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EFFECT OF TIVORTIN ON CARDIOMYOCYTE CELLS AND ITS ROLE IN MYOCARDIAL INFARCTION

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Abstract

The L-arginine-nitric oxide (NO) pathway plays an important role in ischemia-reperfusion injury. In the present study we investigated the role of NO-precursor L-arginine on cardiac and pulmonary function after reversible hypothermic ischemia. Twelve anesthetized dogs underwent cardiopulmonary bypass. After 60 minutes of hypothermic cardiac arrest, reperfusion was started with application of either saline vehicle (control, n = 6) or L-arginine (40 mg/kg i.v. bolus then 3 mg/kg i.v. infusion during the first 20 minutes of reperfusion, n = 6). The vasodilative response to acetylcholine was significantly higher in the L-arginine group ($P < 0.05$). The preload recruitable stroke work of the left ventricle decreased significantly after reperfusion, however remained unchanged in the L-arginine group. Arterial blood gas analysis did not show any difference between the two groups. Plasma L-arginine concentration reached peak level at 20 minutes of administration (675.0 ± 66.6 versus 207.7 ± 14.5 in the L-arginine group, $P < 0.05$) and returned to baseline at 40 minutes, while in the control group remained unchanged during ischemia and reperfusion (276.2 ± 71.6 versus 283.8 ± 38.5, $P < 0.05$). Plasma nitrite concentration followed L-arginine changes parallel, however nitrate levels increased slower. Supplementation with L-arginine during reperfusion prevents myocardial and endothelial dysfunction, however does not have any overriding effect on pulmonary function. Considerably rapid elimination of plasma L-arginine was demonstrated during early reperfusion.

Ischemia-reperfusion injury following cardiac surgery is a common condition, which develops after cardiopulmonary bypass (CPB) operations with cardioplegic arrest. Moreover, temporary dysfunction of the heart can be observed frequently, presumably as a consequence of this phenomenon. Even if cardiac dysfunction is not always clinically remarkable, reduction of myocardial contractility may occur. [1,2] In addition, during CPB there is very little or no blood flow through the pulmonary artery, which may impair pulmonary function or lead to increase of the pulmonary vascular resistance. [3] Extracorporeal circulation is also known to induce systemic inflammatory reaction [4–6] with free radical release, leading to secondary organ injury (ie, in gastrointestinal tract). [7]

Several studies reported that the L-arginine-nitric oxide (NO) pathway plays an important role in ischemia-reperfusion injury. The cardiac NO production is based on the coronary endothelium, cardiac

myocytes, and endocardial cells using oxygen and L-arginine. Nitric oxide plays an important role among others in autoregulatory modulation of coronary blood flow, inhibition of neutrophil-endothelial interaction, and platelet aggregation. However, besides the physiological role (reviewed recently by many authors [8–10]), the pathophysiologi-cal significance of NO still remains unclear. It is shown that NO has a beneficial effect by increasing postischemic blood flow, [11,12] decreasing leukocyte adhesion and expression of cell adhesion molecules, moreover has antioxidative effect. [13] On the other hand some reports are present about the harmful effects of NO during ischemia and reperfusion, presumably due to its direct negative inotropic action or the inhibition of mitochondrial respiration or formation of peroxynitrite. [14,15]

In the present study we investigated the role of NO precursor L-arginine on ischemia-reperfusion injury when applied systemic after reversible deep hypothermic ischemia. The time course of blood L-arginine and NO oxidation products—nitrite and nitrate—were characterized, and compared with the changes of cardiac and lung functions as well as to vascular resistance of the coronary artery.

Oxidative stress conditions associated with atherosclerosis leads to oxidative modification of low-density lipoprotein (LDL). The body's capabilities to inhibit LDL oxidation and to remove or neutralize the atherogenic oxidized LDL (ox-LDL) are limited. When the LDL cholesterol level increases in the blood, it leads to dangerous consequences like atherosclerosis, leading to myocardial infarction. The major effect of an antioxidant in the LDL environment is to prevent the formation of ox-LDL (during atherogenesis. Strategies to reduce LDL oxidation and prevent atherogenesis can involve the enrichment of arterial cells with potent antioxidants that can prevent oxidative damage to the arterial wall. The objective of this study is to evaluate the effect of L-arginine on serum lipid and cholesterol levels in the patients of acute myocardial infarction (AMI). The study consisted of 70 AMI patients and 60 healthy individuals (serving as control) age 55–65 years. Serum levels of total cholesterol, high density lipoprotein (HDL), LDL and Triglycerides were determined on day 1 and day 15 of L-arginine administration (oral dose 3 g/day). The total cholesterol/HDL and the LDL/HDL ratio were calculated and compared. As per the observations, L-arginine administration was found to improve the lipid profile of the subjects. Hence it could be used as an adjuvant therapy for AMI and as a preventive measure for the onset of the disease in the healthy elderly also.

BACKGROUND

Myocardial ischemia followed by reperfusion results in endothelial dysfunction characterized by a reduced release of endothelium-derived relaxing factor (EDRF). Because EDRF has been characterized as nitric oxide, we examined the ability of L-arginine, the substrate for nitric oxide synthesis, to protect in a feline model of myocardial ischemia plus reperfusion.

METHODS AND RESULTS

The effects of L-arginine were investigated in a 6-hour model of myocardial ischemia and reperfusion in pentobarbital-anesthetized cats. A bolus administration (30 mg/kg) of L-arginine, or its enantiomer D-arginine, was given followed by a continuous infusion of 10 mg/kg/min for 1 hour starting 10 minutes before reperfusion. Myocardial ischemia plus reperfusion in cats receiving D-arginine resulted in severe myocardial injury and endothelial dysfunction characterized by marked myocardial necrosis, high cardiac myeloperoxidase activity in ischemic cardiac tissue, and loss of acetylcholine- and A-23187-induced endothelium-dependent relaxation in coronary artery rings. In contrast, myocardial ischemia plus reperfusion cats treated with L-arginine exhibited a reduced area of cardiac necrosis (16 +/- 2% versus 41 +/- 5% of area at risk, p less than 0.01), lower myeloperoxidase activity in the ischemic region (0.3 +/- 0.08 versus 0.8 +/- 0.10 units/100 mg tissue, p less than 0.05), and significant preservation of acetylcholine- (p less than 0.01) and A-23187- (p less than 0.01) induced endothelial-dependent relaxation.

CONCLUSIONS

These results demonstrate the ability of L-arginine to reduce necrotic injury in a cat model of myocardial ischemia plus reperfusion, and this reduction in infarct size is associated with the preservation of endothelial function and attenuation of neutrophil accumulation in ischemic cardiac tissue.

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