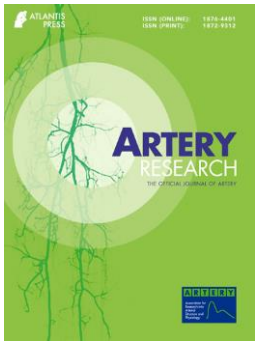

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ENDOTHELIAL AUTOPHAGY AS A KEY MECHANISM IN ARTERIAL DISEASES

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Invited lecture
FETAL PROGRAMMING AND VASCULAR DYSFUNCTION

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Keywords: Cardiovascular risk; vascular dysfunction; epigenetic; fetal programming; preeclampsia; ART
Cardiovascular diseases are the main cause of mortality and morbidity in Western countries, but the underlying mechanisms are still poorly understood. Genetic polymorphisms, once thought to represent a major determinant of cardiovascular risk, individually and collectively, only explain a tiny fraction of phenotypic variation and disease risk in humans. It is now clear that non-genetic factors, i.e., factors that modify gene activity without changing the DNA sequence and that are sensitive to the environment can cause important alterations of the cardiovascular phenotype in experimental animal models and humans. Here, we will review recent studies demonstrating that distinct pathological events during the perinatal (transient perinatal hypoxemia), late foetal (preeclampsia), and early embryonic (assisted reproductive technologies) periods induce profound alterations of the cardiovascular phenotype in humans and experimental animals. Moreover, we will provide evidence that epigenetic modifications are contributing importantly to this problem and are conferring the potential for its transmission to subsequent generations.

Satellite symposium organised in collaboration with servier, New pathways for targeting early vascular aging
ENDOTHELIAL AUTOPHAGY AS A KEY MECHANISM IN ARTERIAL DISEASES

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Paris Cardiovascular Center — PARCC, INSERM, France

Blood flow imposes shear stress on endothelial cells (ECs). ECs are able to convert these mechanical stimuli into intracellular signals that affect cellular function. As deregulated autophagy is associated with an acceleration of a variety of cardiovascular and metabolic diseases where impaired flow-mediated EC responses promote cardiovascular risk, we hypothesized that endothelial autophagy and endothelial function interact.
We found that defective endothelial autophagy, caused by targeted deletion of the *Atg5* gene in ECs alone, results in selective loss of flow-induced vasodilation in mesenteric arteries and in kidneys *ex vivo*; this leads to increased cerebral and renal vascular resistance *in vivo*. Furthermore, we find a crucial pathophysiological role for endothelial autophagy in flow-mediated outward arterial remodelling, prevention of neointima formation following wire injury and recovery after myocardial infarction. Together, these findings unravel a fundamental role for autophagy in endothelial function, linking cell proteostasis to mechanosensing signaling that will be discussed. These findings also open new questions regarding the potential role of endothelial proteostasis in arterial diseases.

VASCULAR CALCIFICATION: FROM INNOCENT BYSTANDER TO CULPRIT RISK FACTOR

Leon J. Schurgers
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Vascular calcification was regarded as an innocent bystander in cardiovascular disease. It was considered to be the passive chemical nucleation of calcium and phosphate ions on cellular debris and therefore the end-stage of atherosclerosis. Currently, vascular calcification is understood to be an actively regulated process involving cellular and humoral contributions that may offer targets for diagnosis and intervention. Vascular calcification is clearly associated with poor cardiovascular outcome, and may result in stiffened vessels and unstable lesions that can rupture and cause acute ischaemic events such as acute myocardial infarction and stroke. In atherosclerotic disease research, calcification is commonly used as a measure of atherosclerotic burden. However, recent data suggest that especially microcalcification have destabilising effects on atherosclerotic plaques. Therefore, the development of novel imaging solutions for early detection of initiation events resulting in microcalcification are of utmost importance. Phenotypic switching of VSMCs plays a key role in vascular disease and is a precondition for vascular calcification, possibly via oxidative stress and shedding of extracellular vesicles. The discovery that vitamin K-dependent processes are involved in the inhibition of vascular calcification has further boosted our mechanistic understanding of the vascular calcification process and has opened up novel avenues. Indeed, the current thrombosis treatment using vitamin-K antagonists (VKAs) paradoxically leads to a high risk of calcification. The treatment of vascular calcification and stiffness using vitamin K supplements is currently under investigation.

TARGETING VASCULAR SMOOTH MUSCLE CELL TO IMPROVE ARTERIAL STIFFNESS

Patrick Lacolley
INSERM, France

Hypertension and arterial aging engage a plethora of key signaling pathways that act in concert to induce vascular smooth muscle cell (VSMC) phenotypic changes leading to vascular degeneration and extracellular matrix (ECM) changes responsible for alterations of the mechanical properties of the vascular wall. This review highlights proof-of-concept examples of components of the extracellular matrix, VSMC receptors which connect extracellular and intracellular structures and signaling pathways regulating changes in mechanotransduction and vascular homeostasis. This presentation presents new directions in the role of vascular smooth muscle cells VSMCs traditionally limited to regulation of contractile properties and synthesis of ECM proteins. VSMCs may exert negative feedback or positive feedback on ECM stiffness and mechanical load via stabilized focal adhesions, activated Rho-ROCK signaling pathways or actomyosin contraction. Understanding the mechanisms of cellular stiffness are also important to appreciate its contribution to mechanical properties at the tissue-level. Many other cell types, including macrophages, could participate to inflammation and VSMC stiffness leading to fibrosis of the arterial wall. In view of the multitude roles of VSMCs and feedback controls, only omic approaches and computational models may extrapolate the overall effects on the vascular wall in light of hemodynamics and complex interactions amongst differentially sized vessels. The use of novel animal models with multiple genetic manipulations of VSMC signaling pathways can provide further insight into the link between large vessel stiffness and small vessel dysfunction.

Focus update
CENTRAL BLOOD PRESSURE MEASUREMENT AND VALIDATION: WHAT IS STILL NEEDED?

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Accurate measurement of blood pressure (BP) is a critical goal for appropriate diagnosis and management of high BP. The measurement reference standard is brachial cuff BP, but recent large-scale meta-analyses show major deficiencies in the accuracy of this method. Indeed, irrespective of cuff technique (e.g. mercury auscultation or oscillometry) brachial cuff BP measures lack precision for representing the BP within both the brachial artery and the central aorta. These data clearly indicate the need to refine and improve methods to measure BP accurately, whether at the brachial or central aortic level, with preference towards the latter as the best representation of pressure loading experienced by the organs at risk from hypertension. The current focus to improve measurement of central aortic BP is on better calibration methods, with mean arterial pressure (MAP) and diastolic BP (DBP) proposed as the best solution. However, the ability to accurately estimate central aortic BP using this calibration method appears to be device-specific and related to the capacity of different devices to accurately measure MAP/DBP using conventional cuff BP. Beyond this, even if we can accurately measure MAP/DBP using non-invasive cuff methods, this does not necessarily provide a final solution because characteristic waveform features and the level of systolic BP amplification still influence accuracy. Thus, altogether, manufacturers of devices purporting to measure central aortic BP need to provide robust evidence about accuracy performance; preferably according to ARTERY Society recommendations.