One of the challenges in the development of molecular models of hypertension as a disease with end organ failure is the multifaceted nature of complications that accompany elevated blood pressure. Comorbidities can be detected even at early stages of hypertension and in patients with family history of hypertension even before blood pressure elevation. Well-documented comorbidities to hypertension include diabetes, cardiac- and large-artery remodeling with hypertrophy and fibrosis, atherosclerosis, and renal pathogenesis. Hypertension is also accompanied by complications such as microvascular rarefaction, immune suppression, and apoptosis. To date, no satisfactory mechanism has been proposed to put this manifold of pathophysiological phenomena under one conceptual roof while at the same time providing an explanation for elevated arterial blood pressure. Oxygen free-radical production in hypertensives could possibly form a bridge between elevated blood pressure and vascular complications. Reactive oxygen species serve as signaling molecules for elevated artery/arteriolar tone by reaction with nitric oxide and are also involved in cell injury. But no molecular details have emerged in any model of hypertension to provide a conclusive picture for the role of free radicals in some of the more specific cell dysfunctions that accompany hypertension.

Instead, an increasing body of evidence implicates an uncontrolled proteolytic process as one of the underlying mechanisms in hypertension, including the family of matrix metalloproteinases (MMPs). MMPs are likely more than just extracellular-matrix-remodeling proteases. Their activity in major complications associated with hypertension (eg, atherosclerosis and stroke) is well-documented.

One is justified to ask: Is there a possibility that MMPs are already involved in the early stages of hypertension? Furthermore, is there a possibility that MMPs are actually the mediators that cause hypertension and at the same time may cause comorbidities? In the article by Dr. Fernandez-Patron and colleagues, evidence is presented in the Angiotensin II (Ang II)–induced hypertensive mouse that MMPs are part of the mechanisms responsible for elevated blood pressure, and are also involved in cardiac wall hypertrophy and fibrosis via a previously unrecognized MMP signaling cascade. Following earlier leads suggesting that the tumor necrosis factor-α converting enzyme (TACE) and MMP-7 mediate cardiac hypertrophy and fibrosis, and that knockdown of TACE serves to attenuate partially MMP-2, the authors demonstrated that TACE and MMP-7 siRNA treatment prevented MMP-2 activity (Figure). The simultaneous knockdown of TACE and MMP-7 also attenuated blood pressure elevation in the Ang II–treated mice as well as the development of cardiac hypertrophy and fibrosis; this is documented by a variety of cardiac indices and fibrictic markers. In contrast, MMP-2 inhibition by gene knockdown and pharmacological means served to prevent only a rise in blood pressure, but it did little to prevent hypertrophy. This evidence points toward a transcriptional regulation of MMP-2 by MMP-7 and TACE. While Ang II–induced cardiovascular disease is signaled via multiple MMP pathways with unique physiological roles, MMP-2 modulates only blood pressure in this model of hypertension. MMP-7, which participates in a number of fibrotic processes, is able to modulate the cardiac hypertrophy, but it needs to activate MMP-2 to modulate blood pressure.

Which molecules could serve as MMP-2 substrates? In addition to cleavage of big endothelin or calcitonin gene-related peptide, shown by the Fernandez-Patron group, adrenomedullin, a vasodilator and inhibitor of myocardial fibrosis expressed in vascular smooth muscle and in endothelium, may serve as a substrate for MMP-2; it generates a series of peptides, which have, in part, vasoconstrictor activity. Thus, MMP-2 may have a dual role and a direct impact on the vascular tone in arteries and arterioles. To what degree this MMP-2–mediated hypertension is unique to the Ang II hypertensive model remains to be determined.

In the spontaneously hypertensive rat, a model with multiple elevated MMP levels, we proposed an alternative hypertensive mechanism by MMP-mediated cleavage of the β2-adrenergic receptor. In the presence of receptor cleavage, normal vasodilatory stimulus provided by this receptor on agonist binding is suppressed; this causes a lack of vasodilatory input to the arterial/arteriolar tone and consequently, arterial blood pressure elevation. An interesting feature of this mechanism is that proteolytic receptor cleavage may affect others, eg, the insulin receptor, thereby causing insulin resistance (ie, type II diabetes), or the vascular endothelial growth factor receptor, causing endothelial apoptosis and capillary rarefaction.
The role of the MMPs in the development of hypertension and its comorbidities is likely to be a fruitful area of exploration. Other MMP-specific signaling cascades for comorbidities in hypertension may be discovered. Diverse leads exist in a rich literature on MMPs. For example, MMP-14 (MT-1 MMP) has been implicated in cell migration through the extracellular matrix via its ability to break down the extracellular matrix proteins, and at the same time is implicated in fibroblast proliferation during cardiac fibrosis.

Future management of MMPs will require a nuanced approach because the MMPs also play a major role in tissue repair. Interventions against MMPs will depend not only on the activity of specific members of the MMP family and their endogenous inhibitors, but also on the organ-specific patterns in which the MMPs are synthesized and activated. Eventually, understanding the genetic and/or environmental cause of MMP activation may be a major requirement for optimal management of hypertension and its complications.

**Figure.** Schematic of MMPs differential signaling in the arterial wall of Ang II-induced hypertension and cardiac wall hypertrophy.

**Sources of Funding**

This work was supported by National Heart, Lung, and Blood Institute grant HL 10881.

**Disclosures**

None.

**References**

Matrix Metalloproteinases Activities in Hypertension: Emerging Opportunities
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Hypertension. 2011;57:24-25; originally published online November 15, 2010;
doi: 10.1161/HYPERTENSIONAHA.110.162032

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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