Commentary

Association between the Molecular Pathobiology of Essential Hypertension and Thrombotic Diseases

Thomas S. Edgington

From the Departments of Immunology and Vascular Biology, The Scripps Research Institute, La Jolla, California

The clinical association of hypertension and heart disease has been recognized for more than a century. However, a direct association between hypertension and thrombosis is not apparent. With the introduction of therapeutic interventional coronary artery ballooning and related procedures including introduction of stents, the occurrence of secondary local vasculopathy as well as thrombosis presents a significant threat. The view that hypertension, which is mediated by angiotensin II, is the immediate driving force for the various forms of associated vasculopathy is naive. Angiotensin II is the product of the renin, angiotensinogen, angiotensin-converting enzyme cascade. Recent studies have identified the cellular effects of angiotensin II as highly pleomorphic.¹ Apart from the well recognized effects of angiotensin II on local vascular tension, namely vascular smooth muscle contraction, it is now recognized that angiotensin II, via engagement of its cognate endothelial surface receptor AT₁, induces biosynthesis and local release of a number of cell modulatory proteins including platelet-derived growth factor, basic fibroblast growth factor, insulin growth factor, transforming growth factor- β , and undoubtedly other molecules, as well as molecules influencing the thrombogenic pathways, such as plasminogen activator inhibitors.² The local effects of angiotensin II include local neointimal thickening³ as well as hypertension and cardiac pathology.⁴ Although most of the pleomorphic cellular products are not directly implicated in the mediation of vasoconstriction and hypertension, indirect effects cannot be entirely excluded.

Available molecular and cellular evidence, coupled with clinical investigations, does not provide an entire map of the molecular pathways associated with angiotensin II effects. The proposition that the effects of hypertension on the coronary artery contributes to atherosclerosis and stenosis remains intact, but hypertension cannot directly account for acute coronary occlusion where an acute thrombotic event is the mechanism. The frequent cause of acute coronary thrombosis and resultant myocardial infarction is now suspected to result directly from the rupture of a susceptible atherosclerotic

plaque rich in tissue factor (TF), the major initiating cell surface receptor and cofactor of the thrombogenic cascade.⁵ Presumably, certain fragile plaques, designated susceptible plaques, are weakened by internal proteolysis of the fibrous cap⁶ and rendered more susceptible to rupture by the hypertensive flow and pressure.

In this issue of *The American Journal of Pathology*,⁷ Müller and coworkers provide an important linkage between the molecular pathology of hypertension and thrombogenic and inflammatory cascades with evidence that angiotensin II, through its endothelial surface receptor AT₁, induces activation of the nuclear factor- κ B (NF- κ B) system with transcription and expression TF by the endothelium *in vivo* in a transgenic model of severe cardiac vasculopathy. This breaks important ground and may add insight into the risk profile of essential hypertension. Notably, current convention and clinical data do not significantly implicate essential hypertension thrombotic risk, except for pulmonary hypertension; however, this may need to be reassessed. In the Bruneck study⁸ there is an association between atherosclerosis and elevated markers favoring thrombosis. The work of Dzau,¹ as well as others, on the effects of hypertension, and more significantly of angiotensin II on vascular pathology, raises issues whether TF expression demonstrated here by local cells in cardiac tissues may contribute to the pathology. Angiotensin II might stimulate increased synthesis of TF in some atherosclerotic plaques and render them more dangerous if they rupture, thus driving local occlusive thrombosis of the subject coronary artery. Equally intriguing, however, is the possibility that the thrombogenic effects of TF are a distraction from other effects that are brought into play. TF, by initiating the coagulation protease cascade, drives a number of cellular responses that are mediated by the protease products that proteolytically activate one or more members of the protease-activated receptor family of cell surface receptors,⁹ the

Accepted for publication May 18, 2000.

Address reprint requests to Thomas S. Edgington, M.D., Departments of Immunology and Vascular Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, C204, La Jolla, CA 92037-1092. E-mail: tse@scripps.edu.

most notable of which, protease-activated receptor-1, is activated in a quite novel manner by thrombin and signals the cell.

In the present study,⁷ Müller et al use an *in vivo* model of transgenic rats carrying and overexpressing a murine renin and a human angiotensinogen gene,⁴ a state of affairs that results in an extremely severe form of cardiac vasculopathy mediated by the product angiotensin II. The life span of untreated rats is a mere 7 weeks; thus, death is a clearly established end point, but not the only one in this carefully executed model of angiotensin II-mediated vasculopathy. The authors use an AT₁ receptor antagonist to demonstrate receptor-specific amelioration of disease and extended life span. Using TF transcription and expression as the indicator, they demonstrate that AT₁ engagement drives activation of activator protein-1 and NF- κ B, well known for their regulation of transcription of a number of inflammatory molecules. It is known that these regulate TF transcription and expression as well, and this is observed to be the case with AT₁ signaling of the cells by angiotensin II. In this transgenic rat model, intravascular microthrombosis has apparently been observed. AT₁ blockade by valsartan provides the specificity and pathology control, and is effective. We are left with questions about the significance of TF expression. Does it contribute directly to this form of severe vasculopathy, or is it more of a marker of NF- κ B activation? Does it occur in humans in association with essential hypertension? And to what degree does this transgenic rodent model parallel a subset of severe angiotensin II-driven hypertensive disease of humans? Nevertheless, the quality of the observations clearly indicates that there may be a link between the pathogenic pathways initiated and driven by TF expression, other NF- κ B inflammatory mol-

ecules, and hypertension associated with elevations of angiotensin II levels *in vivo*.

References

1. Dzau VJ: Angiotensin-converting enzyme as a multimechanistic factor in CAD. *J Myocard Ischemia* 1995, 7(suppl 1):6–14
2. Feener EP, Northrup JM, Aiello LP, King GL: Angiotensin II induces plasminogen activator inhibitor-1 and -2 expression in vascular endothelial and smooth muscle cells. *J Clin Invest* 1995, 95:1353–1362
3. Morishita R, Gibbons GH, Tomita N, Zhang L, Kaneda Y, Ogihara T, Dzau VJ: Antisense oligodeoxynucleotide inhibition of vascular angiotensin-converting enzyme expression attenuates neointimal formation: evidence for tissue angiotensin-converting enzyme function. *Arterioscler Thromb Vasc Biol* 2000, 20:915–922
4. Rossi GP, Sacchetto A, Rizzoni D, Bova S, Porteri E, Mazzocchi G, Belloni AS, Bahcelioglu M, Nussdorfer GG, Pessina AC: Blockade of angiotensin II type 1 receptor and not of endothelin receptor prevents hypertension and cardiovascular disease in transgenic (mREN2)27 rats via adrenocortical steroid-independent mechanisms. *Arterioscler Thromb Vasc Biol* 2000, 20:949–956
5. Edgington TS, Mackman N, Brand K, Ruf W: The structural biology of expression and function of tissue factor. *Thromb Haemost* 1991, 66:67–79
6. Lee RT, Schoen FJ, Loree HM, Lark MW, Libby P: Circumferential stress and matrix metalloproteinase 1 in human coronary atherosclerosis: implications for plaque rupture. *Arterioscler Thromb Vasc Biol* 1996, 16:1070–1073
7. Müller DN, Mervaala EMA, Dechend R, Fiebeler A, Park J-K, Schmidt F, Theuer J, Breu V, Mackman N, Luther T, Schneider W, Gulba D, Ganten D, Haller H, Luft FC: Angiotensin II (AT₁) receptor blockade reduces vascular tissue factor in angiotensin II-induced cardiac vasculopathy. *Am J Pathol* 2000, 157:111–122
8. Willeit J, Kiechl S, Oberhollenzer F, Rungger G, Egger G, Bonora E, Mitterer M, Muggeo M: Distinct risk profiles of early and advanced atherosclerosis: prospective results from the Bruneck study. *Arterioscler Thromb Vasc Biol* 2000, 20:529–537
9. Coughlin SR: How thrombin “talks” to cells: molecular mechanisms and roles *in vivo*. *Arterioscler Thromb Vasc Biol* 1998, 18:514–518