Novel Insights into the Role of Insulin-Like Growth Factor 1 in the Regulation of Myocardial Redox State in Humans

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Background: Myocardial oxidative stress is a key feature in the failing heart. Epicardial Adipose Tissue (EpAT) may be a co-regulator of cardiac function due to its anatomical proximity with the myocardium. Insulin-like Growth Factor 1 (IGF1) is a hormone with pleiotropic effects on human cardiomyocytes, highly expressed in human fat.

Purpose: We explored the role of IGF1 released from EpAT in the regulation of myocardial redox state and function in patients with ischaemic heart disease.

Methods: The study included 600 patients undergoing cardiac surgery. Right atrium appendages were used to quantify superoxide (O2-) production and its individual enzymatic sources using *ex vivo* bioassays and lucigenin-enhanced chemiluminescence. EpAT samples were snap-frozen for gene expression studies. Plasma Brain Natriuretic Peptide (BNP) was measured by a chemiluminescent microparticle assay, whereas plasma IGF1 by ELISA.

Results: The severity of the patients' clinical heart failure syndrome (defined by the NYHA class) was inversely related with plasma IGF1 (A), but it was positively related with local IGF1 expression in EpAT (B). Expression of IGF1 in EpAT was also positively related with plasma BNP (C). High circulating IGF1 was associated with decreased oxidative stress and NADPH oxidase activity (D, E), but it was not linked to the expression of any NOX isoform in the myocardium (F). On the contrary, high expression of IGF1 in EpAT was associated with reduced myocardial O2- production (G, H) and low expression of NOX isoforms (I).

Conclusions: This is the first study identifying IGF1 as a potential new regulator of myocardial redox state in humans. Our results suggest that, as IGF1 is highly expressed in the EpAT surrounding the failing heart, its regulation is likely to consist of a local, paracrine defense mechanism of the human heart against myocardial oxidation.