New Insights on Diabetic Cardiomyopathy

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Diabetes mellitus (DM) is a major cause of death and disability and a large economic burden on healthcare systems across the world. The prevalence of heart failure (HF) is increased both in type I and type II DM and persists after adjustment for differences in coronary artery disease or other relevant risk factors. Indeed, DM gives rise to a specific cardiomyopathy characterized by predominant left ventricular diastolic dysfunction, leading to heart failure with preserved or mildly impaired left ventricular ejection fraction, for which there is no effective treatment.

Using mice models and human myocardial samples, we evaluated whether and by which mechanism increasing the myocardial availability of tetrahydrobiopterin (BH4) prevented or reversed left ventricular dysfunction induced by DM. We showed that increasing myocardial BH4 and nNOS activity by myocardial-specific transgenic overexpression of the rate-limiting enzyme in the synthesis of BH4, GTP-cyclohydrolase 1 (GCH1) does not increase endothelial BH4 or preserve endothelial-mediated vasodilatation but prevents left ventricular dysfunction in diabetic mice—not by averting NOS dysfunction, maintaining phospholamban phosphorylation, or reducing oxidative stress—but by preserving myocardial energetics via a nNOS-mediated increase in glucose uptake through the insulin-independent transporter, GLUT-1. Importantly, oral BH4 supplementation was able to reverse the cardiomyopathic phenotype in diabetic wild type mice. Taken together these findings indicate that GCH1/BH4-based therapeutics may be used to treat as well as prevent diabetic cardiomyopathy.