S28-5 Endothelial and inducible NO synthase in septic shock: Potential therapeutic usefulness of statins

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Septic shock and sequential multiple organ failure remain the leading causes of death in critically ill patients, with an unacceptably high mortality rate. In sepsis, microvascular dysfunction with reduced perfusion and oxygen would result in tissue hypoxia and, ultimately, in the development of organ failure. Vascular endothelium plays a key role in the regulation of tissue perfusion by releasing vasoactive mediators, including nitric oxide (NO), and endothelial injury/dysfunction at macro- and microcirculation levels may lead to the development of multiple organ failure in sepsis. In endotoxin-challenged septic rabbit model and in a cecal ligation and puncture-induced polymicrobial septic mouse model, we found that expression and phosphorylation of endothelial NO synthase (eNOS) were significantly impaired in vascular tissues. The diminished phosphorylated level of eNOS in septic vessels was associated with the impaired PI3-K/Akt pathway. As expected, sepsis induction markedly increased inducible NO synthase (iNOS) expression in vascular tissues. This increase was NF-κB dependent, because it was strongly prevented by in vivo transfection of NF-κB decoy oligonucleotides. Statins, which are well established in the treatment of lipid disorders, restored sepsis-induced eNOS changes in association with the recovery of Akt phosphorylation, and improved survival in sepsis. Thus, it is important to avoid the pathological events associated with endothelial injury during sepsis, and statins may be potentially useful for therapy of sepsis.