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The purpose of the present study was to identify the roles of the three nitric oxide synthase (NOS) isoforms on whole body ischemia-reperfusion injury during cardiopulmonary resuscitation (CPR) with periodic acceleration (pGz) in pigs. Thirty-two anesthetized pigs (27.6±3.4 kg) were monitored for hemodynamics and selected echocardiographic variables. Twenty minutes after NOS inhibition or placebo administration, ventricular fibrillation (VF) was induced and remained untreated for 3 min, followed by CPR with pGz for 15 min, plus 3 min of manual chest compressions and defibrillation attempt. Four groups were studied: (1) saline control; (2) L-NAME (non-selective NOS inhibitor); (3) aminoguanidine (inducible NOS inhibitor); (4) TRIM (neuronal NOS inhibitor). Return of spontaneous circulation (ROSC) to 180 min occurred in 6/8 controls, 4/8 L-NAME, 7/8 aminoguanidine, and 2/8 TRIM animals. The L-NAME group had significantly lower organ blood flow, impaired cardiac function, but higher vascular tone than control group. The aminoguanidine group had the highest organ blood flows and survival rate. Six out of eight TRIM treated animals had initial return of heartbeat; however, with impaired heart contractility and could not survive more than 20 min of ROSC. This study reveals the differential role of endogenous NO produced from the three NOS isoforms during pGz-CPR. Both endothelial and neuronal NOS derived NO show predominantly protective effects while inducible NOS derived NO plays a detrimental role in pGz-CPR. The present study has shown that cardiac arrest and resuscitation appears to be associated with a different expression of NOS isoforms which appear to affect resuscitation outcomes differently.