Plasminogen Activator Inhibitor-1:

A Novel Therapeutic Target for Hypertension?

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Daniel I. Simon, MD, FAHA¹; Norman M. Simon, MD²

¹Dept of Medicine, Harrington Heart & Vascular Institute, University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH; ²Division of Nephrology and Hypertension, NorthShore University HealthSystem, Evanston, IL

Address for Correspondence:
Daniel I. Simon, MD
Director, Harrington Heart & Vascular Institute
University Hospitals Case Medical Center
11100 Euclid Avenue
Cleveland, OH 44106
Tel: 216-844-8151
Fax: 216-983-3202
E-mail: Daniel.simon@uhhospitals.org

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Hypertension is the most common reversible risk factor for stroke, myocardial infarction, and heart failure, affecting greater than 60 million individuals in the United States alone and 1 billion globally\(^1\). According to the World Health Organization, hypertension is now the leading cause of preventable death worldwide\(^2\). Importantly, the prevalence and complications of hypertension increase significantly with age. However, despite the availability of many anti-hypertensive agents of distinct pharmacologic classes and evidence-based guideline recommendations for step-wise, multi-drug regimens, control of hypertension remains suboptimal with target blood pressure achieved in less than 50% of patients\(^1\). Although patient non-compliance and sub-maximal dosing of anti-hypertensive agents contribute to lack of blood pressure control, there is an unmet need for new approaches for treatment of hypertension. In this issue of Circulation, Boe and coworkers\(^3\) report that pharmacological inhibition of plasminogen activator inhibitor-1 (PAI-1) is protective against the development of hypertension, cardiac hypertrophy, and periaortic fibrosis (i.e., arteriosclerosis) in mice treated with \(\text{NO}-\text{nitro-L-arginine methyl ester (L-NAME)}\) to inhibit endothelial nitric oxide synthase (eNOS).

Since the molecular basis for primary or essential hypertension is unknown, the treatment of hypertension, excluding secondary or identifiable hypertension with known causes (e.g., chronic renal disease, renovascular, hyperaldosteronism, Cushing syndrome, pheochromocytoma), has been based largely upon targeting the underlying physiologic determinants of blood pressure—namely, intravascular volume (e.g., diuretics), neurohormonal drive (e.g., centrally-acting agents, renin angiotensin system blockade), systemic vascular resistance (e.g., vasodilators), and cardiac inotropy and chronotropy (e.g., beta-blockers) (Figure 1). Another hallmark of hypertension is vascular remodeling of both small (inward eutrophic remodeling that decreases lumen area and increases systemic vascular resistance) and large
(hypertrophic remodeling that increases medial thickness, extracellular matrix accumulation, and artery stiffness) arteries. Anti-hypertensive agents variably affect vascular remodeling, possibly accounting for differential effectiveness of specific agents in preventing cardiovascular events. Arterial collagen accumulation results in age-related aortic stiffening characterized by increased pulse pressure, which is an independent predictor of heart attack and stroke. Therapeutic approaches specifically targeting structural remodeling represent an important new area in cardiovascular disease.

Boe and colleagues investigated whether a novel, orally active PAI-1 antagonist (TM5441) has a protective effect against L-NAME-induced systemic hypertension, arteriosclerosis, and vascular senescence. Wild-type mice received either L-NAME alone or L-NAME and TM5441 for 8 weeks. TM5441 attenuated the development of hypertension and cardiac hypertrophy compared to animals that had received L-NAME alone. Additionally, TM5441-treated mice had a 34% reduction in periaortic fibrosis. Finally, the development of vascular senescence was investigated by measuring p16Ink4a expression and telomere length in aortic tissue. L-NAME increased p16Ink4a expression levels and decreased telomere length, both of which were prevented with TM5441 co-treatment. Importantly, the favorable blood pressure and remodeling effects of PAI-1 inhibition appear to extend to other models of hypertension. PAI-1 deficiency prevented angiotensin II-induced arteriosclerosis, and in supplemental data in the present study, reduced blood pressure.

The precise mechanism(s) responsible for the blood pressure lowering effect of PAI-1 inhibition is uncertain. The fact that wild-type mice treated with TM5441 alone exhibited no change in blood pressure suggests that inhibition of PAI-1 likely does not affect vascular tone or volume, but rather has structural effects. A closer look at the plasminogen activator system
provides potential insights into TM5441 action. Plasmin is the major protease of the fibrinolytic system and plays an important role in cell migration and tissue remodeling by virtue of the fact that it is capable of degrading extracellular matrix proteins directly (fibrin, fibronectin, thrombospondins, and laminins) or indirectly (collagen, elastin) via the activation of metalloproteases. Plasmin is derived from plasminogen by the endogenous plasminogen activators, tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activators (u-PAs) (Figure 1). The generation of plasmin is regulated by a balance between the plasminogen activators, t-PA and u-PA, and their SERPIN family inhibitors, plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator inhibitor-2 (PAI-2). Two functionally distinct forms of PAI-1, termed active and latent, have been identified. In plasma, most of the PAI-1 circulates in the active form, which deactivates spontaneously with a half-life of 1-2 h and is stabilized by vitronectin. PAI-1 is the primary physiological inhibitor of plasminogen activation. Active PAI-1 acts as a suicide substrate for t-PA and u-PA and rapidly neutralizes these plasminogen activators by forming a covalent complex. In plasma, PAI-1 has a critical role in regulating endogenous fibrinolytic activity and resistance to thrombolysis. In vascular tissues, PAI-1 mediates the response to injury by inhibiting cellular migration and matrix degradation. Excess PAI-1 is known to exacerbate the development of fibrosis in a variety of animal models. The plasminogen activator system also regulates vascular cell growth and remodeling as a consequence of plasmin-dependent processing of various cytokines and chemokines, including transforming growth factor-β, interleukin-1, basic fibroblast growth factor, tumor necrosis factor-α, and monocyte chemotactic protein-1. TM5441 treatment did not fully attenuate the increase in systolic blood pressure due to chronic eNOS inhibition, but almost completely prevented collagen deposition and periaortic fibrosis. Thus, PAI-1 likely
blocks proteolytic pathways that are critical to the maintenance of high blood pressure state as well as hypertension-associated arteriosclerosis.

This study challenges the present paradigm of anti-hypertensive treatments that focus on intravascular volume, neurohormonal drive, systemic vascular resistance, and cardiac inotropy and chronotropy rather than vascular structure and distensibility. Understanding the broader functions of PAI-1 in distinct cellular compartments and environments in vascular homeostasis and disease will be required to determine the clinical significance of these findings. First, is there any evidence that PAI-1 is involved in human hypertension? Indeed, this appears to be the case based upon an analysis of arterial stiffness in the Framingham population. PAI-1 was positively related to measures of conduit artery stiffness (i.e., mean arterial pressure, central pulse pressure, and forward pressure wave amplitude) even after multivariable adjustment.

Second, is selective inhibition of PAI-1 achievable in vivo in humans? If so, what is the most appropriate timing of PAI-1 inhibition—namely, to prevent hypertension in pre-hypertensive individuals or in patients with established hypertension? Third, is it possible for inhibition of PAI-1 to reverse arteriosclerosis and periaortic fibrosis, thereby, for example, lowering pulse pressure? Fourth, will blockade of PAI-1 and unchecked proteolysis be associated with adverse effects, including increased risk of bleeding, intracerebral hemorrhage, and/or unfavorable vascular remodeling that could promote aneurysm formation? Fifth, in genome-wide association studies of hypertension, is there linkage with genes related to the plasminogen activator system or proteolysis? Finally, could targeting PAI-1 be useful in pulmonary hypertension, which is also associated with significant vascular remodeling?

The contribution by Boe et al. 3 in this issue of Circulation highlights the emergence and potential importance of vascular remodeling in animal models of hypertension (chronic
inhibition of eNOS or angiotensin II infusion) that may guide the study of human disease. The involvement of the plasminogen activator system in vascular homeostasis/remodeling and blood pressure, especially in the elderly, has profound implications for our patients. Novel therapeutic approaches available to reduce the increase in pulse pressure and arterial stiffness with age have been proposed previously \(^{25}\). These approaches involve converting enzyme inhibitors, nitrate derivatives, agents acting on collagen cross-linking, spironolactone and vasopeptidase inhibitors. This study suggests a new approach involving structural remodeling of large and small arteries to prevent arteriosclerosis in hypertension. Understanding how to safely and efficiently translate these experimental observations might lead to new clinical applications, perhaps targeting PAI-1.

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**Figure Legend:**

**Figure 1.** Anti-hypertensive agents and sites of target action. Traditional anti-hypertensive agents for essential or primary hypertension target underlying physiologic determinants of blood pressure, including intravascular volume, neurohormonal drive, systemic vascular resistance, and cardiac inotropy and chronotropy. The plasminogen activator system is schematically illustrated (t-PA, tissue-type plasminogen activator; u-PA, urokinase-type plasminogen activator; PAI-1, plasminogen activator inhibitor-1; MMP, matrix.
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