In vivo and *in vitro* toxicity of cobalt in the heart.

Sarunya Laovitthayanggoon[1], Catherine J. Henderson[1], Rothwelle J.Tate[2], Susan Currie[2] Claire McCluskey[2], Margaret MacDonald[2] and M. Helen Grant[1]

[1]Department of Biomedical Engineering, and [2] Strathclyde Institute of Pharmacy & Biomedical Sciences, University of Strathclyde, Glasgow G4 0NW, United Kingdom (sarunya.laovitthayanggoon@strath.ac.uk)

Wear debris from cobalt/chromium (Co/Cr) alloy metal-on-metal bearings in prosthetic hip replacements has created a significant internal source of cobalt exposure in these patients. Co toxicity is suspected to contribute to severe systemic adverse effects, including cardiac and CNS effects, in patients with high circulating Co concentrations. This study investigated the effects of chronic Co exposure to rats (1mg/kg i.p. $CoCl_2$, daily, for 28 days) and Co uptake into primary adult rat cardiac fibroblasts (CFs). Co treatment was associated with accumulation into various organs of the body and significant increases in Co levels were detected in liver, kidney and heart. Echocardiography showed functional changes that correlated with compromised cardiac contractility. Fractional shortening was significantly reduced in $CoCl_2$-treated rats following 28 days treatment compared to the control group (54.01±0.90% and 60.29±0.53% respectively), providing evidence of contractile dysfunction. Cellular studies examined uptake of $CoCl_2$ into both CFs and 3T3 fibroblasts using inductively coupled plasma mass spectrometry (ICP-MS) to measure intracellular metal content. The range of Co uptake increased proportionally (0-50 µg/L) for the 3T3 cells, as well as for the CFs (about 0-120 µg/L) when the $CoCl_2$ concentration in the medium was increased between 0 and 72 mg/L. Uptake of Co into CFs was significantly greater than into 3T3 cells. The greater accumulation of $CoCl_2$ into CFs suggests Co ions in vivo could accumulate in these cells, leading to functional consequences on cardiac performance. Future work will focus on determining the underlying uptake mechanism which could have important therapeutic implications.