238 **RAT PLASMA EXOSOMES ARE CARDIOPROTECTIVE**

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Background The restoration of blood and oxygen to ischaemic myocardium under threat of infarction is of paramount importance, but reperfusion paradoxically exacerbates injury (IR injury). Exosomes are extracellular, lipid bilayer vesicles that range from 30 to 100nm in diameter. Exosomes released from *in vitro* cultured stem cells have been shown to be cardioprotective. Exosomes are also present in the blood of healthy individuals, but their properties are unknown. We hypothesized that plasma exosomes have cardioprotective properties.

Aim To characterize the circulating exosomes of healthy rats, and to determine whether they protect against IR injury in HL-1 cardiac cells, in a Langendorff isolated, perfused rat heart model, and in an *in vivo* rat model of IR injury.

Methods and Results Exosomes were isolated from rat plasma using the standard ultracentrifugation protocol. Their identity as exosomes was confirmed by their typical diameter of 87±2 nm measured by nanoparticle tracking analysis, their typical-shape morphology by electron microscopy, and by their expression of exosome marker proteins CD63 and HSP70. An average concentration of $2.5\pm1.1\text{x}10^{11}$ exosomes per ml of rat plasma was measured (N=5 rats). Similar results were obtained with human exosomes.

After in vitro IR injury, 21±5% of HL-1 cells remained alive. Addition of exosomes increased survival to 49±6%. Control perfused rat hearts subject to IR had infarct sizes of 35±3 % (N=6). Perfusion with purified exosomes significantly reduced infarct size after IR to 23 ±2 % (N=10,P<0.01). In the in vivo model, i.v. injection of exosomes reduced infarct size from 47±4 % to 24±11 % (N=3-6, P<0.01).

Conclusion This is the first data showing that circulating endogenous exosomes from healthy rats are capable of conferring cardioprotection. This contrasts with data suggesting larger microvesicles in the blood are detrimental to the cardiovascular system. Disease states which alter exosome number might potentially alter innate cardiac resistance to IR injury. Possible mechanisms will be discussed.