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NO GENERATION, BLOOD PRESSURE AND VASCULAR STIFFNESS: LESSONS FROM THE ANGIOTENSIN AT2 RECEPTOR

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designs remain to be fully characterised, although shear stress, wall tensile stress and metabolic stimuli are likely candidates.^{4,5} I will also review evidence that deviations from a minimal cost condition or optimal design may provide both a measure of disease severity and insights into the underlying disease mechanism.

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Invited Lecture

NO GENERATION, BLOOD PRESSURE AND VASCULAR STIFFNESS: LESSONS FROM THE ANGIOTENSIN AT2 RECEPTOR

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Vascular remodeling participates in the development and progression of cardiovascular conditions such as hypertension, atherosclerosis or aneurysm. This process is fine-tuned by neuro-humoral regulatory pathways: the renin-angiotensin system (RAS), being one of the most important. Chronic RAS activation, via AT1 receptor (AT1R) stimulation sets on a series of pro-proliferative, pro-fibrotic, pro-inflammatory signals that promote vascular remodeling and lead to adverse cardiovascular outcomes. The prevention of these outcomes after the blockade of this "deleterious" RAS might be at least in part mediated by the activation of the "protective" RAS. The "protective" RAS involves the AT2 receptor (AT2R) with anti-proliferative, anti-fibrotic, anti-inflammatory and anti-oxidant effects. Some of these protective actions of AT2R stimulation are mediated by AT2R-induced NO generation. Stimulation of AT2R with the new selective, orally active AT2R agonist, Compound 21, in L-NAME hypertensive rats reduced vascular stiffness (pulse wave velocity) and induced vascular structural improvements without lowering blood pressure. These effects cannot be ascribed to NO generation. Alternative effector pathways include activation of protein phosphatases that inactivate the pro-fibrotic MAPKs or anti-apoptotic Bcl-2, down-regulation of MAPKs with NADPH oxidase inhibition and subsequent attenuation of oxidative load, inhibition of NF- κ B activity by epoxidation of 11,12-epoxy-eicosatrienoic acid, direct and indirect anti-inflammatory action with augmented IL-10 production and T cell differentiation, and, finally, heterodimerization of the AT2R with AT1R that abrogates the AT1R-dependent pro-fibrotic effects.

McDonald Lecture

CROSS-SECTIONAL ARTERIAL MECHANICS: THE RENAISSANCE

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These last years, the widespread use of regional pulse wave velocity in clinical practice has overlooked the usefulness of local arterial stiffness. Indeed, the elastic properties of large superficial arteries (carotid, femoral, brachial and radial) can be assessed locally through the systolic-diastolic variations in arterial lumen diameter and thickness using high resolution echotracking systems, and local pulse pressure using aplanation tonometry. The mechanical properties of deep arteries like the thoracic aorta can be assessed using cine magnetic resonance imaging (MRI).

The aim of this review is to discuss how the measurement of the geometrical and functional properties of large arteries contributed to important conceptual achievements in arterial mechanics. Several aspects are discussed that concern the pathophysiology, pharmacology and epidemiology of arterial stiffness. We explain (1) how the precise phenotyping of the changes

in large and small artery during essential hypertension can enter a vicious circle of aggravation named large/small artery cross-talk; (2) how the understanding of the wall material elastic properties that are associated with arterial wall hypertrophy in essential hypertension, has led to the discovery of putative novel mechanisms involved in arterial stiffness; (3) how local measurements of arterial stiffness can help to find the true pathway followed by the pressure wave, when a single-site measurement/arm cuff oscillometric method is used; (4) how the study of arterial remodeling and mechanics during long-term antihypertensive treatment can unmask a blood-pressure independent reduction in arterial stiffness; and, finally (5) how carotid stiffness can predict cardiovascular events independently of regional pulse wave velocity.

Debate

CENTRAL PRESSURE SHOULD BE USED IN CLINICAL PRACTICE

J. Sharman

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The original purpose for developing the technique to record brachial blood pressure (BP) more than 100 years ago was to estimate aortic (central) BP. While high brachial BP is an important cardiovascular risk factor, it is clear that major differences in central systolic BP (SBP; e.g. >30 mmHg) can occur among people with similar brachial SBP. It is also proven that central SBP responses to antihypertensive therapy can differ substantially from brachial SBP responses, such that true treatment effects cannot be gauged from conventional brachial BP. Importantly, assessment of central BP results in: 1) improved predictive accuracy of future cardiovascular events beyond brachial BP and other cardiovascular risk factors; 2) superior diagnostic accuracy over brachial BP and; 3) different patient management than usual care guided by brachial BP. Collectively the above data satisfy criteria for central BP being a better cardiovascular risk biomarker than brachial BP. As with all medical advances there are areas of research need and international consensus is required on issues such as standardization of techniques. However, central BP can now be accurately estimated (with appropriate waveform calibration) using brachial cuff methods in an approach that is familiar to clinicians, acceptable to patients and amenable to widespread use. In other words, this modern BP technique finally satisfies the original purpose for measuring BP as intended more than 100 years ago. Although the tipping point towards routine use is yet to be reached, the body of evidence continues to favour the view that central BP should be used in clinical practice.

Debate

CENTRAL PRESSURE SHOULD BE USED IN CLINICAL PRACTICE

G. Mitchell

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The heart, brain and kidneys are key targets of pulsatile damage in older people and in patients with longstanding hypertension. These central organs are exposed to central systolic and pulse pressures, which may differ from the corresponding peripheral pressures measured in the brachial artery. Studies employing the generalized transfer function as a means to estimate central pressure have demonstrated a large difference between central and peripheral systolic and pulse pressure that diminishes with age but remains substantial even in octogenarians. As a result of this persistent difference, some have advocated that central pressure may represent a more robust indicator of risk for target organ damage and major cardiovascular disease events. From the perspective of risk prediction, it is important to acknowledge that a new technique must add incremental predictive value to what is already commonly measured. Thus, in order to justify the added complexity and expense implicit in the measurement, central pressure must be shown to add significantly to a risk factor model that includes standard cardiovascular disease risk factors. A limited number of studies have shown marginally better correlations between central pressure pulsatility and continuous measures of target organ damage in the heart. A similarly limited number of prospective studies in unique cohorts have suggested that central pressure may provide marginally better risk stratification, although no reclassification analysis has been published. Thus, currently available evidence does not provide sufficient justification for widespread adoption and routine use of central pressure measurements in clinical practice.