

CRITICAL SPLANCHNIC ARTERY HYPOPERFUSION CAUSES IRREVERSIBLE HYPODYNAMIC SHOCK BY INTESTINAL ENKEPHALIN-INDUCED INCREASE OF PLASMA NITRIC OXIDE LEVELS

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The old hypothesis that (critical) splanchnic artery hypoperfusion is the factor of hemodynamic irreversibility during all advanced systemic shock states has yet to be demonstrated. Splanchnic artery occlusion-reperfusion (SAO) shock models cannot give, in this regard, suitable and conclusive information, and discouraging clinical results have been obtained with drugs blocking a series of mediators thought to play a leading role in hemodynamic shock states of different etiology (e.g. antioxidant compounds, nonselective opioid receptor antagonists and nitric oxide [NO] synthase [NOS] inhibitors, antiinflammatory drugs).

In the present study, barbiturate-anesthetized male New Zealand rabbits developed irreversible hypodynamic shock and metabolic acidosis (with death occurring within 240-300 minutes) when the superior mesenteric artery was critically hypoperfused at 25-20% of its baseline mean blood flow. A series of hemodynamic and hematochemical parameters were monitored including systolic, diastolic and mean blood pressure, heart rate, positive and negative dP/dt, stroke volume, arterial blood flow as well as arterial and venous pO₂, pCO₂ and pH. The observed cardiovascular changes did not involve catecholamines, angiotensin II, bradykinin (BK), adenosine, acetylcholine, serotonin and histamine, and were not prevented or reversed by non-steroidal antiinflammatory drugs (e.g. fenoprofen) or corticosteroids (e.g. hydrocortisone). Shock induction and irreversibility were indeed due to increased plasma levels of leu⁵- and met⁵- enkephalins (ENKs, determined by HPLC), which appeared to be released by the intestine. ENKs in turn increased NO (determined as L-citrulline by HPLC) in the systemic circulation. Such NO increase was the consequence of ENK-induced activation of the cardiovascular δ -opioid receptors, inhibition of kininase II activity (with consequent kininase I-mediated higher availability of BK-derived C-terminal L-arginine for NO synthesis in the endothelium), and increase of iNOS activity. Only selective δ -opioid receptor blockers (ICI 174864, naltrindole) and/or iNOS inhibitors (AMT, \pm 2-amino-5,6-dihydro-6-methyl-4H-1,3-thiazine, HCl) were able to improve the shock condition and/or prevent its progression to irreversibility (by restoring cardiac output more than by improving heart rate and vascular tone). These findings may have important therapeutical implications for the management of circulatory shock conditions.