Cobalt cardiotoxicity - effects on the contractile and non-contractile cells of the heart

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Exposure to cobalt is known to cause cardiotoxicity and a common source of cobalt exposure is from metal-on-metal bearings used in prosthetic joint replacements. Acute and chronic effects of cobalt at a cellular level in the heart are not well understood. This study investigated the effects of cobalt ($CoCl_2$) treatment on contractile and non-contractile cells of the heart. We have used isolated adult rat ventricular papillary muscles to investigate the effects of $CoCl_2$ on basal and isoprenaline-stimulated contractile responses. In addition, we used freshly isolated primary adult rat ventricular fibroblasts maintained in short-term culture to assess the effects of $CoCl_2$ on cell viability and proliferation. Stimulation of isolated ventricular papillary muscles with the positive inotrope isoprenaline (1uM) resulted in a consistent increase (~35% increase) over the basal contractile response as expected. Following treatment with $CoCl_2$ (1uM) for 4h, there was a dramatic reduction in both the basal and isoprenaline-stimulated contractile responses (both~40% reduction). This effect was not due to a time-dependent decrease in contractility since in separate parallel control preparations consistent increases in contraction were observed following 1uM isoprenaline challenges at time zero and after 4h without $CoCl_2$. Examination of the effects of $CoCl_2$ on cardiac fibroblast proliferation and viability was performed using a range of assays. To assess effects on proliferation, MTT, neutral red and crystal violet assays were all used to compare effects of increasing concentrations of $CoCl_2$ on the Swiss 3T3 fibroblast cell line and primary cardiac fibroblasts. Over 72h, increasing $CoCl_2$ concentrations (up to 500uM) resulted in decreased proliferation. The MTT and Crystal violet assays showed the most reproducible results with IC50 values for $CoCl_2$ in the range of ~300uM. Interestingly, further experiments using BrdU incorporation to assess proliferation suggested that cardiac fibroblasts were more sensitive to $CoCl_2$ treatment than Swiss 3T3s. In the former, after either 48h or 72h there was ~80% reduction in proliferation with 25uM $CoCl_2$ and almost no proliferation following 100–150uM $CoCl_2$. Cell viability in increasing concentrations of $CoCl_2$ (up to 500uM) was assessed using CFDA and propidium iodide staining. The ratio of live:dead cells decreased dramatically with increasing $CoCl_2$. Phalloidin-FITC was also used to examine cell viability and structure following treatment. With increasing $CoCl_2$ there was evidence for increased disruption of actin filaments. In conclusion, short-term low dose $CoCl_2$ treatment of ventricular preparations results in compromised contractile function. Treatment of non-contractile cardiac fibroblasts with higher concentrations results in decreased ability of cells to proliferate as well as long-term cell damage and death. It is likely that the cardiotoxic effects of $CoCl_2$ are manifest in both contractile and non-contractile cells of the heart. The underlying cellular mechanisms involved have yet to be established.