

24. Pharmacological activation of the soluble guanylate-cyclase prevents the transition from pressure overload-induced left ventricular hypertrophy to heart failure

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Background: Chronic pressure overload of the left ventricle (hypertension, aortic stenosis) induces left ventricular hypertrophy (LVH), which in the long term leads to chamber dilatation and progressive deterioration of cardiac function. Cardiomyocyte apoptosis has been reported to be involved in the transition from LVH to heart failure (HF). However, the nitric oxide/ soluble guanylate-cyclase (sGC)/ cyclic guanosine monophosphate pathway has been identified not only as an effective anti-hypertrophic and but also as an anti-apoptotic signaling.

Purpose: Therefore we investigated the effect of the sGC activator cinaciguat in a rat model of pressure overload-induced LVH and HF.

Methods: Pressure overload was induced in Sprague-Dawley rats by abdominal aortic banding (AB) for 6 or 12 weeks. Sham operated animals served as controls. The experimental groups were treated from the 7th to the 12th postoperative week, with 10 mg/kg/day cinaciguat (Cin) or with placebo (Co) p.o., respectively. Development of LVH and its transition to HF was investigated by serial echocardiography and electrocardiography. In addition, after the 12th week, left ventricular pressure-volume analysis was carried out. Besides the functional experiments, histological and molecular biological measurements were also performed.

Results: Chronic activation of the sGC enzyme effectively inhibited the functional decompensation of LVH (ejection fraction: 47.4 vs. 63.7%, slope of end-systolic pressure-volume relationship: 1.47 ± 0.13 vs. 2.05 ± 0.25 mmHg/ μ l, corrected QT interval: 91.0 ± 1.9 vs. 81.2 ± 1.8 ms $p < 0.05$ AB 12th week-Co week vs. AB 12th week-Cin). Apoptosis was increased in the AB 12th week-Co group compared to the 6th week AB group, and also to the Sham 12th-Co group, as reflected by TUNEL staining, and by the increased expression of Bax, Caspase-3 and Caspase-9 and the decreased expression of Bcl2. Furthermore, Masson's trichrome staining revealed that reactive myocardial fibrosis was also enhanced in the AB 12th week-Co group, providing further evidence for the myocardial cell loss. Cinaciguat administration proved to be protective in all respects, since all of these molecular/cellular changes were inhibited in the AB 12th week-Cin group.

Conclusion: Our results demonstrate that chronic activation of the sGC enzyme prevents the transition from pressure overload-induced LVH to HF and inhibition of the apoptotic cell death in the myocardium contributes to the protective effect.