

The phosphodiesterase-5 inhibitor vardenafil protects against diabetic cardiomyopathy in type-2 diabetes mellitus

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Purpose: Diabetes mellitus (DM) is associated with a special heart disease, termed diabetic cardiomyopathy. The pathophysiological role of cyclic guanosine monophosphate (cGMP) signalling has been intensively investigated in DM. The second messenger cGMP, broken down by the phosphodiesterase-5 enzyme (PDE5), has been shown to exert cytoprotective effects. We investigated the effect of chronic inhibition of PDE5 by vardenafil in type-2 DM related cardiomyopathy.

Methods: For type-2 DM Zucker Diabetic Fatty (ZDF; homozygous recessive (fa/fa)) rats were used. Heterozygous (fa/+) or homozygous dominant (+/+) ZDF Lean (ZDFL) rats served as controls. Animals received either vehicle (ZDFL, ZDF) or 10mg/kg BW vardenafil per os (ZDFLVard, ZDFVard) from 7 to 32 weeks of age. Cardiac morphology was followed by echocardiography. Left ventricular (LV) function was assessed using a pressure-volume (PV) conductance microcatheter system. Gene expression analysis of atrial natriuretic factor (ANF; qRT-PCR), cardiomyocyte diameter/tibia length (CD/TL) and Masson's staining (fibrosis score (FS)) were used to prove pathological myocardium hypertrophy.

Results: Cardiac hypertrophy (echocardiography: LV anterior wall thickness in systole (LVAWs): 2.81 ± 0.1 mm; relative wall thickness (RWT): 0.49 ± 0.02 ; LVmass/TL: 0.30 ± 0.01 g/cm; CD/TL: 3.53 ± 0.02 μ m/cm; ANF: 3.04 ± 0.26 vs ZDFL (LVAWs: 2.53 ± 0.04 mm; RWT: 0.43 ± 0.02 ; LVmass/TL: 0.23 ± 0.004 g/cm; CD/TL: 3.09 ± 0.02 μ m/cm; ANF: 0.92 ± 0.17); $p < 0.05$) and fibrotic remodelling (FS: 1.05 ± 0.09 vs ZDFL (0.57 ± 0.13); $p < 0.05$) have been observed in ZDF. Drug treatment significantly decreased myocardial hypertrophy and fibrosis (LVAWs: 2.47 ± 0.05 mm; CD/TL: 3.15 ± 0.02 ; ANF: 1.39 ± 0.21 ; FS: 0.59 ± 0.08 vs ZDF; $p < 0.05$) in DM. PV analysis showed impaired diastolic function and increased cardiac stiffness (time constant of LV pressure decay (τ): 9.17 ± 0.25 ms; slope of end-diastolic pressure volume relationship (EDPVR): 0.078 ± 0.002 mmHg/ μ l vs ZDFL (τ : 8.18 ± 0.13 ms; EDPVR: 0.045 ± 0.003 mmHg/ μ l); $p < 0.05$) while contractility parameters and blood pressure remained unchanged in ZDF. Vardenafil improved diastolic parameters (τ : 8.62 ± 0.34 ms, EDPVR: 0.062 ± 0.006 mmHg/ μ l vs ZDF; $p < 0.05$). Vardenafil did not have effect in ZDFL.

Conclusions: We reported that chronic administration of vardenafil prevents DM associated myocardial complications. PDE5 inhibition might be an important target to improve the cardiovascular outcome in diabetic patients in the future.