Hypertension Highlights

Integrins, Vascular Remodeling, and Hypertension

Egidius H.J. Heerkens, Ashley S. Izzard, Anthony M. Heagerty

At the level of the resistance artery, hypertension also brings about a thickening of the vascular wall and inward encroachment on the lumen. This has been reported as being attributable to hypertrophy or hyperplasia of vascular smooth muscle cells (VSMCs), but studies have appeared suggesting that growth is not apparent in arteries at this level of the circulation. In addition, detailed structural and mechanical analyses have shown that eutrophic inward remodeling can narrow the vascular lumen without precipitating hypertrophy. A small amount of hypertrophy may be observed, and in some pathological states, hypertrophy may supervene and is an adverse prognostic sign. For the remainder of this section, we consider the reasons why resistance arteries respond to hypertension in this manner.

To understand how hypertension produces the above nonhypertrophic changes in small arteries, one must look at the role of the resistance vasculature. At physiological pressures, these vessels typically exhibit a level of contraction (myogenic tone) independent of neurohormonal influences. This response enables blood vessels to constrict or dilate in response to changes in pressure. This process, known as the myogenic response, is only observed in smaller resistance arteries, which mediate autoregulation of blood flow and stabilize capillary pressure.

Hypertrophy is observed in vessels that do not possess myogenic tone, whereas, in smaller resistance arteries, an initial increase in pressure will bring about increased myogenic constriction, which, if prolonged, will lead to inward eutrophic remodeling and/or a reduced arterial distensibility. This structural difference between large conduit and resistance arteries is apparent in many models of hypertension, for example, in a hypertensive model bought on by chronic NO synthase inhibition. In addition, the magnitude and duration of an increase in intraluminal pressure plays a role in determining the remodeling process. It has become evident that the extracellular matrix (ECM) integrin–cytoskeleton axis plays an essential role in the mecanosensory apparatus, which enables VSMCs to detect and respond to changes in intraluminal pressure, allowing eutrophic inward remodeling of resistance arteries in hypertension.

Eutrophic Inward Remodeling

Inward eutrophic remodeling is a process of structural adaptation observed in most forms of hypertension, including the onset of hypertension and milder hypertensive states. However, a few animal models of hypertension, such as a model developing hypertension independent of the renin–angiotensin system (BPH-2 mice), show hypertrophy as the predominant structural change. Inward eutrophic remodeling is a relatively fast functional adaptation observed after prolonged vasoconstriction and is thought to be an energetically favored mechanism to preserve a reduced lumen diameter for long periods. The process is also the preferred physiological mechanism by which wall stress can be normalized while maintaining vasomotor tone.

In our studies of the well-characterized TGR(mRen2)27 rat, which develops hypertension from 4 weeks of age, we found that eutrophic inward remodeling occurs from 4 weeks and depends on integrin αV/β3, a multifunctional ECM receptor (Figure 1). Hypertrophy also begins to appear at between 6 and 8 weeks of age. Hypertrophy and a reduced distensibility are also observed in cerebral vessels of the stroke-prone spontaneously hypertensive rat when the animals are given a high-salt/low-protein diet compared with the spontaneously hypertensive rat, before strokes occur. The spontaneously hypertensive rat, in contrast, is stroke resistant, and cerebral vessels from young spontaneously hypertensive rats display eutrophic inward remodeling compared with the Wistar-Kyoto rat but exhibit a reduced distensibility in adulthood. Finally, subcutaneous small arteries of patients with type 2 diabetes and microalbuminuria exhibit hypertrophy, which coincides with an impaired myogenic response irrespective of whether there is hypertension or not. Therefore, current evidence suggests that an increase of hypertrophy might ensue as a compensatory mechanism when eutrophic remodeling is inadequate to normalize wall stress, because the stimulus for remodeling (ie, vasoconstriction) is impaired.

Integrins, Mechanotransduction, and Cytoskeletal Reorganization

The ECM of resistance arteries is subject to tensile force exerted by blood pressure, which is transferred through integrins across the cell membrane and linked by signaling complexes to the cytoskeleton. Specific integrin subtypes are initially used for mechanotransduction of pressure. It has been shown by the use of peptides and specific antibodies that...
integrins $\alpha V\beta 3$ and $\alpha 5\beta 1$ indirectly regulate the myogenic response by control of $Ca^{2+}$ flow through ion channels. $\alpha 5\beta 1$ is responsible for the initial $Ca^{2+}$ influx required to establish vessel tone and $\alpha V\beta 3$ to mediate force maintenance by a $Ca^{2+}$ sensitzation of contractile components.19–21 These integrins can form complexes that regulate cytoskeletal dynamics to maintain a vascular myogenic force at a given pressure. This is abrogated on cytoskeletal disruption.22,23 Cytoskeletal proteins, such as heat-shock protein 27, activated by RhoA/Rho-kinases, have been shown to regulate myogenic contractility.24 It is now clear that RhoA signaling plays a central role in both calcium sensitization pathways and regulation of actin dynamics in resistance artery remodeling (elegantly reviewed in references25–26). In contrast to molecular signaling mechanisms behind the vascular myogenic response, relatively few data are available on the role of integrins and the underlying biochemical pathways of the next stage of vascular adaptation to hypertension that is the migration of VSMCs toward a narrowed lumen.

Integrins and VSMC Migration

Remodeling involves a migratory process after prolonged constriction, whereby existing VSMCs in the vascular wall reposition. A characteristic of migrating cells in vitro is the presence of lamellipodial and filopodial protrusions containing focal adhesion kinases (FAKs), which provide a substrate for other cytosolic proteins, such as Src, and interact with actin-associated cytoplasmic components.27 Evidence for the formation of these structures at the VSMC periphery in resistance arteries is inconclusive. However, it has been shown recently that migration of VSMCs of arteries in vivo is more subtle and limited to elongation of tapered VSMCs and an increase in cell overlap.13 It is thought that cytoskeletal rearrangements and subsequent force generation play a cen-

![Figure 1](image1.png)

**Figure 1.** VSMC integrins and matrix associations. Integrin $\alpha 5\beta 1$ is the main receptor for fibronectin and mediates the influx of $Ca^{2+}$ through L-type calcium channels. $\alpha V\beta 3$ is a multifunctional integrin receptor that binds to the RGD sequences found in components of the vascular extracellular matrix (vitronectin, osteopontin, and thrombospondin but not von Willebrandt factor, fibrinogen, and sialoprotein which are absent from the smooth muscle extracellular space). $\alpha V\beta 3$ is necessary for migration during pressure induced remodeling of arteries.

![Figure 2](image2.png)

**Figure 2.** The involvement of vascular smooth muscle integrins in cytoskeletal reorganization during remodeling. Signaling complexes found at the edge of VSMCs in arteries contain integrins, and the cytoplasmic terminal complex (eg, vinculin, paxillin, talin, and p130Cas) associate with the actin cytoskeleton. Src and FAK in arteries are phosphorylated on integrin engagement and are essential in the actin (dis)assembly possibly regulated by RhoA/Rho-kinases. Permanent placement of VSMCs in the remodeled vasculature involves tissue-transglutaminase (tTG) fixation.
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