons as an approach to control body weight ***(Johnstone, 2007)***. Although weight reduction diets are well documented in reducing the severity of coronary heart disease risk factors, such as dyslipidemia and hypertension, data from patients receiving starvation diets have reported hypotension and sudden death ***(Ahmed et al., 2001)***. In addition, the incidence of typical and atypical angina was found to be surprisingly high among patients with anorexia nervosa (***Birmingham et al., 1999***).

Following short-term starvation, ***Ayobe et al. (1992)*** reported that cardiac dysfunction in the form of attenuation of inotropic reserve in response to β-adrenergic stimulation, together with reduction in the coronary flow rate.

Increased oxygen free radicals could play an important role in development of dysfunction of starved hearts. Experimental studies have shown that short-term starvation decreased the endogenous free radical scavenging defense mechanisms in rat hearts ***(Wohaieb and Godin, 1987)***. Recently, ***Hamilton*** (***2007***) reported that enhancing oxidant-scavenging capacity would

protect against some of the cardiac disturbance and help salvage of myocardial tissue during ischemia reperfusion.

Aim of work

The aim of this work is to elucidate the effect of the potent antioxidant vitamin E (α-tocopherol) on the cardiac performance in short-term starved rats.

Site of research

Physiology Department, Faculty of Medicine - Ain Shams University.

Experimental protocol

Animals: The study is performed on 30 female Wistar rat.

Animal models: Short-term starvation is achieved by complete food deprivation for 6 days, with free access to water. Animals are allocated into the following groups:

1) Normally-fed control group.
2) Short-term starved group.
3) Vitamin E-supplemented starved group.

Experimental procedure

All rats will be subjected to the following interventions:

1) Evaluation of body weight: Including initial and final body weights as well as the body mass index (BMI).
2) Recording of ECG.
3) In vitro studying of isolated hearts in modified Langendorff preparation, including:

   a- Study of intrinsic activity of heart under basal conditions.

b- Study of responses to β-adrenergic stimulation.

c- Study of responses to global ischemia followed by reperfusion.

Assessment of cardiac activity will be performed by recording the following parameters: Heart rate, peak developed tension, time to peak tension, half relaxation time, and myocardial flow rate.

4) Measurement of cardiac weights.

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Introduction

Total fasts are undertaken for religious reasons and for treatment of obesity. Extreme degrees of food restriction in non-obese are a consequence of starvation in famine, prisoners of war, and in victims of hunger strike. Food restriction is the only known invention that reduces the incidence and severity of the age-related diseases and retards physiological decline associated with aging. However, food restriction was shown to increase circulating levels of catecholamines.

In the opinion of the **Fogerty Task Force**, total starvation is recommended as a line of treatment to patients with severe obesity in whom weight loss appears to be vital. This form of treatment has several advantages over the traditional slower calorie restricted diets.

However, in all the above-mentioned states several cardiovascular complications of starvation have been reported. These include among others cardiac arrhythmias; and decreased thyroid activity, and even sudden death has been reported.

There is little knowledge regarding the precise effect of food restriction and starvation on the intrinsic myocardial function. Therefore a study of the function of the heart and its response to circulating catecholamines is worthy being done.

Aim of the work

Disturbance of cardiac function amounting to arrhythmia and sudden death, are problems mandating extreme caution with the use of total starvation in the management of obese patients.

The aims of the present study were to investigate the effects of total fasting on cardiac intrinsic function and to determine the value of using vitamin E, an endogenous antioxidant that could have a potential clinical value in the management of cardiac dysfunction induced by starvation.

REVIEW OF LITERATURE

Adult humans often undertake acute fasts for cosmetic, religious (as in Ramadan fast) and medical reasons as an approach to control body weight.

In disease states as anorexia nervosa rhythm disturbance, hypotension and bradycardia were noticed; also anorexia nervosa causes decrease in the heart dimensions ***(Gottdiener et al., 1978)***. Loss of weight in anorexia nervosa is associated with significant morbidity and mortality much involving the cardiovascular system was noticed. Physiologic consequences of anorexia nervosa include rhythm disturbances, systolic and diastolic ventricular dysfunction ***(Schocken et al., 1989)***. In addition, the incidence of typical and atypical angina was found to be surprisingly high among patients with anorexia nervosa (***Birmingham et al., 1999***),

Although weight reduction diets are well documented in reducing the severity of coronary heart disease risk factors, such as dyslipidemia and hypertension, data from patients receiving starvation diets have reported hypotension and sudden death ***(Ahmed et al., 2001)***.

Data on hunger strike revealed many adverse events including even death in rare circumstances. Ventricular fibrillation is the major cause of death in those people subjected to prolonged starvation ***(Altun et al., 2004).***

Prolonged use of very low calorie weight reduction regimens consisting entirely or largely of protein caused death due to ventricular arrhythmia ***(Sours et al., 1981)***. The major concern following the use of starvation or semistarvation diets for weight reduction in severely obese people has been the reports of sudden death due to ventricular arrhythmia ***(Fisler, 1992)***.

Siem et al., (1995) showed that ECG made after being off a very low caloric diet taken by women revealed sinus bradycardia which was the most common abnormality. Also, ST-T wave abnormalities and prolonged QTc were observed in some cases.

Most medical complications resulting from starvation can be reversed with a well-planned refeeding program. A potentially catastrophic treatment complication is the **refeeding syndrome**, which may result in cardiovascular collapse ***(Mehler, 1996)***, arrhythmia, tachycardia, congestive heart failure, and sudden cardiac death ***(Casiero and Frishman, 2006)***.

Regarding myocardial metabolic changes during starvation, increased lipid content in the rabbit myocardium occurring at fasting provides the heart with the energy substrate required to preserve its contractile function ***(Nepomniashchikh et al., 1979)***. Studies by ***Crescimanno et al., (1989)*** showed that high myocardial loads of free fatty acid induced by 3-day periods of food deprivation in mice involved

the peroxisomal enzymes in the β-oxidation process. This resulted in increased production of hydrogen peroxide which could be partly responsible for myocardial injury caused by fasting.

The heart is known for its ability to produce energy from fatty acids because of its important β-oxidation equipment, but it can also derive energy from several other substrates including glucose, pyruvate, and lactate ***(Grynberg and Demaison, 1996)***.

During fasting, when overall metabolism changes, the contribution of glucose and fatty acids to cardiac energy production alters as well. ***Van der Lee et al.,(2001)*** studied the effect of 46 hours fasting in rats; they found that the adult rat heart responds to change in nutritional status, through adjustment of glucose as well as fatty acids metabolism at level of gene expression. Meanwhile, food restriction did not significantly change the pattern of cardiac energy utilization of isolated, isovolumically beating hearts ***(Klebanov et al., 2002)***.

Experimental studies showed that fasting in female Wistar rats leads to decrease of the diffusion distance between the capillary and the cardiomyocyte for metabolites and thus improving cellular energy supply and offering a relative protection of the metabolism in malnourished myocyte ***(Vandewoude, 1995)***.

Fasting was also reported to elevate myocardial glycogen in rats ***(Poland et al., 1982).*** This high glycogen level may be beneficial to the ischemic heart by providing glycolytic ATP or detrimental by increasing intracellular lactate and protons ***(Cross et al., 1996).***

Impaired cardiac function due to high plasma concentration of free fatty acids was reported by ***Hammer et al., (2008);*** this could be due to caloric restriction which induces a dose dependent increase in myocardial triglycerides content and a dose dependent decrease in diastolic function in lean healthy men.

Free fatty acids may contribute to myocardial dysfunction and are proarrhythmic, and their oxidation requires more oxygen than does glycolysis ***(Pilz and März, 2008).*** However an earlier report by ***Wang et al., (1979)*** showed that fasted male students for 66 hours had elevated plasma free fatty acids without inducing arrhythmias.

Han et al., (2004) showed that after brief periods of fasting (4 and 12 hours) in murines, there was selective loss of long-chain polyunsaturated fatty acids which altered the physical properties of the myocardial membranes; on the other hand, there was no decrease in triacylglycerol mass in the myocardium during fasting. These results demonstrate the dramatic alteration in the membrane composition of mildly fasted mammalian myocardium that identifies the unanticipated

plasticity of myocardial phospholipids to adapt to modest chemical and physical perturbations.

Cicogna et al., (2000) demonstrated that food restriction for 60 days does not alter blood pressure in spontaneously hypertensive rats and causes no more mechanical changes in the hypertrophied myocardium than in the normal heart. Although food restriction has a tendency to attenuate the cardiac hypertrophy in the spontaneously hypertensive rats, the myocardial function is minimally affected, presenting only a lengthening in time to peak tension.

Chang et al., (2001) showed that food restriction in rats for 6 months prevented the reduction in myocardial contractility that occurred between 18 and 24 months of age in ad libitum fed rats. However, food restriction did not affect the age-related changes in ventricular internal resistance. Also, food restriction preserves the ventricular function in any aging heart, maintaining normal blood flow essential for the metabolic needs of tissues and/or organs.

In Wistar-kyoto (WKY) rats subjected to different periods of food restriction (30, 60, and 90 days) had altered cardiac performance. While food restriction for 30 days produces disparate effect on myocardial performance, food restriction for 60 and 90 days prolongs the contraction period. Also, food restriction for 90 days increased time from peak