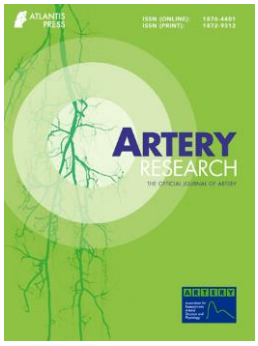

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PROTEOMICS OF THE VESSEL WALL

Manual Mayr

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Invited Speaker Abstracts

Opening Lecture
IMAGING OF THE CARDIOVASCULAR SYSTEM

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MR and PET vessel wall imaging have progressed substantially in the past decade and considerable technical improvements have been made in image acquisition and the development of cell and protein specific contrast agents that allow plaque characterization both on a morphological and molecular/cellular level. Studies in animal models of experimental atherosclerosis and small single center pilot clinical studies have demonstrated the feasibility of molecular MR and PET vessel wall imaging in the carotid artery, the aorta and the coronary arteries. These studies demonstrate the potential of those techniques for the non-invasive quantification of plaque burden and molecular composition, which could lead to improved risk stratification in patients with cardiovascular disease. With the advent of PET/MRI and continued development of target specific contrast agents, these novel techniques have potential to be useful for the non-invasive assessment of atherosclerosis and for monitoring response to treatment in clinical practice.

Career Development Lecture
ARTERIAL STIFFENING ACROSS MULTIPLE LENGTH SCALES

Riaz Akhtar
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It is well established that aortic stiffness increases with age, and as a result of a number of risk factors including diabetes. Most quantitative measurements of arterial stiffness involve the use of in vivo techniques such as pulse wave velocity or ex vivo techniques such as tensile testing. However, the aorta has a complicated and intricate structure, governed by the properties and composition of the microstructural components of the vessel wall. Hence, these methods provide an average macroscopic response of the material properties and little is known about the effects of ageing and disease on individual components of the aorta.
We present data obtained with novel materials science techniques that allow us to localise mechanical property changes at the microstructural and molecular scale. The scanning acoustic microscope (SAM), when operated at frequencies close to 1 GHz, can provide quantitative measurements of acoustic wave speed (related to tissue stiffness) with a spatial resolution around 1 μm. We have employed SAM to examine changes in the aorta due to ageing, diabetes and Cardiotrophin-1 treatment using animal models. In each case, the inter-lamellar regions of the media have been found to be a key determinant of the overall mechanical and structural properties of the aorta. At the molecular level, we examine the role of fibrillin microfibrils on aorta properties using atomic force microscopy (AFM). These data are compared with the in vivo and macroscopic response of the vessel.

Career Development Lecture – ARTERY 13
CARDIOVASCULAR AGING: INSIGHTS FROM MAGNETIC RESONANCE IMAGING

Alban Redheuil
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Aortic stiffness is now established as an independent marker of cardiovascular aging and cardiovascular risk. However, the specific role of the proximal aorta, specifically the ascending aorta, remains understudied. Magnetic resonance imaging (MRI), a non invasive technique has recently been proposed to measure new local and regional stiffness indices in the thoracic aorta. We will here review the available data on aortic stiffness assessed by MRI. We will discuss the methodological advantages and challenges of MRI, combined with applanation tonometry, to evaluate local aortic distensibility and pulse wave velocity (PWV) and summarize available results concerning the distribution of such parameters in both the general population and disease and their prognostic value.
Aortic distensibility has been shown to be an early subclinical marker of vascular target organ damage in the general population and expected ranges for ascending aortic distensibility and aortic arch pulse wave velocity assessed in MRI have been described in the general population and in disease. Changes in aortic distensibility and arch PWV have been related to age-related geometric changes, specifically lengthening, enlargement and unfolding of the thoracic aorta. Increased proximal aortic stiffness measured by MRI has also been related to decreased systolic and diastolic function and concentric remodeling of the left ventricule in healthy individuals. Data are now available for proximal aortic stiffness in diabetes, hypertension and aortic diseases such as bicuspid aortic valve or Marfan syndrome. We will review data on aortic distensibility as an independent predictor of mortality and incident cardiovascular disease in the general population.

Special Guest Lecture
PROTEOMICS OF THE VESSEL WALL

Manual Mayr, Professor
Senior Fellow of the British Heart Foundation and Professor of Cardiovascular Proteomics, King's College London, UK

Proteomics has made tremendous progress over the recent years. Initiatives, such as the Human Protein Atlas project, provide a great resource by capturing the *in vivo* location of proteins in different tissues and by making these data publically available (www.proteinatlas.org). Apart from the inherent limitations of antibody-based detection (antibody specificity, epitope masking, etc.), the only cardiovascular relevant tissue in the Human Protein Atlas is the heart. No large blood vessels are included in the tissue bank. At present, functional analysis tools do not capture some of the vascular proteins because these proteins are either only expressed during disease and/or not annotated as vascular proteins in the public databases.
Our group introduced new methods for the use of proteomics to study the vascular extracellular matrix and applied them to uncover extracellular

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matrix degradation during aneurysm formation. Our current understanding of extracellular matrix remodeling during vascular diseases is limited to a few molecules of interest that are investigated intensively whilst others are not studied at all. Moreover, data on specificities or commonalities between the extracellular matrices of different vessels is sparse. It will be essential that high-quality vascular proteomic data investigating changes in the vessel wall with aging and diseaseare made publically accessible to advance the field (adapted from Mayr M. Vascular Proteomics — the forgotten blood vessels. *Proteomics Clin Appl.* 2013 Aug;7(7-8):463.).

FOCUS: FUNCTIONAL IMAGING – MRI AND PET

Ian Wilkinson, Reader, BHF WE Parkes Senior
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The ground-breaking developments in non-invasive imaging over the last 50 years has provided a range of exciting new tools for physiologists and clinicians interested in large artery structure and function. The main focus of my lecture will be on MRI and PET/CT.
MRI can be used in a number of different ways to provide useful information about large arteries, including: arterial diameter, wall thickness, endothelial function, neovascularization, and the distribution of plaque. However, perhaps the most common is the assessment of vessel stiffness. This can be done by measuring distension waveforms or pulse wave velocity (PWV). Particular advantages of MRI are that measurement sites is not limited by anatomy, and accurate path lengths can be obtained for PWV estimation. However, temporal resolution is limited, which means that most waveforms are a composite average over several heartbeats or minutes. Nevertheless, MRI has provided useful information about regional age-related changes in structure and stiffness within the aorta.
A number of PET ligands are in clinical use, the most common being FDG. Uptake depends on metabolic activity, which is often used as a surrogate of inflammation. FDG PET/CT can aid the diagnosis of vasculitis and response to anti-inflammatory therapy. Emerging data suggests that chronic inflammatory diseases such as rheumatoid arthritis and COPD are associated with aortic inflammation, which may explain why they are also associated with increased, but reversible aortic stiffening. Other potentially interesting ligands are NaF (calcium), and FMISO (hypoxia).

FOCUS: FUNCTIONAL IMAGING - ULTRASOUND

Chris L. de Korte, Hendrik H. G. Hansen
Medical UltraSound Imaging Centre (MUSIC), Department of Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

Introduction: Intravascular Elastography has proven to be a sensitive tool to identify vulnerable plaques in coronary arteries. It is a technique to assess the deformation (strain) due to the pulsatile blood pressure of the vessel wall and plaque. However, for screening asymptomatic patients, a noninvasive technique is required. Using linear array transducers, the carotid artery can be imaged noninvasively. However, in contrast to intravascular ultrasound catheters, the ultrasound field is not co-aligned with the radial strain in the arterial wall for cross-sectional imaging. We developed a compounding technique to circumvent this problem and to reconstruct radial strain images of the carotid artery and plaques.
Methods: Linear array transducers are capable of emitting the ultrasound field under different angles. By compounding strain images acquired under different angles, the radial strain can be determined for the full cross-section of the carotid artery. The method was validated using phantoms of arteries with and without plaque. In vivo data was acquired in patients before an endarterectomy procedure was performed allowing validation of the technique by histology.
Results: Using the noninvasive elastographic compounding technique, high quality elastograms of arterial tissues and plaque can be obtained. Phantom experiments revealed that the quality of these elastograms is similar to that of elastograms obtained with intravascular elastography. Receiver operating curves demonstrate high correlations with histologically determined vulnerable plaque features. For the detection of lipid content and superficial macrophages sensitivities and specificities were 80% & 70%, and 100% & 100%, respectively.
Conclusions: Noninvasive vascular elastography using compounding is a promising technique to assess vulnerable plaque features in patients.

Invited Lecture
CENTRAL AORTIC PRESSURE AND ARTERIAL STIFFNESS: ROLE IN ASSESSMENT OF BLOOD PRESSURE VARIABILITY AND BARORECEPTOR FUNCTION

Alberto Avolio
Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

Blood pressure variability (BPV) is due to complex interaction of cardiac and vascular factors and is influenced significantly by baroreceptor control. The cardiovagal baroreflex sensitivity (BRS) has been shown to depend on vascular compliance and this may explain recent epidemiological association between BPV and arterial stiffness. Although baroreceptors are centrally located (in carotid arteries and aortic arch), BPV and BRS are generally assessed using arterial pressure measurement in a peripheral location (brachial artery or finger) However, the pressure pulse is amplified between the aorta and periphery, with amplification depending on heart rate due to the frequency dependency of the brachial transfer function. In addition, the degree of pulse amplification reduces with increased aortic stiffness as occurs with age. Thus, if BRS is determined by systolic BPV and concomitant changes in heart rate, the relationships will not be similar if assessed from a peripheral or central pressure measurement. The spontaneous sequence technique is used for computation of BRS from the slopes of linear relationships of systolic pressure (SBP) and pulse interval (PI) of contiguous cardiac cycles, where SBP and PI change in the same direction. With this method, BRS computed using central pressure has no consistent relationship to BRS computed using peripheral blood pressure measurements, with differences also being dependent on the lag between SBP and PI. With improvements in technology for continuous non-invasive measurements of central aortic pressure, characterisation of BPV and BRS will be enhanced by the inclusion of effects of arterial stiffness on the pressure waveform.

McDonald Lecture
WAVES, RESERVOIRS & ARTERIES

Kim H. Parker
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It is commonly assumed that pressure and flow in the arteries are purely the result of forward and backward travelling waves. We will show that various observations of arterial behaviour are difficult to explain using this assumption. In particular we will look at what happens to arterial pressure under different conditions: during ectopic beats (or extended periods of cardiac arrest), in experimental studies of pressure and flow when the aorta is totally occluded at different locations, in a computational study of the input impedances of randomly generated networks of arteries and when pressure and velocity are measured at different distances along the aorta.
We show that all of these observations can be explained using wave intensity analysis, a method of analysis developed in gas dynamics which will be described very briefly. We further show that this analysis suggests that it is useful to separate arterial pressure into a reservoir pressure that accounts for the overall compliance of the arterial system and an excess pressure that is determined by local conditions.
Evidence has accumulated in the decade since the introduction of the reservoir-wave hypothesis that the reservoir/excess pressure separation can be useful in interpreting the results of vasoactive drugs on cardiovascular performance and that parameters based on the reservoir/excess pressure are significant predictors of cardiovascular events.
We argue that reservoir/excess pressure exists as a concept simply because it has been defined. The real question is the usefulness of the concept in the interpretation, physiologically and clinically, of the infinitely complex behaviour of the cardiovascular system. We conclude that the evidence suggests that it is a worthwhile topic for future research.