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**GLUCAGON-LIKE PEPTIDE-1 PROTECTS AGAINST
CARDIAC DYSFUNCTION AND EXTRACELLULAR
MATRIX REMODELLING IN EXPERIMENTAL DIABETES**

doi:10.1136/heartjnl-2012-303148a.3

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Glucagon-like peptide-1 (GLP-1) is an insulin-releasing hormone with established cardiovascular actions. Here, we investigated effects of exendin-4, a stable GLP-1 mimetic, on cardiac remodelling in experimental diabetes. Male C57BL/6J mice were injected with streptozotocin (STZ; 50 mg/kg/day for 5 days) or vehicle control prior to starting infusion with exendin-4 (25 nmol/kg/day) at 4 weeks. Continuous treatment with exendin-4 for 8 weeks had no effect on body weight but reduced blood glucose in STZ-treated animals (HbA1c: control 6.6 ± 0.3 vs STZ saline 11.8 ± 1.1 , $p < 0.01$; exendin-4 9.4 ± 0.9 vs STZ exendin-4 $6.5 \pm 0.3\%$, $p = \text{NS}$; $n = 4-9$). Echocardiography indicated that systolic function, assessed by fractional shortening, was similar between groups. However, diastolic dysfunction observed after STZ treatment was attenuated by exendin-4 (mitral valve E/A: STZ saline 1.17 ± 0.04 vs STZ exendin-4 1.51 ± 0.09 , $p < 0.05$; $n = 3-8$). Interestingly, these functional effects were associated with an improved pro-fibrotic gene expression profile, as assessed by real-time RT-PCR. For example, expression of procollagen I mRNA was reduced in STZ animals after exendin-4 treatment (STZ saline 4.32 ± 0.27 vs STZ exendin-4 3.02 ± 0.37 arbitrary units, $p < 0.05$; $n = 5-8$), and similar patterns were observed for procollagen III and fibronectin. Furthermore, differential STZ-induced effects on mRNA expression of matrix metalloproteinase-2 (MMP-2) (control 7.30 ± 0.46 vs STZ saline 9.21 ± 0.49 , $p < 0.05$; exendin-4 6.50 ± 0.11 vs STZ exendin-4 7.70 ± 0.45 arbitrary units, $p = \text{NS}$; $n = 5-7$) and MMP-9 (STZ saline 1.70 ± 0.35 vs STZ exendin-4 3.84 ± 0.63 arbitrary units, $p < 0.05$; $n = 5-8$) were inhibited by exendin-4. These data indicate that GLP-1 protects against adverse cardiac remodelling in diabetes via modulation of the extracellular matrix, although the underlying mechanisms remain unclear.