**CYSTATHIONINE-GAMMA-LYASE: A NOVEL THERAPEUTIC TARGET IN TREATING SEPTIC SHOCK**

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Hallmark of septic shock is profound vasodilation and hypotension, as a result of markedly impaired vasoregulation, microcirculatory dysfunction, shunting, and critical organ hypo-perfusion. A proposed mechanism causing this pathophysiologic phenomenon is endothelial cell (EC) activation and dysfunction mediated by mediators like reactive oxygen species and nitric oxide (oxidative / nitrosative stress). Hydrogen sulfide (H2S), generated by cystathionine-gamma-lyase (CSE) in ECs, has been identified as an Endothelial Derived Hyperpolarization Factor, which mediates its effects by, a novel redox-sensitive posttranslational modification, sulfhydration. We hypothesized that sepsis up-regulates H2S/CSE to cause vasoplegia, hypotension and organ hypoperfusion. We used a cecal ligation puncture model (CLP) to induce sepsis in WT and CSE-/- mice. We measured CSE activity, vascular reactivity, hemodynamics (blood pressure (BP) and heart rate (HR)), and survival. CSE activity is significantly reduced in control CSE-/- vs. control WT mice. CSE activity is significantly increased in CLP WT vs. control WT mice, but not in CLP CSE-/- mice. Vasoconstriction to alpha-1 agonist phenylephrine is significantly impaired in WT CLP mice but is unaffected by CLP in CSE-/- mice. While BP is not significantly depressed in CLP WT mice, HR is markedly elevated, a phenomenon not observed in CSE-/- mice. Finally CLP CSE-/- have significantly improved survival compared to their CLP WT cohort. CSE activity and H2S production is induced in sepsis contributing to vasoplegia and cardiovascular compromise. Knockout of CSE protects against sepsis induced vascular dysfunction, cardiovascular compromise, and improves survival. Thus CSE may be a critical target in treatment of septic shock.