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The Renin-Angiotensin-Aldosterone System (RAAS) and Cardiac Arrhythmias

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Abstract

The role of the renin-angiotensin-aldosterone system (RAAS) in many cardiovascular disorders, including hypertension, cardiac hypertrophy, and atherosclerosis is well established, whereas its relationship with cardiac arrhythmias is a new area of investigation. Atrial fibrillation and malignant ventricular tachyarrhythmias, especially in the setting of cardiac hypertrophy or failure, appear to be examples of RAAS-related arrhythmias, since treatment with RAAS modulators, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers and mineralocorticoid receptor blockers, reduces the incidence of these arrhythmias. RAAS has a multitude of electrophysiological effects and can potentially cause arrhythmia through a variety of mechanisms. We review new experimental results that suggest RAAS has pro-arrhythmic effects on membrane and sarcoplasmic reticulum ion channels and that increased oxidative stress is likely contributing to the increased arrhythmic incidence. A summary of ongoing clinical trials that will address the clinical usefulness of RAAS modulators for prevention or treatment of arrhythmias is presented.

Keywords

arrhythmias; renin-angiotensin-aldosterone system; oxidative stress; gap junction; angiotensin converting enzyme inhibitor; angiotensin receptor blocker; mineralocorticoid receptor blocker; atrial fibrillation

Introduction

The renin-angiotensin-aldosterone system (RAAS) is a major endocrine/paracrine system involved in the regulation of a myriad of cardiovascular processes.¹ Its role in the pathogenesis of hypertension, cardiac hypertrophy, and atherosclerosis is well established. Early in heart failure, RAAS is activated as a compensatory mechanism, but with the progression of the disease, it assumes a detrimental role, responsible for increased preload and afterload, which are the hallmarks of clinical heart failure syndrome.

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The octapeptide angiotensin II (AngII) is the primary mediator of this system, but other active peptides, such as renin, aldosterone and angiotensin (1–7) have important biological roles in health and disease states.^{2,3} RAAS modulators, such as angiotensin converting enzyme inhibitors (ACEI),^{4–7} angiotensin receptor blockers (ARB),^{8–11} and mineralocorticoid receptor blockers (MRB)^{12,13} are mainstays of treatment in various cardiovascular disorders. Direct renin inhibitors are a new addition to the RAAS-modulating drugs.¹⁴

An emerging paradigm is the role of RAAS in the pathogenesis of cardiac arrhythmias and the corollary potential beneficial effects of RAAS inhibitors in prevention or treatment of rhythm disorders. The body of evidence that RAAS contributes to arrhythmia is largest for atrial fibrillation (AF). Patients with AF have increased levels of ACE and angiotensin II (AngII) type 1 receptors in the left atrium.^{15,16} At least two prospective clinical trials have tested the hypothesis that ACEIs or ARBs reduce the recurrence rate of AF. The two-month recurrence rate of AF was 15% in a group of patients with persistent AF who underwent electrical cardioversion and were treated with irbesartan, compared to 37% in the placebo group.¹⁷ Addition of an ACEI to amiodarone in patients with chronic AF after cardioversion lowered the recurrence rate of AF after 270 days by 22.9%.¹⁸ Treatment with an ACEI decreased the number of cardioversion attempts needed for AF¹⁹ and, in a retrospective trial, the likelihood of AF.²⁰ In a prospective study of 9193 hypertensive patients, losartan, an ARB, reduced the incidence of new onset AF (relative risk 0.55–0.83) compared to atenolol after an average follow-up of 4.8 years (LIFE study).²¹ Trandolapril therapy, a long-acting ACEI, reduced the incidence of AF after myocardial infarction in the TRACE study.²² In AFFIRM, patients with left ventricular systolic dysfunction who were on ARB or ACE inhibitor had a lower recurrence rate of AF.²³

Sudden cardiac death because of ventricular tachyarrhythmias, especially in the setting of low left ventricular ejection fraction, is linked also to RAAS activation. In the Heart Outcomes Prevention Evaluation Study, treatment of high-risk patients with the ACEI ramipril was associated with a relative risk reduction of 0.66 in sudden cardiac death.²⁴ In The Randomized Aldactone Evaluation Study (RALES), there was 30% less mortality in the group of heart failure patients treated with spironolactone compared to placebo, which occurred in part from a reduction in lethal arrhythmias.²⁵ Eplerenone, another MRB, reduced sudden death by 21% in patients with severe heart failure.²⁶

Traditionally, the effect of RAAS on promoting atrial and ventricular arrhythmias is explained based on increased cardiac hypertrophy, fibrosis, and heterogeneity of the cardiac tissue.²⁷ Nevertheless, such a model fails to explain the observed reversal of the proarrhythmic effects upon treatment with ACEIs or ARBs, suggesting other electrophysiological effects of RAAS activation. RAAS has manifold effects on the cardiovascular system and various possible pathways have been proposed as the link underlying the relationship between RAAS and arrhythmias. Only a few previous reviews have discussed the link between RAAS and arrhythmias, especially AF.^{28–30} In this manuscript, our focus is on novel mechanisms of atrial and ventricular arrhythmia in the setting of RAAS activation.

RAAS, Oxidative Stress, and Arrhythmias

Oxidative stress is one such pathway. AngII activates endothelial and endocardial NADPH oxidase and upregulates NF- κ B and related inflammatory genes.^{31–33} The NADPH oxidase family of enzymes plays a central role in generation of reactive oxygen species (ROS) in cardiovascular disorders.^{34–36} It catalyzes the formation of superoxide anion ($O_2^{\bullet-}$), which in turn is reduced to hydrogen peroxide (H_2O_2) by superoxide dismutases. While not a free radical, hydrogen peroxide is an oxidant capable of initiating lipid peroxidation chain reaction and also acts as a signaling molecule to activate smooth muscle cell proliferation.³⁷ In addition,

in the presence of transitional metals, hydrogen peroxide is decomposed into hydroxyl radical ($\text{OH}\bullet$), one of the most reactive of ROS.

More is known about the relationship between oxidative stress and atherosclerosis than between oxidative stress and other cardiovascular disorders. A simple but surprisingly powerful model in atherosclerosis is that the balance between detrimental ROS (including $\text{O}_2^{\bullet-}$, H_2O_2 , and $\text{OH}\bullet$) and protective nitric oxide ($\text{NO}\bullet$) determines the state of health of the endothelium. The major risk factors for atherosclerosis, including hypertension, diabetes mellitus, smoking, and hypercholesterolemia affect the endothelium and change the balance toward increased ROS, resulting in endothelial dysfunction and, eventually, atherosclerosis.

A remarkable observation is that AF shares many of the same risk factors as atherosclerosis,^{38–41} suggesting these two diseases may have a related pathogenesis. Multiple lines of evidence have strongly implicated oxidative stress in the pathogenesis of AF. Carnes et al. demonstrated the beneficial effects of ascorbate, an anti-oxidant and peroxynitrite decomposition catalyst, on AF prevention and reduction of electrical remodeling in pacing-induced AF in dogs.⁴² Kim et al. demonstrated that the major source of ROS in the right atrial appendage of patients with AF was an increase in myocardial NADPH oxidase activity with a smaller contribution from uncoupling of the endothelial nitric oxide synthase (eNOS).⁴³ We observed downregulation of endothelial eNOS in the left atrium and left atrial appendage associated with a reduction in $\text{NO}\bullet$ production,⁴⁴ and an increase in generation of $\text{O}_2^{\bullet-}$ in a rapid atrial pacing porcine model of AF.⁴⁵ While NADPH oxidase activity was increased in this model, the individual subunits of the cardiac NADPH oxidase remained unchanged. Detailed analysis showed activation of Rac1 (a Rho family GTPase), which is part of the signaling chain from AngII to NADPH oxidase.⁴⁶ Overexpression of Rac1 can cause AF.⁴⁷ Further, we confirmed the relationship of oxidative stress to AF in humans by measuring derivatives of reactive oxidative metabolites (DROMs) and the ratios of oxidized to reduced glutathione and cysteine (as a quantitative measure of oxidative status) in the serum of patients with and without AF. The presence of AF was associated with increased oxidative, but not inflammatory, markers.⁴⁸

ROS seem to contribute also to ventricular arrhythmias. Torok et al. showed that treatment with a synthetic free radical scavenger protects against ventricular fibrillation in a dog infarct model.⁴⁹ Later studies have reproduced this result after treatment with vitamin E analogues⁵⁰ and the anti-oxidant BHT.⁵¹ Interestingly, in a hypertrophied rat heart model of low flow ischemia, an ARB (losartan) but not an ACEI reduced the rate of reperfusion ventricular arrhythmias.⁵²

RAAS and Ion Channels

Oxidative stress has direct effects on ion channels, which may explain how ROS promotes arrhythmias. Caouette et al. showed that addition of H_2O_2 to Chinese hamster ovary cell line expressing Kv1.5 gene (I_{Kur} current) increased this current.⁵³ Oxidized glutathione, a sulfhydryl group modifier, reduced transient outward potassium current (I_{to}) in rat ventricular myocytes,⁵⁴ while t-butyl hydroperoxide (TBHP, an oxidant) treatment decreased I_{to} in rat atrial cells.⁵⁵ Treatment with TBHP reduced the amplitude fast sodium current (I_{Na}) in feline ventricular myocytes.⁵⁶ In both human embryonic kidney cells and cultured atrial myocytes, sodium current was reduced after treatment with TBHP or E2-isoketal, a highly selective agent causing lipid peroxidation.⁵⁷ Recently, we showed that treatment of myocytes more chronically with AngII significantly reduced sodium channel protein and current through H_2O_2 -dependent activation of NF- κ B and subsequent transcriptional downregulation of the channel.⁵⁸

AngII and aldosterone also have been shown to have direct modulatory effects on membrane ion channels. AngII induces L-type calcium channels in neonatal rabbit cardiomyocytes⁵⁹ and rat portal vein vascular myocytes.⁶⁰ The I_{to} current in the canine ventricular cardiomyocytes incubated in AngII has a slower recovery from inactivation.⁶¹ Similarly, in rat ventricular myocytes, AngII stimulation reduces I_{to} current amplitude.⁶² Aldosterone downregulates I_{to} and increased L-type calcium current in rat ventricular cells.^{63,64} The net effect of enhanced calcium and reduced potassium currents would be action potential duration prolongation and repolarization dispersion. Both of which promote arrhythmias.

Intracellular calcium cycling is another target of RAAS activation. The stored calcium in the sarcoplasmic reticulum (SR) is released through the ryanodine receptor, RyR2 in heart, in systole and is restored during diastole by SR Ca^{2+} -ATPase (SERCA pump). Abnormalities of Ca^{2+} handling appear to be arrhythmogenic. For example, mutations in RyR2 cause catecholaminergic polymorphic ventricular tachycardia.⁶⁵ Heart failure is a high AngII state, and both SERCA pump and RyR2 are suppressed in heart failure.^{66,67} The effect of AngII on SERCA pump is, at least partly, mediated through NADPH oxidase and ROS.⁶⁸ In multiple experimental models of heart failure, treatment with ACEI or ARB normalizes the intracellular calcium handling,^{69–71} possibly contributing to the reduction their antiarrhythmic effects in this condition.

Modulation of gap junctions is a newly described proarrhythmic effect of RAAS. Connexins are a family of at least 15 different proteins that form hexameric connexon hemichannels. After translocation to the membrane, two hemichannels from adjacent cardiac cells provide a low resistance pathway (gap junction) for electrical conduction between myocytes.⁷² Cardiac gap junctional complexes are constituted mainly of connexins 37, 40, 43 and 45.

Quantitative or qualitative abnormalities of various connexins have been implicated in the pathogenesis of different arrhythmias; for example, mutation of the connexin 40 is associated with idiopathic AF.⁷³ Reduction or abnormal distribution of Cx43, the major component of the mammalian ventricular gap junctional complex, has been observed in various pathological conditions, including cardiomyopathies,⁷⁴ ventricular hypertrophy,⁷⁵ and in the infarct border zone.⁷⁶ Slowing of the conduction velocity resulting from reduction in Cx43 may contribute to the increased arrhythmia incidence, especially VT and VF.^{77,78} Such abnormalities can slow conduction velocity, increase heterogeneity, and exaggerate anisotropic properties of ventricles,⁷⁹ all of which facilitate the initiation or maintenance of arrhythmias.

Functional Cx43 is usually phosphorylated on multiple serine residues. Conversely, dephosphorylation of Cx43 is associated with loss of function. In general, *in vitro* studies have found that AngII increases total Cx43 and phosphorylation,^{80,81} whereas *in vivo* studies under various pathological conditions have demonstrated the beneficial effects of ARBs in preventing Cx43 dephosphorylation.⁸² We observed dramatic reductions in total and phosphorylated Cx43 in transgenic mice with cardiac-specific ACE overexpression and elevated levels of AngII in heart tissue. These mice showed VT and sudden death in the absence of structural heart disease.⁸³ Treatment with captopril, an ACEI, or losartan, an ARB, resulted in partial reversal of Cx43 abnormalities and significant reduction in VT inducibility and sudden death.⁸⁴ Similarly, rats with humanized renin and angiotensinogen genes exhibited increased sudden death after treatment with AngII, were prone to VT, had depressed levels of Cx43, and partially recovered after treatment with losartan.⁸⁵

Current Clinical Trials

There is abundant data supporting the link between RAAS and cardiac arrhythmias. RAAS modulators (i.e. ACEI, ARB, MRB) have salutary effects in prevention and treatment of arrhythmias. Fortunately, many patients have an indication for these classes of drugs based on

their underlying conditions, e.g. hypertension, systolic heart failure, and previous myocardial infarction. Nevertheless, there remains a group of patients, who are at risk of RAAS-related arrhythmias and have no indication for taking ACE or ARB based on the current standard of care. Currently, many studies are actively recruiting patients to test RAAS modulators in the management of AF. ARBs, ACEI, or spironolactone are being tested for reducing recurrence of paroxysmal AF (ClinicalTrials.gov identifiers: NCT00098137, NCT00376272 and NCT00461903), preventing AF recurrence after electrical cardioversion (ClinicalTrials.gov identifier: NCT00130975) or catheter ablation (ClinicalTrials.gov identifier: NCT00438113), reducing AF burden after cardiac surgery (ClinicalTrials.gov identifier: NCT00134862), especially coronary artery bypass surgery (ClinicalTrials.gov identifier: NCT00141777), and preventing AF in patients with dual chamber pacemaker and frequent high atrial rate episodes who have increased incidence of AF (ClinicalTrials.gov identifier: NCT00225667). Another study (ClinicalTrials.gov identifier: NCT00352560) is trying to gain mechanistic insight into the link between RAAS and AF by measuring electrophysiological parameters, including atrial refractory period, in patients with paroxysmal AF who are treated with an ARB.

Summary

RAAS activation appears to be arrhythmogenic (Fig. 1 summarizes the possible mechanisms). Modulating RAAS activation is likely to be a successful strategy to reduce incidence of arrhythmia in certain patients. At least part of the arrhythmic effect of RAAS activation involves alterations in ion channels mediated in part by increased oxidative stress. Moreover, exploring the molecular mechanisms by which RAAS activation causes arrhythmia is likely to give a rationale for development of new antiarrhythmic agents, such as anti-oxidants for the management of AF (e.g. using thiazolidinediones as an anti-oxidants in ClinicalTrials.gov identifier: NCT00321204) or gap-junction enhancers (e.g. rotigaptide) for the treatment of atrial or ventricular tachycardia.⁸⁶

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Abbreviations

ACEI, angiotensin converting enzyme inhibitors
 AF, atrial fibrillation
 AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management
 AngII, angiotensin II
 ARB, angiotensin receptor blockers
 DROM, derivatives of reactive oxidative metabolites
 eNOS, endothelial nitric oxide synthase

LIFE, Losartan Intervention for Endpoint Reduction
MRB, mineralocorticoid receptor blockers
NADPH, nicotinamide adenine dinucleotide phosphate
RAAS, renin-angiotensin-aldosterone system
RALES, Randomized Aldactone Evaluation Study
ROS, reactive oxygen species
RyR2, ryanodine receptor
SERCA, sarcoplasmic reticulum Ca^{2+} -ATPase
SR, sarcoplasmic reticulum
THBP, t-butyl hydroperoxide
VF, ventricular fibrillation
VT, ventricular tachycardia

Figure 1.

A summary of the pro-arrhythmic RAAS effects on electrophysiological targets. The primary mediator of the effects is AngII, which acts mainly through type-1 AngII receptor (AT₁) and triggers multiple signaling pathways. Activation of NADPH oxidase (Nox) results in the generations of superoxide ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) by the action of superoxide dismutase (SOD). Electrophysiological important targets include sarcolemma ion channels (sodium, potassium, and calcium channels), the sarcoplasmic reticulum Ca²⁺-ATPase (SERCA), the sarcoplasmic reticulum Ca²⁺ release channel (RyR2), and gap junctional proteins, such as connexin 43 (Cx43).