Primary aldosteronism (PA), first characterized by Conn in 1955, results in hypertension secondary to the excessive production of aldosterone by the adrenal cortex—in many cases because of the presence of a benign aldosterone-producing adenoma. The prevalence of PA among hypertensive patients has been estimated to range between 4% and 20%, depending on the criteria used for patient selection, the specific diagnostic methods used, and the severity of hypertension. Hyperaldosteronism is associated with damage to the heart, kidneys, and cardiovascular system, in turn affecting clinical outcomes and patient survival. PA is the most common form of secondary hypertension, and in comparison with patients with essential hypertension, PA patients exhibit more severe cardiovascular damage, including left ventricular hypertrophy, diastolic dysfunction, myocardial infarction, stroke, and atrial fibrillation. Early detection of PA is essential for avoiding the adverse effects of aldosterone independently of the degree of high blood pressure.

A common feature of patients with PA is the development of cardiac fibrosis, characterized by the increased deposition of extracellular matrix (ECM) components, such as type I collagen. By changing the compliance of the myocardium, extracellular matrix (ECM) components, such as type I collagen, are upregulated in response to higher concentrations of aldosterone. The relative balance between synthesis and degradation in contributing to ECM accumulation in PA, thus, remains unclear.

In the current issue of Hypertension, Hung et al provide new evidence for a functional link between a high concentration of circulating aldosterone and cardiac expression of tissue inhibitor of metalloproteinases-1 (TIMP-1), suggesting that fibrosis subsequent to PA may be because of a reduction in ECM degradation, rather than an increase in ECM gene expression (Figure). In a small prospective study, this group has previously shown that serum TIMP-1 and measures of diastolic dysfunction in patients with aldosterone-producing adenoma were significantly elevated compared with patients with essential hypertension. At 1-year follow-up after adrenalectomy, a significant reduction in serum TIMP-1 correlated with improved diastolic function, but without changes in MMP2 expression. Although this study did not directly measure fibrosis in these patients, it nonetheless suggested the intriguing possibility that aldosterone may directly or indirectly influence TIMP-1 expression to induce diastolic dysfunction.

This article expands on this earlier work using data from patients with PA, an animal model of hyperaldosteronism and isolated human cardiac fibroblasts treated with aldosterone to demonstrate for the first time the induction of TIMP-1 expression by aldosterone via a glucocorticoid receptor (GR)/PI3K-Akt/nuclear factor-kB-mediated pathway. In patients with PA, the authors demonstrated a positive and significant correlation between plasma TIMP-1 and 24-hour urinary aldosterone, as well as between plasma TIMP-1 and indicators of cardiac dysfunction, including left ventricular mass, interventricular septal thickness, and tissue Doppler E/E′ ratio, a measure of diastolic dysfunction. Direct administration of aldosterone to isolated human cardiac fibroblasts caused a time- and dose-dependent increase in TIMP-1 expression, an effect that was abolished by administration of siRNA targeting the GR but not the mineralocorticoid.
receptor (MR). RU486, which can act via the GR but not MR, exhibited a similar attenuation of aldosterone-induced TIMP-1 expression. As early as 7 days after implantation of timed release aldosterone pellets in mice, serum TIMP-1 level and cardiac TIMP-1 expression similarly increased. As in the in vitro studies, GR blockade with RU486 prevented aldosterone-induced increases in TIMP-1, whereas MR blockade with eplerenone failed to show a similar effect.

Aldosterone induced the phosphorylation of Akt in isolated fibroblasts, and pharmacological blockade of PI3K-Akt signaling with LY294002 attenuated aldosterone-mediated TIMP-1 upregulation, implicating this pathway in the underlying regulatory mechanism, whereas blockade of extracellular signal-regulated kinase or p38 mitogen-activated protein kinase signaling had no effect. Further insight was gained into the downstream transcriptional effector of aldosterone by the demonstration that TIMP-1 upregulation could be blocked with a nuclear factor-κB decoy, and that aldosterone-induced nuclear factor-κB nuclear localization and transcriptional activity which could be blocked by GR or PI3K inhibition.

In an elegant series of experiments, the authors demonstrated that, although aldosterone induced accumulation of type I collagen in cardiac fibroblasts, this effect seems to be because of a reduction in collagen degradation, rather than an increase in de novo synthesis. siRNA targeting TIMP-1 completely attenuated collagen accumulation, whereas aldosterone itself had no effect on collagen mRNA synthesis. Furthermore, although aldosterone had no effect on MMP-1 expression at either the mRNA or protein level, MMP-1 activity decreased in a dose-dependent manner with aldosterone administration, implicating TIMP-mediated effects.

This work provides important new insight into a potential contributory mechanism underlying fibrosis resulting from hyperaldosteronism. Although alterations in ECM remodeling by MMPs are frequently observed in many fibrotic diseases, there is typically an accompanying increase in collagen synthesis. Aldosterone-induced fibrosis may represent an exception to this paradigm, given the surprising finding reported here that aldosterone failed to alter collagen mRNA synthesis, and in fact required TIMP-1 for collagen accumulation to occur. Nonetheless, many important questions remain that will require further study. The authors observed a clear increase in cardiac fibrosis after aldosterone administration in vivo in agreement with previous studies, and noted an increase in TIMP-1 expression that was specifically dependent on GR signaling; however, they did not directly test whether GR or MR inhibition blocked aldosterone-induced cardiac fibrosis in this model. This is an important question, as eplerenone and spironolactone, which are generally considered to work primarily via MR-mediated mechanisms, are both effective in reducing cardiac fibrosis in humans (Figure).9 Notably, eplerenone failed to block aldosterone-induced TIMP-1 upregulation in isolated cells in this study, suggesting that TIMP-1 upregulation by aldosterone cannot explain all of its profibrotic effects. A model-specific effect cannot be ruled out at present. These results also introduce the possibility that eplerenone and spironolactone may act indirectly on cardiac fibrosis by affecting the function of other cells in the myocardium, rather than by having a direct effect on cardiac fibroblasts—perhaps by altering the expression of profibrotic paracrine factors.

It also remains to be seen whether aldosterone-mediated induction of TIMP-1 expression may occur via additional mechanisms besides the GR/PI3K-Akt/nuclear factor-κB pathway described here. Rapid, nongenomic effects of aldosterone have been described for many years, suggesting that other mechanisms could be at work. The use of human fetal cardiac fibroblasts in this study also raises the question of whether the same mechanism also occurs in adult cells.

The true extent of the role of TIMP-1 in PA will require significant additional inquiry. TIMP-1 gene deletion is protective in the setting of myocardial infarction, resulting in decreased cardiac collagen content, and elevated expression of TIMP-1 and TIMP-2 in human pressure-overloaded hearts is associated with increased collagen content and diastolic dysfunction.10,11 PA may thus represent another condition in which increased TIMP-1 contributes to the underlying cardiac pathology. It is critical that the specific roles of not only the individual TIMPs but also their MMP and non-MMP targets, continue to be uncovered, particularly because these roles may well vary depending on the
specific cardiac pathology in question. Therapeutic blockade of TIMP-1 in PA-induced cardiac diastolic dysfunction may ultimately prove to be an attractive strategy for patient management.

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References

Tissue Inhibitor of Metalloproteinases-1 Regulation by Aldosterone: Breaking the Balance in Cardiac Fibrosis
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