

**Adams JA, Wu D, Bassuk J, Arias J, Lozano H, Kurlansky P, Lamas GA. Nitric oxide synthase isoform inhibition before whole body ischemia reperfusion in pigs: Vital or protective? Resuscitation 2007;74:516-25**

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**BACKGROUND:** Nitric oxide (NO) is a critical regulator of vascular tone, and signal transduction. NO is produced via three unique synthases (NOS); endothelial (eNOS), and neuronal (nNOS) are both constitutively expressed and inducible (iNOS) produced primarily after stimulation. NO has been implicated during and after ischemia reperfusion injury as both a detrimental and cardioprotective mediator. Since cardiopulmonary resuscitation (CPR) in ventricular fibrillation (VF) is a model of whole body ischemia reperfusion injury, it provides an opportunity to assess the effects of NO from the three NOS isoforms. **OBJECTIVE:** To determine the differential role of nitric oxide synthase isoforms inhibition in ventricular fibrillation CPR and investigate whether inhibition of the NOS isoforms afford any cardioprotection in this model. **METHODS:** Thirty-two pigs, weight range 25-35 kg, were assigned to four groups of eight animals each. The animals were randomized to receive (1) N(G)-nitro-L-arginine methyl ester (LNAME), a non-selective endothelial nitric oxide synthase inhibitor, (2) 1-(2-trifluoromethylphenyl) imidazole (TRIM), a selective neuronal NOS inhibitor, (3) aminoguanidine (AMINOG), a selective inducible NOS inhibitor or (4) saline control (Control) in equal volumes, 30 min before induction of ventricular fibrillation (VF). After 3 min VF with no intervention, the animals received standard chest compressions using an automated chest compression device (Thumper) for 15 min. After 18 min of VF, single doses of vasopressin and bicarbonate were given and defibrillation attempted. Hemodynamics, regional blood flows, and echocardiography and were performed, before and after drug infusion, during CPR, and after return of spontaneous circulation (ROSC). **RESULTS:** ROSC for 3 h occurred in 5/8 (63%), 1/8 (13%), 0/8 (0%), and 6/8 (75%) in Control, LNAME, TRIM, and AMINOG treated animals, respectively. After infusion of LNAME, there was a significant increase from baseline in blood pressure [127 $\pm$ 6 mmHg versus 169 $\pm$ 3 mmHg,  $p < 0.002$ ] and coronary perfusion pressure [119 $\pm$ 6 mmHg versus 149 $\pm$ 6 mmHg,  $p < 0.003$ ]. During CPR, there were no differences among groups in hemodynamics or regional blood flow. In surviving animals, AMINOG had significantly better myocardial function (left ventricular ejection fraction, fractional shortening, and wall motion score index) than control or LNAME treated animals, and attenuated the post-resuscitation hyperemic response in heart and brain. **CONCLUSIONS:** Intact basal nNOS activity is vital for survival from whole body ischemia reperfusion injury. iNOS inhibition prior to ischemia reperfusion, protects myocardial function after ROSC and decreases myocardial and brain hyperemic response after ROSC.