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THE EFFECT OF SUB PHYSIOLOGICAL OXYGEN ON PRO ANGIOGENIC POTENTIAL OF CARDIOSPHERE DERIVED CELLS (CDCS)

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Background Pre-clinical and clinical studies have applied cardiosphere derived cells (CDCs) as a source of stem cells to the injured heart, with the aim of rescuing cardiac function following myocardial infarction (MI). These stem cells, cultured from heart tissue biopsies, are usually prepared at atmospheric oxygen levels (20%) prior to delivery. We hypothesised that pre-conditioning in low oxygen (3%) would prepare the transplanted cells for survival in the hypoxic environment of the ischemic heart and could improve their pro-angiogenic potential.

Methods and Results We used mouse heart tissue as a source of CDCs and characterized them based on the expression of endothelial and stem cell markers. We also confirmed the cellular response to hypoxia by monitoring HIF-1α protein expression and induction of vascular endothelial growth factor (VEGF) expression. The effect of hypoxia on the expression of several stem cell markers (Sca1, c-Kit and Abcg2) was analysed using qPCR (quantitative PCR) and FACS (fluorescent activated cell sorting). We found that hypoxia treatment resulted in higher levels of the mesenchymal stem cell marker Sca-1 and Abcg2 in CDCs, although there was no significant change in the expression of c-Kit. These results indicate the potential benefit of hypoxia on increasing some aspects of the 'stemness' of cardiac progenitor cells, which could improve outcomes following cell transplantation post MI. To evaluate the potential ability of CDCs to promote angiogenesis in vivo, GFP labelled CDCs were mixed with matrigel, and injected as a subcutaneous plug in adult mice. Immunohistochemical analysis of the plug after 14 days revealed that although most CDCs were not retained in the matrigel plugs, there was an increase in angiogenesis, indicated by increased CD31 expression (in comparison to the group which received matrigel only). To investigate whether pretreatment of CDCs with hypoxia could improve their pro-angiogenic ability, matrigel containing GFP labelled CDCs precultured in sub-physiological O2 were injected subcutaneously into adult mice. Subsequent immunohistochemical analysis showed that culturing CDCs in sub-physiological O2 increased their pro-angiogenic effect compared to CDCs cultured in normoxia. These data suggest that the pro-angiogenic potential of CDCs is likely to be enhanced by preconditioning in sub-physiological O2 and this may be useful for pro-angiogenic therapy following myocardial infarction.