ACUTE TREATMENT WITH THE RUTHENIUM-BASED NITRIC OXIDE SCAVENGER, AMD6221, IMPROVES CARDIOVASCULAR FUNCTION IN RATS WITH STREPTOZOTOCIN-INDUCED DIABETES

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Excess nitric oxide (NO) production by inducible nitric oxide synthase (iNOS) has been implicated in cardiovascular dysfunction associated with the acute phase of diabetes mellitus. Based on previous work in our laboratory (Cheng *et al.*, 2004). The aim of the present study was to examine if acute administration of the selective NO scavenger, AMD6221 cardiovascular function in rats with streptozotocin -induced diabetes. The *in vivo* NO-scavenging activity of AMD6221 has been previously demonstrated in a rat model of bacterial lipopolysaccharide-induced septic shock (Fricker *et al.*, 1997).

Diabetes was induced in male Wistar rats (300-400g) by injection of streptozotocin (60 mg/kg, i.v.). The effects of noradrenaline infusion (16.5 nmol/kg/min) on several cardiovascular variables were measured in anaesthetized diabetic and control rats (n = 7 per group) before and after acute administration of AMD6221 (80 mg/kg). Results are presented as the mean ± S.E.M. The effects of AMD6221 were analysed using two-way repeated-measures ANOVA with planned comparisons of variables before and after AMD6221 administration for each group made using Dunn-Bonferroni post-tests.

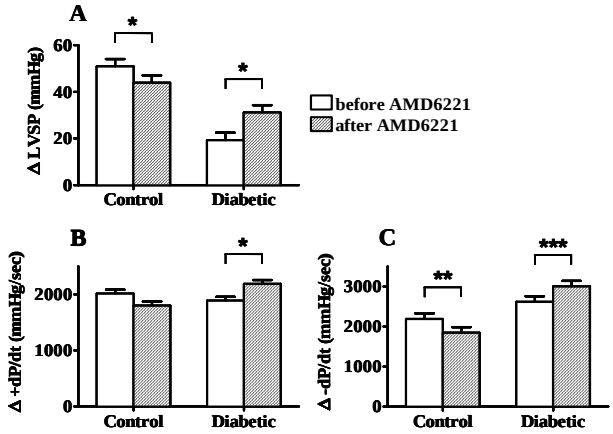

Figure 1 – Responses (mean ±S.E.M.) to noradrenaline infusion for peak left ventricular systolic pressure (ΔLVSP; *A*), maximal rate of increase of left ventricular pressure during systole (Δ +dP/dt; *B*) and maximal rate of decrease of left ventricular pressure during diastole (Δ - dP/dt; *C*) prior to and after administration of AMD *P<0.05; **P<0.01; ***P<0.001

The increases in heart rate (415±15 vs. 366±6 beats/min; $p < 0.05$), mean arterial pressure (147±5 vs. 119±4 mmHg; $p < 0.05$) and LVSP (162±7 vs. 127±5 mmHg; $p < 0.05$) in response to noradrenaline infusion were markedly higher in control compared with diabetic rats. Acute treatment with AMD6221 significantly augmented the LVSP, +dP/dt and –dP/dt responses to noradrenaline in diabetic but not control rats (Figure 1).

In conclusion, these results suggest that selective scavenging of nitric oxide by AMD6221 increases the cardiovascular responsiveness to noradrenaline in rats with streptozotocin-induced diabetes.

Cheng, X. *et al.* (2004). *Cardiovasular Research*. **64**; 298-307.
Fricker, S.P. *et al*. (1997). *British Journal of Pharmacology*. **122**; 1441-1449.