

'The response of the dysfunctional endothelium to elevated flow - implications for plaque disruption'

Abstract text (max. 1500 characters without spaces)

Atherosclerosis primarily occurs at bifurcations and curved sections of arteries, implicating local haemodynamics in the initiation and progression of disease. Endothelial mechanosensitivity, which translates the frictional force exerted by blood flow (shear stress) into a biological response, underlies this association. Endothelial cells in regions of the vasculature exposed to normal laminar flow adopt a quiescent anti-inflammatory phenotype that resists the development of atherosclerosis. This contrasts with cells exposed to disturbed flow, which triggers an increase in permeability, reduces the bioavailability of nitric oxide and amplifies the response to inflammatory mediators. As atherosclerosis develops, the endothelium overlying stenotic plaques can be exposed to very elevated shear stress, which depending on the degree of stenosis can be >15-fold higher than in non-diseased sections. The response of the endothelium to elevated shear stress has received little attention, despite stenotic plaques being more likely to suffer plaque rupture or endothelial erosion, the two principle causes of acute coronary syndromes. We particularly focus on endothelial erosion of plaques and have identified that endothelial erosion frequently occurs towards the throat of stenotic plaques, exposing the endothelium to elevated shear stress, and that elevated shear modifies endothelial behaviour. Histopathology has demonstrated an association of erosion with smoking, suggesting endothelial dysfunction may affect the response of the endothelium to elevated flow and contribute to detachment. In addition, our work implicates a hyperactivation of the antioxidant system as a potential contributor to this process.