The Antiarrhythmic Potential of Angiotensin II Antagonism: Experience With Losartan
Irene Gavras and Haralambos Gavras

A large body of literature accumulated over the past several years supports the notion that inhibition of the renin-angiotensin system protects the heart and other target organs from hypertensive complications. Various studies have shown that angiotensin-converting enzyme inhibitors reduce morbidity and mortality in the setting of ischemic heart disease and/or congestive heart failure. The improvement in survival has been attributed in part to a significant decrease in the incidence of sudden deaths, possibly due to a decrease in complex arrhythmia episodes. Recently, the angiotensin II type 1 receptor antagonist losartan was shown to reduce mortality by 46% compared with captopril in older patients with chronic congestive heart failure. This paper briefly reviews the arrhythmogenic properties of angiotensin II and the possible pharmacologic mechanisms for the antiarrhythmic potential of losartan. Am J Hypertens 2000;13:512–517 © 2000 American Journal of Hypertension, Ltd.

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Evidence that angiotensin-converting enzyme (ACE) inhibitors have a cardioprotective effect has been reviewed extensively elsewhere.1,2 This evidence, derived from early experimental and clinical studies and from large multicenter trials involving patients with ischemic heart disease and/or congestive heart failure (CHF), shows reduced mortality due to ACE inhibition. The reduction has been attributed to a significant decrease in the incidence of sudden deaths, possibly due to fewer episodes of complex arrhythmias.3,4 Although this finding, which has been corroborated by animal studies,5 has been attributed to blockade of the renin-angiotensin system (RAS), ie, the angiotensin-mediated effects of ACE inhibition, a number of experimental investigations have attributed the decrease in sudden death to the bradykinin-mediated effects of ACE inhibition.6,7 It therefore was surprising that the first trial comparing an ACE inhibitor (captopril) with an angiotensin II type 1 (AT1) receptor antagonist (losartan) in older patients with chronic CHF reported that losartan reduced mortality by 46% as compared with captopril and that this was primarily due to fewer sudden cardiac deaths.8 This outcome suggests that complete blockade of AT1 receptors may be more effective in preventing arrhythmias than the combined results of ACE inhibition, ie, inhibition of angiotensin II formation along with potentiation of bradykinin.9 Bradykinin appears to have both antiarrhythmic and proarrhythmic activity,9,10 and the latter may have played a mechanistic role in captopril’s higher incidence of sudden death reported in the Evaluation of Losartan in the Elderly (ELITE) heart failure trial.8 The following paper reviews the mechanisms involved in the arrhythmogenic properties of Ang II
TABLE 1. PROPOSED ARRHYTHMOGENIC MECHANISMS OF ANGIOTENSIN II

<table>
<thead>
<tr>
<th>Proposed Arrhythmogenic Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct positive inotropic effect on the heart</td>
<td>Increases contractility</td>
</tr>
<tr>
<td>Altered electrolyte channels</td>
<td>Affects ion transport</td>
</tr>
<tr>
<td>Decreased intracellular electrical resistance</td>
<td>Reduces cellular resistance</td>
</tr>
<tr>
<td>Increased conduction velocity</td>
<td>Increases impulse propagation</td>
</tr>
<tr>
<td>Shorter refractory period for cardiac myocytes</td>
<td>Reduces time for recovery</td>
</tr>
<tr>
<td>Indirect positive chronotropic and proarrhythmic effect via enhanced sympathetic activity</td>
<td>Activates sympathetic nervous system</td>
</tr>
<tr>
<td>Inhibition of cardiac vagal afferents in the central nervous system</td>
<td>Reduces vagal tone</td>
</tr>
<tr>
<td>Enhanced release of endothelin-1</td>
<td>Promotes vasoconstriction</td>
</tr>
</tbody>
</table>

and the pharmacologic actions that may explain the antiarrhythmic properties of losartan.

THE ARRHYTHMOGENIC EFFECTS OF ANGIOTENSIN II

The arrhythmogenic properties of Ang II appear to be mediated by several mechanisms (Table 1). Ang II influences cardiac rate and rhythm by acting directly on cardiac myocytes and by stimulating the release of neurohumoral factors, such as catecholamines and endothelin, which exert their own proarrhythmic effect on the heart. Activation of the AT1 receptor by Ang II triggers a series of intracellular responses, including mobilization of calcium, stimulation of Na⁺/H⁺ exchange, metabolism of inositol phosphate, production of diacyl glycerol, activation of protein kinase C and other kinases, activation of phosphorylation pathways, and alteration of cytoplasmic proteins. This also triggers the release of intracellular growth factors, which, among other functions, also control the expression of contractile proteins. Changes in electrolyte channels, especially calcium channels, along with the enhanced shortening of cardiac fibers due to protein alterations, tend to increase the contractility of cardiac myocytes and vascular smooth muscle cells. This explains the direct positive inotropic effect of Ang II described two and three decades ago.

A high density of AT1 receptors has been demonstrated in the cardiac conduction system. Stimulation of these receptors on the sinoatrial and atrioventricular nodes, and the Purkinje fibers, can generate spontaneous electrical activity or alter responses to electrical stimulation. Evidence suggests that Ang II decreases intracellular resistance and significantly increases conduction velocity. This effect is believed to be mediated via activation of protein kinase C and increased calcium current. It has been demonstrated that Ang II shortens the refractory period in cardiac myocytes. This direct effect is best seen in vitro in cultured neonatal rat myocytes; in this model, Ang II increases the spontaneous beating rate, whereas the Ang II antagonist Sar¹, Ala³-Ang II blocks this action. In addition to its direct AT1-receptor-mediated cellular actions, Ang II exerts an indirect positive chronotropic and proarrhythmic effect by enhancing sympathetic activity and suppressing vagal activity. Ang II exerts a permissive effect on norepinephrine release from presynaptic sympathetic nerve endings. Facilitation of sympathetic neurotransmission in cardiac adrenergic nerve terminals and sympathetic ganglia is partly responsible for the previously mentioned positive inotropic, as well as the chronotropic and proarrhythmic, properties of Ang II. Furthermore, an inhibitory action of Ang II on cardiac vagal afferents in the central nervous system has been reported.

Disequilibrium between sympathetic and parasympathetic influences is one aspect of decompensated CHF, which is associated with activation of several neurohormonal systems, including the sympathetic and renin-angiotensin systems. This autonomic imbalance with the attendant loss of parasympathetic restraint is incriminated in part for the high rate of malignant ventricular arrhythmias and sudden death that are characteristic of CHF. Finally, activation of AT1 receptors also stimulates the expression of the endothelin-1 gene in endothelial cells and enhances the release of endothelin-1. Like other pressor substances, endothelin also has independent, direct proarrhythmic effects.

At this time, it is unclear to what extent the arrhythmogenic properties of Ang II are due to circulating or locally generated Ang II. Evidence suggests that cardiacmyocytes and cardiac fibroblasts may be able to produce Ang II because presence of mRNA has been demonstrated for all the components of the renin-angiotensin system. Therefore, locally generated Ang II could act in a paracrine, autocrine, or even intracrine manner on these cells. However, so-called “endocrine” Ang II generated via renin of renal origin circulates in much higher amounts, and it is the plasma levels of renin and angiotensin that have been statistically associated with adverse cardiovascular outcomes. Elevated circulating levels after experimental infusion of exogenous Ang II in rabbits produced widespread foci of myocardial necrosis, and patients who died suddenly after being exposed to surges of endogenous Ang II displayed cardiac pathology indistinguishable from that of the experimental animals. We have shown that the coronary vasculature is particularly sensitive to the vasoconstricting effect of Ang II. It is therefore likely that patients exposed to excess levels of circulating Ang II develop areas of focal myocardial necrosis, which, if they involve the path of the conduction system, will then become a focus of abnormal electrical activity and trigger episodes of arrhythmia. Finally, the long-term myocardial remodeling after acute ischemic necrosis leads to asymmetrical hypertrophy and replacement of myocytes by fibrotic tissue.
These changes markedly alter ventricular conduction and promote reentrant arrhythmias.

**ANTIARRHYTHMIC PROPERTIES OF ACE INHIBITION**

It is now well established that ACE inhibitors have a cardioprotective action as shown by the diminished mortality of patients in heart failure with or without prior myocardial infarcts. To a large extent, mortality in such patients is due to sudden death attributable to ventricular arrhythmia. A surge in plasma neurohormone levels (including Ang II, norepinephrine, and endothelin) is characteristically associated with acute ischemic episodes, the postischemic reperfusion phase, and episodes of acute decompensation of chronic heart failure. All of these conditions are also characterized by increased frequency and complexity of ventricular arrhythmias.

In several animal models of acute myocardial ischemia followed by reperfusion, the ensuing metabolic, functional, and anatomical damage was associated with electrophysiologic instability and high incidence of malignant arrhythmias. Parenteral, oral, or local administration of various ACE inhibitors in these models was invariably shown to suppress these arrhythmias and restore electrical stability. This beneficial influence represents the sum of a number of interactive events triggered by ACE inhibition, with the following results: the formation of Ang II decreases but is not completely abolished because alternative enzymatic pathways can also form Ang II (e.g., chymase); the local release of norepinephrine and endothelin is partially inhibited; and the degradation of kinins is retarded, leading to the local accumulation of bradykinin, which has both a direct antiarrhythmic action and an indirect proarrhythmic effect mediated via enhanced local release of norepinephrine. The fact that selective bradykinin receptor blockade reverses, in part, the stabilizing effect of ACE inhibition in this setting suggests that the antiarrhythmic effect outweighs any proarrhythmic influence of bradykinin. Nevertheless, the clinical observation that the incidence of sudden death in CHF was more significantly decreased, in conjunction with a greater probability of survival, with losartan than with captopril suggests that a complete blockade of the AT1 receptor may exert a more effective antiarrhythmic influence than the sum of the downstream events triggered by ACE inhibition. A direct in vitro comparison of captopril versus losartan’s metabolite, EXP 3174, in human atrial tissues lends support to this conclusion.

**ANTIARRHYTHMIC PROPERTIES OF LOSARTAN**

AT1 receptors of Ang II are believed to mediate most of the physiologically important actions of Ang II, as the amount of AT2 receptors declines sharply after birth. Blockade of AT1 receptors appears to abolish the multiple actions of Ang II, including the arrhythmogenic (chronotropic/inotropic) action described herein, as well as its trophic, mitogenic, metabolic, thrombotic, and other systemic and local effects.

Many studies have investigated the antiarrhythmic properties of Ang II antagonists (Table 2). Several experimental studies in vivo have demonstrated the capacity of losartan to counteract arrhythmogenic stimuli. In acute experiments, rats were submitted to left main coronary artery ligation followed by removal of the ligature; animals pretreated with losartan had significant reductions in infarct size and significant decreases in incidence of ventricular tachycardia/fibrillation and overall mortality, compared with those receiving placebo. Experiments with spontaneously hypertensive rats compared various antihypertensive treatments in terms of effects on electrophysiologic parameters, which mark susceptibility to malignant ventricular arrhythmias. Results showed that rats treated with an ACE inhibitor and rats treated with Ang II antagonist had significant regression of left ventricular hypertrophy and had indices of electrophysiologic stability similar to normotensive rats. In contrast, rats treated with hydralazine had no regression of left ventricular hypertrophy, and their electrophysiologic markers were similar to placebo-treated hypertensive rats, despite blood pressure lowering to
TABLE 2. SUMMARY OF STUDIES INVOLVING ANGIOTENSIN II ANTAGONISTS*

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Pitt et al</td>
<td>There was a significant decrease in the incidence of sudden death in</td>
</tr>
<tr>
<td></td>
<td>CHF patients with losartan compared with captopril.</td>
</tr>
<tr>
<td>Lee et al</td>
<td>Pretreatment with losartan significantly reduced infarct size, incidence</td>
</tr>
<tr>
<td></td>
<td>of ventricular tachycardia/fibrillation, and overall mortality in rats.</td>
</tr>
<tr>
<td>Kohya et al</td>
<td>Hypertensive rats showed a significant regression in left ventricular</td>
</tr>
<tr>
<td></td>
<td>hypertrophy when treated with an Ang II antagonist.</td>
</tr>
<tr>
<td>Matsuo et al</td>
<td>The incidence of ventricular tachyarrhythmias was reduced in dogs</td>
</tr>
<tr>
<td></td>
<td>treated with losartan prior to coronary occlusion.</td>
</tr>
<tr>
<td>Fleetwood et</td>
<td>An Ang II antagonist was effective in decreasing the duration of</td>
</tr>
<tr>
<td>al</td>
<td>ventricular fibrillation in isolated rat hearts with global ischemia</td>
</tr>
<tr>
<td></td>
<td>followed by reperfusion.</td>
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</tbody>
</table>

* Ang II = angiotensin II; CHF = congestive heart failure.

The notion that losartan possesses antiarrhythmic properties is based on the observation that treatment of chronic heart failure with losartan reduces the incidence of sudden death more than with captopril. This suggests that losartan is effective at suppressing complex ventricular arrhythmias, a common cause of death in patients with chronic heart failure. This brief review of the molecular and cellular events underlying the arrhythmogenic properties of Ang II and the experimental evidence from recent literature supporting the antiarrhythmic properties of losartan suggest that this is not a spurious observation, but is indeed consistent with generally known mechanisms of action, despite occasional discrepancies. The data require, however, further confirmation by large clinical trials and detailed clinical studies measuring the effects of treatment on electrophysiologic parameters in populations at risk.

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