

Prevention of the development of heart failure with preserved ejection fraction by the phosphodiesterase-5A inhibitor vardenafil in rats with type 2 diabetes

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Aims

Heart failure with preserved ejection fraction (HFpEF) has a great epidemiological burden. The pathophysiological role of cyclic guanosine monophosphate (cGMP) signalling has been intensively investigated in HFpEF. Elevated levels of cGMP have been shown to exert cardioprotective effects in various cardiovascular diseases, including diabetic cardiomyopathy. We investigated the effect of long-term preventive application of the phosphodiesterase-5A (PDE5A) inhibitor vardenafil in diabetic cardiomyopathy-associated HFpEF.

Methods and results

Zucker diabetic fatty (ZDF) rats were used as a model of HFpEF and ZDF lean rats served as controls. Animals received vehicle or 10 mg/kg body weight vardenafil per os from weeks 7 to 32 of age. Cardiac function, morphology was assessed by left ventricular (LV) pressure–volume analysis and echocardiography at week 32. Cardiomyocyte force measurements were performed. The key markers of cGMP signalling, nitro-oxidative stress, apoptosis, myocardial hypertrophy and fibrosis were examined. The ZDF animals showed diastolic dysfunction (increased LV/cardiomyocyte stiffness, prolonged LV relaxation time), preserved systolic performance, decreased myocardial cGMP level coupled with impaired protein kinase G (PKG) activity, increased nitro-oxidative stress, enhanced cardiomyocyte apoptosis, and hypertrophic and fibrotic remodelling of the myocardium. Vardenafil effectively prevented the development of HFpEF by maintaining diastolic function (decreased LV/cardiomyocyte stiffness and LV relaxation time), by restoring cGMP levels and PKG activation, by lowering apoptosis and by alleviating nitro-oxidative stress, myocardial hypertrophy and fibrotic remodelling.

Conclusions

We report that vardenafil successfully prevented the development of diabetes mellitus-associated HFpEF. Thus, PDE5A inhibition as a preventive approach might be a promising option in the management of HFpEF patients with diabetes mellitus.

Keywords

Vardenafil • cGMP • Diabetic cardiomyopathy • Diastolic dysfunction • Cardiomyocyte stiffness

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