Elevated cardiac AngII exacerbates structural and mechanical diabetic myocardial pathology in normotensive mice

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Diabetic cardiopathology involves left ventricular dysfunction, associated with activation of the renin–angiotensin (AngII) system. Inhibition of cardiac AngII results in improved systolic and diastolic function in diabetic rodents (Masuda *et al*., 2012). Enhanced cardiac AngII in a non-diabetic setting results in hypertrophy and severe contractile abnormalities with absence of increased workload (Huggins *et al*., 2003). The aim of this study was to characterise the role of cardiac AngII in the pathogenesis of diabetic cardiomyopathy in a setting of normotensive cardiac hypertrophy.

Male wildtype (Wt) and cardiac-specific angiotensinogen overexpressing (AOGN-Tg) mice on a C57/Bl6J background were utilised (n = 6-8 /group). Diabetes was induced at 15 weeks by intraperitoneal injection of 55 mg/kg streptozotocin (STZ) for 5 consecutive days (*vs* control treatment of citric acid vehicle). Tail vein blood glucose level (BGL) was measured at 7 weeks post-diabetes induction. Mice were anaesthetized after 8 weeks with tribromoethanol (2.5% solution, 0.01 ml/g) and echocardiography was performed using a Vivid 9 Dimension (GE Vingmed) 15 MHz i13L linear phased array probe.

STZ-induced comparable increases in BGL in Wt and AOGN-Tg, and body weight (BW) remained unchanged between groups. The increase in cardiac weight index (CWI) in AOGN-Tg was less pronounced with diabetes. An overall significant effect of diabetes on septal wall thickness (IVSd) and posterior wall thickness (LVPWd) was observed. In Wt, septal wall thickness was moderately reduced by STZ treatment (8.33%), an effect accentuated in the AOGN-Tg (14.15%). The STZ-associated reduction in posterior wall thickness was apparent in both Wt and AOGN-Tg diabetic mice to a similar extent. The diabetes-associated increase in chamber diameter (LVIDd) was significantly greater in the AOGN-Tg mice compared to the Wt mice. Functional data demonstrated an overall significant reduction in ejection fraction (EF) linked with STZ treatment, and this reduction was more pronounced in the AOGN-Tg mice when compared with Wt (Wt 11.58% decrease; AOGN-Tg 30.28% decrease).

	Wt		**AOGN-Tg**	
	Vehicle	**STZ**	**Vehicle**	**STZ**
BGL (mmol/L)	8.4 ± 0.2	24.8 ± 1.07*	8.4 ± 0.3	22.7 ± 6.3*
BW (g)	28 ± 0.5	29.9 ± 1.0	29.5 ± 0.7	29.2 ± 0.5
CWI (mg/mm)	8.4 ± 0.3	7.8 ± 0.3	10.9 ± 0.6$^{\#}$	8.5 ± 0.5*
IVSd (mm)	0.84 ± 0.03	0.77 ± 0.02	1.06 ± 0.3$^{\#}$	0.91 ± 0.04*
LVPWd (mm)	1.0 ± 0.04	0.9 ± 0.03*	1.2 ± 0.08	1.0 ± 0.06*
LVIDd (mm)	3.6 ± 0.17	3.9 ± 0.06	3.4 ± 0.15	4.2 ± 0.18*
EF (%)	70 ± 4	65 ± 1*	77 ± 3	64 ± 1*

*$p < 0.05$ *vs* respective Vehicle $^{\#}p < 0.05$ *vs* respective Wildtype

Overall, these results confirm occurrence of modest ventricular dilatation accompanied by reduced functional performance with diabetes in wildtype. In the context of cardiac-specific elevation of AngII, this dilation and dysfunction is exacerbated. These AngII-related responses are observed in equivalent hyperglycaemic and normotensive conditions. These findings provide evidence that elevated cardiac AngII compounds the diabetic myocardial pathology even when there is no influence on hemodynamic loading.

Huggins CE, Domenighetti AA, Pedrazzini T, Pepe S, Delbridge LMD. (2003) *Journal of Renin-Angiotensin-Aldosterone System* **4**, 186–90.

Masuda T, Muto S, Fujisawa G, Iwazu Y, Kimura M, Kobayashi T, Nonaka-Sarukawa M, Sasaki N, Watanabe Y, Shinohara M, Murakami T, Shimada K, Kobayashi E, Kusano E. (2012) *American Journal of Physiology: Heart and Circulatory Physiology* **302**, H1871–83.