Evolving understanding of the renin-angiotensin-aldosterone system: Pathophysiology and targets for therapeutic intervention

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Since its discovery in the late 19th century, our conceptual understanding of the renin-angiotensin-aldosterone system (RAAS) has undergone a process of continuous evolution. Renin was first described by Tigerstedt and Bergman, who, in 1898, documented pressor effects of tissue extracts from rabbit kidneys. Later investigators established that the downstream products of renin's enzymatic activity functioned as key physiologic regulators of vascular tone, salt and water balance, and blood pressure (BP). It was later found that the most important of these products, angiotensin II (AII), also regulates cellular processes at the tissue level that are central to cardiovascular structure and function.

Recently, discovery of the (pro)renin receptor and experimental evidence that binding to this receptor amplifies renin's enzymatic activity, activates prorenin, and directly stimulates important intracellular signaling pathways has added a further dimension to an evolving comprehension of exactly how the RAAS works and the mechanisms by which it contributes to human disease.

The development of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) has allowed RAAS suppression to be extensively tested as a therapeutic strategy for both the prevention and treatment of cardiovascular disease. The ACEIs and ARBs reduce the effects of AII either by reducing its production or by directly blocking its interaction with the angiotensin-1 (AT1) receptor. Agents from both classes have proven effective in reducing the risk of serious cardiovascular events in patients with hypertension, heart failure (HF), and proteinuric renal disease.

When given as monotherapy, ACEIs and ARBs increase renin secretion by interfering with feedback inhibition of its release. This leads to downstream RAAS activation that may limit the degree of RAAS suppression that is achievable with these drugs. Recognition of this phenomenon has led to the hypothesis that blocking multiple RAAS targets might produce more complete RAAS blockade and further improve cardiovascular outcomes. This article and others in this supplement will review the concepts and data that support and oppose this hypothesis as well as their clinical implications.

Renin-angiotensin-aldosterone system

From an evolutionary perspective, the RAAS exists to maintain homeostasis in times of stress or injury. Activation of the system in acute situations is directed toward preservation of intravascular volume, maintenance of BP, and repair of tissue injury. In contrast to its protective effects in acutely stressful circumstances, chronic stimulation of the RAAS exerts effects that are detrimental to long-term cardiovascular health. The effects are mediated by a number of pathogenic processes including chronic vasoconstriction, elevation of BP, vascular smooth muscle cell growth/migration, endothelial dysfunction, oxidative stress, the release of cytokines and immune/inflammatory cell activation, fibrosis, and thrombosis. Through these mechanisms, chronic RAAS activation contributes to development of vascular and myocardial hypertrophy, left ventricular remodeling, atherosclerosis, and glomerulosclerosis.

These structural alterations form the permissive anatomic substrate that precedes catastrophic cardiovascular events such as myocardial infarction (MI), stroke, and end-stage renal disease.

Most of these effects—both acute and chronic—are mediated directly or indirectly by AII. The first reaction and rate-limiting step in the production of AII is the cleavage of angiotensinogen by the circulating enzyme renin. Angiotensin-converting enzyme converts the inactive product of this reaction, angiotensin I (AI), into the active octapeptide AII. The serine proteases, chymase and cathepsin G, are also capable of converting AI to AII independent of ACE activity. Only approximately 10% of ACE circulates in the plasma, whereas 90% is found in the tissues such as heart, brain,
kidney, and arteries.\(^2\) The circulating RAAS that controls acute hemodynamic modulation is an ACE-dependent system that regulates BP by inducing vasoconstriction and Na\(^+\)/water retention and acutely enhancing myocardial contractility. Tissue-specific RAAS uses local AI to form AII.\(^3\)

Angiotensin II acts on both the AT\(_1\) and angiotensin-2 (AT\(_2\)) receptors (Figure 1).\(^4\) Angiotensin-1 receptor stimulation mediates most of the acute effects of the RAAS, including vasoconstriction, aldosterone release, central sympathetic activation, and renal Na\(^+\)/water retention.\(^5,6\) The deleterious effects of AII on the vasculature are also mediated by AT\(_1\) receptor stimulation, which promotes endothelial dysfunction, smooth muscle cell proliferation, atherosclerosis, and vascular hypertrophy. Angiotensin-1 receptor stimulation of cardiac myocytes results in hypertrophy, gene reprogramming, and necrosis. Activation of the AT\(_1\) receptor on cardiac fibroblasts results in proliferation and up-regulation of transforming growth factor-\(\beta\), collagen (type I and III), and fibronectin, leading to tissue fibrosis.\(^7\) The effects of AT\(_1\) receptor stimulation on cardiac myocytes and fibroblasts ultimately lead to left ventricular hypertrophy. In most, but not all, experimental situations, AT\(_2\) receptor stimulation mediates effects that are thought to be beneficial, such as vasodilation, nitric oxide release, increased renal Na\(^+\) excretion, and inhibition of cellular hypertrophy and proliferation.\(^8,9\)

Angiotensin II plays an important role in atherosclerosis via pathogenic processes that affect several cell types involved in plaque development, including endothelial cells, platelets, and vascular smooth muscle cells.\(^10,11\) Angiotensin II induces endothelial cell dysfunction via oxidative stress and impairment of nitric oxide synthesis, lipid oxidation via lectin-like oxidized low-density lipoprotein receptors, and cellular proliferation and fibrosis via transforming growth factor-\(\beta\).\(^12\) Vascular inflammation is a key pathogenetic process in atherosclerosis development and its complications, including plaque rupture and thrombosis. Angiotensin II contributes to inflammation via up-regulation of interleukin-6 and platelet-derived growth factor, and platelet adhesion via vascular cell adhesion molecule and intercellular adhesion molecule integrins.\(^12\)

The recent description of renin receptors by Nguyen et al\(^13\) and the finding that this receptor also binds prorenin are further expanding our understanding of the multidimensional mechanisms by which the RAAS contributes to human disease. The (pro)renin receptor is a 350-amino acid protein with a transmembrane domain that binds both renin and prorenin. The (pro)renin receptor was first described in cultured human renal mesangial cells and is also expressed in the brain, heart, vasculature, and cells of the distal and collecting tubules of the renal parenchyma. The rate of AI generation in vitro was 4- to 5-fold higher with receptor-bound renin than renin in solution, indicating increased catalytic activity.
Prorenin, previously thought to be merely an inactive precursor of renin, becomes enzymatically active when bound to the (pro)renin receptor and demonstrates AI-generating activity. This latter finding points to a pathophysiologic role for prorenin in vascular and renal disease consistent with clinical findings that it constitutes a marker of small vessel disease in patients with diabetes. Prorenin has a unique “gate and handle” structure. It is postulated that the active catalytic site of prorenin is covered by the gate; however, when the handle region of prorenin binds the (pro)renin receptor, the gate is opened, exposing the active site (Figure 2), a process referred to as nonproteolytic activation. Receptor-bound prorenin catalyzes AI generation in a fashion comparable with renin.

Receptor-mediated renin and prorenin activation leads to increased generation of AI in the tissues, which may cause harmful effects. Interestingly, stimulation of the (pro)renin receptor by either renin or prorenin also leads to activation of mitogen-activated protein kinase intracellular signaling pathways, which promote tissue fibrosis and hypertrophy. These receptor-mediated effects are independent of AI generation.

Combination therapy

Because stimulation of the AT_1 receptor suppresses renin release, ACEIs and ARBs interfere with feedback inhibition of the RAAS. Renin-angiotensin-aldosterone system blockade by either approach results in increased renin levels and concurrent RAAS activation. In patients receiving ACEIs, increased renin release results in augmented production of AI. This increase contributes to the phenomenon of “ACE escape,” that is, the process by which circulating AI levels are restored nearly to baseline levels in patients receiving chronic therapy with ACEIs. Thus, in patients receiving chronic treatment with enalapril, an initial decline in plasma AI levels was followed by a progressive increase in these levels over 6 months despite the fact that the drug effectively suppressed plasma ACE levels throughout the treatment period.

In patients receiving ARBs, augmented renin release leads to chronic elevation in plasma renin activity (PRA), AI, and AII levels. In the presence of an AT_1 receptor blocker, increased AI levels are generally thought to “overstimulate” beneficial AT_2 receptors. There is evidence from animal studies to support this concept, for example, the finding that AT_2 receptor stimulation has an anti-remodeling effect after experimental MI. However, the functions of these receptors are incompletely understood and, under certain experimental conditions, mediate deleterious effects on the cardiovascular system. It is also possible that compensatory RAAS activation and AI elevation may exert other effects that limit the therapeutic effectiveness of ARBs.

Combined ACEI/ARB therapy has been postulated to be more effective than ACE inhibition alone because the potentially deleterious effects of AI produced through ACE escape would be blocked by the ARB at the level of the AT_1 receptor. Conversely, reducing circulating AI levels with simultaneous ACE inhibition could overcome any potentially negative effects of increased AI levels resulting from ARB monotherapy. Combined ACEI/ARB therapy also preserves the increase in levels of the vasoactive peptide bradykinin, which occurs with ACE inhibition and which is thought to contribute to the beneficial effects of these agents.

The introduction of the renin inhibitor aliskiren creates additional opportunities for assessing combined strategies of RAAS blockade. In a study conducted in normal volunteers who were Na” depleted to activate the RAAS, the ARB valsartan increased PRA, AI, and AII levels. By suppressing the enzymatic activity of renin, the addition of aliskiren blocked the compensatory increase in AI and AII. In a study evaluating the combination of aliskiren
and valsartan for the treatment of hypertension, PRA increased by 160% in patients receiving valsartan alone but was suppressed by 44% in those receiving the combination of the renin inhibitor/ARB.22

Clinical end point studies using dual RAAS blockade

Several important randomized, controlled end point trials have evaluated the efficacy of dual RAAS blockade with ACEIs and ARBs in different high-risk patient populations. Detailed reviews of clinical results are provided in the other articles in this supplement. Several studies conducted in different patient populations have found greater target-organ protection with dual RAAS blockade. These findings are consistent with the hypothesis that, in patients with HF or proteinuric renal disease, combined ACEI and ARB can provide more complete RAAS blockade, resulting in benefits additional to BP lowering.

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) was the first major end point trial designed to evaluate RAAS blockade with maximal doses of an ACEI and an ARB alone and in combination.23 This large, randomized, double-blind trial involved 25,620 patients in 40 countries who were at least 55 years of age with a history of coronary artery disease, peripheral arterial disease, cerebrovascular disease, or diabetes with end-organ damage but with controlled BP and no HF. Patients were randomly assigned to receive telmisartan 80 mg/d, ramipril 10 mg/d, or combination of telmisartan/ramipril (80/10 mg/d). The primary outcome was the composite end point of cardiovascular mortality, nonfatal stroke, acute MI, and hospitalization for congestive HF.24

The results of ONTARGET showed that monotherapy with telmisartan is as effective as monotherapy with ramipril in reducing the risk of reaching the primary composite end point.24 Individuals in the telmisartan-only group were significantly less likely to discontinue study treatment due to cough (P < .001 compared with ramipril only) or angioedema (P = .01 compared with ramipril only), despite enrollment criteria excluding patients known to be intolerant to ACEIs. An increase in the number of discontinuations due to hypotension was noted among the telmisartan recipients (P < .001 compared with ramipril only), but no syncope was observed in either treatment group. No added benefit in reducing the risk of reaching the primary end point was found with combination therapy compared with ramipril alone (risk ratio 0.99, 95% CI 0.92-1.07). This lack of benefit was seen despite a 2.4/1.4-mm Hg additional reduction in BP, an effect that previous studies suggested would reduce the risk of the primary end point by 4% to 5%. Moreover, combination therapy was less well tolerated than either monotherapy and was associated with a significantly greater incidence of discontinuation due to hypotensive symptoms (relative risk 2.75, P < .001) and renal impairment (relative risk 1.58, P < .001).24

The results of ONTARGET are consistent with those of the VALIANT study in which valsartan (160 mg, twice daily) monotherapy was found to be as effective as captopril (50 mg, 3 times daily) in reducing cardiovascular risk.25 No benefit was observed with combination therapy using a lower dose of valsartan (80 mg, twice daily) added to a maximal dose of captopril (50 mg, 3 times daily)26 in patients with reduced ventricular function or HF after acute MI. These findings differ from those of the CHARM-Added study, which showed benefit when candesartan was added to an ACEI in patients with HF resulting from impaired systolic ventricular function.26

Perspective

Chronic activation of the RAAS is detrimental to long-term cardiovascular health through physiologic mechanisms that include BP elevation, chronic vasoconstriction, and cellular effects that promote atherosclerosis and cardiovascular remodeling. Blockade of the RAAS is valuable in patients with hypertension and becomes increasingly important in the presence of end-organ disease. Although the therapeutic utility of RAAS blockade is unequivocal, there remains considerable uncertainty regarding the best pharmacologic strategy for achieving optimal RAAS inhibition.

There are currently 3 pharmacologic targets within the synthetic pathway that leads to the production of AII. Angiotensin-converting enzyme inhibitors were the first clinically useful RAAS inhibitors and have been available since the 1980s; ARBs were introduced in 1995. Although there have been numerous clinical trials evaluating ACEIs and ARBs in patients with hypertension, HF, and proteinuric renal disease, few direct-comparison studies have been conducted. In this context, the results of ONTARGET are particularly noteworthy. Conducted in a broad population of patients with established vascular disease and/or diabetes, this study confirms earlier observations suggesting that, in terms of end point protection, the long-term efficacy of these 2 classes of agents is similar. Thus, the occurrence rates of the primary composite cardiovascular end point were almost identical in patients receiving the ARB telmisartan and the ACEI ramipril. Nonsignificant trends suggest that perhaps there is a small advantage with telmisartan in terms of stroke reduction and with ramipril in terms of MI prevention, but the overall results indicate therapeutic equivalence. Consistent with earlier observations, telmisartan was better tolerated despite the fact that patients with clear-cut intolerance to ACEIs were excluded during the open-label run-in phase.

A number of theoretical considerations suggest that dual RAAS inhibition might offer advantages to
monotherapy in preventing the deleterious end-organ consequences of RAAS stimulation. All RAAS blockers interfere with feedback inhibition of renin release. Many have postulated that the compensatory RAAS activation that results might limit the effectiveness of either ACE inhibition or angiotensin receptor blockade. Data from previous clinical trials—although conflicting—have also tended to support the hypothesis that ACEIs and ARBs in combination might be superior to either drug alone, at least in certain patient populations.

The results of ONTARGET indicate that, in the population studied, this particular strategy of dual RAAS blockade offers no advantages in terms of end point reduction. Indeed, combined administration of telmisartan and ramipril adversely affected tolerability and was associated with an increased incidence of adverse renal outcomes. This latter finding was unexpected given earlier studies demonstrating additional reduction in both proteinuria and, in 1 study, “hard” renal end points in patients receiving ACEI/ARB combination therapy. It is perhaps ironic that, shortly after the release of the ONTARGET results, The Lancet published an analysis calling into question the credibility of the 1 renal end point study (COOPERATE) that reported improvement in long-term renal outcomes in patients receiving dual ACEI/ARB blockade.  

As will be reviewed elsewhere in this supplement, advantages have been seen in long-term clinical trials of HF patients when an ARB was added to ACEI monotherapy. However, a recent metaanalysis suggested that the price in terms of tolerability and potentially serious adverse effects such as hyperkalemia counterbalances any outcome advantage that may occur with dual RAAS blockade. In another large-scale clinical trial, no additional benefit was seen with ACEI/ARB combination therapy compared with respective monotherapies in patients with left ventricular dysfunction after acute MI. Although one cannot exclude utility in selected patient populations, there is presently little evidence to support the routine use of dual RAAS blockade using ACEIs and ARBs in most patient subgroups.

Several ongoing studies are assessing the efficacy of combined treatment with the direct renin inhibitor aliskiren and an ARB on long-term cardiovascular and renal end points. Because aliskiren inhibits the enzymatic activity of renin, it is theorized that any deleterious downstream effects of compensatory RAAS activation related to ARB therapy would be blocked by the concomitant administration of a direct renin inhibitor. In addition, there is evidence that aliskiren inhibits the enzymatic activity of renin and prorenin when they are bound to the (pro)renin receptor and, in so doing, might make a unique contribution to RAAS blockade. Whether this approach will prove superior to combination therapy with an ACEI and an ARB will await the results of these studies.

In summary, our understanding of the RAAS and the drugs that block it continues to evolve. Recent discoveries including the description of the (pro)renin receptor raise many fascinating questions regarding the mechanisms by which the RAAS contributes to human disease. Clinical trials including ONTARGET have definitively established the therapeutic equivalence of ACEIs and ARBs in most relevant patient populations. ONTARGET did not, however, demonstrate additional value of dual RAAS blockade using an ACEI and an ARB. Nevertheless, dual RAAS blockade remains the subject of active investigation.

Disclosures

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References