

## **The soluble guanylate cyclase activator cinaciguat prevents pressure overload-induced cardiac hypertrophy**

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**Purpose:** Pathological cardiac hypertrophy is observed in pressure overload of the left ventricle. Elevated intracellular cGMP-levels have been reported to prevent the development of pathological myocardial hypertrophy. We investigated the effects of chronic activation of the cGMP producing enzyme, soluble guanylate cyclase (sGC) by cinaciguat in a rat model of pressure overload-induced cardiac hypertrophy.

**Methods:** We performed aortic banding (AB) to evoke pressure overload-induced cardiac hypertrophy in our rats. Sham operated animals served as controls. Experimental groups were treated with 10 mg/kg/day cinaciguat (Cin) or with placebo (Co) p.o., respectively. Development of cardiac hypertrophy was investigated by echocardiography. We performed left ventricular (LV) pressure-volume analysis with a pressure-conductance microcatheter to assess cardiac function. In addition to our functional experiments, histological and molecular biological measurements were carried out.

**Results:** Echocardiography showed marked myocardial hypertrophy in the AB-Co group (left ventricular mass index (LVMI):  $3.15 \pm 0.09$  AB-Co vs.  $2.13 \pm 0.04$  g/ttkg Sham-Co) which was verified by post mortem investigation of the hearts (heart weight/tibial length ratio (HW/TL):  $0.384 \pm 0.015$  AB-Co vs.  $0.293 \pm 0.008$  g/cm Sham-Co) and by histology (cardiomyocyte diameter (CD):  $17.37 \pm 0.04$  AB-Co vs.  $14.55 \pm 0.12$   $\mu$ m Sham-Co). Increased left ventricular dimensions (left ventricular end-diastolic volume:  $414 \pm 19$  AB-Co vs.  $341 \pm 19$   $\mu$ l Sham-Co) were observed while ejection fraction and fractional shortening remained unchanged. Cinaciguat did not alter blood pressure but effectively attenuated left ventricular hypertrophy (LVMI:  $2.64 \pm 0.06$  g/ttkg, HW/TL:  $0.339 \pm 0.009$  g/cm, CD:  $15.08 \pm 0.10$   $\mu$ m,  $p < 0.05$  vs. AB-Co).

**Conclusions:** Our results demonstrate that chronic stimulation of the NO-cGMP signalling by pharmacologically activating soluble guanylate cyclase might be a novel therapeutic approach in the prevention of pathological myocardial hypertrophy.

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