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Critical role IL-37 to ameliorate endotoxemic cardiac depression in aging mice: a critical role of suppression cardiodepressant cytokines

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Purpose: Aging exaggerates myocardial injury caused by sepsis and up-regulated the expression of cytokines. IL-37 is an anti-inflammatory cytokine, mice with transgenic expression of IL-37 are protected against endotoxic shock, exhibiting reduced lung and kidney damage. We tested the hypothesis that IL-37 protects the aging heart against endotoxemic cardiac depression via suppression of myocardial inflammatory responses. Methods: WT and IL-37 transgenic (tg) mice, males of adult (4-6 months) and aging (18-20 months), were treated with endotoxin (E. coli 011:B4; 0.5 mg/kg i.v.). Left ventricular (LV) function was measured with a pressure-volume microcatheter at 1-6 h after injection. Plasma and myocardial tissue homogenate were prepared for analysis of MCP-1, TNF-α and IL-1β by ELISA. Results: Endotoxin caused greater depression of LV function in WT aging mice, TNF-α and IL-1β in comparison to WT adult mice. Aging IL-37Tg mice had improved ejection fraction and cardiac output after LPS injection that were associated with lower myocardial levels of cytokines. To determine the role of MCP-1 in myocardial production of TNF-α and IL-1β, as well as in LV dysfunction, we treated WT aging mice with MCP-1-neutrlizing antibody and found that neutralization MCP-1 reduced myocardial TNF-α and IL-1β levels and improved LV function. Conclusions: Endotoxemia results in worse LV functional injury in aging WT mice. MCP-1 plays an important role in mediating the production of cardiac depressant cytokines and resultant LV dysfunction. IL-37 improves LV function in aging mice during endotoxemia through suppression of myocardial production of MCP-1 and cardiodepressant cytokines. Thus, IL-37 has the therapeutic potential for cardiac protection in the elderly against functional injury associated with major surgeries.

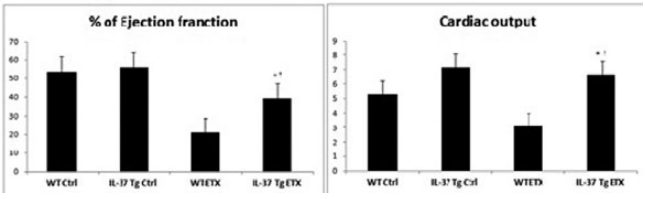

Figure: Aging IL-37 Tg mice LV function