ABSTRACTS

16

In Situ Measurements of Cross-bridge Dynamics and Lattice Spacing in Diabetic Rat Hearts using X-ray Diffraction

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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 (I1,0/I1,1) 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.

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17

Losartan Improves Survival and Cardiac Function in a Double-mutant Mouse Model of Severe Hypertrophic Cardiomyopathy

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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.

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18

Phosphoinositide 3-Kinase p110alpha is a Master Regulator of Exercise-induced Cardiac Protection, Acting Independently of Heat Shock Protein 70

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

We hypothesised that phosphoinositide 3-kinase p110α (PI3K) is critical for exercise-induced protection, as PI3K is activated in cardiomyocytes during exercise and is critical for heart growth following long-term training (athlete's heart).

Methods: Cardiac-specific transgenic mice with elevated or reduced PI3K activity (caPI3K and dnPI3K mice, respectively) and non-transgenic controls underwent four weeks of swim training followed by pressure-overload (ascending aortic banding, $n = 5$–9 per group). Systolic function was assessed by echocardiography one week post-surgery and heart tissue collected for histological and molecular analyses. Aortic banding was also performed in dnPI3K mice overexpressing heat shock protein 70 (Hsp70) to assess the relative importance of PI3K versus Hsp70 in mediating cardioprotection.

Results: Exercise training protected non-transgenic mice from developing heart failure following banding [improved systolic function ($P < 0.001$) and less cardiac hypertrophy ($P < 0.05$), lung congestion ($P < 0.001$) and fibrosis ($P < 0.05$) compared with untrained controls]. Banded caPI3K mice were protected from developing heart failure regardless of whether or not mice were exercised prior to banding (fractional shortening (FS) = 58%, no significant difference vs sham-operated caPI3K controls). In contrast, exercise had no protective effect in banded dnPI3K mice (FS = 30–35%; depressed vs non-transgenic, $P < 0.05$). Transgenic overexpression of Hsp70 did not improve the cardiac phenotype of banded dnPI3K mice.

Conclusion: PI3K is critical for mediating the protective effects of long-term exercise training in a mouse model of pressure-overload. Future studies will use a gene therapy approach to investigate the therapeutic potential of PI3K in heart failure.

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Vascular/Hypertension

19

2011 Draft Position Statement on the Use of Ambulatory Blood Pressure Monitoring in Australia: National Heart Foundation (NHF) & High Blood Pressure Research Council (HBPRCA)

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20

A Novel Framework to Assess Neural and Peripheral Characteristics in Hypertension using Baroreflex Equilibrium Diagram

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Background: Sympathetic nervous hyperactivity as well as the cardiovascular abnormality (arterial atherosclerosis and cardiac hypertrophy) has long been suspected to contribute to the pathogenesis of hypertension. However, quantitative, simultaneous and individual assessment of the neural and the peripheral characteristics responsible for increased arterial pressure has been difficult.

Methods: We investigated the open-loop characteristics of baroreflex function in anesthetised spontaneously hypertensive rats (SHR, $n = 7$) and normotensive Wistar Kyoto rats (WKY, $n = 6$) by isolating the carotid sinus baroreceptor. Carotid sinus pressure (CSP) was controlled at various pressures and the sympathetic nervous activity (SNA) and arterial pressure (AP) responses were recorded simultaneously. The transfer function from CSP to SNA [neural arc], and from SNA to AP [peripheral arc] were described in a baroreflex equilibrium diagram. Peripheral characteristics were additionally estimated by measuring plasma norepinephrine concentrations (NE) before and after autonomic blockade, and by examining AP response to phenylephrine administration.