Soluble factors secreted into cardiac veins during PICSO enhance cardiomyocyte proliferation

W. Mohl1; W. Mohl1; C. Khazen1; T. Aschacher1; A. Alabadi1; N. Khatami1; V. Wagh2; R. Lieber3; K. Macfelda3; RM. Mader4
1Cardiac Surgery Medical University Vienna, Vienna, Austria; 2Harvard medical school, Massachusetts General hospital, Boston, United States of America; 3Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria; 4Medical university Vienna, Oncology, Vienna, Austria

Background: We have previously reported that Pressure controlled Intermittent Sinus Coronary Occlusion (PICSO) – a coronary sinus intervention, applied primarily to reduce myocardial injury by redistributing flow into underperfused zones and inducing washout clearing the ischemic/reperfused microcirculation, is able to enhance the proliferation of human fibroblasts in culture. To test whether PICSO is also clinically feasible to treat patients with advanced heart failure we studied the proliferation potential of human cardiomyocytes cultivated from recipient hearts during cardiac transplantation. We supposed that vascular cells activated by temporal elevation of venous pressure release hitherto unknown molecules into coronary venous blood of heart failure patients, inducing proliferation of cardiomyocytes in cell cultures as surrogate for regenerative pathways by reactivating developmental processes (“embryonic recall”).

Design: Blood samples from cardiac veins were collected from 8 cardiomyopathy patients in the interventional group and 24 in controls during the surgical intervention of resynchronization therapy, pre and post-20-minutes of PICSO and compared to controls. Cardiomyocytes from the septum of the heart of a 67 years old patient with dilatative cardiomyopathy collected during cardiac transplantation were cultivated together with the serum of cardiomyopathy patients treated with or without PICSO during device implantation for resynchronization therapy. In vitro cellular proliferation was measured with the xCELLigence System as a quantitative analysis. Serum samples were tested for miRNA, growth factors and protein patterns.

Results: In the proliferation assay test serum samples of treated individuals showed a significant increase in the capability to proliferate cardiomyocytes compared to both control groups (+/-PICSO and pre and post values). This was supported by a significant difference in serum born miRNA patterns normally secreted during cardiac development, however not by a fraction of tested growth factors.

Conclusions: The in vitro data on cardiomyocyte proliferation and the secretion of differential miRNA patterns indicate, that recovery of injured myocardium is possible by reiterating molecular pathways evoking developmental processes and that these effects are responsible for the beneficial effects of PICSO clinically, since 5 year follow up of this patient group suggested favorable outcome in treated individuals.