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.

doi:10.1016/j.hlc.2011.05.021

Vascular/Hypertension

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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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Due to confidentiality reasons, the text of this abstract has been withheld from publication.

doi:10.1016/j.hlc.2011.05.022

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

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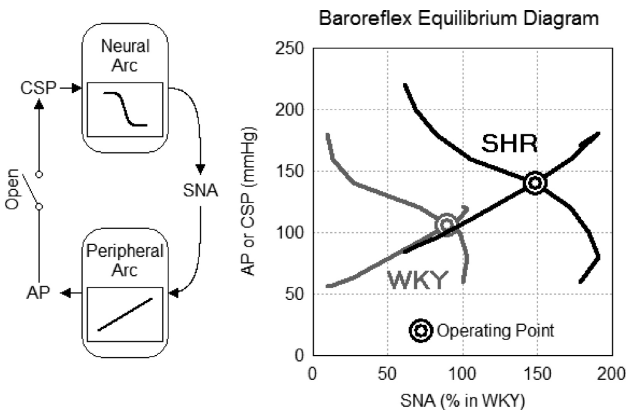
Background: Sympathetic nervous hyperactivity as well as the cardiovascular abnormality (arterial atherosclerosis and cardiac hypertrophy) has long been suspected to contribute to the pathogenesis of hypertension. However, quantitative, simultaneous and individual assessment of the neural and the peripheral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



Results: Although slope and offset of the baroreflex peripheral arc (linear relation) were similar, the neural arc response (inverted sigmoid curve) range was attenuated in SHR ($71 \pm 2\%$ vs. $91 \pm 3\%$, $P < 0.01$). The operating-point AP was higher in SHR than in WKY (144 ± 6 mm Hg vs. 109 ± 5 mm Hg, $P < 0.01$).

Although NE was higher in SHR at baseline condition (403.1 pg/ml vs. 203.2 pg/ml, $P < 0.01$), AP response to phenylephrine was similar (linear relation), suggesting preserved peripheral response to sympathetic activity.

Conclusion: The baroreflex equilibrium diagram indicates that baroreflex regulation of SNA rather than the cardiovascular response to SNA plays a critical role in the development of hypertension in SHR.

doi:10.1016/j.hlc.2011.05.023

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A Novel Recombinant CD39 Targeting Activated Platelets via a Fused Single-chain Antibody: Achieving Efficient Anti-coagulation While Minimising Bleeding Side Effects by Clot Directed Enrichment

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Introduction: CD39, an NTPDase with strong antithrombotic properties, has previously been shown to be protective in models of stroke, transplantations, pulmonary embolism and myocardial infarctions by hydrolysing/removing the platelet agonist ADP. However CD39's high potency comes at the cost of an increased bleeding risk. We hypothesise that targeting CD39 to activated platelets allows localised enrichment at the growing thrombus despite a low and safe systemic concentration.

Methods and results: CD39 was recombinantly fused to a single-chain antibody specific to activated platelets via selective binding to the active conformation of GPIIb/IIIa. The fusion construct was produced in Hek293 and purified using a His-tag chromatography step. Targeted-CD39 was significantly more effective at preventing platelet activation (flow cytometry) and platelet aggregation (aggregometry) with ADP and collagen as agonist than its non-targeted control (CD39 fused to a non-functional mutated single-chain antibody). Most importantly in a mouse model of ferric chloride-induced carotid artery thrombosis, targeted-CD39 was protective against vessel occlusion at a concentration at which the non-targeted-CD39 was ineffective ($p < 0.005$). At the same concentration no tail bleeding prolongation was observed for the targeted-CD39 while the ineffective non-targeted-CD39 showed a bleeding tendency ($p < 0.01$).

Conclusion: Targeting CD39 to its desired site of action enables administration of such a low concentration as to avoid the previously observed bleeding tendencies while still being a highly effective antithrombotic drug. Thus, enriching CD39 to activated platelets at growing thrombi prevents the previously limiting bleeding side effects and advances CD39 towards potential clinical use.

doi:10.1016/j.hlc.2011.05.024

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Acute Pulmonary Embolism (PE)—Is Echocardiography Underutilised in Regional Australia

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Background: Echocardiography is recommended after acute pulmonary embolisms (PE) to risk stratify patients at risk of developing chronic thromboembolic pulmonary hypertension (CTEPH) and then at six to eight weeks if elevated pulmonary artery systolic pressure (PASP) is found initially. The true incidence of CTEPH is unknown but ranges from 0.01% to 3%. PASP >50 mm Hg and age >70 years are risk factors for CTEPH. CTEPH is insidious in onset and missed in many patients. It is potentially curable if diagnosed early.

Methods: A retrospective one year case note review was undertaken of all confirmed (CT pulmonary angiography proven) PE cases (66 patients) admitted in Ballarat Base Hospital. Clinical variables, management and echocardiography reports were reviewed.

Results: Mean age was 59 years. Forty-seven percent of patients had troponin measured at diagnosis (Males 48%, females 44%) those with elevated troponin I (>0.04 ng/L) had prolonged hospital stay compared to normal result (10 days versus 5.4 days). Sinus tachycardia was most common ECG finding (30.3%).S1Q3T3 pattern on ECG was found in six patients. Deep venous thrombosis (DVT) accompanying PE was confirmed in 33% (22) patients. Echocardiogram was done in 45% (30) patients, with three patients (10%) all aged <70 years having pulmonary artery systolic pressure >50 mm Hg. Thus 33 eligible patients did not have echocardiogram.

PE patients	Echo	No echo	PASP > 50 mm Hg
66	30	33	3