Calpain Inhibition Decreases Ischemia-Reperfusion Induced Pulmonary Hypertension and Cardiopulmonary Dysfunction by Decreasing Endothelin-1 in Neonates

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Objective:
Cardiopulmonary bypass (CPB) in infants and children can result in cardiopulmonary dysfunction through ischemia-reperfusion unjury. Inhibition of calpain, a cysteine protease, has been shown to inhibit reperfusion injury. The hypothesis is that calpain inhibition can alleviate cardiopulmonary dysfunction after reperfusioin in neonates.

Methods:
Crossbred piglets (5-7 kg) were cooled on CPB to 18° C followed by deep hypothermic circulatory arrest (DHCA) for 120 min. Animals were re-warmed to 37° C on CPB, and maintained for 120 min. Six animals were administered calpain inhibitor (*carbobenzoxy-leucinyl-leucinyl-tyrosine-flurormethyl ketone*; 1mg/kg, IV) 120 min. prior to CPB. Nine animals were administered saline as a control. Plasma endothelin-1 levels were measured by enzyme-linked immunosorbent assay.

Results:
Calpain inhibition prevented the increase in pulmonary vascular resistance (PVR) compared with controls (95.7 ± 39.4 vs. 325.3 ± 83.6 dyne•s/cm5, respectively; $p<0.06$). This decrease was associated with reduced plasma endothelin-1 levels (4.91 ± 1.72 after calpain inhibition vs. 10.66 ± 6.21 pg/mL in controls, $p<0.05$). Pulmonary function 120 min. after reperfusion was improved with calpain inhibition compared with controls; PO2/FiO2 ratio (507.2 ± 46.5 vs. 344.7 ± 140.5, respectively; $p<0.05$) and alveolar-arterial gradient (40.0 ± 17.2 vs. 128.1 ± 85.2 mm Hg, respectively; $p<0.05$). In addition, oxygen delivery was increased with calpain inhibition compared to controls (759 ±171 vs. 277 ± 46 mL/min., respectively; $p<0.001$).

Conclusions:
Calpain inhibition resulted in decreased endothelin-1 and an associated reduction in pulmonary vascular resistance. Improved gas exchange and cardiopulmonary function suggests that calpain inhibition may be advantageous in alleviating post-operative cardiopulmonary dysfunction commonly associated with neonatal cardiopulmonary bypass.