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Chronic phosphodiesterase-5 inhibition prevents the development of diabetic cardiomyopathy in a rat model of type-2 diabetes mellitus

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Purpose: Diabetes mellitus (DM) is associated with characteristic structural and functional changes of the heart, termed diabetic cardiomyopathy. The pathophysiological role of cGMP signaling has been intensively investigated in DM. Elevated levels of the second messenger cGMP have been shown to exert cardioprotective effects in various heart diseases. We investigated the effect of chronic inhibition of the cGMP-degrading enzyme phosphodiesterase-5 (PDE5) by vardenafil in type-2 DM related cardiomyopathy.

Methods: For type-2 DM Zucker Diabetic Fatty (ZDF) rats were used. 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 by pressure-volume (P-V) analysis. Gene expression measurements 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 P-V 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 any effects in ZDFL.

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

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Bicoronary infusion of nitroglycerin and atrial natriuretic peptide improves diastolic distensibility in healthy pigs.A Alogna¹; M Manning²; B Zirngast³; M Schwarz⁴; P Steendijk⁵; B Pleske¹; H Post¹

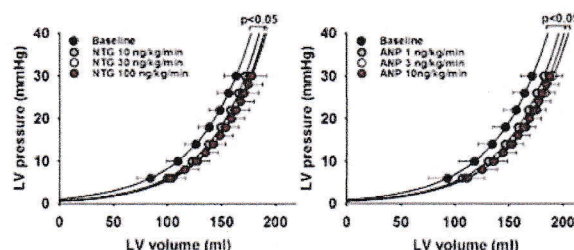
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Background: Experimental data indicate that the acute post-translational modification of the myofilament titin spring by cGMP-activated protein kinase G can increase left ventricular (LV) end-diastolic distensibility (LVed-Dist). Intracellular cGMP production can be stimulated either by nitric oxide via the soluble guanylate cyclase (sGC), or by the natriuretic peptides via the particulate guanylate cyclase (pGC). We tested the hypothesis that acute intracoronary infusion of nitroglycerin (NTG) or atrial natriuretic peptide (ANP) would exert direct myocardial effects and improve LVed-Dist in healthy myocardium.

Methods: 5 anaesthetized, closed-chest pigs (59 ± 2 kg) were acutely instrumented with a left ventricular (LV) pressure-volume catheter, a Swan-Ganz catheter and an aortic balloon catheter. Two 5F coronary catheters were positioned in the right and left coronary ostia via femoral access. Pressure-volume relationships were derived from short aortic occlusions. Following baseline measurements, NTG was infused bicoronarily at 10, 30 and 100 ng/kg/min over 20 min, respectively. After 30 min wash-out, the same protocol was repeated with ANP at 1, 3 and 10 ng/kg/min. *: $p < 0.05$ vs baseline

Results: LV peak pressure slightly decreased at the highest dose compared to baseline (NTG: $87 \pm 3^*$ vs 94 ± 4 , ANP: $85 \pm 4^*$ vs 96 ± 6) while systemic vascular resistance was not altered during NTG infusion and to a minor extent during the highest dose of ANP ($11.1 \pm 0.6^*$ vs 12.7 ± 0.7 mmHg/l/min). The maximum rate of positive LV pressure change, LV dP/dt_{max}, decreased and the calculated end-systolic volume at 100 mmHg end-systolic pressure increased dose-dependently, indicating a negative inotropic effect. The end-diastolic pressure volume relationships (EDPVR, graph) before and during infusion of NTG and ANP were shifted rightwards compared to the respective baseline (see graphs).

Conclusion: The acute pharmacological stimulation of cGMP-dependent signalling improves LV end-diastolic distensibility in healthy pigs in vivo. The molecular mechanisms mediating such acute modulation of LV distensibility may represent pharmacological targets to treat a pathological loss of LV distensibility as, for instance, heart failure with preserved ejection fraction (HFpEF).



EDPVRs baseline vs NTG-ANP

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Intravenous administration of CoQ10 evokes increase in NO-mediated blood vessels relaxation

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Introduction: The presence of endothelial dysfunction is associated with an increased mortality risk in patients with chronic heart failure. Coenzyme Q10 (CoQ10) is recommended for treatment of patients with congestive heart failure, but due to its low bioavailability it is necessary long term administration in order to reach therapeutic effect. One of the proposed mechanisms of beneficial effects of CoQ10 is improvement in the vasodilating NO-mediated function of endothelium.

Purpose: Investigation of the fast effects of CoQ10, administered intravenously, on the NO-mediated vasorelaxation, evoked by acetylcholine. **Methods.** Male Wistar rats (300-350g) were anaesthetized with chloralhydrate (400 mg/kg, ip) and placed on a heated surgical pad at constant body temperature 37 ± 0.5 °C. 3% water-based solution of CoQ10 (30 mg/kg) or saline (0.9% NaCl, 1 mL/kg) were administered intravenously via the femoral vein. 2 h after drugs administration the animals were anaesthetized by chloralhydrate over dose (600 mg kg⁻¹, ip) and decapitated. The descending thoracic aorta was carefully excised and cut into ring segments 3 mm in length and then transferred into 10-ml organ baths containing Krebs solution bubbled with a mixture of 95% O₂ and 5% CO₂. The rings were precontracted with 0.3 μ M Phenylephrine (PE), and after a steady-state tension had been reached, increasing concentrations of ACh (0.001 μ M - 30 μ M) were cumulatively added to the organ bath.

Results: ACh elicited a concentration-dependent relaxation of rat aortic rings. The maximum relaxation (E max, %) was obtained at a ACh concentration of 30 μ M. In the CoQ10-treated group the relaxant responses to ACh were markedly potentiated when compared with the control (saline) group ($94.2 \pm 2.0\%$ vs $68.1 \pm 4.4\%$, respectively, $p < 0.01$). It was significant difference in pD₂ (-lg EC₅₀,) values of the control and treatment groups (5.79 ± 0.29 vs 8.14 ± 0.65 , $p < 0.05$).

Conclusion: 2h duration of CoQ10 (30 mg/kg) action is enough for improving the vasodilating NO-mediated function of endothelium. This mechanism could be partially responsible for positive effects of CoQ10 in congestive heart failure.

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Prolonged dipyridamole use is associated to amelioration of myocardial perfusion disturbance in experimental chronic Chagas cardiomyopathy

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Background: Microvascular ischemia is a conspicuous finding in chronic chagasic cardiomyopathy (CCC) that may be involved in the development of left ventricular systolic dysfunction (LVSD).

Purpose: We aimed at assessing the effect of the prolonged use of dipyridamole (DIPY) on myocardial perfusion and left ventricle systolic function in a model of CCC.

Methods: We investigated 3 groups of female hamsters: animals infected with T. cruzi and treated with DIPY (CH+DIPY, n=15), infected and treated with saline (CH+Saline, n=15), non-infected and treated with DIPY (CO+DIPY, n=12) or treated with saline (CO+Saline, n=11). After 6 months of infection (baseline condition), the animals were submitted to echocardiography and to Sestamibi-Tc99m SPECT