Metabolic deregulation in myocardial infarction is mediated by PGC-1 alpha pathway

Purpose: In the context of myocardial infarction (MI) the availability of metabolites is clearly restricted, therefore a fuel metabolic shifts takes place. Previous studies have indicated that peroxisome proliferator activated receptor co-activator alpha (PGC-1α) pathway is a crucial regulator of cardiac metabolism in response to cardiac stress. Here we address the role of PGC-1α in regulating metabolic changes of MI.

Methods: We studied a group of 12 common swine in which anterior MI was induced by means of angioplasty balloon inflation. A series of 6 swine were sacrificed at 48h post-infarction (acute infarction group) and another series of 6 swine were sacrificed at 3 weeks (chronic infarction group). Metabolites such as: glucose, pyruvate, ketone bodies, and lipids were analyzed in serum (mmol/L) at baseline, 75 min after balloon inflation, 2 h, 48 h and 3 weeks after reperfusion by means of enzymatic analysis. Results were compared to baseline levels. Genes related to PGC-1α such as: PGC-1α, ERR-α, PPAR-α, and HIF-1α, were analysed (fold change) in infarcted, adjacent and remote areas of porcine hearts 48h or 3 weeks post-infarction by molecular biology. Results were compared to 5 control swine without infarction.

Results: In all groups, after 2h of infarction, a striking increase of lactate (3.2 ± 0.6 vs. 0.8 ± 0.3) and non-esterified fatty acids (0.6 ± 0.2 vs. 1.8 ± 0.3) was observed in serum compared to baseline (p < 0.001 in both cases). Conversely, a significant decrease of glucose (5.2 ± 0.3 vs. 3.8 ± 0.2) and β-Hydroxybutyrate (1.8 ± 0.5 vs. 0.6 ± 0.2) occurred at the same time (p < 0.001 in both cases).

All values reverted progressively to baseline after 3 weeks. In comparison with controls, molecular biology analysis of acute infarcted hearts revealed a significant decrease of expression in mRNA and protein levels of transcription factors related to lipid and mitochondrial metabolism: PGC-1α (0.3 ± 0.1 vs. 1.2 ± 0.2 fold), ERR-α (0.8 ± 0.3 vs. 1.6 ± 0.2 fold) and PPAR-α (0.9 ± 0.3 vs. 1.7 ± 0.2 fold) (p < 0.01 in all cases). Values didn't change after 3 weeks. However genes related to glucose metabolism were significantly increased in acute infarcts compared to controls: GLUT-1 (3.8 ± 0.4 vs. 1.1 ± 0.3 fold), HIF-1α (4.2 ± 1.3 vs. 1.0 ± 0.2 fold) (p < 0.01 in both cases). These values recovered control levels after 3 weeks.

Conclusion: A metabolic deregulation mediated by PGC-1α decreased expression takes place in the context of acute MI. This is mediated by a decrease of fatty acid oxidation and an increase of glucose utilization and it reverts after 3 weeks.