Renin-Angiotensin System Inhibitors and Atrial Fibrillation

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Atrial fibrillation is the most frequently encountered arrhythmia in clinical practice [1,2]. The prevalence of AF increases with age [1], and currently stands at 4% in the adult population. The essential mechanisms for AF include triggers, mostly originating from the pulmonary veins [3], and substrate that maintains the AF [4,5]. Direct-current cardioversion is the most effective treatment for the restoration of sinus rhythm, but it may be hampered by a high percentage of recurrence [6]. Chances to revert AF decrease with its duration, and paroxysmal AF turns to persistent AF over time – both phenomena supporting the concept of "AF begets AF." These self-perpetuating mechanisms of AF over time are not completely understood, but they include electrical as well as structural remodeling of the atria by ongoing AF [7]. Remodeling usually involves several stages: a) short-term electrical remodeling due to functional changes in ion channels, b) true electrical remodeling mediated by changes in channel gene expression, and c) structural changes in the atrium. Each one of these stages has its underlying mechanisms.

Currently, AF is managed by a variety of tools, including anti-arrhythmic drugs, pacing, and radiofrequency ablation. The development of therapy directed against remodeling could result in an important change in the management of patients with AF [6,8–19]. There are few known therapies that prevent remodeling. Several drugs have demonstrated effectiveness in the treatment of various stages of electrical remodeling, such as calcium blockers [9,10] or beta blockers [11,12].

Angiotensin-converting enzyme inhibitors are widely used for controlling hypertension and for treating cardiac dysfunction [19,20] and atherosclerotic vascular disease even in patients without left ventricular dysfunction [21,22]. ACE inhibitors do not have a direct effect on ion channels. However, there is accumulating evidence that supports a possible role for ACE inhibitors and angiotensin II receptor blockers in the prevention and treatment of AF by effecting electrical remodeling. The present review presents recent evidence supporting this claim.

Animal studies

Several studies have explored the pathophysiologic basis of electrical remodeling and its association with the rennin-angiotensin system. Several mechanisms have been proposed to explain the positive effect of ACE inhibitors and angiotensin II receptor blockers [6,11,19,23]:

- Preventing the shortening of the refractory period in the atrium during AF, one of the mechanisms of electrical remodeling
- Lowering end-diastolic left ventricular pressure and subsequently left atrial pressure that exists in hypertension and diastolic dysfunction
- Preventing atrial fibrosis that is promoted by angiotensin
- Modifying the sympathetic tone
- Modulating refractoriness of the atria.

Wijffels et al. [5] conducted a landmark study in 1995, supporting the concept that "AF begets AF" by electrical remodeling. They showed that rapid atrial pacing decreases effective refractory periods and reverses physiologic rate adaptation of refractoriness. Twelve goats were chronically instrumented with multiple electrodes sutured to the epicardium of both atria. The animals were connected to a fibrillation pacemaker that artificially maintained AF by rapid atrial pacing. Maintenance of AF resulted in a progressive increase in the duration of spontaneous AF that became sustained (>24 hours) after 7.1 ± 4.8 days (in 10 of 11 goats). During the first 24 hours of AF the median fibrillation interval shortened from 145 ± 18 to 108 ± 8 msec, and the inducibility of AF by a single premature stimulus increased from 24% to 76%. The atrial effective refractory period was shortened from 146 ± 19 to 95 ± 20 msec (-35%) (S1S1, 400 msec). Sinus rhythm was restored and all electrophysiologic changes were found to be reversible within 1 week. The authors concluded that rapid atrial rate results in electrical remodeling of the atria, rendering them more prone to atrial fibrillation.

The renin-angiotensin system has an important role in maintenance of atrial fibrillation

The following studies looked at the relationship between this response and the rennin-angiotensin aldosterone system. Nakashima and co-workers [18] examined the results of ACE inhibitors and ARBs on atrial remodeling in AF in 24 dogs. Rapid atrial pacing

AF = atrial fibrillation
ACE = angiotensin-converting enzyme
ARB = angiotensin II receptor blockers

at 800 beats/min was maintained for 180 minutes. Atrial effective refractory period was measured before, during, and after rapid atrial pacing at 800 bpm for 180 minutes, while administering saline, angiotensin II, ACE inhibitor (captopril) or an ARB (cadensartan). They showed that in the saline and angiotensin II infusion treatment groups a similar shortening of the atrial effective refractory period occurred 30 minutes after the pacing was initiated. In addition, there was a loss of physiologic rate adaptation due to atrial effective refractory period shortening. In contrast, the captopril and cadensartan groups did not show such changes. Furthermore, atrial effective refractory period recovered almost to baseline within 10 minutes in the control group, whereas angiotensin II markedly delayed the recovery after the cessation of rapid pacing. This showed, for the first time, that angiotensin II is involved in the mechanism of atrial electrical remodeling and that any blockade of angiotensin II may hamper this effect.

Another study that demonstrated angiotensin II-dependent remodeling was conducted in 2003 by Cardin et al. [24], who subjected dogs to tachypacing for periods of up to 5 weeks. They described significant apoptosis in histologic specimens within 24 hours after the tachypacing and subsequent return to baseline. Apoptosis was preceded by an increase in tissue angiotensin II concentration and enhanced expression ratio of pro-apoptotic protein Bax to anti-apoptotic protein Bcl-2. Apoptosis was followed by interstitial fibrosis. Enalapril prevented an increase in tissue angiotensin II and reduced tissue fibrosis and cellular apoptosis. The authors concluded that remodeling of the atria involves angiotensin II-dependent pathways and that ACE inhibitors can partially prevent the remodeling.

Another study [19] testing the relationship between heart failure and AF was performed in dogs. Ventricular tachypacing (220–240 bpm) for a 5 week period caused heart failure in 20 dogs (10 treated with enalapril and 10 with placebo). Their hearts demonstrated atrial fibrosis, lower atrial conduction velocity, and a predisposition to AF due to fast pacing. In addition, there was an increased concentration of angiotensin II and of expression mitogen-activated protein kinase. Angiotensin II and mitogen-activated protein kinase were shown to be involved in promoting atrial structural remodeling in other studies by promoting the proliferation of fibroblasts and hypertrophy of cardiomyocytes [25–28]. These changes were significantly attenuated in dogs that were treated with enalapril. An additional arm, treated with isosorbide mononitrate and hydralazine, did not alter atrial fibrosis or AF promotion despite positive hemodynamic effects on heart failure. Therefore, ACE inhibition proved to be effective in preventing aberrant signal transduction leading to electrical and structural remodeling that propagated to AF.

Tsai and associates [29] evaluated genetic polymorphism of the cardiac atrial renin-angiotensin system. They compared eight genetic polymorphisms of the atrial renin-angiotensin system genes in 250 patients with documented non-familial structural AF and 250 controls. The controls were matched to cases on a one-to-one basis with regard to age, gender, presence of left ventricular dysfunction, and presence of significant valvular heart disease. The ACE gene insertion/deletion polymorphism, the T174M, M235T, G-6A, A-20C, G-152A, and G-217A polymorphisms of the angiotensinogen gene, and the A1166C polymorphism of the angiotensin II type I receptor gene were genotyped. In multi-locus haplotype analysis, the angiotensinogen gene haplotype profile was significantly different between cases and controls (chi-square = 62.5, $P = 0.0002$). In single-locus analysis, M235T, G-6A, and G-217A were significantly associated with AF. Frequencies of the M235, G-6 and G-217 alleles were significantly higher in cases than in controls ($P = 0.000$, 0.005, and 0.002, respectively). The odds ratios for AF were 2.5 (95% confidence interval 1.7–3.3) with M235/M235 plus M235/T235 genotype, 3.3 (95% CI 1.3–10.0) with G-6/G-6 genotype, and 2.0 (95% CI 1.3–2.5) with G-217/G-217 genotype. Therefore, this study demonstrates the association of atrial renin-angiotensin system gene polymorphisms with non-familial structural AF.

ACE inhibitors and ARBs have both been shown to play a role in primary and secondary prevention of atrial fibrillation

Clinical studies

The first published paper [13] to investigate the effect of ACE inhibitors on AF was a substudy of the TRACE trial, published in 1999, which studied the effect of trandolapril on the incidence of AF in patients with reduced left ventricular function secondary to acute myocardial infarction. In this substudy 1,577 patients with normal sinus rhythm on the ECG at randomization were randomized to trandolapril treatment (790 patients) versus placebo (787 patients) on days 3 to 7 after a myocardial infarction. All patients were >18 years of age, with a left ventricular ejection fraction of <36%. The study compared the long-term occurrence of AF in both groups of patients, with the time to first occurrence of AF as a primary endpoint. Trandolapril significantly reduced the risk of developing AF by 55% ($P < 0.01$) over a 2 to 4 year follow-up period, compared to placebo. Overall, 5.3% (n=42) developed AF in the placebo group compared to 2.8% (n=22) in the trandolapril group ($P < 0.05$).

In 2003, Vermes et al. [14] published a similar retrospective study based on observations from the Study of Left Ventricular Dysfunction (SOLVD) trial. They analyzed 374 patients during a follow-up of 2.9 years. All patients had an ejection fraction of <35% and were randomized into two groups: enalapril and placebo. Incidental electrocardiograms obtained during the trial were used to diagnose new AF. In a multivariate analysis, there was a 78% risk reduction of AF in the enalapril group, which was statistically significant ($P < 0.0001$).

Madrid and team [6] published a prospective study that examined the use of an angiotensin receptor blocker on patients with AF of at least 7 days duration, who were candidates for cardioversion.

CI = confidence interval

A combination of irbesartan and amiodarone was administered to 79 patients, while 75 others received amiodarone only. All patients were scheduled for cardioversion 3 weeks following initiation of therapy; 29 patients (38.6%) from the amiodarone group and 33 (42%) from the amiodarone plus irbesartan group converted spontaneously before scheduled cardioversion ($P = 0.693$), and 37 versus 41 patients, respectively, underwent successful cardioversion ($P = 0.270$). After 2 months of follow-up, the group of patients treated with amiodarone plus irbesartan demonstrated fewer recurrent AFs (Kaplan-Meier analysis 84.79 vs. 63.16%, $P = 0.008$). They also showed a longer time to first recurrence although this was not significant. This study showed an increase in efficacy of an angiotensin receptor blocker in the prevention of recurrences following cardioversion, especially during the first 254 days (range 60–710) following cardioversion. Although other studies have shown a beneficial effect of spontaneous conversion to sinus rhythm [14], this study did not show such an effect.

Another recent study by Madrid et al. [8] demonstrated similar findings. They conducted a randomized study with three arms. The first group was treated with amiodarone 400 mg, the second, amiodarone plus irbesartan 150 mg and the third group, amiodarone plus irbesartan 300 mg. Patients treated with amiodarone 400 mg plus irbesartan 300 mg had a greater probability of remaining free of AF (77% vs. 52% for amiodarone and 65% for amiodarone + irbesartan 150 mg); hazard ratio for a recurrence in the third group was 0.47 (95% CI 0.27–0.82, $P = 0.001$). This study demonstrated the beneficial effect of an ACE inhibitor in the treatment of atrial fibrillation. In addition, a dose-response effect was observed.

Another similar study demonstrated a significant effect of adding an ACE inhibitor to amiodarone to prevent of AF recurrence following cardioversion [16]. This study showed a lower rate of immediate recurrence (4.3% vs. 14.7%, $P = 0.067$) in the group that received enalapril in addition to amiodarone. Furthermore, in the same group, Kaplan-Meier analysis demonstrated a higher probability of remaining in sinus rhythm at 4 weeks (84.3% vs. 61.3%, $P = 0.002$).

An article describing a substudy of the LIFE trial [17] published in 2003 also demonstrated the beneficial effect of ACE inhibitors, by comparing losartan (ARB) to atenolol (beta blocker) in the treatment of hypertension in 9,193 patients (46% men). Patients were followed for at least 4 years, and demonstrated a 4.9% overall incidence for developing AF. The results of the LIFE study showed a close to 50% risk reduction in sudden death in losartan-treated patients with diabetes, compared to those treated with atenolol. In addition, there was a 30% risk reduction in new-onset AF (relative risk 0.71, 95% CL 0.58–0.86, $P < 0.001$). Therefore, a possible explanation for the improved outcome could be the favorable effect of angiotensin receptor blockade on atrial remodeling over time. This advantage over beta blockers was independent of the antihypertensive effect. Moreover, another substudy of the LIFE trial population demonstrated that even in patients with preexisting AF, the rate of stroke was decreased as compared to similar patients treated with beta blockers [30].

L'Allier and colleagues [31] recently reported their study that compared calcium channel blockers with ACE inhibitors. In this retrospective comparative study 10,926 patients (mean age 65 years) with hypertension were divided equally between those receiving ACE inhibitors and those receiving calcium channel blockers. A regression model was used for patient evaluation. The adjusted incidence ratio for AF-related hospitalization was 0.74 (95% CI 0.62–0.89) and for new-onset AF 0.85 (95% CI 0.74–0.97). This study might offer additional insight into preferring ACE inhibitors for treating hypertension compared with calcium channel blockers.

Zaman et al. [32] demonstrated the beneficial effect of ACE inhibitors in patients with prolonged atrial fibrillation. They followed 47 patients for one year. They divided the patients into two groups according to their treatment, with the attending physician deciding whether the patient required an ACE inhibitor. Twenty-four patients received ACE inhibitors and 23 did not. Over the 1 year study period, the patients treated with ACE inhibitors demonstrated fewer admissions, defibrillation attempts, and lower mean energy levels for defibrillation. The investigators also showed that signal-averaged p-wave duration, which is prolonged in atrial fibrillation, significantly shortens with ACE inhibitors. However, as the editorial written on this study [33] states, this study was small and non-randomized, highlighting the need for randomized clinical trials intended to define the role of ACE inhibitors in the management of atrial fibrillation.

The exact role of these medications in the routine treatment of AF patients remains to be determined

Madrid et al. [34] recently conducted a meta-analysis of seven randomized controlled studies involving 11,328 patients and 13,521 controls. The study compared the likelihood of developing atrial fibrillation in patients receiving ACE inhibitors or ARBs. The patients were taken from studies that focused on the treatment of hypertension, diabetes mellitus, ischemic heart disease, or heart failure. The authors demonstrated a significant risk reduction in the treatment group (OR 0.57, 95% CI 0.39–0.84, $P = 0.003$) for occurrence or recurrence of atrial fibrillation.

Conclusion

The above-mentioned studies illustrate the favorable effect of ACE inhibitors and ARBs on atrial remodeling, which in turn has a therapeutic effect on the treatment of AF. Blocking the renin-angiotensin system with ACE inhibitors or ARB results in regression of electrical as well as structural remodeling and partial prevention of AF occurrence and recurrence. It should be noted that most of the above data come from retrospective studies and therefore require further substantiation. Hence, larger prospective randomized trials are needed before ACE inhibitors can be recommended as a preventive and therapeutic drug for AF. Nevertheless,

OR = odds ratio

in hypertensive patients for whom a preferred drug type has to be chosen, the existence of concomitant AF may be used as an argument in favor of prescribing ACE inhibitors or ARBs.

References

1. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med* 1995;155:469–73.
2. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba follow-up group. *Am J Med* 1995;98:476–84.
3. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N *Engl J Med* 1998;339:659–66.
4. Nattel S. New ideas about atrial fibrillation 50 years on. *Nature* 2002;415:219–26.
5. Wijffels MCEF, Kirchlof CJHJ, Dorland R, Allessie M. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation* 1995;92:1954–68.
6. Madrid AH, Bueno MG, Rebollo JMG, et al. Use of Irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation. A prospective and randomized study. *Circulation* 2002;106:331–6.
7. Allessie MA. Atrial electrophysiological remodeling. Another vicious cycle? J *Cardiovasc Electrophysiol* 1998;9:1378–93.
8. Madrid AH, Marin IM, Cervantes CE, et al. Prevention of recurrences in patients with lone atrial fibrillation. The dose-dependent effect of angiotensin II receptor blockers. J *Renin Angiotensin Aldosterone Syst* 2004;5:114–20.
9. Villani G, Piepoli M, Terracciano C, et al. Effects of diltiazem pretreatment on direct-current cardioversion in patients with persistent atrial fibrillation: a single blind, randomized, controlled study. *Am Heart J* 2000;140:437–43.
10. Simone A, Stabile G, Vitale DF, et al. Pretreatment with verapamil in patients with persistent or chronic atrial fibrillation who underwent electrical cardioversion. J *Am Coll Cardiol* 1999;34:810–14.
11. Kühlkamp V, Schirdewan A, Stangl K, et al. Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation. J *Am Coll Cardiol* 2000;36:139–46.
12. Workman AJ, Kane KA, Russell JA, Norrie J, Rankin AC. Chronic beta-adrenoceptor blockade and human atrial cell electrophysiology: evidence of pharmacological remodeling. *Cardiovasc Res* 2003;58:518–25.
13. Pedersen OD, Bagger H, Kober L, et al. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. *Circulation* 1999;100: 376–80.
14. Vermes E, Tardif JC, Bourassa MG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction. *Circulation* 2003;107:2926–31.
15. Capucci A, Villani GQ, Aschieri D, et al. Oral amiodarone increases the efficacy of direct-current cardioversion in restoration of sinus rhythm in patients with chronic atrial fibrillation. *Eur Heart J* 2000;21:66–73.
16. Ueng KC, Tsai TP, Yu WC, et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. *Eur Heart J* 2003;24:2090–8.
17. Lindholm LH, Dahlöf B, Edelman JM, et al. Effect of losartan on sudden cardiac death in people with diabetes: data from the LIFE study. *Lancet* 2003;362:619–20.
18. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. *Circulation* 2000;101:2612–17.
19. Li D, Shinagawa K, Pang L, et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. *Circulation* 2001;104:2608–14.
20. Klein L, O'Connor CM, Gattis WA, et al. Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: review of trial and practical considerations. *Am J Cardiol* 2003;91(Suppl):18–40F.
21. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin converting-enzyme inhibitor, ramipril, on death from cardiovascular causes, myocardial infarction and stroke in high-risk patients. N *Engl J Med* 2000;342: 145–53.
22. The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicenter trial (the EUROPA study). *Lancet* 2003;362: 782–8.
23. Pandozi C, Santini M. Update on atrial remodeling owing to rate. *Eur Heart J* 2001;22:541–53.
24. Cardin S, Li D, Thorin-Trescases N, et al. Evolution of the atrial fibrillation substrate in experimental congestive heart failure: angiotensin-dependent and -independent pathways. *Cardiovasc Res* 2003;60(2):315–25.
25. Goette A, Staack T, Rocken C, et al. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. J *Am Coll Cardiol* 2000;35:1669–77.
26. Yano M, Kim S, Izumi Y, et al. Differential activation of cardiac c-Jun amino-terminal kinase and extracellular signal-regulated kinase in angiotensin II-mediated hypertension. *Circ Res* 1998;83:752–60.
27. Sugden PH, Clerk A. Cellular mechanisms of cardiac hypertrophy. J *Mol Med* 1998;76:725–46.
28. Komuro I, Kaida T, Shibazaki Y, et al. Stretching cardiac myocytes stimulates proto-oncogene expression. J *Biol Chem* 1990;265: 3595–8.
29. Tsai CT, Lai LP, Lin JL, et al. Renin-angiotensin system gene polymorphisms and atrial fibrillation. *Circulation* 2004;109:1640–6.
30. Dalhöf B, et al. Presented at the European Society of Cardiology Congress, Berlin, August 2002. Poster 2163.
31. L'Allier PL, Ducharme A, Keller PF, et al. Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation. J *Am Coll Cardiol* 2004;44:159–64.
32. Zaman AG, Kearney MT, Schecter C, Worthley SG, Nolan J. Angiotensin-converting enzyme inhibitors as adjunctive therapy in patients with persistent atrial fibrillation. *Am Heart J* 2004;147:823–7.
33. Al-Khatib SM. Angiotensin-converting enzyme inhibitors: a new therapy for atrial fibrillation? *Am Heart J* 2004;147:751–2.
34. Madrid AH, Peng J, Zamora J, et al. The role of angiotensin receptor blockers and/or angiotensin converting enzyme inhibitors in the prevention of atrial fibrillation in patients with cardiovascular diseases: meta-analysis of randomized controlled clinical trials. *Pacing Clin Electrophysiol* 2004;27:1405–10.

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