Cardioprotective and functional effects of levosimendan and milrinone in mice with cecal ligation and puncture-induced sepsis

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Abstract

***Background*:** Levosimendan, and milrinone may be used in place of dobutamine to increase cardiac output in septic patients with a low cardiac output due to impaired cardiac function. We examined the effects of the two inotropic agents on cardiac inflammation and left ventricular (LV) performance.

***Methods*:** Polymicrobial sepsis was induced by cecal ligation and puncture (CLP) in BALB/c mice.

***Results*:** Septic mice displayed significant cardiac inflammation, as indicated by highly increased mRNAs of pro-inflammatory cytokines and increased staining of myeloperoxidase, an index of neutrophil infiltration, in ventricular myocardial tissues. When these agents were continuously given, levosimendan prevented but milrinone exaggerated cardiac inflammation. However, both levosimendan and milrinone significantly reduced the elevations in plasma cardiac troponin-I and heart-type fatty acid-binding protein, clinical markers of cardiac injury, suggesting that they retain the cardioprotective properties. Echocardiographic assessment of cardiac function showed that the effect of levosimendan, given by an intravenous bolus injection, on LV

performance was impaired in CLP mice compared with sham-operated controls, whereas milrinone produced inotropic responses equally in sham-operated and CLP mice. Similarly, a lesser effect of levosimendan on LV performance in the CLP group was also found in spontaneously beating Langendorff-perfused hearts *ex vivo*. In ventricular myocytes isolated from both CLP mice and sham-operated controls, levosimendan, but not milrinone, caused a large increase in the L-type calcium current.

***Conclusions*:** This study represents that, while both levosimendan and milrinone are cardioprotective against septic cardiac injury, they provide different advantages and drawbacks to cardiac inflammation and LV dysfunction in sepsis.

***Keywords*:** Cardiac inflammation, Cardiac injury, Cardioprotection, Inotropic agentLeft ventricula function, L-type calcium current, Polymicrobial