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 non-hypertrophic 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 contract 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 mechanosensory 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 αVβ3, 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 αVβ3 and α5β1 indirectly regulate the myogenic response by control of Ca²⁺ flow through ion channels. α5β1 is responsible for the initial Ca²⁺ influx required to establish vessel tone and αVβ3 to mediate force maintenance by a Ca²⁺ sensitization of contractile components. 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. Cytoskeletal proteins, such as heat-shock protein 27, activated by RhoA/Rho-kinases, have been shown to regulate myogenic contractility. 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 (elegantely reviewed in references). 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. 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. It is thought that cytoskeletal rearrangements and subsequent force generation play a cen-
Integrins, Vascular Remodeling, and Hypertension

3

We thank Maureen Speed for her assistance in preparing this work.

Sources of Funding

We thank the Wellcome Trust and British Heart Foundation for supporting our research. Our clinical studies are carried out in the Manchester Wellcome Trust Clinical Research Facility.

Disclosures

None.

References

17. Endemann DH, Pu Q, De Cuiucis C, Savoia C, Virds A, Neves MF, Touyz RM, Schiffrin EL. Persistent remodeling of resistance arteries in...


Integrins, Vascular Remodeling, and Hypertension
Egidius H.J. Heerkens, Ashley S. Izzard and Anthony M. Heagerty

Hypertension. 2007;49:1-4; originally published online December 4, 2006;
doi: 10.1161/01.HYP.0000252753.63224.3b
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/49/1/1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/