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Calpain-1 inhibitor prevent loss of dystrophin in experimental septic cardiomyopathy induced by cecal ligation and puncture (CLP)

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Evidences from our laboratory demonstrated that cytosolic calcium overload caused increase activation of intracellular calcium-dependent proteases, such as calpain-1 resulting in sarcolemal dystrophin disruption in severe sepsis induced by CLP in mice.

This study was designed to determine the hypothesis that N-Acetyl-L-leucyl-L-leucyl-L-norleucinal (ALLN), calpain-1 inhibitor, could attenuate dystrophin disruption and cardiac contractile proteins loss/reduction in experimental sepsis induced by CLP. Male C57Bl/6 mice were subjected to sham and severe septic injury (SSI) induced by CLP. Half of animals from each group were treated with ALLN (3mg/kg, SSI+ALLN; SH+ALLN) 4hs after surgery. In SSI+ALLN mice reduced amounts of myocardial calpain-1 were associated with increased actin/myosin expression as compared to SSI mice. Additionally, ALLN treatment of septic mice significantly prevented loss of dystrophin and β-dystroglycan as compared to SSI mice. Concurrently, SSI+ALLN mice presented an increased survival rate.

Calpain inhibitor, ALLN, suppressed the increased calpain-1 expression and prevented myocardial structural injury caused by experimental severe sepsis. These observations reinforce the concept that calpain-1 activation represents a key target in dystrophin disruption behind cardiac dysfunction in severe sepsis/septic shock. Further studies are needed to elucidate this mechanism that may provide new interventional pathways to prevent septic cardiomyopathy.

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