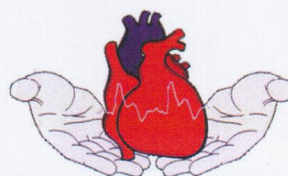


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Abstracts

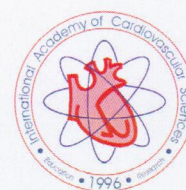


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considerably from those in the non-diabetic controls. Nevertheless, during postischemic reperfusion, diabetic hearts exhibited significantly better recovery of LVDP, $+dP/dt_{\max}$ and $-dP/dt_{\max}$ (all $P<0.05$) in comparison to controls. This indicated that diabetic hearts adapted to pseudo-hypoxia accompanying the disease might be also more tolerant against ischemia. 30 min ischemia decreased the membrane fluidity and Mg^{2+} -ATPase activity to approximately similar extent in healthy and in diabetic heart mitochondria. However, 40 min reperfusion led to a further decline of enzyme activity and membrane fluidity in controls, whereas in the diabetics mitochondrial membrane fluidity was slightly increased and the activity of Mg^{2+} -ATPase recovered even above the baseline pre-ischemic levels ($P<0.05$). Our findings indicate that hearts become adapted to diabetes-accompanying pseudo-hypoxia already in acute phase of the disease and this will increase their tolerance also against additional ischemic impulses. Mitochondria are essentially participating in the mechanism of adaptation of the diabetic myocardium to hypoxia and/or ischemia.

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CA²⁺-SENSITIZING EFFECTS OF OR-2828 IN PERMEABILIZED CARDIOMYOCYTES

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OR-2828, a potential calcium-sensitizer drug with a molecular structure similar to that of levosimendan have a dextrorotatory (R-OR-2828) and a levorotatory (L-OR-2828) stereoisomer. The aim of this study was to characterize the hypothetical Ca²⁺-sensitizer effects of these optical isomers in isolated permeabilized cardiomyocytes.

Force measurements were performed in myocyte-sized preparations derived from left ventricular preparations of guinea pigs, as well as from failing human hearts with dilated cardiomyopathy. Isolated and permeabilized cardiomyocytes, attached between a force transducer and an electromagnetic motor were exposed to test solutions with increasing concentrations of the two optical isomers of OR-2828 (between 10 nM and 100 μ M) to test their concentration dependencies on force production and on its Ca²⁺-sensitivity.

10 μ M L-OR-2828 significantly ($P<0.05$) increased Ca²⁺-sensitivity of force production in myocyte-sized preparations derived from guinea pigs hearts (pCa_{50} : 5.76, vs. the drug free control of 5.69; $n=8$) and from failing human hearts with dilated cardiomyopathy (pCa_{50} : 6.18, vs. a drug free control of: 6.07; $n=14$). The EC_{50} value for L-OR-2828 effect was 2.44 μ M in guinea pig hearts. L-OR-2828 had no effect on force generation at maximal Ca²⁺ concentration (pCa 4.75) and on Ca²⁺-independent passive force. R-OR-2828 did not affect Ca²⁺-sensitivity of force production in cardiomyocytes of guinea pig hearts.

Our data illustrated L-OR-2828 as a positive inotropic agent, exerting its cardiotonic effect similarly to levosimendan via a Ca²⁺-sensitizing mechanism.

THE SOLUBLE GUANYLATE CYCLASE ACTIVATOR CINACIGUAT PROTECTS AGAINST DIABETIC CARDIOMYOPATHY IN A RAT MODEL

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Introduction: Diabetic cardiomyopathy is associated with fibrotic remodeling of the myocardium and deterioration of systolic and diastolic function leading to the development of chronic heart failure. Enhancement of cyclic guanosine monophosphate (cGMP) signalling has been reported to evoke antihypertrophic and antifibrotic activities. In this study we investigated the effects of the soluble guanylate cyclase activator cinaciguat in a rat model of diabetic cardiomyopathy.

Methods: Diabetes mellitus was induced in Sprague-Dawley rats by a single injection of streptozotocin (60 mg/kg). Cinaciguat (10 mg/kg/d, treatment groups) or vehicle (control groups) were applied orally for 8 weeks. Cardiac function was assessed in vivo by left ventricular pressure-volume analysis in a closed chest model by using a microtip Millar pressure-conductance catheter. Plasma cGMP, myocardial mRNA and protein expressions were investigated by ELISA, qRT-PCR, immunohistochemistry and Western blotting, respectively.

Results: Diabetes was associated with increased myocardial expression of transforming growth factor beta (TGF- β) and fibrotic remodeling of the myocardium as evidenced by Masson's trichrome staining along with enhanced gene expression for matrix metalloproteinase-9 and atrial natriuretic peptide, which were all reversed after increasing cGMP-levels by cinaciguat treatment. The impaired systolic (end-systolic elastance, E_{es} : 0.72 ± 0.10 vs. 1.82 ± 0.13 mmHg/ μ l) and diastolic function (end-diastolic pressure, LVEDP: 9.7 ± 0.7 vs. 7.0 ± 0.6 mmHg) of diabetic animals were significantly improved by cinaciguat (E_{es} : 1.20 ± 0.15 mmHg/ μ l, LVEDP: 7.3 ± 0.6 mmHg in the diabetes+cinaciguat group). The treatment had no effects in non-diabetic control animals.

Discussion: Our results demonstrate that cinaciguat inhibits diabetes-associated fibrotic remodeling and prevents the development of chronic heart failure in our rat model. Pharmacological soluble guanylate cyclase activation might represent a novel therapy approach for diabetic cardiomyopathy.

CONCENTRATION OF L-ARGININE AND ASYMMETRIC DIMETHYLARGININE (ADMA) IN PERICARDIAL FLUID IN PATIENTS UNDERGOING OPEN HEART SURGERY

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Background: The primary function of pericardial fluid (PF) to ensure a proper friction between the pericardium and the heart. However, recent findings suggest that PF contains several biological active substances, which may reflect the functional condition of the heart. Such molecules are L-arginine and its methylated derivative asymmetric dimethylarginine (ADMA). Previous studies have shown that ADMA reduces the bioavailability of nitric oxide (NO) and elicits oxidative stress. We hypothesized that L-arginine and ADMA are present in PF, and their concentrations are different in CABG and VR groups, and correlated with morphological parameters of the heart.

Patients and methods: Thus plasma and PF were collected from patients undergoing open coronary artery bypass graft (CABG, $n=28$) and valve replacement (VR, $n=15$) surgeries and the concen-