Vascular growth factors and stem cell therapy in ischaemic heart disease

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ABSTRACT

The work presented in this dissertation was carried au7 in Department of Cardiology, The Heart Centre, H:S Rigshospitalet from 2002 to 2005.

Angiogenic therapies in animals have demonstrated the development of new blood vessels in ischaemic myocardium. However, results from clinical protein and gene angiogenic trials have been less impressive. Moreover, the safety and efficacy of mobilized bone marrow stem cell by G-CSF treatment in human chronic myocardial ischemia needs to be defined. We investigate angiogenic genes expression in human chronic ischemic myocardium and the influence of acute ischemia and reperfusion on their expression, and investigated the spontaneous occurrence of circulating mesenchymal stem cells (MSC) and angiogenic factors in patients with ST-elevation myocardial infarction (STEMI). In a clinical phase I safety and efficacy study, we evaluated the safety and clinical effect of stem cells mobilisation by G-CSF.

We demonstrated identical baseline expression of VEGF-A and -C mRNA in human chronic ischaemic myocardium compared with non-ischaemic myocardium. They could be increased following short-term acute ischaemia and reperfusion in both two-tissue regions. These suggested the non-conclusive VEGF gene therapy trials in patients with chronic coronary artery disease was not due to a pre-existing up-regulation of VEGF in chronic ischaemic myocardium. There might be a room for further therapeutic angiogenesis in chronic ischaemic myocardium. In addition, we found a decrease in circulating MSC with endothelial characteristics in the patients with acute STEMI treated by primary PCI. There was an increase in plasma SDF-1, which might be important for stem cell mobilization and homing within the first four weeks after the infarction. In the same period, VEGF-A and FGF-2 increased. Based on the demonstrated spontaneous variation of MSC and the increase in vascular growth factor levels after STEMI, the optimal time point for an additional stem cell therapy should be three weeks after STEMI to obtain the maximal effects by the stimulation of endogenous growth factors on delivered stem cells.

The treatment with G-CSF in patients with chronic ischaemic heart disease was safe and improved clinical symptoms of myocardial ischaemia. The importance of numbers of mobilized stem cells for clinical effects was supported by the facts that treated effect was seen only in patients with increased circulating mobilized CD34+ stem cells. However, the myocardial perfusion was not influenced by the treatment and an adverse effect on ejection fraction could not be excluded. Large planned randomised, double blind and placebo-controlled clinical trials are considered to clarify the effectiveness of G-CSF treatment with present or higher dose in patient with severe occlusive coronary artery disease.