High-fat diet induced cardiac dysfunction is associated with altered myocardial insulin signaling in rats

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Background: Patients with type 2 diabetes have a high risk to develop coronary artery disease and congestive heart failure. Even asymptomatic diabetic subjects exhibit myocardial structural and functional changes, which are ascribed to diabetic cardiomyopathy (DCM). Changes in myocardial energy metabolism, resulting from altered cardiac substrate supply and utilization, may underlie the development of DCM. We assessed whether long-term exposure to excessive alimentary fat, inducing a type 2 diabetic phenotype in rats, results in myocardial dysfunction and whether this occurs through the interference with myocardial insulin signaling.
Methods: Male rats received isocaloric high- (HF) or low-fat (LF) diets (8 weeks). Thirty min prior to sacrifice, rats received insulin or saline (i.p.). Contractile function was assessed in isolated perfused papillary muscles. Insulin signaling was determined in ventricular cell lysates.
Results: Fasting as well as post-load blood glucose levels were increased in HF vs. LF-rats (both $p<0.01$). Mean body weight was similar, however, heart weight was increased in HF-rats ($p<0.03$). Hearts from HF-rats showed structural changes and myocardial triglyceride-accumulation. Papillary muscles from HF-rats developed contractile forces, but showed an impaired response compared to LF-rats at higher workloads. The protective effect of insulin against Ca^{2+}-overload was also reduced in HF-rats. Finally, in HF vs LF-rats, a 40-60% reduction in insulin-induced stimulation of IRS1-associated PI 3'-kinase activity, phosphorylation of PKB, GSK3, eNOS and the forkhead transcription factors was observed (all $p<0.05$).
Conclusions: HF-diet induced a hypertrophy-like cardiac phenotype, characterized by a higher basal contractile force, decreased contractile reserve and reduced protective effect of insulin against Ca^{2+}-overload. The cardiac functional changes were associated with abnormal myocardial insulin action as demonstrated by the impaired activation of the IRS1/PI 3'-kinase/PKB-dependent signaling pathway. Our data indicate that impaired myocardial insulin signaling caused by exposure to excessive alimentary fat may be the key mechanism underlying DCM.

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