Integrins in Hypertensive Remodeling

Ed VanBavel, Michael J. Mulvany

As nurse Abby in the popular television series “E.R.” well knew (http://www.erheadquarters.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 could affect remodeling. First, the α3β3 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 α3β3-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 α3β3 integrin blockade could be caused by a vasodilator action on the basis of the tone-remodeling hypothesis of Bakker et al,3,10 stating that inward remodeling is a consequence of maintained deep tone. Consistent with this, Mogford et al11 demonstrated vasodilation by arginine-glycine-aspartate (RGD) peptides binding to the smooth muscle α3β3 integrin, whereas Martinez-Lemus et al12 found involvement of both α3β3 and α2β1 integrins in myogenic responsiveness to pressure changes. The tone-remodeling hypothesis is based on mainly cultured vessel experiments. However, a clinical role for vasoconstriction in the remodeling process has been supported indirectly by the observation that vasodilator therapy causes outward remodeling.13 Whether such a vasodilator effect of α3β3 integrin blockade was involved in the present study is not known, since tone could not be monitored. In any event, as our studies have shown, using both in vitro and in vivo models, the effect of the activated smooth muscle on the extracellular matrix is mediated by transglutaminases, enzymes that are closely associated with integrins.15 There are thus several ways by which the blocking of integrins in the study by Heerkens could have affected remodeling, and these possibilities deserve future attention.

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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 al16 found no change in passive diameter on cytochalasin B in rat posterior cerebral arteries, whereas Boer et al17 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 al4 clearly demonstrates the involvement of the αvβ3 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

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