Integrins in Hypertensive Remodeling

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A
ds nurse Abby in the popular television series “E.R.” well knew (http://www.erahedquarters.com/episodes/10/10204.htm), the law of Laplace states that wall stress equals pressure times radius divided by wall thickness. This law leaves 2 options for a vessel to normalize its wall stress in hypertension: either reorganize the available material around a smaller lumen or undergo hypertrophy. In various forms of hypertension, including human essential hypertension, the resistance arteries choose the first option, eutrophic inward remodeling, whereas large vessels demonstrate hypertrophy.1,2 The mechanisms by which the vessels make this choice are not clear.

Previous investigations have suggested that integrins, in particular the β3 integrin, is involved in the eutrophic remodeling process.3 The article by Heerkens et al4 is the first to test this hypothesis as regards remodeling during hypertension. The authors use the well-characterized TGR(mRen2)27 rat5 as a genetic hypertension model. These Ren2 rats start developing hypertension from the age of 4 weeks, probably as a result of increased activity of the renin–angiotensin system,6 and have previously been shown to be associated with inward eutrophic remodeling of mesenteric small arteries.7 No measurements of lumen diameter are reported by Heerkens et al, but in a private communication the authors informed us that lumen diameters of the vessels from Ren2 animals were significantly reduced relative to those from control animals by 14%, 29%, 18% at, respectively, 5 weeks, 6 weeks, and 8 weeks; lumen diameters were identical at 4 weeks. Thus, inward remodeling occurred at all ages after 4 weeks. From their measurements of media cross-sectional area, the authors show that the remodeling is eutrophic at 5 weeks and in part hypertrophic at 6 weeks and 8 weeks. However, even at the latter times, a substantial part of the remodeling was eutrophic, as indicated by the remodeling indices (ie, the percentage of the change that can be ascribed to redistribution of material), which in both cases were above 90%.

The remodeling was at all time points associated with increased expression of the αv integrin. Moreover, intraperitoneal injection of the αv integrin blocking peptide cRGDfV (Calbiochem, United Kingdom) increased the growth response and also greatly reduced the calculated remodeling index. The β3 integrin was found to coprecipitate with the αv integrin antibody, from which the authors conclude that αvβ3 integrin (the vitronectin receptor) mediates the remodeling. This integrin is known to interact with fibronectin, and indeed mRNA expression of the fibronectin splice form EIIIA+ was doubled in the Ren2 rats. Thus, to the extent that the αv integrin blocking peptide is having a specific effect, and future experiments need to determine this, the results point to an important role for this integrin in the remodeling process. Furthermore, because the antibody did not block the hypertrophic process, indeed enhanced it, this suggests that the αv integrin could be specifically involved in eutrophic remodeling. This would be consistent with previous work showing that the αvβ3 integrin is upregulated in resistance vessels of spontaneously hypertensive rats compared with Wistar-Kyoto controls.8

There seem to be several ways by which αvβ3 blocking could affect remodeling. First, the αvβ3 integrin may, as suggested by Heerkens et al,4 be involved in length autoregulation, a concept introduced by Martinez-Lemus et al.9 Using isolated vessels, those authors demonstrated that during maintained vasoconstriction the SMC relengthen while keeping the vessel constricted. This response, occurring in the course of hours, can be considered to be an acute form of remodeling. It is quite likely that the reshaping of the SMC depends on integrins cyclically binding to and releasing the extracellular matrix, and the αvβ3-fibronectin bond is one of the candidates in this process. The results of the current study, although demonstrating the involvement of this bond, do not include length of the SMC after remodeling. Second, the action of αvβ3 integrin blockade could be caused by a vasodilator effect of the αvβ3 integrin antibody, from which the authors conclude that αvβ3 integrin (the vitronectin receptor) mediates the remodeling. This integrin is known to interact with fibronectin, and indeed mRNA expression of the fibronectin splice form EIIIA+ was doubled in the Ren2 rats. Thus, to the extent that the αv integrin blocking peptide is having a specific effect, and future experiments need to determine this, the results point to an important role for this integrin in the remodeling process. Furthermore, because the antibody did not block the hypertrophic process, indeed enhanced it, this suggests that the αv integrin could be specifically involved in eutrophic remodeling. This would be consistent with previous work showing that the αvβ3 integrin is upregulated in resistance vessels of spontaneously hypertensive rats compared with Wistar-Kyoto controls.8

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A more basic question that remains to be addressed is the contribution of cells versus matrix elements in determining the caliber of a relaxed vessel. The classical views explain the passive pressure–radius relation in terms of elastin and collagen fiber arrangement only, with no contribution of cells under relaxed conditions. Another possibility is that the diameter of the vessel at full vasorelaxation is influenced by the mechanical properties of the smooth muscle cell cytoskeleton, which through integrins and matrix constituents forms a continuous system of load-bearing elements. The sparse evidence on this question is conflicting: Cipolla et al\(^1\) found no change in passive diameter on cytochalasin B in rat posterior cerebral arteries, whereas Boer et al\(^17\) found increased compliance in pulmonary arteries following this treatment. We would suggest a combination of the 2 views: sustained vasoconstriction causes cross-linking of the extracellular matrix such that in time the active vasoconstriction is replaced by a structural change and the reduced lumen can be maintained with minimal energy expenditure. In a vessel that has recently experienced remodeling, the cytoskeleton may still carry part of the tension in the passive vessels, but in more stable vessels, the smooth muscle cells have remodeled their matrix such that during vasodilation all tension is carried by the collagen and elastin. This view, however, needs to be tested.

In conclusion, the study by Heerkens et al\(^4\) clearly demonstrates the involvement of the \(\alpha_v\beta_3\) integrin in inward microvascular remodeling in hypertension. The work adds to growing excitement that we are at last gaining some understanding of the molecular processes leading to the remodeling of the vasculature, a remodeling which is a hallmark of hypertension. The work generates the desire to derive an integrative model for the biomechanics of the remodeling vessel. Such a model would be based on organization and mechanical properties of both matrix elements and the cytoskeleton, their coupling through integrins, and physiological principles: tone-remodeling coupling, smooth muscle cell length autoregulation, and regulation of wall stress in hypertension.

References


