

Featured research

Abstracts and commentaries

Ischemia/reperfusion-induced death of cardiac myocytes: possible involvement of nitric oxide in the coordination of ATP supply and demand during ischemia

Kawahara K, Hachiro T, Yokokawa T, Nakajima T, Yamauchi Y, Nakayama Y. *J Mol Cell Cardiol.* 2006; 40:35–46.

Nitric oxide has been shown to have various functional and pathological roles as an intracellular and intercellular messenger in the heart. In particular, it has been suggested recently that production of NO represents one paracrine/autocrine mechanism coordinating energy supply and demand in tissues [1]. Normal myocardium generates more than 90% of its ATP by oxidative metabolism and less than 10% by anaerobic glycolysis. This means that ischemic cardiac myocytes must drastically reduce ATP demand or utilization to meet the needs for survival, and thus balance reduced ATP supply with reduced demand during severe ischemia. The activity of the enzyme nitric oxide synthase (NOS), which produces nitric oxide from arginine, is stimulated by ischemia and it has also been shown that the activated NOS produces nitric oxide after the onset of ischemia. In this study using cultured neonatal rat cardiac myocytes, the authors investigated whether nitric oxide produced during ischemia was involved in the coordination of ATP supply and demand.

Commentary

In all experiments, cell viability was analyzed 24 h after the start of reperfusion, because delayed death of cardiac myocytes could be observed long after the ischemic insult in some cases. Unexpectedly, the survival rate of myocytes after 24 h of reperfusion after 3 h of simulated ischemia was increased compared with that after 2 h of simulated ischemia. This meant that, as the duration of the ischemia increased, the survival of cardiac myocytes increased. Investigation of the metabolic status of cardiac myo-

cytes during simulated ischemia led to the observation that the cellular concentration of ATP 3 h after the start of simulated ischemia was increased compared with that at 2 h, and was almost the same as that before the start of ischemia. Either the inhibition of NOS activity which produces nitric oxide, or the scavenging of nitric oxide during ischemia for 3 h resulted in the significant decrease in cellular ATP. These results suggested that nitric oxide produced during ischemia was involved in the preservation of cellular ATP. To investigate the possible implication of NOS-derived nitric oxide in the preservation of cellular ATP and in the protection from reperfusion-induced cell death, cultured cells were pretreated with NOS inhibitors or nitric oxide modulators (ie, donors or scavengers). Results obtained after each of these treatments indicated that nitric oxide produced during ischemia by NOS was crucially involved in the coordination of cellular ATP supply and demand, in addition to survival rate. Mechanisms that may be responsible for the nitric oxide induced decrease in ATP utilization by cardiac myocytes during ischemia are currently unknown, and further studies will be needed to clarify this. It is important to note here that the experimental conditions used in this study are far from situations obtained in vivo, because ischemia was simulated in cultured cardiac myocytes. However, these data are of interest in that they point to a critical role of myocardial nitric oxide production, and probably nitric oxide dependent signaling, in balancing energy supply and demand during ischemia, and therefore in protecting cardiac cells from ischemia/reperfusion injury.

REFERENCE

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Danielle Feuvray

Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial

Howard BV, Van Horn L, Hsia J, et al. *JAMA*. 2006;295:655–666.

Several epidemiologic studies and some trials have linked diet with prevention of cardiovascular disease (CVD), but long-term intervention data are needed. We tested the hypothesis that a dietary intervention, intended to be low in fat and high in vegetables, fruits, and grains to reduce cancer, would reduce CVD risk. This was a randomized controlled trial (clinical trials registration: ClinicalTrials.gov Identifier: NCT00000611) in 48 835 postmenopausal women aged 50–79 years, of diverse backgrounds and ethnicities, who participated in the Women's Health Initiative Dietary Modification Trial. The women were randomly assigned to an intervention (19 541 [40%]) or control group (29 294 [60%]) in a free-living setting. Study enrollment occurred between 1993 and 1998 in 40 US clinical centers; mean follow-up in this analysis was 8.1 years. Participants underwent group and individual sessions of intensive behavior modification designed to reduce total fat intake to 20% of calories and increase intakes of vegetables/fruits to 5 servings/day and grains to at least 6 servings/day. The comparison group received diet-related education materials. Fatal and nonfatal coronary heart disease (CHD), fatal and nonfatal stroke, and CVD (composite of CHD and stroke) were the main outcome measures. By year 6, mean fat intake decreased by 8.2% of energy intake in the intervention group compared with the control group, with small decreases in saturated (2.9%), monounsaturated (3.3%), and polyunsaturated (1.5%) fat; increases occurred in intakes of vegetables/fruits (1.1 servings/day) and grains (0.5 serving/day). Low-density lipoprotein cholesterol concentrations, diastolic blood pressure, and factor VIIc concentrations were significantly reduced, by 3.55 mg/dL, 0.31 mm Hg, and 4.29%, respectively; concentrations of high-density lipoprotein cholesterol, triglycerides, glucose, and insulin did not significantly differ in the intervention and control groups. The numbers who developed CHD, stroke, and CVD (annualized incidence rates) were 1000 (0.63%), 434 (0.28%), and 1357 (0.86%) in the intervention and 1549 (0.65%), 642 (0.27%), and 2088 (0.88%) in the control group, respectively. The diet had no significant effects on incidence of CHD (hazard ratio [HR] 0.97; 95% confidence interval [CI] 0.90 to 1.06), stroke (HR 1.02; 95% CI 0.90 to 1.15), or CVD (HR 0.98; 95% CI 0.92 to 1.05). Excluding participants with baseline CVD (3.4%), the HR (95% CI) values for CHD and stroke were 0.94 (0.86 to 1.02) and 1.02 (0.90 to 1.17), respectively.

Trends toward greater reductions in CHD risk were observed in those with lower intakes of saturated fat or trans fat or greater intakes of vegetables/fruits. Over a mean of 8.1 years, a dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of CHD, stroke, or CVD in postmenopausal women and achieved only modest effects on CVD risk factors, suggesting that more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk.

Commentary

This clinical trial is significant in that it involved the random allocation to groups of more than 19 000 postmenopausal women to a diet low in fat and high in fruits, vegetables, and grains. The control group of non-dieters involved 29 000 women, bringing the total number of study participants to 48 835. Also impressive was the 8.1-year period of analysis. As a result, this study is the largest clinical trial yet performed that examined the role of dietary intervention on the risk of developing cardiovascular disease. Somewhat disappointing, however, is that the study found that dietary intervention that reduces total fat intake and increased intake of vegetables, fruits, and grains did not significantly reduce the risk of coronary heart disease (CHD). The incidence of myocardial infarctions, CHD deaths, revascularization, stroke, and total cardiovascular deaths was not significantly different between the dietary intervention group and the non-dieters, regardless of whether the data analyzed were from all participants or from participants without a history of cardiovascular disease (CVD). The authors conclude that “to achieve a significant public health impact on cardiovascular events, a greater magnitude of change in multiple macronutrients and micronutrients and other behaviours that influence CVD disease risk factors may be necessary.” However, this statement also hints at one of the significant weaknesses of the study. The original goal of the study was to have 20% calories from fat in the dietary intervention group and 40% of calories from fat in the non-dieters. This, unfortunately, was not achieved and, 6 years into the study, the dietary intervention group was obtaining 29% of calories from fat, while the non-dieters were obtaining 37% of calories from fat. While replacing saturated fatty acids with polyunsaturated fatty acids may also benefit CVD, 6 years into the study the difference in polyunsaturated fatty acid intake was minimal between the dietary intervention group (6.1%) and the non-dieting group (7.5%). This minimal difference in fat intake may have contributed to the relatively small trends toward reduction in CHD risk in individuals

with lower saturated fat intake or greater intake of vegetables/fruits. Finally, this study is part of the Women's Health Initiative, which was examining whether dietary intervention can decrease the incidence of breast cancer in women. It therefore does not provide any insights into whether dietary intervention can decrease the incidence of CHD in men. As a result, the jury is still out as to the potential benefits of a low fat diet on the risk of developing CHD.

Gary Lopaschuk

Cardiac efficiency and oxygen consumption measured with ^{11}C -acetate PET after long-term cardiac resynchronization therapy

Lindner O, Sorensen J, Vogt J, et al. *J Nucl Med.* 2006;47:378–383.

Cardiac resynchronization therapy (CRT) is a treatment option in patients with severe heart failure and left bundle-branch block (LBBB). This study evaluated the effects of 4 and 13 months of CRT on myocardial oxygen consumption (mVO_2) and cardiac efficiency as compared with patients with mild heart failure without LBBB. Sixteen patients with severe heart failure and LBBB as a result of idiopathic cardiomyopathy were studied at baseline and after 4 and 13 months of treatment. Thirteen patients with mild heart failure without LBBB served as a control group. The clearance rate (k_2) of [^{11}C]acetate was measured with positron emission tomography (PET) to assess mVO_2 . Stroke volume was derived from the dynamic PET data according to the Stewart–Hamilton principle; cardiac efficiency was calculated using the work metabolic index. After 4 months of CRT, stroke volume index (SVI) increased by 50% ($P = 0.012$) and cardiac efficiency increased by 41% ($P < 0.001$). Global k_2 remained unchanged, but regional k_2 demonstrated a more homogeneous distribution pattern. The parameters showed no significant changes during treatment. Under CRT, cardiac efficiency, SVI, and the distribution pattern of regional k_2 did not differ from those in patients with mild heart failure without LBBB. We conclude that CRT improves cardiac efficiency for

at least 13 months, as demonstrated by a greater SVI, whereas mVO_2 remains unchanged. Cardiac efficiency, SVI, and the pattern of distribution of mVO_2 reach values observed in patients with mild heart failure without LBBB. The unfavorable hemodynamic performance in heart failure with LBBB is effectively restored by long-term CRT, to the level of an earlier disease state.

Comments

Resynchronization therapy is a relatively new treatment for patients with heart failure. Implantation of a biventricular pacemaker results in improved exercise tolerance, quality of life, and symptoms, reduces left ventricular volumes, and improves prognosis. The mechanisms underlying this improvement are partly understood. Studies have shown that the improvement is closely related to the effect of resynchronization of the left ventricular contraction and that cessation of biventricular pacing immediately results in deterioration of contraction. Conversely, prolonged biventricular pacing may result in chronic reverse remodeling, with sustained improvement in cardiac volumes.

In the present study, the authors studied oxygen consumption and volumes of the heart – using [^{11}C]acetate PET imaging – before resynchronization therapy and 4 and 13 months thereafter. The results showed that, in patients, stroke volume increased over time, whereas oxygen consumption remained unaltered. From these data the authors calculated cardiac efficiency, which is defined by the amount of oxygen used given a certain amount of cardiac work (in this study the product of heart rate, stroke volume, and blood pressure). The cardiac efficiency increased significantly from baseline to 4 months and showed a trend to further improvement at 13 months. The values of oxygen consumption were almost normal at 13-month follow-up. Thus cardiac oxidative metabolism and function show sustained improvement after biventricular pacemaker implantation in patients with heart failure.

Frans C. Visser
