PROF MURRAY ESLER

A cardiologist with clinical and research interests in:
• the human sympathetic nervous system
• stress, and its effects on the heart and blood pressure
• causes and treatment of high blood pressure and heart failure
• neurotransmitters of the human brain

Prof Esler’s principal research contribution has been the development of isotope dilution methodology to study the human sympathetic nervous system, and the application of this tool in the investigation of the sympathetic neural physiology of circulatory control, aging, exercise and mental stress responses, and the neural cardiovascular pathophysiology of obesity, orthostatic intolerance, panic disorder and depressive illness, cardiac failure and essential hypertension. This research was pivotal to the emergence of the field of human cardiovascular neuroscience. The demonstration of a high level of activation of the cardiac sympathetic outflow in patients with heart failure provided the theoretical backdrop for the evaluation of beta-adrenergic blockers in this condition. More recently, the demonstration of activation of the renal sympathetic outflow in essential hypertension was the stimulus for the development of a new therapy for hypertension, radio-frequency ablation of the renal sympathetic nerves with a purpose-designed renal artery catheter. Prof Esler is the chief investigator of a trial describing the successes achieved with this new treatment published in the Lancet (2010;376:1903-1909) and Circulation (2012;126:2976-2982)

Research Brief
The primary continuing focus of my research, conducted with colleagues Gavin Lambert, Markus Schlaich and Elisabeth Lambert, is:

1. **Resistant Hypertension** The “sympathetic nervous system renaissance” in hypertension management, primarily taking the form or catheter-based renal denervation in resistant hypertension and centred in Melbourne, continues.

2. **Orthostatic Intolerance Syndromes** Disorders of postural circulatory control are common, very poorly understood and consequently not rationally treated. The simultaneous application of measurements of sympathetic nerve firing and transmitter release, coupled with sympathetic nerve protein analysis is proving productive.

3. **Psychogenic Cardiovascular Disease** Research of my group on the psychological dimensions of cardiovascular medicine continues, now with a focus specifically on understanding and quantifying the psychological benefits of renal denervation in resistant hypertension.

Methodologies
The key research tools are isotope dilution measurement of noradrenaline spillover to quantify sympathetic activity in internal organs; single fibre sympathetic nerve recording; western blot quantification of sympathetic nerve proteins in biopsied subcutaneous forearm veins; sympathetic nerve immunohistochemistry; psychometric scaling

Selected Publications
- Symplicity HTN-2 Investigators. Renal sympathetic denervationin patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomized controlled trial (Chief Investigator and Corresponding Author). Lancet 2010;376:1903-1309.
Catheter-Based Renal Denervation for Hypertension Treatment

The catheter-based renal denervation treatment of drug-resistant essential hypertension was initiated in Melbourne. Safety, efficacy and durability of the procedure have been established. Our pilot studies indicate the value of the method also in renal hypertension. The current areas we are pursuing are:
1. Application in milder grades of hypertension, attempting a “cure”
2. Applying renal denervation in cardiac failure
3. Development of an on-line measure of renal denervation on the study day (which is lacking at present)
4. Evaluating whether the well documented progressive fall in BP after renal denervation is due to cardiovascular remodelling
5. Establishing the optimal level of denervation for BP-lowering

Neural Circulatory Mechanisms of Orthostatic Intolerance

Orthostatic intolerance can be due to neural degenerative disease, of sympathetic nerves (Pure Autonomic Failure) or the CNS (Multiple System Atrophy, Parkinsonism), or due to regulatory disorders in an anatomically intact sympathetic nervous system. The three phenotypic variants of the latter we report (Intern Med J 2010;40:554-560) are Postural Tachycardia Syndrome (POTS), Vasovagal syndrome with low (< 90 mm Hg) supine blood pressure, and Vasovagal syndrome with normal supine BP. Analysis of sympathetic proteins (accessed from a subcutaneous forearm vein biopsy, depicted below) has identified a “molecular signature” of each. For POTS, this is markedly reduced noradrenaline transporter (NET) protein, which magnifies the effect of nerve firing, and underlies the postural tachycardia, and the CNS neural vasoconstriction causing the syncope (Circ Arrhythmia Electrophysiol 2008;1:103-109). In Vasovagal syndrome with normal supine BP, sympathetic nerve NET protein is increased, augmenting clearance of noradrenaline from the sympathetic synapse and reducing the postural neuroeffector sympathetic response (Circ Arrhythmia Electrophysiol 2011;4:711-718). For Vasovagal syndrome with low (< 90 mm Hg) supine blood pressure, reduction in tyrosine hydroxylase protein (rate-limiting in noradrenaline synthesis) and consequently noradrenaline release is key (Circ Arrhythmia Electrophysiol 2011;4:711-718).

Sympathetic Nerve Proteins: Molecular analysis on a vein biopsy

![Sympathetic Nerve Proteins](image-url)