Atherogenic vascular stiffness and hypertension: cause or effect?

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Blood vessels function as conduits for distribution of blood throughout the circulatory system. Large arteries, in addition to the essential conduit function, also serve to dampen the effect of pulsatile ventricular ejection that generates pulsatile pressure with each cardiac cycle; that is, they exhibit a 'cushion' function. The conduit function can be compromised by intimal effects that cause obstruction to flow, generally attributed to plaque formation due to intimal changes affected by atherosclerotic processes. The cushion function is affected by medial changes altering the wall stiffness, and so the capacity of arteries to absorb pulsatile energy. This modulates pulse pressure through changes in wall stiffness and vessel compliance and characteristics of wave propagation. In addition, these changes are further affected by arterial pressure. Intimal changes related to obstructive phenomena are generally thought to be related to *atherosclerosis,* and medial change affecting vessel buffering capacity related to *arteriosclerosis*. This lecture explores aspects that characterise the potential inter-relationship between the two phenomena and arterial pressure.

With advances in molecular biology, imaging and computational modelling, pathways involved in cell-signalling affecting intimal changes through endothelial function and medial changes through both endothelial and smooth muscle function are increasingly being identified. The nitric oxide pathway has been shown to influence protein expression affecting the stiffness of the extracellular matrix through alteration of cross-link formation. In turn, bioavailablity of endothelial nitric oxide is also affected by wall stiffness. Changes in distribution of internal wall stress due to altered structure of the wall matrix can alter the mechanotransduction effects on the endothelial cell, modifying intimal changes. The phenotypic transdifferentiation of the smooth muscle cell is associated with changes in structural integrity of medial elastin, leading to arterial calcification and altered arterial stiffness. The changes in smooth muscle function are also affected by anchoring properties of integrins, in turn modifying wall properties. Superimposed on the cell-signalling phenomena modulating intimal and medial function is the modification of wall properties due to distending pressure.

The task of assessing whether the relationship between atherosclerosis and arteriosclerosis and hypertension constitutes a cause or effect presents a formidable challenge. However, emerging evidence suggests that investigating the inter-relationships may elucidate potential feedback signalling pathways that may be interrogated to possibly delay the ill effects of compromised vascular function and development of hypertension.