The Renin–Angiotensin–Aldosterone System: Approaches to Cardiac and Renal Therapy

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Abstract: *The renin–angiotensin–aldosterone system (RAAS) plays a prominent role in the pathophysiology of cardiac and renal diseases. Aldosterone leads to local effects of vasoconstriction, sodium resorption, and possibly inflammation and fibrosis in several organs. Pharmacologic manipulation of the RAAS may involve renin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II–receptor blockers, and aldosterone antagonists.*

At a Glance

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The renin–angiotensin–aldosterone system (RAAS) plays a significant role in preserving hemodynamic stability in response to the loss of blood volume, salt, and water.[1,2] It is primarily associated with the kidneys, but its activity also affects the brain, heart, blood vessels, and adrenal glands.[3] These local systems may respond with vascular inflammation and fibrosis. As a result of research into its activity in local tissue, manipulation of the RAAS has become the mainstay of therapy for cardiac and renal diseases.

Normal Function of the Renin–Angiotensin–Aldosterone System

The RAAS comprises a renin-triggered cascade of hormones with systemic effects (**FIGURE 1**). Renin is secreted from the juxtaglomerular apparatus of the afferent renal arterioles.[4] Stimuli for the release of renin include β_1-adrenergic activity, decreased renal perfusion, and reduced sodium resorption by the renal tubules.[3] Renin cleaves the substrate angiotensinogen to form angiotensin I (Ang I), which is later converted to angiotensin II (Ang II). Angiotensinogen is an α_2-globulin secreted by the liver and stored in the plasma.[3,4]

Angiotensin-converting enzyme (ACE) changes Ang I (inactive) to Ang II (active) and angiotensin III (active, but less potent than Ang II). It also inactivates bradykinin, a potent vasodilator. ACE is found in most tissues and circulates in plasma, but its activity in the lungs is particularly high.[4] Nonrenin and non-ACE pathways allow the production of Ang II either directly from angiotensinogen or from Ang I. Both mechanisms are especially active in the vascular endothelium.[1]

Ang II mediates all systemic effects of the RAAS by activating two receptor subtypes. Angiotensin type 1 (AT1) receptors are widely distributed in the vasculature, kidneys, adrenal glands, heart, liver, and brain.[3] Angiotensin type 2 (AT2) receptors are similarly dispersed in the fetus, but in adults, they are found only in the adrenal medulla, uterus, ovary, vascular endothelium, and certain regions of the brain.

The activation of AT1 receptors by Ang II stimulates the adrenal zona glomerulosa to produce aldosterone, the final step of the RAAS cascade. Major stimuli for aldosterone production include the release of Ang II and corticotropin and elevated potassium levels.[3]

Angiotensin

The physiologic activities of Ang II are mediated by the AT1 receptors (**BOX 1**). Ang II is a potent vasoconstrictor that stimulates aldosterone production and promotes sodium and water retention, inflammation, fibrosis, and myocyte hypertrophy. The pressor effects are mediated by direct vasoconstriction via stimulation of

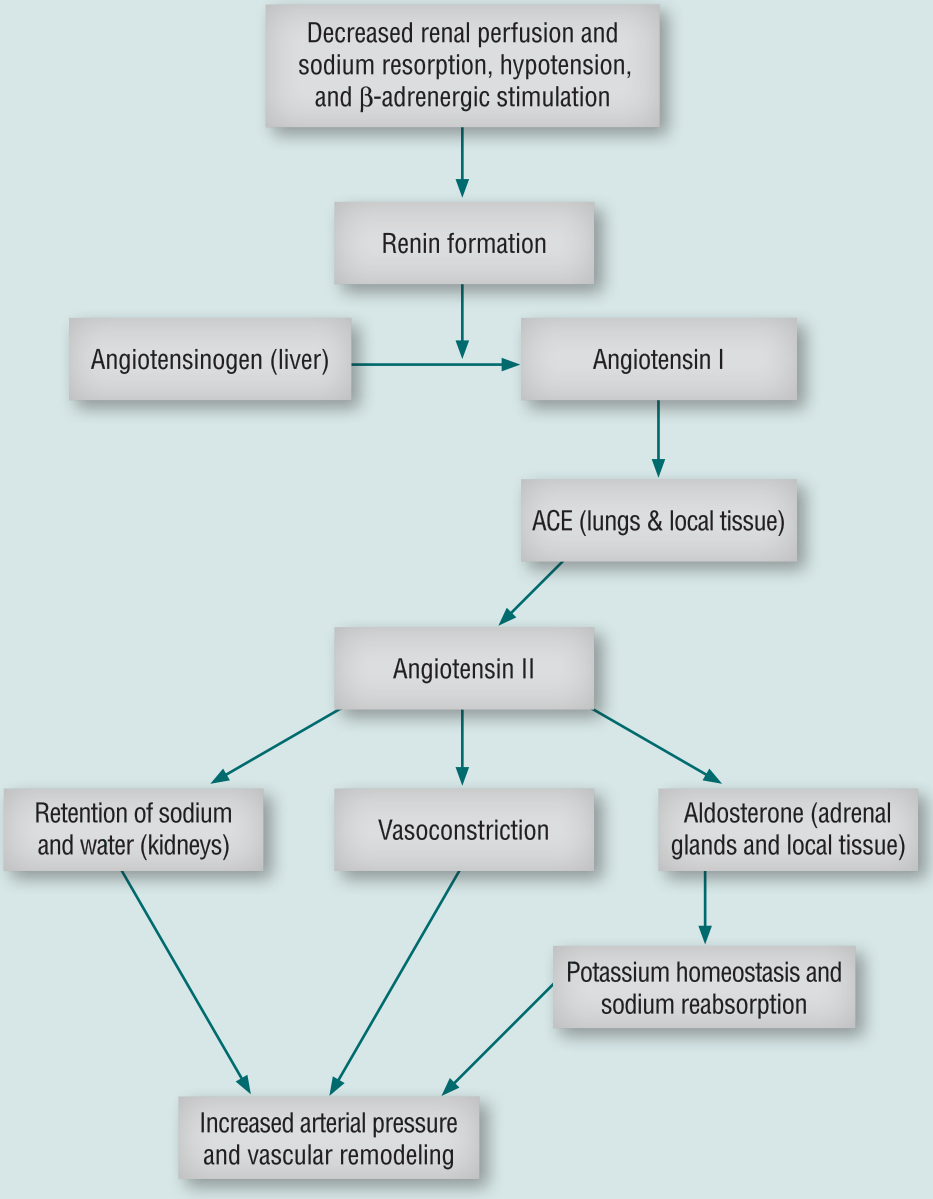
the sympathoadrenal system (centrally and peripherally) and by inhibition of vagal control of the heart rate.[5] Ang II also stimulates sodium resorption in the kidneys by acting on the basolateral and luminal membranes of the proximal tubule, the medullary thick ascending limb, and the cortical collecting ducts.

Ang II has mitogenic properties, stimulating the release of cytokines and growth factors. The production of transforming growth factor β (TGF-β), platelet-derived growth factor, and nuclear factor-κβ leads to inflammation, fibroblast formation, and collagen deposition.[1] In response to decreased plasma volume, Ang II, in conjunction with the sympathetic nervous system, promotes the release of vasopressin from the posterior pituitary. Vasopressin has weak vasoconstriction and inotropic effects on the heart and stimulates water resorption through the aquaporin-2 water channels in the renal collecting ducts.[3] The final result is systemic vasoconstriction and water retention.

One of the key effects of Ang II is the regulation of aldosterone. Ang II acts via AT1

FIGURE 1

Overview of the RAAS



*Quick***Notes**

The RAAS affects tissue throughout the body.

BOX 1

Actions of Angiotensin II[1,3,5,7]

Angiotensin receptor 1
- Increases sodium resorption
- Stimulates aldosterone release
- Stimulates vasopressin release
- Promotes inflammation
- Promotes fibrosis
- Promotes myocyte hypertrophy
- Promotes vasoconstriction
- Promotes glomerular capillary hypertension
- Inhibits vagal control

Angiotensin receptor II
- Affects fetal organ development
- Promotes vasodilation
- Inhibits proliferation
- Inhibits inflammation

receptors in the adrenal zona glomerulosa to cause the release of aldosterone. Sodium depletion up-regulates AT1 receptors for Ang II, while excess sodium decreases the zona glomerulosa receptors.[6] Ang II and aldosterone help regulate sodium and water balances and maintain vascular pressure.[3]

In contrast to AT1 receptors, AT2 receptors modulate organ development in the fetus and possess vasodilatory and antiproliferative effects on the vessel endothelium in select organs. The AT2 receptors appear to antagonize the actions of the AT1 receptors.[1]

Aldosterone

Aldosterone has properties similar to those of Ang II (**BOX 2**). It binds to receptors in the cortical collecting duct of the nephron, allowing sodium and water resorption and potassium secretion. It also promotes sodium resorption in the salivary glands, sweat glands, and colon, resulting in expansion of intravascular volume.[5] Like Ang II, aldosterone has mitogenic and profibrotic properties, directly increasing the expression and production of TGF-β to cause fibrosis and inflammation. Both aldosterone and Ang II are involved in blood coagulation through increased platelet production, plasminogen activator inhibitor type 1 (PAI-1) activity, and aggregation and activation of platelets.[2,7]

Hypokalemia, atrial natriuretic peptide (ANP), and dopamine all inhibit aldosterone release, whereas plasma sodium levels have little or no direct effect. Dopamine has a direct negative effect on aldosterone by inhibiting adrenal response to exogenous Ang II. ANP is produced by atrial cardiac myocytes in response to left atrial enlargement and tachycardia, and it inhibits renin secretion and blocks the action of Ang II on aldosterone secretion.[5]

Pathophysiology

Cardiac Disease

Heart failure is now recognized as a complex syndrome that involves increased activity of the adrenergic nervous system, activation of the RAAS, overexpression of ANP and brain natriuretic peptide (BNP), and increased release of vasopressin, endothelin-1, and tumor necrosis factor.[3,8] Reduced cardiac output and decreased blood pressure activate the adrenergic nervous system, resulting in increased heart rate, peripheral vasoconstriction, and increased myocardial contractility. These mechanisms increase blood flow to vital centers.[3,8] However, chronic activation of the adrenergic nervous system can lead to myocardial cell dysfunction and cell death, peripheral vasoconstriction, myocardial hypertrophy and fibrosis, tachycardia, and arrhythmias.

Mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles can sense arterial underfilling. Decreased activation of these receptors due to reductions in systemic arterial pressure, stroke volume, renal perfusion, or peripheral vascular resistance leads to an increase in sympathetic outflow from the central nervous system, activation of the RAAS, and release of vasopressin.[9,10] Renin release is stimulated by β_1-adrenergic stimulation, decreased renal perfusion, and reduced sodium delivery to the renal tubules. Renin release contributes

BOX 2

Actions of Aldosterone[2,5,7]

- Promotes potassium homeostasis
- Promotes platelet aggregation and activation
- Promotes vasoconstriction
- Stimulates thirst
- Increases sodium resorption
- Promotes fibrosis
- Promotes vascular remodeling

QuickNotes

Manipulation of the RAAS is the cornerstone of therapy for heart failure.

to further sodium and water retention. Renal renin concentrations have been shown to be elevated in cats with hypertrophic cardiomyopathy.[11] Ang II and aldosterone can directly affect the myocardium and vasculature, leading to hypertrophy and fibrosis.[3,8]

In six major canine studies, ACE inhibitors (e.g., enalapril, benazepril) were found to reduce morbidity and mortality in dogs with dilated cardiomyopathy and mitral valve disease.[8] However, there are concerns regarding the effects of long-term ACE inhibitor use on renal function. It has been demonstrated that dogs with severe compensatory mitral valve disease receiving enalapril for 2 years had no statistical difference in serum urea nitrogen and creatinine levels from those in healthy dogs, suggesting that long-term enalapril use does not adversely affect renal function.[12] ACE inhibitors do reduce Ang II and aldosterone production, but non–ACE-mediated pathways can enable continued aldosterone production during long-term ACE inhibitor therapy (i.e., aldosterone escape). This can cause persistent sodium retention, potassium loss, myocardial fibrosis, and diuretic resistance. The use of aldosterone antagonists (e.g., spironolactone) in addition to ACE inhibitors may further reduce morbidity and mortality.[8]

*Quick***Notes**

ACE inhibitors are not contraindicated in azotemic patients.

Vasopressin is activated through stimulation of the sympathetic nervous system, Ang II release, and reduced plasma volume sensed by stretch receptors in the atria and large veins. Vasopressin activation leads to vasoconstriction and water retention via the renal collecting ducts.[3,8] Elevated vasopressin levels have been detected in patients with congestive heart failure. Arterial underfilling and activation of carotid baroreceptors may be the cause of this paradoxical vasopressin release. Use of the vasopressin receptor blocker conivaptan to offset this effect is being studied in people and dogs.[8]

Natriuretic peptides have a role in counterbalancing the effects of the RAAS and the sympathetic nervous system. ANP release is triggered by atrial distention, causing arteriole dilation, increasing renal excretion of sodium and water, exerting an antihypertrophic effect on myocytes, and degrading Ang II, bradykinin, and endothelin.[8] BNP, which is primarily released from the left ventricle in response to increased filling pressures, exerts similar effects.[8]

Endothelin helps modulate vascular tone. It is produced by vascular endothelial cells in response to hypoxia, stretch, and the release of Ang II, norepinephrine, growth factors, cytokines, and bradykinin. It promotes vasoconstriction and increases myocardial contractility and aldosterone secretion, eventually leading to hypertrophy of the vascular smooth muscle and myocardium.[3] In the setting of congestive heart failure, the plasma norepinephrine concentration is inversely correlated with survival.[9]

Levels of tumor necrosis factor α are increased in congestive heart failure, causing left ventricular dilation and remodeling. Cachexia in dogs with heart failure correlates with high levels of tumor necrosis factor α. Supplementation with fish oils has been evaluated in dogs to help counteract the effects of this factor and other cytokines. Dogs that received this supplementation appeared to have improved cachexia scores compared with those in a placebo group.[8]

Renal Disease

As with cardiac disease, the RAAS has an integral role in the progression of renal disease. Chronic renal disease in dogs and cats begins with nephron injury that results in hyperfiltration, glomerular capillary hypertension, glomerulosclerosis, and interstitial fibrosis.[7,13] Activation of the RAAS helps protect renal function in the early stages, but prolonged renal ischemia and direct insult from Ang II and aldosterone eventually exacerbate renal injury through several mechanisms.[1] Ang II increases the production of TGF-β, a fibrogenic cytokine that stimulates the production of extracellular matrix, contraction of smooth muscle, and proliferation of glomerular mesangial cells—the major cells involved in the development of glomerulosclerosis. Ang II also increases the production of PAI-1, thereby deactivating renal proteases and allowing further accumulation of the extracellular matrix.[13] Ang II activates inflammatory cells by direct chemotaxis and the release of proinflammatory mediators and mononuclear cells to the interstitium and glomeruli. Increased glomerular capillary pressure, extracellular matrix accumulation, and aldosterone stimulation all contribute to glomerulosclerosis and interstitial fibrosis.[13]

Ang II promotes renal efferent arteriolar vasoconstriction in an effort to increase the glomerular filtration rate. However, this vasoconstriction also leads to glomerular capillary hypertension, an increase in glomerular permeability, and excessive protein filtration. Proteinuria may also be worsened through RAAS disruption of nephrin expression. Nephrin is a transmembrane protein located in the slit diaphragm of the glomerular podocyte that limits protein loss by maintaining slit diaphragm integrity. Protein in the urine is also toxic to the tubules, resulting in additional tubulointerstitial inflammation and scarring.[7]

Manipulation of the RAAS is becoming the mainstay of therapy for some forms of renal disease. The American College of Veterinary Internal Medicine (ACVIM) published a consensus statement in 2004 regarding the management of canine and feline proteinuria, which is both a marker of glomerular damage and a cause of progression in renal failure.[14] In dogs with marked proteinuria, ACE inhibitors may have renoprotective effects and reduce the magnitude of proteinuria[14,15] because they decrease efferent glomerular arteriolar resistance. They also decrease the formation of Ang II and aldosterone, potentiate the vasodilatory effects of bradykinin, and lower glomerular transcapillary hydrostatic pressure. Treatment with enalapril may counteract proteinuria and delay the onset or progression of azotemia in dogs with idiopathic glomerulonephritis.[14,15] The ACVIM consensus statement recommends that patients with persistent renal proteinuria be treated with an ACE inhibitor, an appropriate high-quality protein diet, and omega-3 fatty acid supplementation.[14]

ACE inhibitors have been evaluated in dogs and cats with renal failure.[13,16,17] One study in cats with experimentally induced renal failure found that those treated with benazepril had either no change or an increase in whole-kidney glomerular filtration rate compared with cats receiving a placebo; all subjects were mildly azotemic and were monitored for only 6 months.[16] Benazepril has been approved in Europe for the treatment of feline chronic renal failure.[13]

Many clinicians are uncomfortable with the use of ACE inhibitors in azotemic patients, believing that they may further increase serum creatinine levels and worsen hyperkalemia.

TABLE 1 Drugs for Direct Manipulation of the Renin–Angiotensin–Aldosterone System[1,2,18,20–24]

Class	Generic Names[a]	Mechanism of Action
Renin inhibitors	Aliskiren	Interfere with the first rate-limiting step in the synthesis of Ang I from angiotensinogen
ACE inhibitors	▸ Benazepril[b] ▸ Captopril ▸ Enalapril[b,c] ▸ Imidapril ▸ Lisinopril ▸ Ramipril	Inhibit the conversion of Ang I into Ang II
Angiotensin receptor antagonists	▸ Candesartan ▸ Irbesartan ▸ Losartan ▸ Valsartan	Block the binding of Ang II to AT1 receptors
Aldosterone antagonists	Spironolactone[b]	Block the binding of aldosterone to principal cells of the renal collecting ducts

[a]Not all available drugs are listed.
[b]These drugs are routinely used in veterinary medicine.
[c]This drug is available in a veterinary-approved form.

Researchers have found that human patients whose serum creatinine levels increase but stabilize within 2 months have the greatest long-term delay in progression of renal failure.[1,18] A study of dogs with experimentally induced renal failure evaluated the pharmacokinetics of enalapril and benazepril. The metabolites of benazepril were eliminated in both bile and urine, whereas the metabolites of enalapril were eliminated in urine. Thus, dogs with renal disease can clear benazepril from the system, but those treated with enalapril may need lower doses.[19] The optimal dose of ACE inhibitors in patients with renal disease is still unknown. Serum creatinine and potassium concentrations should be checked 7 days after ACE inhibitor therapy is initiated.

Ang II receptor blockers (ARBs) have a greater affinity for AT1 receptors than for AT2 receptors and do not inhibit the breakdown of bradykinin. They should be more effective than ACE inhibitors at decreasing the deleterious effects of angiotensin because they are

not affected by production of Ang II by non-ACE mechanisms (i.e., angiotensin escape).[18] In addition, they may reduce proteinuria and retard the progression of nondiabetic kidney disease.[7,18] Researchers have suggested that dual blockade with ACE inhibitors and ARBs may provide renal benefit beyond therapy with either drug alone.[7,18]

Pharmacologic Manipulation

The use of drugs to manipulate the RAAS is the mainstay of therapy for canine and feline cardiac and renal diseases (**TABLE 1**).

Renin Inhibitors

Renin inhibitors interfere with the initial rate-limiting step in the synthesis of Ang II by binding directly to renin.[20] The first generation of renin inhibitors was not effective because of poor bioavailability. Aliskiren, a type of renin inhibitor, appears to successfully lower blood pressure and may provide end-organ protection in the presence of hypertension.[21,22]

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors prevent the conversion of inactive Ang I into active Ang II[23] and are considered first-line therapy for many cardiovascular and renal diseases. They decrease morbidity in dogs with dilated cardiomyopathy and mitral valve disease, and their use has been approved in England for cats with chronic renal disease. An additional benefit of ACE inhibitors is decreased degradation of bradykinin. However, the potential for angiotensin and aldosterone escape may necessitate additional treatment options.

Angiotensin II Receptor Blockers

ARBs act by selectively blocking the binding of Ang II to AT1 receptors. They do not act on AT2 receptors. Early clinical trials demonstrated that ARBs effectively lower blood pressure and may offer renal and cardiac protection. Human studies have shown that ARBs may reverse left ventricular hypertrophy, improve congestive heart failure, and slow the progression of renal disease in diabetic patients,[24] but effects in dogs and cats are still being studied.

Aldosterone Antagonists

Spironolactone blocks aldosterone's actions on the principal cell of the renal collecting duct. Because it is an aldosterone receptor antagonist, it may help combat aldosterone escape. Spironolactone reduces blood pressure by enhancing renal sodium excretion. Several human studies have shown positive evidence for the use of spironolactone in conjunction with an ACE inhibitor and a loop diuretic (e.g., furosemide) in the treatment of congestive heart failure.[1,2]

Conclusion

The RAAS plays an integral role in maintaining vascular tone, sodium and water balance, and blood pressure. Its activity has been defined in cardiac and renal diseases and is being evaluated in the dysfunction of other organs. Renin and aldosterone ratios are being characterized in dogs to help identify primary hypoadrenocorticism and primary hypoaldosteronism.[25] Further studies are expected to examine the role of the RAAS in conditions such as hypoadrenocorticism, hypertension, thyroid disease, and liver disease. As more findings emerge, drug therapies for manipulating the RAAS will be developed for dogs and cats. C

*Quick***Notes**

ACE inhibitors and angiotensin receptor blockers may have protective effects on the kidneys.

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1. _____ does not trigger renin secretion.
- **a.** β_1-adrenergic stimulation
- **b.** Decreased renal perfusion
- **c.** Decreased potassium resorption by the renal tubules
- **d.** Decreased sodium resorption by the renal tubules

2. Which is not a stimulus for aldosterone production?
- **a.** hyperkalemia
- **b.** Ang II release
- **c.** corticotropin release
- **d.** hypernatremia

3. Which is a direct result of AT1 receptor activation by Ang II?
- **a.** sodium resorption
- **b.** antiinflammation
- **c.** potassium resorption
- **d.** vasodilation

4. _____ is not involved in congestive heart failure.
- **a.** The RAAS
- **b.** The adrenergic nervous system
- **c.** Parathyroid hormone
- **d.** ANP

5. The roles of ANP and BNP include
- **a.** arteriole dilation and increased renal sodium excretion.
- **b.** vasoconstriction and increased renal sodium excretion.
- **c.** arteriole dilation and increased renal sodium resorption.
- **d.** vasoconstriction and increased renal sodium resorption.

6. Which is an action of Ang II on the kidneys during renal failure?
- **a.** antiinflammation
- **b.** decreased production of PAI-1
- **c.** renal efferent arteriolar vasoconstriction
- **d.** increased nephrin expression

7. Which type of agent is recommended for treating persistent renal proteinuria in dogs?
- **a.** loop diuretic
- **b.** corticosteroid
- **c.** β-blocker
- **d.** ACE inhibitor

8. What is aldosterone escape?
- **a.** production of aldosterone by non-ACE mechanisms during ACE inhibitor administration
- **b.** production of Ang II during angiotensin receptor blocker administration
- **c.** production of Ang I from angiotensinogen during ACE inhibitor administration
- **d.** production of ACE during angiotensin receptor blocker administration

9. Which medication does not directly manipulate the RAAS?
- **a.** enalapril
- **b.** furosemide
- **c.** aliskiren
- **d.** spironolactone

10. What is the mechanism of action of spironolactone?
- **a.** It blocks conversion of Ang I to Ang II.
- **b.** It inhibits sodium resorption in the thick ascending loop of Henle.
- **c.** It antagonizes aldosterone's actions on the principal cell of the renal collecting duct.
- **d.** It inhibits renin production.