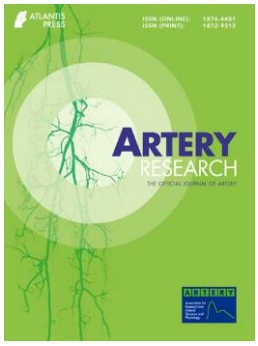

Artery Research

ISSN (Online): 1876-4401 **ISSN (Print): 1872-9312**
Journal Home Page: https://www.atlantis-press.com/journals/artres

WAVE POTENTIAL: A UNIFIED MODEL OF ARTERIAL WAVES, RESERVOIR PHENOMENA AND THEIR INTERACTION

Jonathan P. Mynard, Joseph J. Smolich

To cite this article: Jonathan P. Mynard, Joseph J. Smolich (2016) WAVE POTENTIAL: A UNIFIED MODEL OF ARTERIAL WAVES, RESERVOIR PHENOMENA AND THEIR INTERACTION, Artery Research 16:C, 45–46, DOI: https://doi.org/10.1016/j.artres.2016.10.148

To link to this article: https://doi.org/10.1016/j.artres.2016.10.148

Published online: 7 December 2019

Artery Research (2016) 16, 45–47

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

ARTERY Conference 16 — Speaker

Opening Lecture
REMODELLING SMALL ARTERIES AND PHD TRAINING: A JOURNEY

Michael J. Mulvany, Professor
Professor emeritus, Department of Biomedicine, Aarhus University, Denmark Aarhus University, Aarhus, Denmark

Abstract
Biomedical research is increasingly based on the efforts of PhD students. This talk will trace the development of the author's research, and show how this experience can be used to optimize PhD training. The basis of the research has been that essential hypertension is associated with increased peripheral resistance due to narrowing of the small arteries and arterioles. The author's PhD training ended in 1978 with development of a technique that enabled accurate measurement of the structure and function of small arteries. The technique was adopted by many laboratories world-wide, and also formed the basis for the author to establish a research group (with 22 PhD students over the years) that elucidated excitation-contraction properties and the morphology of small arteries, and how these were altered in essential hypertension. Vessels showed increased media:lumen ratio with inward eutrophic remodelling and limited functional changes. The remodelling was found to have prognostic consequences. The inward remodelling was found to be due to the vasoconstriction itself, mediated through multiple cellular pathways. The remodelling can be prevented by vasodilators and the results have had clinical effect. While this career path points to some success, it would unlikely happen in today's academic environment in that the author's PhD training took about 10 years. Through being head of the faculty graduate school and vice-president of the organization ORPHEUS (Organization for PhD education in Biomedicine and Health Sciences in the European System), the author has sought to establish procedures to ensure that today's PhD students are able to prepare for successful careers — within or outside of academia — even within the normal 3-4 year time constraints.

Special Guest Lecture
STEM CELL THERAPY FOR CARDIOVASCULAR DISEASES

Jean Sebastien Silvestre, Professor
INSERM UMRS 970, Paris Cardiovascular Research Center, Université Paris Descartes, Sorbonne Paris Cité, Paris, France

Abstract
Stem cell-based therapies for vascular regeneration in patients with cardiovascular ischemic diseases initially relied on a very simple concept: therapeutic stem/progenitor cells might differentiate into vascular cells, mainly of endothelial phenotype, increasing new vessel formation and tissue perfusion in the ischemic milieu. This exciting notion challenged the scientific community to start the quest for the Holy Grail in vascular regenerative medicine: the search for the ideal source of endothelial stem/progenitor cells. This concept leads to the development of salutary approaches based on the use of therapeutic autologous adult stem cells thought to contain such bona-fide endothelial progenitor cells such as bone marrow- or peripheral blood-derived mononuclear cells. Beside the classical technical caveats including modalities of cell transfer and optimization of cell engraftment, the negative impact of cardiovascular risk factors as well as the low rate of incorporation of adult stem cells in the targeted vasculature likely explain the mixed results obtained in numerous phase I-II clinical trials incorporating patients with peripheral artery or cardiac diseases. Hence, alternative sources of stem cells have been considered to leverage their intrinsic pluripotentiality and drive them towards a vascular lineage. Both embryonic stem cells and induced pluripotent stem cells have then been tested in various experimental models of post-ischemic vascularization. However, as for their adult counterpart, these "embryonic" cells do not structurally integrate within the recipient vascular network but likely release biomolecules that fine-tune endogenous repair processes. A precise characterization of the cell-released factors purportedly accounting for their benefits still remains elusive. However, there are mounting evidences to suggest that stem cells can release extracellular membrane vesicles that may contain vascular regenerative entities. Hence, the natural evolution of the stem cell theory for vascular regeneration may end with the development of cell-free strategies with multiple cellular targets including vascular cells but also other infiltrating or resident cells.

Invited Lecture
ARTERIAL PROTEOMICS: LESSONS IN RELATION TO STIFFNESS, ANEURYSMS, DIABETES AND OTHER CONDITIONS

Lars Melholt Rasmussen, Professor
Clinical Biochemistry, Odense University Hospital, Odense, Denmark

Abstract
Proteins are the main molecular components of the arterial wall. Alterations in the amounts of specific proteins in both the extracellular matrix and in vascular cells are believed to be associated with different arterial pathologies, however only sparse data is currently available, particularly in relation to human arteries.
Proteome analysis is large scale analysis of the quantity of many proteins in a single analytical run from biological samples. Combining "state of the art" proteome analysis by LC-MS (liquid chromatography-mass spectrometry) with access to samples from a large human artery biobank, we have obtained knowledge about protein changes in arteries from patients with various cardiovascular conditions. Specific alterations in matrix proteins are for example present in relation to increased arterial stiffness and to diabetes, whereas alterations in non-matrix proteins are associated with the growth rate of aortic aneurysms.
Such new knowledge about changes of arterial proteins in specific vascular conditions can direct our attention towards pathophysiological understandings and display routes to new potential treatment targets and novel biomarkers for arterial diseases.

Career Development Lecture
WAVE POTENTIAL: A UNIFIED MODEL OF ARTERIAL WAVES, RESERVOIR PHENOMENA AND THEIR INTERACTION

Jonathan P. Mynard, Joseph J. Smolich
Heart Research, Clinical Sciences, Murdoch Childrens Research Institute, Department of Paediatrics, University of Melbourne, Australia

Abstract
Models of haemodynamics play a central role in current research directed to understanding and addressing cardiovascular disease. Although

conventional windkessel and wave models are very useful, they are incompatible due to conflicting assumptions and neither comprehensively explain the basis and interdependencies of pressure/flow waves, mean pressure and reservoir filling/discharge phenomena. The hybrid reservoir-wave model was proposed to address this gap, but is not widely accepted due to theoretical inconsistencies and negative results from validation studies. We recently described a unified model of haemodynamics based on the concept of 'wave potential', which identifies physically meaningful information from the absolute values of the forward/backward components of pressure and flow. Within this paradigm, hydraulic power may also be separated into forward/backward components, thus allowing study of time-dependent cardiac and vascular effects that influence hydraulic power output and efficiency. Based on in vivo and numerical experiments, it has been shown that 1) absolute values of the pressure/flow/power components represent wave potential, spatial gradients of which produce waves that transfer hydraulic energy, 2) mean pressure is generated by waves, 3) wave potential is a measure of local conduit arterial reservoir function and stored hydraulic energy, and 4) the diastolic pressure decay and associated 'self-cancelling' diastolic waves can be explained purely on the basis of wave reflection and distal leakage of wave potential. Wave potential provides a unified and analytically simple paradigm of arterial haemodynamics that extends and is fully compatible with conventional wave separation, while overcoming the difficulties encountered with the reservoir-wave paradigm.

Career Development Lecture
VASCULAR DYSFUNCTION: AT THE HEART OF CARDIOVASCULAR DISEASE, COGNITIVE IMPAIRMENT AND DEPRESSIVE SYMPTOMS

Dr Thomas van Sloten
Maastricht University Medical Centre, Maastricht, The Netherlands

Vascular dysfunction may be an important pathway through which ageing and other factors, such as diabetes and obesity, can cause diseases of the heart and brain. Vascular dysfunction includes dysfunction of large arteries (due to arterial stiffness), the microcirculation (microvascular dysfunction) and endothelium (endothelial dysfunction). We have investigated, in a series of epidemiological studies, the role of vascular dysfunction in the pathogenesis of cardiovascular disease, dementia and depression. Data were used of The Hoorn Study, The AGES-Reykjavik Study, The Maastricht Study and The SUVIMAX2 Study. In addition, we did two systematic reviews and an individual participant data meta-analysis.
We found that stiffening of the carotid artery is independently associated with incident stroke, but not with coronary heart disease. Furthermore, carotid stiffness improved stroke risk prediction beyond Framingham and cfPWV. In addition, femoral artery stiffening was independently associated with incident cardiovascular disease.
Brain MRI studies showed that cerebral small vessel disease is associated with cognitive decline and incident depressive symptoms. In addition, arterial stiffening was associated with cognitive impairment and depressive symptoms, and this association was mediated by cerebral small vessel disease. We also found that endothelial dysfunction is associated with more depressive symptoms. Finally, we showed the presence of interaction (synergy) with regard to cardiovascular risk, between endothelial dysfunction and type 2 diabetes.
From a clinical point of view, these associations are important as they suggest that efforts at favourably influencing vascular dysfunction can have significant public health implications via prevention of cardiovascular disease, dementia and depression.

Career Development Lecture
ARTERIAL INFLAMMATION, BLOOD PRESSURE AND CENTRAL HEMODYNAMICS — THE ABC OF DIABETIC ANGIOPATHY

Simone Theilade
Steno Diabetes Center, Gentofte, Denmark

Aim: In diabetes patients, we explored relationships between markers of diabetic angiopathy, diabetic complications and adverse outcome.

Methods: Patients were recruited from 3 observational studies from Steno Diabetes Center, Denmark and one randomized, double-blind, international, multicentre study.
We investigated inflammatory proteins, blood pressure (BP) and central hemodynamics as markers of diabetic angiopathy.
Inflammatory proteins were soluble urokinase plasminogen activator receptor and placental growth factor, measured from frozen blood samples (suPARnostic®, ViroGates, Denmark and Elecsys®, Roche, Germany). Sphygmomanometry and/or tonometry measured BPs.
PWV and PWA recordings were obtained with SphygmoCor (Atcor, Sydney, Australia) and Bpro (HealthStats, Singapore) (only PWA). PWA recordings included central BPs, augmentation pressure, augmentation index and subendocardial viability ratio.
Results: We demonstrated increased arterial inflammation and arterial stiffness, and altered central hemodynamics in diabetes. These changes were augmented with longer diabetes duration. Furthermore, diabetic angiopathy measures were related to diabetic complications and predictive of adverse outcome.
We demonstrated significant discrepancies between office and 24-hour BPs, documenting considerable undertreatment of patients and a substantiated need for 24-hour BP recordings.
We demonstrated significant differences in central and brachial BPs, and proposed reference values for central BP in diabetes patients.
Conclusions: Our data show added diagnostic and prognostic value of measurements of diabetic angiopathy evaluated as measures of arterial inflammation, 24-hour ambulatory BP, central BP, arterial stiffness and pulse wave reflection.
Perspectives: Evaluating markers of diabetic angiopathy, may help identify patients at higher risk for development of diabetic complications. These patients may be suited for advanced and earlier medical treatment.

Special Guest Lecture
WHY DOES NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) CONTRIBUTE TO CARDIOVASCULAR OUTCOMES?

Hannele Yki-Järvinen, Professor
Professor of Medicine, Department of Medicine University of Helsinki, Helsinki, Finland

Take home messages

1. Both 'Metabolic NAFLD' and the features of insulin resistance/the metabolic syndrome (MetS) increase the risk of cardiovascular disease (CVD), even independent of obesity
2. 'Metabolic NAFLD' and insulin resistance share common pathophysiology, which may explain their link with CVD
3. 'Metabolic NAFLD' may be even a better predictor of CVD as it measures more directly abnormal metabolism than the MetS
4. Carriers of the I148M gene variant in PNPLA3 with NAFLD have steatosis but not features of insulin resistance implying that steatosis and insulin resistance and the risk for CVD dissociate

Features of insulin resistance/the metabolic syndrome (MetS) predict cardiovascular disease (CVD), even independent of obesity. NAFLD, diagnosed by liver enzymes, ultrasound or a liver biopsy, has also been shown in at least 14 prospective studies to predict CVD independent of obesity.
The MetS and NAFLD share common pathophysiology. The liver is the site of production of two of the key components of the MetS, fasting serum glucose and very-low density lipoprotein. In subjects with NAFLD, the ability of insulin to normally suppress production of glucose and VLDL is impaired resulting in hyperglycemia and hyperinsulinemia and hypertriglyceridemia combined with low HDL cholesterol. The liver, once fatty, also overproduces many other markers of cardiovascular risk such as C-reactive protein, fibrinogen, coagulation factors and plasminogen activator inhibitor-1.
The increases in markers of insulin resistance and of cardiovascular risk in NAFLD are associated with endothelial vascular dysfunction and could in part explain why NAFLD predicts CVD. NAFLD may be an even better predictor of the risk of CVD than the MetS. Whether this is because measurement of liver fat content provides a more direct estimate of the risk of CVD than the MetS, which can be diagnosed using 10 different combinations of its 5 components or other mechanisms is unclear.