

## **The cardiac actions of the nitroxyl (HNO) donor Angeli's salt are thiol-sensitive and cGMP-dependent: impact of diabetes**

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**Introduction:** HNO is a novel redox sibling of NO with multiple cardioprotective actions, including potent enhancement of left ventricular (LV) function and vasodilatation, favourable therapeutic properties for heart failure. Both cGMP and CGRP are putative mediators of HNO actions. In the diabetic heart, impaired LV function is accompanied by impaired inotropic responsiveness, but the impact of diabetes on cardiac HNO effects are unknown.

**Aims:** To explore the cardiac mechanisms of action of the HNO donor Angeli's salt in the intact heart, and the impact of diabetes on these effects.

**Methods:** Hearts from anaesthetised male Sprague-Dawley rats (350-400g, 100mg/kg Ketamine + 12mg/kg Xylazine i.p.) were subjected to Langendorff perfusion at constant pressure. LV function and coronary flow were monitored continuously. Dose-response curves to Angeli's salt were performed following precontraction with U46619 to ~50% of baseline coronary flow. Hearts isolated from rats subjected to 8 weeks streptozotocin (55mg/kg i.v.) diabetes or their vehicle shams were also studied.

**Results:** In normal hearts, Angeli's salt (10pmol-10 $\mu$ mol) elicited significant dose-dependent increases in LV systolic function (LV systolic pressure, LV developed pressure, LV+dP/dt), LV diastolic function (LV end-diastolic pressure, LV-dP/dt) and coronary flow. All of these effects were significantly inhibited by co-administration of the HNO scavenger L-cysteine (4mM) or the soluble guanylyl cyclase inhibitor ODQ (10 $\mu$ M), but were insensitive to the CGRP antagonist CGRP<sub>8-37</sub> (0.1 $\mu$ M). The positive inotropic effects of Angeli's salt remained evident in diabetic hearts (albeit slightly blunted); whereas diabetes markedly impaired inotropic responsiveness to isoprenaline (0.1nmol). The enhanced LV diastolic function elicited by Angeli's salt was preserved in diabetic hearts, whilst the vasodilator actions were markedly attenuated.

**Discussion:** Our results demonstrate that the inotropic and vasodilator effects of Angeli's salt are mediated by HNO and cGMP, but not CGRP. HNO donors may represent additional options for inotropic support for the diabetic heart.