CHRONIC PRESSURE OVERLOAD IN RATS REDUCES MITOCHONDRIAL RESPIRATORY CAPACITY BUT NOT COUPLING TO ATP-PRODUCTION

ACC Poster Contributions
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Objectives: Two mitochondrial mechanisms have been suggested for the development of pressure-overload heart failure: mitochondrial dysfunction both through uncoupling of ATP production or through a reduction in respiratory capacity due to downregulation of the mitochondrial master regulator PGC-1α. We assessed respiratory capacity and coupling to ATP-production, PGC-1α and downstream target gene-expression, as well as fatty acid oxidation in rat hearts subjected to chronic pressure overload developing heart failure.

Results: Transverse aortic constriction for 20 weeks resulted in heart failure with dyspnoea, pleural effusions and decreased ejection fraction (EF: 53±8% vs. 75±6% sham, p<0.05). Maximal respiratory capacity (state 3 respiration) of isolated mitochondria was reduced with all substrates (natomsO/min/mg protein: glutamate 239±64 vs. 503±91, palmitoyl-carnitine 241±27 vs.521±83, pyruvate 198±14 vs.615±107; p<0.05). This decrease was associated with reduced PGC-1α expression, reduced fatty acid oxidation gene expression (MCAD, LCAD) and reduced rates of fatty acid (μmol/min/g dry: 0.28±0.04 vs. 1.02±0.04) and glucose oxidation (0.16±0.03 vs. 0.38±0.08) in the isolated working heart. Cardiac power related to ATP production was significantly reduced, suggesting decreased efficiency. However, coupling of mitochondrial oxygen consumption to ATP production was not affected in heart failure (ratio: 2.33±0.12 vs. 2.30±0.20) suggesting that inefficiency is not due to uncoupling. The expression of mitochondrial uncoupling proteins was also not altered in failing hearts.

Conclusion: These results suggest that downregulation of the mitochondrial oxidative machinery, possibly through dysregulation of PGC-1α, and not uncoupling of the respiratory chain is involved in the development of pressure overload heart failure in rats.