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In Situ Measurements of Cross-bridge Dynamics and Lattice Spacing in Diabetic Rat Hearts using X-ray DiffractionM. Jenkins^{1,2,*}, A. Edgley^{1,2}, T. Sonobe³, Y. Fujii³, H. Ishibashi-Ueda³, D. Kelly¹, D. Schwenke⁴, N. Yagi⁵, M. Shirai³, J. Pearson^{2,6}¹ Department of Medicine, St Vincents Hospital, University of Melbourne, Melbourne, Australia² Department of Physiology, Monash University, Melbourne, Australia³ National Cardiovascular Center Research Institute, Suita, Japan⁴ Department of Physiology, Otago University, Dunedin, New Zealand⁵ Japan Synchrotron Radiation Research Institute, Harima, Japan⁶ Australian Synchrotron, Melbourne, Australia

Independent of hypertension and coronary artery disease diabetes is associated with a specific diabetic cardiomyopathy. The use of synchrotron radiation (SR) as a source for small-angle X-ray diffraction allows the assessment of myocyte cross-bridge dynamics in situ and in real time. This study aimed to investigate cross-bridge dynamics and myosin interfilament lattice spacing, in situ, in diabetic rat hearts using SR.

Experiments were conducted at the Japanese Synchrotron, SPring-8 using anaesthetised Sprague-Dawley rats three weeks after treatment with either vehicle (control) or streptozotocin (diabetic; 65 mg/kg i.p.). Rats were thoracotomised and myocardial diffraction patterns were digitally recorded. Cardiac function was assessed simultaneously via cardiac catheterisation of the left ventricle (LV).

Preliminary analysis of our data shows that cross-bridge cycling in the beating hearts of diabetic rats is abnormal in the diastolic phase. Furthermore, recordings obtained from the anterior and posterior walls of the LV in diabetic rats at different depths within the myocardium reveals a transmural gradient of contractile depression not observed in controls. At progressively deeper layers within the diabetic heart wall (subepicardium and endocardial layers) diastolic intensity ratio (I_{1,0}/I_{1,1}) is elevated 4.0–8.0 versus 2.0–3.0 in controls, and is higher than that previously reported for resting muscle or arrested hearts 3.0–3.5. This suggests that in diabetic hearts myosin heads are forced further from actin filaments during diastole than normal.

Using synchrotron X-ray diffraction in situ, this preliminary analysis uncovers for the first time a significant impairment in the regulation of myosin head order in diabetic hearts during relaxation.

doi:10.1016/j.hlc.2011.05.019

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Losartan Improves Survival and Cardiac Function in a Double-mutant Mouse Model of Severe Hypertrophic CardiomyopathyR. Shephard^{1,2,*}, T. Tsoutsman^{1,2}, C. Semsarian^{1,2,3}¹ Centenary Institute, Sydney, Australia² University of Sydney, Australia³ Royal Prince Alfred Hospital, Sydney, Australia

Background: Hypertrophic cardiomyopathy (HCM) is an inherited disease of the myocardium, caused by sarcomere protein mutations. Five percent of HCM patients harbour multiple mutations leading to a more severe clinical phenotype (increased LV hypertrophy and incidence of sudden cardiac death events). Currently, there are no pharmacological therapies that have definitively been shown to prevent or cause regression of HCM. This study sought to investigate the role of the angiotensin II receptor inhibitor losartan in mice with severe HCM.

Methods: The TnI-203/MHC-403 mouse model, which expresses two HCM-causing mutations and results in a severe phenotype resulting in heart failure and 100% mortality by 21 days, was used. This model mimics a subset of HCM patients who develop a dilated phenotype and heart failure. TnI-203/MHC-403 and non-transgenic (NTg) mice were treated with either losartan (100 mg/kg, oral, daily) or water alone (control group). Outcome measures included survival and cardiac function.

Results: A total of $n = 125$ mice were treated with either losartan ($n = 67$) or water ($n = 58$). Losartan treatment significantly improved survival of TnI-203/MHC-403 mice, extending maximum lifespan by 35% (mean, 17.3 ± 1.6 days vs 23.3 ± 1.4 days; $p < 0.0001$). Echocardiographic analysis showed losartan treatment improved cardiac function in TnI-203/MHC-403 mice compared to water-treated TnI-203/MHC-403 mice (fractional shortening $54 \pm 4\%$ vs $40 \pm 14\%$; $p = 0.013$). The improvement in survival in losartan-treated mice was independent of gender.

Conclusion: Losartan treatment is beneficial in improving survival and cardiac function in a double-mutant mouse model of severe HCM. Further studies to investigate the molecular mechanisms underlying this response are warranted.

doi:10.1016/j.hlc.2011.05.020

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Phosphoinositide 3-Kinase p110alpha is a Master Regulator of Exercise-induced Cardiac Protection, Acting Independently of Heat Shock Protein 70K. Weeks^{1,2,*}, X. Gao¹, H. Kiriazis¹, M. Febbraio¹, X. Du¹, J. McMullen¹¹ Baker IDI Heart and Diabetes Institute, Australia² Department of Biochemistry and Molecular Biology, University of Melbourne, Australia

Background: Molecular mechanisms that mediate exercise-induced cardiac protection are not well defined.