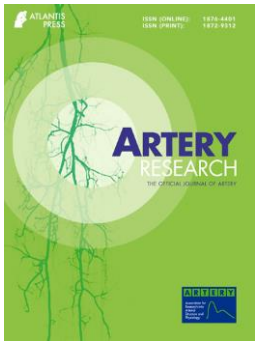

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WHY DOES NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) CONTRIBUTE TO CARDIOVASCULAR OUTCOMES?

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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.

Common genetic forms of NAFLD such as the I148M variant in PNPLA3 ('PNPLA3 NAFLD') are characterized by steatosis but not insulin resistance or an increased risk of CVD or diabetes. The molecular mechanisms underlying this dissociation in the human liver and its implications for CVD will be discussed.

Invited Lecture
CONSTITUENT BASED MODELLING OF ARTERIAL WALL MECHANICS

Lydia Aslanidou [1], Rodrigo Araujo Fraga da Silva [1], Patrick Segers [2], Nikos Stergiopulos [1]
[1]*Institute of Bioengineering, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland*
[2]*IBiTech-bioMMeda, Ghent University-iMinds Medical IT, Ghent, Belgium*

Abstract
In the preclinical setting, Angiotensin-II infusion has been the most popular model for mouse aneurysm research in the last 15 years. Nonetheless, little is known about the ascending aortic aneurysm pathobiology of this model and several lingering questions regarding the abdominal aortic aneurysm pathology (AAA) have long remained unaddressed, namely the suprarenal location of the murine AAA, the large morphological variation of the lesions and the presence of intramural thrombus. Technological advancements in both in vivo and ex vivo imaging techniques have significantly enhanced our understanding of the mechanisms driving the Angiotensin-II mouse model pathology. Our implementation of the groundbreaking PCXTM imaging modality has challenged the existing paradigm on this model while yielding unprecedented insight into previous observations on murine dissecting AAA. The detailed 3D PCXTM images have unveiled a previously unknown pivotal role for small, supraceliac and thoracic side branches to the onset of the disease. Mural ruptures in the vicinity of small side branches lead to apparent luminal dilatation and intramural hematoma. The PCXTM-based observations are in line with -seemingly incongruous- previous findings obtained with other imaging techniques, thereby raising a point on the importance of the implemented imaging modality when characterizing this aneurysm model.

Focus Lecture
ARTERIAL STIFFNESS IN INFLAMMATORY DISEASE

Dr Kaisa Maki-Petaja
University of Cambridge, Cambridge, UK

Abstract
Many inflammatory conditions are associated with an increased risk of cardiovascular disease (CVD) and mortality. As well as accelerated atherosclerosis, increased plaque instability and endothelial dysfunction; arterial stiffness has been proposed as one of the potential mechanisms underlying the increased CVD in these patients. Indeed, patients with chronic inflammatory conditions such as rheumatoid arthritis (RA), lupus erythematosus, human immunodeficiency virus, chronic obstructive pulmonary disease (COPD), and inflammatory bowel disease have been shown to have increased arterial stiffness. This appears to correlate with the level of inflammation, suggesting that arterial stiffness may be reversible with anti-inflammatory treatment. Numerous small-scale interventional studies have demonstrated that anti-inflammatory and cholesterol-reduction therapies with pleiotropic effects can reduce arterial stiffness in certain inflammatory conditions.
The association between increased arterial stiffness and inflammation appears obvious, yet the mechanism is poorly understood. One of the proposed mechanisms is arterial inflammation. In FDG PET/CT studies, patients with psoriasis, COPD and RA have been shown to have sub-clinical aortic inflammation. Arterial inflammation can subsequently lead to changes in the hydration state of the arterial wall and the composition of extracellular matrix, such as changes in glycosaminoglycan (GAG) synthesis. Indeed, animal studies have shown that overproduction of GAGs in the aorta resulted in thinning of the elastic lamellae and therefore aortic stiffening. Also, inflammatory cytokines can cause vascular smooth muscle cell proliferation, and phenotypic transformation resulting in an increased bioapatite formation, which can lead to calcification and stiffening. Furthermore, the release of matrix metalloproteinases from leukocytes can degrade elastin fibres within the arterial media.