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## Novel Mechanisms of Ischemic Injury and Repair

# Abstract 1062: A Single Intracoronary Injection of Midkine Reduces Ischemia/reperfusion Injury in Swine Hearts: A Novel Therapeutic Approach for Acute Coronary Syndrome

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**Background:** Several growth factors were shown to be effective for salvaging viable

myocardium and limiting infarct size in experimental studies using small animals, but their benefit in large animals and feasibility in clinical practice remains to be elucidated. In this study, we investigated the cardioprotective effect of midkine (MK), a heparin-binding growth factor, in swines subjected to ischemia/reperfusion (I/R).

**Methods and Results:** I/R was created in pigs under anesthesia by coronary (LAD) occlusion for 45 min using a percutaneous over-the-wire balloon catheter. MK protein (200 microg) was injected as a bolus through the catheter at the initiation of reperfusion, and the consequences were assessed 24h thereafter (MKT, n=9). Saline was injected in controls (CONT, n=12). MKT showed a significantly higher survival rate than CONT (89% vs. 67%), and smaller infarct size/area at risk ( $8.1 \pm 6.0\%$  vs.  $38.6 \pm 6.8\%$ ,  $P < 0.01$ ). Echocardiography in MKT revealed a significantly higher percent wall thickening of the interventricular septum ( $17.6 \pm 6.7\%$  vs.  $10.7 \pm 3.3\%$ ), a higher % fractional shortening ( $27.1 \pm 4.0\%$  vs.  $22.4 \pm 3.0\%$ ) and a lower  $E/e'$  ( $9.8 \pm 3.3\%$  vs.  $14.2 \pm 4.6\%$ ) compared with CONT ( $P < 0.05$ ). LV catheterization in MKT showed a lower LVEDP ( $8.4 \pm 2.6$  mmHg vs.  $11.9 \pm 2.8$  mmHg,  $P < 0.05$ ), and a higher  $dP/dt_{max}$  ( $1843 \pm 242$  mmHg/s vs.  $1259 \pm 402$  mmHg/s,  $P < 0.05$ ) compared with CONT. Western blotting of LV tissue (periinfarct zone) from MK showed an increased activation of ERK-1/2 (phosphorylated fraction:  $73 \pm 19.4\%$  vs.  $44 \pm 20.3\%$ ,  $P < 0.05$ ) and a higher expression of Bcl-2 compared with CONT.

**Conclusions:** A single intracoronary injection of MK protein to pigs at the commencement of reperfusion dramatically reduced infarct size, mortality and systolic/diastolic LV dysfunction, and this beneficial effect was associated with a stimulation of antiapoptotic signals. These results suggest that MK application during percutaneous coronary intervention could be a next promising adjunctive therapy of acute coronary syndrome.