

Hypertension Research in Perth



This month's article focuses on Hypertension Research in our most Western Capitol, Perth. We have contributions from three groups at the Royal Perth Hospital. Founded in 1829, the 855 bed hospital admits over 67,000 patients per year performing nearly 16,000 operations annually. It is not surprising then that RPH is a major teaching and research Hospital in Western Australia. The Hospital has a close association with the School of Medicine at the University of Western Australia, and with other state universities involved in the training of nursing and other health professionals. Its research output is outstanding with over 150 articles per year. There is also a great contribution from Jackie Philips now at the School of Veterinary and Biomedical Sciences at Murdoch University.

Neurocardiology Research Group : Royal Perth Hospital



Professor Leonard Arnolda heads the Royal Perth Hospital – based West Australian Neurocardiology Research Group (WANCR) of the School of Medicine and Pharmacology, University of Western Australia. The core members of the group (see photo) include **Dr Doug McKitrick** (current membership secretary HBPRCA) and **Dr Vasyl Holobotovskyy**. The group is independently involved in projects examining centrally organized cardiovascular reflexes, and the control of thirst and vasopressin secretion in hypertension, heart failure, cirrhosis and renal disease. **Mr Varun Malik** is currently completing a BMedSci degree investigating nitric oxide mechanisms involved in blood pressure control in spinal cord autonomic pathways and **Dr Kooi Ang** recently completed his Ph.D. examining mechanisms of thirst and vasopressin secretion in heart failure. There are

numerous associated student members working with the RPH group on collaborative projects (see below).

With **Dr Livia Hool** (UWA Physiology), **Drs Marie Bogoyevitch** and **Peter Arthur** (UWA Biochemistry) and **A/Prof Kevin Croft** (UWA Medicine), WANCR is completing studies investigating cardiac mitochondrial changes and systemic oxidative stress in mice exposed to chronic reno-vascular hypertension. The project employs a West Australian Institute for Medical Research – funded post-doc, **Dr Carla Di Maria**.

In collaboration with **A/Prof Steve Wilton** and **Dr Susan Fletcher** of the Australian Neuromuscular Research Institute, WANCR is investigating the pathophysiology and treatment of heart failure and intestinal smooth muscle dysfunction in the MDX mouse model of Duchene muscular dystrophy. WANCR supervises **Mr Joshua Steinhaus** (Ph.D candidate) in the project.

Cardiac Transplant Research Group: RPH

The Cardiac Transplant Research Group originated as a collaboration between **Roger Taylor** (Prof Cardiology RPH), **Gerry O'Driscoll** (Head Cardiac Transplant Unit RPH) and **Danny Green** (Assoc Prof UWA).



Over the past decade studies have focussed on the impact of various interventions, including cardiovascular medications (ACEI, ARB, statins, anti-TNF agents), antioxidants (vitamins, allopurinol) and exercise and exercise training interventions, on vascular structure and function in vivo. Studies have been performed across the continuum of health and disease, from elite athletes from the Institutes of Sport through type 2 diabetes and obesity in children to end stage heart failure patients on ventricular assist devices and post cardiac transplantation. Recent studies, in collaboration with **Len Arnolda** and **Doug McKitrick**, have also considered the impact of

cardiopulmonary baroreceptors and chemoreflex function on vasomotor control in humans.

The group currently consists of postdoctoral fellows and a number of post-graduates at Masters, PhD and Hons levels. Some of the outcomes of the studies performed in the past decade include: early studies providing evidence for pleiotropic roles of statins and ACE inhibitors (Circulation 1997;95:1126-1131; J. Clin. Invest. 1997;100:678-684; Diabetic Medicine 2000;17:553-554), evidence for a role of bradykinin sparing in vascular effects of ACE inhibitors (J. Am. Coll. Cardiol. 2000;36:1461-66; J. Am. Coll. Cardiol. 1999;33:1506-1511), benefits of antioxidant strategies in some groups with elevated oxidant stress (Clin. Sci. 1995;89:343-348; Clin. Exp. Pharm. Physiol. 1999;26:853-856; Clin. Sci. 1998;95:361-367), lack of effect of xanthine oxidase inhibition in vivo (Clin. Exp. Pharm. Physiol. 1999;26:779-783), systemic benefits of exercise training in the vasculature (J Physiol 2004;561:1-25; J. Am. Coll. Cardiol. 2001;38:860-866; Am. J. Physiol. 2000;279:H1999-H2005; Eur Heart J 24: 1681-1689, 2003), differential effects of exercise modalities on vascular shear stress in vivo (J Physiol 2004;561:1-25; J Physiol 562:617-628, 2005), significant effects of cardiopulmonary baroreceptors in vasomotor control in vivo (J Physiol: 560:919-27, 2004). A feature of the groups work has been the development and patenting, in collaboration with **Chris Reed** (Medical Physics RPH), of novel imaging tools for assessment of vascular structure and function in humans (J. Appl. Physiol. 2001;91:929-37; J. Appl. Physiol. 2002;93:361).

Molecular Neurobiology Laboratory : Murdoch University

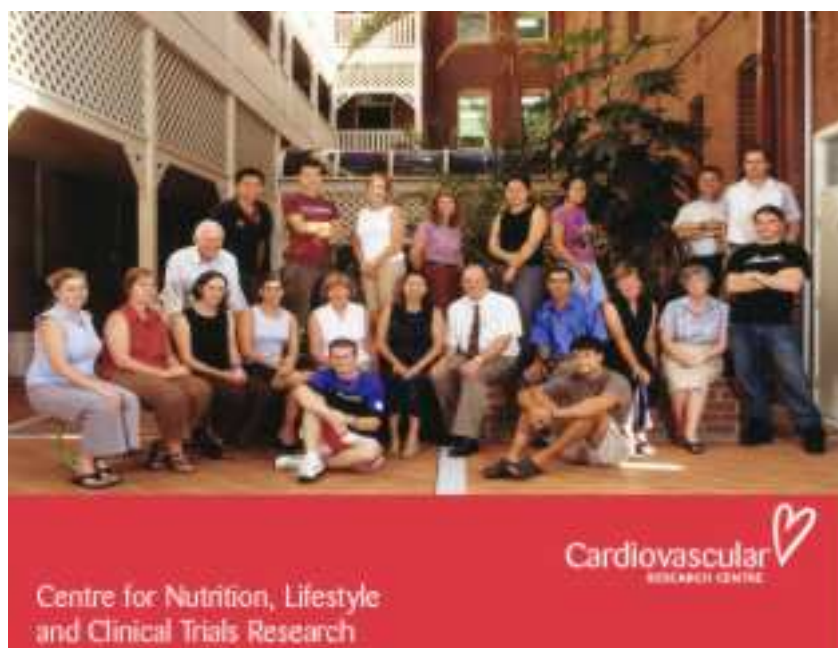


Jacqueline Phillips is based at Murdoch University and set up the Molecular Neurobiology Laboratory in January 2001, having moved from Auckland NZ (and prior to that from Canberra ACT). There are currently 7 people in the group, including **Rhonda Loxley** and **Courtney Reddrop** (RA's), **Kellysan Powers-Martin**, **Paula Fuller** and **Susannah Cleary** (PhD Students) and **Raihana Nordin** (Honors Student). Our primary research focus in the laboratory is on central nervous control of the circulation, with a focus on hypertension in both the spontaneous hypertensive rat model and renal hypertension. We are particularly interested in the neuro-anatomical

makeup of pathways controlling arterial pressure throughout the neuraxis, especially those cell populations within the rostral ventrolateral medulla (RVLM) and the sympathetic preganglionic neurons (SPN) in the spinal cord. The activity of RVLM neurons and their subsequent level of activity is regulated not only by baroreceptor input via the nucleus tractus solitarius and caudal ventrolateral medulla but also by synaptic inputs from many other areas of the central nervous system including the paraventricular nucleus of the hypothalamus. An increase in sympathoexcitatory output from the RVLM has been reported in different forms of hypertension, despite different initiating mechanisms. We are interested in altered nitric oxide (NO) signaling in both the RVLM and SPN in hypertension, and have been examining NO Synthase (NOS) isoform expression in these regions. NO can exert its effects by S-nitrosylation of proteins including the NMDA receptor and the activation of guanylyl cyclase/cGMP and we have also been looking at these pathways in the RVLM and SPN populations.

In a new project, we have been examining the role played by the sympathetic nervous system in driving hypertension in different models of renal disease. Renal failure and hypertension commonly occur hand-in-hand, and both conditions have significant impact on the well being of Australians today, not to mention their high costs on the health system. Much of our work is carried out in collaboration with the Neurocardiology Research Group at Royal Perth Hospital. Other projects in the laboratory included a study of the molecular mechanisms influencing the phenotypic expression of the adrenal medullary tumour pheochromocytoma, sympathetic nervous innervation of the skin in patients with complex regional pain syndrome and the role of neuromodulators in regulating contractile responses at the neuromuscular junction.

Cardiovascular Research Centre: RPH



The Cardiovascular Research Centre was formed in 2003 and is based at Royal Perth Hospital. The centre is part of the School of Medicine and Pharmacology at the University of Western Australia. Our mission of is to reduce cardiovascular disease through clinical trials and laboratory research with a focus on nutrition and lifestyle. The team includes [Professor Ian Puddey](#) (director), [Professor Lawrie Beilin](#), [Associate Professor Kevin Croft](#), [Dr Valerie Burke](#), [Dr Trevor Mori](#), [Dr Anne Barden](#), [Dr Kay Cox](#) and [Dr Jonathan Hodgson](#) who all have a long association with the School and studies of the effects of nutrition and lifestyle on cardiovascular risk. The research combines carefully controlled lifestyle interventions and population studies that are overseen by [Lawrie Beilin](#) and [Ian Puddey](#) and underpinned by laboratory expertise

that allows us to explore mechanisms of action. The centre holds an NH&MRC Clinical Centre of Excellence grant, NH&MRC project grants, and grants from the NHF, Healthway and the ARC.

[Lawrie Beilin](#), is currently examining the effect of genetic polymorphisms in both children and their parents and gene-environment interaction on phenotypes of cardiovascular health. This study is part of the ongoing Western Australian Pregnancy Cohort Study that has followed 2,860 children from birth to adolescence.

The department has a strong background in analytical chemistry and biochemistry. The Biomedical Mass Spectrometry Unit run by [Kevin Croft](#) and [Trevor Mori](#) has enabled the group to be at the frontiers of research into oxidative stress and fatty acid metabolism in relation to the pathogenesis of atherosclerosis.

[Kevin Croft](#) and [Jonathan Hodgson](#) have been examining the effects of γ -tocopherol, one of the major forms of vitamin E in the diet, and comparing its effects to those of α -tocopherol. Although α -tocopherol is a stronger antioxidant, γ -tocopherol differs in that it is capable of trapping reactive nitrogen species and its major metabolite has anti-inflammatory and natriuretic properties. They are undertaking a randomised controlled trial of 6 weeks supplementation with either mixed tocopherols (high in γ -tocopherol), α -tocopherol or placebo in subjects with Type 2 Diabetes. The end points are markers of oxidative stress and inflammation; vascular function and blood pressure. [Anne Barden](#) and [Kevin Croft](#) are examining the role of cytochrome P450 metabolites of arachidonic acid in the metabolic syndrome. This study will examine the effects of weight loss on vasodilator and vasoconstrictor cytochrome P450 metabolites of arachidonic acid in relation to their role in vascular function, blood pressure regulation and glucose and lipid metabolism.

The unit has a longstanding interest in the effects of long chain fatty acids derived from fish on cardiovascular risk. [Trevor Mori](#) is testing the hypothesis that supplementation with fish oils and coenzyme-Q10 (CoQ) will have independent and additive effects in improving the cardiovascular risk profile of patients with mild renal impairment. The primary aim is to determine whether a combined approach has additive effects in improving blood pressure, vascular function and arterial compliance. Secondary aims are to determine whether there are beneficial effects on ventricular function, markers of inflammation and oxidative stress.

[Ian Puddey](#) has established an international reputation for his studies of the effects of alcohol on blood pressure. To date intervention trials of the effects of alcohol have been confined to men. In collaboration with [Trevor Mori](#) and [Jonathan Hodgson](#), he has been conducting two trials examining the effects of alcohol on blood pressure and cardiovascular risk factors in women and in Type 2 diabetics.

[Kay Cox](#) has conducted a number of randomised controlled trials of the effects of exercise on blood pressure and cardiovascular risk and is now taking her exercise programs into the community setting. Focusing on the older adult population she is developing a training program for walk leaders and age-peer mentors from the community. A physical activity promotion package is being developed and will be used in a large-scale controlled intervention where its effects on long-term physical activity adherence will be assessed.

[Valerie Burke](#), [Trevor Mori](#) and [Lawrie Beilin](#) are conducting a 2 yr follow-up study of participants in the ADAPT trial, a health, promotion program for withdrawal of antihypertensive drugs in overweight hypertensives. The trial compared a usual care group, with a health promotion program incorporating improved dietary habits including increased fish consumption, weight control and physical activity. The study was a randomised controlled trial with initial 4 months of counselling, planned drug withdrawal and further 12 months follow-up. The program achieved improvements in a range of health-related behaviours and

cardiovascular risk factors in overweight men and women being treated with drugs to control hypertension. Program group individuals achieved a greater weight loss, a greater decrease in waist circumference, cholesterol and triglycerides, systolic and diastolic blood pressure and heart rate at the end of the program and at follow-up. The program was associated with a greater proportion of men with drug treatment withdrawn at the end of the program. The 2 year follow-up will be completed at the end of 2005.

Trevor Mori and Jonathan Hodgson are collaborating with the food industry evaluating the effects of novel foods based on a unique combination of soy and dairy products. This project is a new collaboration between So Natural Foods, and the Universities of Wollongong, South Australia and Western Australia. The aims are to develop novel foods based on a combination of soy and dairy and to determine if the combination of soy/dairy foods results in cholesterol reduction and other health benefits of soy, similar to soy alone. These studies are currently being carried out and are due to be completed by the end of 2005.