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

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See related article, pp 1309–1320

Primary aldosteronism (PA), first characterized by Conn in 1955,1 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.2 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.3,4 By changing the compliance of the myocardium, of cardiac fibrosis, characterized by the increased deposition 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.3,4 By changing the compliance of the myocardium, fibrosis interferes with both systolic and diastolic cardiac function, and furthermore contributes to arrhythmogenesis because of altered electric properties, particularly with atrial fibrosis. Fibrosis thus represents not only a pathological outcome of underlying disease but also a risk factor for further exacerbation of cardiac dysfunction and poorer patient outcomes in its own right. Steady-state ECM levels represent a balance between synthesis by cardiac fibroblasts, and degradation, typically by matrix metalloproteinases (MMPs) arising from a variety of cell sources. In fibrosis, this balance is upset, resulting in increased synthesis, decreased degradation, or a combination of perturbations to both processes, resulting in progressive deposition of ECM. Numerous studies have reported the antifibrotic benefits of adrenalectomy or aldosterone antagonism via the use of spironolactone and its derivatives in patients with PA, yet previous examinations of the effects of aldosterone in the heart have generally reported that aldosterone does not alter ECM or collagen gene expression directly, and in some cases have noted decreased collagen expression in response to higher concentrations of aldosterone.5,6 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 al7 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.8 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-κB–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.
TIMP-1 upregulation, implicating this pathway in the under-
signaling with LY294002 attenuated aldosterone-mediated
lated fibroblasts, and pharmacological blockade of PI3K-Akt
blockade with eplerenone failed to show a similar effect.
aldosterone-induced increases in TIMP-1, whereas MR
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 iso-
lated fibroblasts, and pharmacological blockade of PI3K-Akt
signaling with LY294002 attenuated aldosterone-mediated
TIMP-1 upregulation, implicating this pathway in the under-
lying regulatory mechanism, whereas blockade of extracellu-
lar 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-xB decoy, and that aldosterone-induced
nuclear factor-xB nuclear localization and transcriptional
activity which could be blocked by GR or PI3K inhibition.

In an elegant series of experiments, the authors demon-
strated that, although aldosterone induced accumulation
of type I collagen in cardiac fibroblasts, this effect
seems to be because of a reduction in collagen degrada-
tion, rather than an increase in de novo synthesis. siRNA
targeting TIMP-1 completely attenuated collagen accumu-
lation, whereas aldosterone itself had no effect on colla-
gen 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-depen-
dent 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 remod-
eling by MMPs are frequently observed in many fibrotic
diseases, there is typically an accompanying increase in
collagen synthesis. Aldosterone-induced fibrosis may rep-
resent 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 ques-
tions 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 spe-
cifically dependent on GR signaling; however, they did not
directly test whether GR or MR inhibition blocked aldoste-
rone-induced cardiac fibrosis in this model. This is an impor-
tant 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).^7 Notably, eplerenone failed to block aldo-
stone-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 intro-
duce 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 expres-
sion 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-xB
pathway described here. Rapid, nongenomic effects of aldo-
steroine 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 pro-
tective in the setting of myocardial infarction, resulting in
decreased cardiac collagen content, and elevated expres-
sion 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, particu-
larly 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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**Disclosures**

None.

**References**


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