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EDITORIAL

Biomechanical factors in cardiovascular disease

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This Spotlight issue is focused on the influence of biomechanical forces induced by flowing blood on the development, function, and pathophysiology of the vasculature. The velocity and direction of blood flow vary at a temporal level with each heartbeat and changes spatially according to vascular anatomy. This concept appears to have been already appreciated in the early sixteenth century by the renaissance polymath Leonardo Da Vinci, who depicted swirling motions of blood following its interaction with the aortic valve,[1] detailed drawings of which can be found in the Royal Library in Windsor Castle (http://www.royalcollection.org.uk/collection/919082/the-aortic-valve and http://www.royalcollection.org.uk/collection/919083/blood-flow-through-the-aortic-valve). The relationship between blood flow and the spatial location of atherosclerotic lesions was also noted by Virchow in 1856[2] and was brought into the modern era by Caro *et al.*,[3] Nerem and Seed,[4] Fry and colleagues,[5] and Friedman *et al.*,[6] who pioneered cross-disciplinary approaches by combining engineering with biology to assess vascular biomechanical responses.

The vascular endothelium is a thin monolayer of cells that line the luminal side of all blood vessels. It serves as a barrier for the exchange of fluid, electrolytes, macromolecules, and cells between the intravascular space and surrounding tissue. It regulates leucocyte adhesion and trans-endothelial migration as well as platelet aggregation and smooth muscle function through the expression of adhesion and junctional molecules and by the biosynthesis of vasoactive substances, such as nitric oxide, prostacyclin, and endothelin-1. The endothelium is highly sensitive to haemodynamic shear stresses acting at the vessel luminal surface in the direction of blood flow. Although the mechanisms and structures by which endothelial cells sense wall shear stress are largely unknown, it is widely recognized that mechanical forces are an important determinant of endothelial cell function, gene expression, and structure. Ando and Yamamoto[7] develop this concept by reviewing several candidate shear stress sensors, including ion channels, cell membrane receptors, the cytoskeleton, adhesion molecules, the glycocalyx, caveolae, and primary cilia. They also point us to the obligatory subtlety and specificity of mechanical sensors; namely, the arterial endothelium is not only subjected to shear stress, but the pulsatile changes in blood pressure generate simultaneously a powerful stretching tension of these cells. Mechanoreceptors convert mechanical cues into a myriad of biological signals which control cell physiology and epigenetic, genomic, and proteomic levels. The review article from Frueh *et al.*[8] embraces this complexity and describes the current challenges of large data sets and the application of systems biology in the exploration of the effects of blood flow on endothelial function. The review pays special attention to the Krüppel-like factor family of transcription factors which function as central regulator of physiological responses to shear stress by inducing anti-inflammatory and anti-coagulant transcripts.[9]

Mechanical forces regulate most aspects of vascular physiology and function and play a key role in vascular development and homeostatic mechanisms as well as during arterial disease. The former processes are discussed by Hoefer *et al.*,[10] who described the rapid effects of shear stress on vascular tone and its more sustained influence on outward and inward vascular remodelling. Atherosclerotic lesions develop predominantly near side branches of arteries where blood flow is disturbed, or at the lesser curvature of bends of the arterial tree where blood flow rates are relatively low.[11] Using site-specific endothelial isolation and systems biology combined with reductionist *in vitro* experiments and probing of the mechanistic information *in vivo*, Davies *et al.*[12] introduce us to the concept of pre-lesional atherosusceptibility, an adaptive chronic low-level inflammatory state that ensures continued endothelial function at the expense of increased susceptibility to atherogenesis. It remains one of the major challenges of this research field to complete the abundant information that is nowadays available on the *spatial* differences of flow-induced endothelial type with *temporal* information on the endothelial phenotypic changes during the progression towards atherosclerosis. Meens *et al.*[13] describe the critical role of gap junction proteins (connexins) in co-ordinating responses within groups of endothelial cells towards mechanical forces; the formation of so-called communication compartments might contribute to the maintenance of the *spatial* differences in endothelial phenotype observed between atheroprotected and atherosusceptible regions.

Blood flow governs vascular inflammation at multiple levels by regulating leucocyte margination and rolling on endothelial surfaces[14] and also by controlling endothelial inflammatory activation. Recent evidence indicates that wall shear stress may not only critically regulate the gene expression in endothelial cells, but may also directly modulate macrophage phenotype and finally atherosclerotic plaque stability, as described in the review of Seneviratne *et al.*[15] Thin-cap fibroatheromas are vulnerable plaques, generally identified by a thin rupture-prone fibrous cap, a large necrotic core, and a high content of inflammatory

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cells,[16] the development of which is promoted by low (laminar) shear stress. In contrast, oscillatory shear stress seems to promote the development of atherosclerotic lesions with a more stable phenotype. The above-mentioned review[15] as well as the review from Weber and colleagues[17] describe in detail the recent implication of microRNAs in flow-dependent change in endothelial and macrophage phenotype. MicroRNAs are endogenous non-coding small RNAs and have appeared as key regulators of gene expression by repressing target mRNAs, determining cell function under physiological and disease conditions.[18] Further insights into the regulation of microRNAs by biomechanical forces may open up towards potentially interesting diagnostic or therapeutic applications. In addition to its effects on vascular inflammation, shear stress also has important effects on platelet adhesion to the vessel wall and subsequent generation of a thrombus. The review article from Heemskerk and colleagues[19] discusses the underlying mechanism, which involves direct mechanical effects on the molecular structure of von Willebrand factor that unfolds in response to shear for subsequent capture of circulating platelets.

Bäck *et al.*[20] focus their review on the biomechanical factors involved in the development of aortic valve stenosis and aortic aneurysms. Of note, they suggest that differences in the mechanical environment at the aortic and ventricular sides of the valve may relate to differences in tissue morphology, calcification, and lesion formation. The authors also describe the mechanical forces in the aorta and how their pertubation (e.g. associated with bicuspid aortic valves) relate to the formation of aneurysms.

Vascular repair processes are also exquisitely sensitive to mechanical forces. This is highlighted by the reviews of Chaabane *et al.*[21] and Van der Heiden *et al.*,[22] which are concerned with the responses of arteries to stent implantation. Chaabane *et al.*[21] describe the response of arteries to stretch and strain which can promote vascular remodelling by stimulating smooth muscle cell migration/proliferation, conversion of smooth muscle cells from contractile to synthetic phenotype, and alterations in extracellular matrix production and production of matrix metalloproteases. This is complemented by Van der Heiden *et al.*,[22] who discuss the effects of shear stress on endothelial repair in stented arteries, a process that involves migration and proliferation of mature endothelial cells as well as the mobilization of vascular stem cells. Of note, both groups of authors agree that there is a requirement for novel stents that maintain a patent lumen while minimizing the deleterious effects of stenting on vascular structure and function.

Xu and colleagues[23] also focus on the biomechanical effects on vascular injury and repair and, in particular, the influence of mechanics on the maturation of circulating or resident stem cells into functional vascular cells. The authors summarize the evidence for the existence of vessel-resident and blood-borne vascular progenitor cells and discuss the influence of mechanical forces on their differentiation into smooth muscle cells (driven by stretch) and endothelial cells (promoted by shear stress).

Finally, Saxer *et al.*[24] highlight recent advances in the development of novel approaches to exploiting vascular mechanical forces to activate diagnostic systems or mechanosensitive drug delivery systems (e.g. shear stress-sensitive nanoparticle aggregates). Thus, although mechanical forces contribute to vascular pathophysiology, they may also be harnessed to develop novel pharmacological treatments for vascular injury and disease.

In conclusion, this special issue on 'Biomechanical factors in cardiovascular disease' highlights multiple aspects of the interface between mechanical forces and vascular biology. The stresses and strains experienced by arteries, and other parts of the cardiovascular system, have profound effects on cardiovascular physiology and disease. Several important challenges remain in this field. This is emphasized by Peiffer *et al.*,[25] who performed a systemic review of the literature linking focal atherosclerosis with the distribution of haemodynamic factors. The authors note that although numerous studies have correlated low and/or oscillatory shear with atherosclerosis, further work is required to identify the particular metrics, e.g. magnitude, oscillations, direction (or a combination of these) that influence disease. Current challenges also include the identification of mechanoreceptors and the application of systems biology approaches to discern the molecular mechanisms underlying vascular responses to mechanical force. On the other hand, further studies are required to elucidate the influence of mechanical forces on vascular repair processes (e.g. following stenting or grafting). A limiting factor in this field is the lack of technologies to apply realistic mechanical forces to vascular cells under sterile conditions; thus, future technological developments of novel bioreactors that generate complex forces *in vitro* will lead to a step-change in our capacity to identify and study novel mechanosensitive pathways. The realization of these aims will rely on a multidisciplinary approach that integrates engineers, physicists, mathematicians, and other members of the physical sciences with biomedical science.

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