ASYMMETRIC DIMETHYLARGININE (ADMA) INDUCES VASCULAR ENDOTHELIUM IMPAIRMENT AND AGGRAVATES MYOCARDIAL ISCHEMIA-REPERFUSION INJURY IN RATS

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Asymmetric dimethylarginine (ADMA) is a naturally occurring inhibitor of nitric oxide (NO) synthesis that accumulates in a variety of diseases associated with endothelial dysfunction and enhanced atherosclerosis. Thus ADMA, which was identified as circulating in human plasma at concentration ten times that of N^G-monomethyl-L-arginine, is considered the most important regulator of the L-arginine/NO pathway *in vivo*
This study investigated whether ADMA (10 mg/kg day for 14 days) affected endothelial function and aggravated post-ischemic ventricular dysfunction in the perfused rat heart. Systolic blood pressure and heart rate, plasma levels of ADMA and nitrite/nitrate were measured in vehicle- and ADMA-treated rats. Perfused hearts were submitted to global ischemia-reperfusion and vascular endothelial dysfunction was examined with angiotensin II in coronary vessels and aortic rings. Endothelial NO synthase (eNOS) and angiotensin-converting enzyme (ACE) mRNA expression in aortic and cardiac tissues were measured. ADMA-treated rats had higher systolic blood pressure (1.3-fold, $P<0.01$) and slower heart rate (16%, $P<0.05$) than controls. Plasma ADMA rose (1.9-fold, $P<0.01$) and nitrite/nitrate concentration decreased 59% ($P<0.001$). Ventricular contraction (stiffness) increased significantly, with worsening of post-ischemic ventricular dysfunction. In preparations from ADMA-treated rats the coronary vasculature's response to angiotensin II was almost doubled ($P<0.01$) and the maximal vasorelaxant effect of acetylcholine in aortic rings was significantly lower than in preparations from vehicle-treated rats. In cardiac and aortic tissues eNOS mRNA and ACE mRNA levels were similar in controls and ADMA-treated rats. The increased plasma levels of ADMA presumably cause endothelial dysfunction because of a deficiency in NO production, which also appears involved in the aggravation of myocardial ischemia-reperfusion injury.