Upstream Therapy for Atrial Fibrillation

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There are multiple factors for the etiology of atrial fibrillation (AF), including stretch, autonomic imbalance, hyperthyroidism, and inflammation. Of these factors for AF, stretch and inflammation increase the angiotensin II level, thereby inducing calcium over load, and inducing ectopic focal activities that initiate AF. Angiotensin II activates the Erk cascade through the AT₁R and induces interstitial fibrosis of the atria, which compromises intra-atrial conduction. Short atrial refractoriness and slow conduction form multiple re-entry, before maintaining AF. Anti-arrhythmic drugs used for downstream therapy can suppress the focal activities and re-entry, but cannot prevent the development of a structural substrate. In contrast, angiotensin-converting enzyme, angiotensin II type 1 receptor blocker and statins might constitute upstream therapy through the prevention of structural remodeling that promotes AF. (*Circ J* 2007; **Suppl A**: A-75–A-81)

Key Words: Angiotensin; Arrhythmia; Atrial fibrillation; Inflammation; Statins

Anti-arrhythmic drugs can suppress the ectopic focal activities and re-entrant excitations, therefore, they are usually used for the treatment of atrial fibrillation (AF). However, these drugs cannot prevent the structural substrate development. It is well known that architectural alterations of the atria, including atrial dilatation and tissue fibrosis, are associated with atrial dysfunction.^{1,2} Several studies have shown that activation of the renin-angiotensin system is associated with the mechanism of AF.^{3–5} We previously reported that the blockade of angiotensin II receptors prevented the electrical and structural remodeling induced by rapid atrial pacing.^{6,7} Thus, an activation of the renin-angiotensin system during long-term rapid atrial excitation participates in the mechanisms of AF maintenance through the creation of structural abnormalities.

Possible Mechanisms of AF Promotion

Previous studies have shown that shortened atrial effective refractory period (AERP) and loss of its adaptation to rate, which have been referred to as electrical remodeling, are observed in the pacing-induced AF model.^{8–10} Wijffels et al reported the AERP shortening and increased vulnerability to AF in the goat model.¹¹ However, there was a discrepancy in the time-course between these 2 changes. AERP shortening began within 24h, whereas it took longer than a week for the induced AF to stabilize. These results indicated that a decreased wavelength, which is caused by a shortened AERP and decreased conduction velocity, might play a critical role in the development of chronic AF. Moreover, Everett et al demonstrated that a shortened AERP returned to the baseline level in 7–14 days after 6 weeks of rapid atrial pacing.¹² Despite the complete normalization of AERP, the structural abnormalities of the atria persisted. Based on these results, not only AERP shortening but also

other additional factors, including conduction and structural abnormalities of the atria, might be involved in the promotion of AF.

Therefore, we investigated the effects of an angiotensin II type 1 receptor blocker (ARB), candesartan, on the long-term structural remodeling in a canine model of rapid pacing-induced AF.⁷ Although the degree of the shortening of AERP was similar between the candesartan group and controls, treatment with candesartan significantly decreased the conduction delay by suppressing interstitial fibrosis. These results indicate that angiotensin II might be involved in the mechanism of structural remodeling in chronic AF, and might lead to therapies to prevent both electrical and structural substrate development. In this study, AERP was significantly shortened in the first week, and there was no further shortening of AERP at the later period. In contrast, the intra-atrial conduction time was gradually and progressively prolonged up to 5-week pacing. Furthermore, the inducibility of AF and its mean duration was increased significantly from the first week to the fourth and fifth weeks in parallel with the intra-atrial conduction slowing. These findings indicate that conduction slowing might contribute to the initiation and maintenance of AF.

Role of the Renin-Angiotensin System on Electrical Remodeling

Previous studies have shown that atrial tachycardia-induced electrical remodeling, which is composed of AERP shortening and loss of physiological rate adaptation, is responsible for the increase of AF inducibility and stability.^{1–4} The intracellular calcium overload during high-frequency atrial activation is supposed to contribute to this phenomenon of electrical remodeling.^{9,10,13,14} Accordingly, a L-type calcium channel blocker, verapamil, has been suggested to prevent short-term electrical remodeling in animal and human studies.^{9,10,13,14} However, several studies have demonstrated that verapamil does not prevent AERP shortening and loss of its rate adaptation following AF induced by long-term tachycardia, and that verapamil increases the duration of AF induced.^{15–18} We reported previously that verapamil increased intra-atrial conduction delay and frag-

(Received December 16, 2006; revised manuscript received December 28, 2006; accepted January 9, 2007)

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Fig 1. Effects of angiotensin II type 1 receptor blocker on atrial remodeling in a canine model of rapid pacing-induced atrial fibrillation (AF). Time-course of the percent changes in the atrial effective refractory period (AERP) of the right atrial appendage and intra-atrial conduction time (CT) from the right atrial appendage to the lower right atrial wall at a basic cycle length of 300 ms, and the mean duration of induced AF in the control and candesartan groups. The degree of AERP shortening was similar between the 2 groups; the intra-atrial CT in the candesartan group was significantly shorter than that in the control group, and the mean AF duration in the candesartan group was significantly shorter than that in the control group. The percentage of fibrosis of the free walls and appendages in both atria after 5 weeks of pacing was shown. The percentage of fibrosis in all atrial regions in the candesartan group was markedly lower than that in the control, although greater than that in the sham group. * $p < 0.001$ compared with the control group. * $p < 0.05$ compared with the sham group. RAA, right atrial appendage; RAFW, right atrial free wall; LAA, left atrial appendage; LAFW, left atrial free wall (Reproduced from *J Am Coll Cardiol* 2003; 41: 2197–2204, with permission). § $p < 0.01$, * $p < 0.05$ compared with the control group.

mented activity in patients with paroxysmal AF¹⁹ These results suggested that intracellular calcium overload might contribute to a mechanism of electrical remodeling only in the short-term, but not in the long-term. Shinagawa et al found that amiodarone prevented tachycardia-induced atrial electrical remodeling in a dog model, in terms of both atrial electrical properties and ion-channel subunit expression.²⁰ Because amiodarone can share T-type Ca^{2+} -channel-inhibiting actions, it is tempting to speculate that the T-type blockade plays a central role.

We previously reported that the angiotensin converting-enzyme inhibitor (ACEI) and ARB prevented AERP shortening in a canine short-term rapid pacing model.⁶ The beneficial effects of these drugs might be ascribed, in part, to a reduction of atrial stretch in response to rapid atrial activation. We also examined the effects of an ARB, candesartan, on the long-term atrial electrical remodeling. Candesartan did not prevent AERP shortening after 1 week of rapid pacing, suggesting that long-term electrical remodeling cannot be explained solely by calcium overload (Fig 1). Shinagawa et al also reported that the ACEI, enalapril, did not prevent AERP shortening after 7 days of rapid pacing, suggesting apparent differences in the pathogenesis of short-term and long-term remodeling.²¹ They suggested that short-term remodeling is primarily caused by functional changes such

as Ca^{2+} - and voltage-dependent I_{CaL} inactivation, whereas long-term remodeling is caused by changes in ion channel expression at transcriptional and/or post-transcriptional levels. This might explain why candesartan inhibited the short-term electrical remodeling, but not the long-term electrical remodeling. However, candesartan significantly decreased the inducibility and the duration of AF after 5 weeks of rapid atrial pacing, probably by preventing the development of conduction slowing (Fig 1). Therefore, the blockade of angiotensin II might attenuate the arrhythmogenic substrate, which might promote the transition to chronic AF.

Role of the Renin-Angiotensin System on Structural Remodeling

AF is associated with progressive structural changes of the atria, resulting in atrial dilatation and increased interstitial fibrosis.^{1,12} Li et al reported that decreased AERP and increased AERP heterogeneity were not observed in a dog model of heart failure, while AF inducibility and duration were significantly increased compared to those in control dogs.² Local conduction slowing, its heterogeneity, and the interstitial fibrosis of the atria were prominent in dogs with heart failure. Therefore, the changes in local atrial conduc-

Fig2. Effects of angiotensin II type 1 receptor blocker on atrial remodeling in a canine model of rapid pacing-induced atrial fibrillation. Representative histological sections of the right atrial free wall from each group (Masson trichrome stain) from a sham dog (A), a fifth week rapid pacing dog (B), and a fifth week rapid pacing with a candesartan-treated dog (C). In a sham dog, the intracellular space appeared normal. In a control dog, extensive interstitial fibrosis, evidenced by Masson trichrome stain, was found. In a candesartan-treated dog, interstitial fibrosis was attenuated (Reproduced from *J Am Coll Cardiol* 2003; 41: 2197–2204, with permission). Magnification: $\times 400$.

Fig3. Effects of statin on atrial fibrillation (AF) in a canine sterile pericarditis model. Left: Comparison of C-reactive protein (CRP) levels between the control and atorvastatin groups before and after operation. Before the operation, there were no significant differences in the CRP levels between 2 groups. On the second postoperative day, the CRP was significantly increased in both groups; however, it was significantly lower in the atorvastatin group than in the control. [#] $p < 0.0001$ compared with before the operation. ^{*} $p < 0.0001$ compared with the control group. Right: Comparison of the duration of induced atrial fibrillation between the control and atorvastatin groups before and after operation. Before the operation, there were no significant differences in atrial fibrillation duration between 2 groups. On the second postoperative day, the atorvastatin group had a shorter atrial fibrillation duration than the control (Reproduced from *Cardiovasc Res* 2004; 62: 105–111, with permission). [#] $p < 0.0001$ compared with before the operation. ^{*} $p < 0.0001$ compared with the control group.

tion properties caused by interstitial fibrosis favor the maintenance of AF in dogs with heart failure.

Recently, Goette et al demonstrated that the expression of angiotensin converting-enzyme and Erk1/Erk2 was enhanced in patients with AF.³ Willems et al established that the development of AF by rapid pacing was associated with an increase in the plasma level of angiotensin II in a sheep model.²² In animal studies, it has been reported that high atrial pressure directly caused AERP shortening and increased AERP dispersion, resulting in increased vulnerability to AF.^{23–25} In addition to these direct effects on electrophysiological properties, increased atrial stretching activates the Erk cascade through the AT₁R, which might induce interstitial fibrosis of the atria.^{3,26} More interestingly, treatment with ACEI decreased the level of an activated Erk1/Erk2.³ ARB might also have similar inhibitory effects

on these kinases, resulting in decreasing atrial fibrosis (Figs 2,3). The inhibition of local angiotensin II can prevent the promotion of AF by suppressing the development of the structural substrate. In addition, ARB has been reported to decrease atrial pressure.²⁷ Therefore, it is possible that a decrease in atrial stretching by ARB might directly precipitate electrophysiological changes to prevent AF.

Role of Inflammation on AF

Structural changes in the atria in association with inflammation might promote AF persistence. Recently, Chung et al reported that C-reactive protein (CRP) was elevated in patients with AF and was higher in patients with persistent AF compared to those with paroxysmal AF.²⁸

Evidence for an inflammatory contribution to at least

Fig4. Effects of statin on atrial fibrillation in a canine sterile pericarditis model. Representative histological sections of the right atrial free wall from each group were taken. (A) A sham dog sample stained with haematoxylin-eosin, (B) a control dog sample stained with haematoxylin-eosin, (C) an atorvastatin-treated dog sample stained with haematoxylin-eosin, (D) a sham dog sample stained with Masson trichrome, (E) a control dog sample stained with Masson trichrome, and (F) an atorvastatin-treated dog sample stained with Masson trichrome. In a sham dog, the intracellular space appeared normal. In a control dog, active perimyocarditis was found, which consisted of inflammatory infiltrate with lipid degeneration, was confined to the atrial myocardium and extensive interstitial fibrosis, evidenced by Masson trichrome stain. In contrast, these pathological abnormalities of atrial tissues were attenuated in an atorvastatin dog (Reproduced from *Cardiovasc Res* 2004; **62**: 105–111, with permission). Magnification: $\times 400$.

Fig5. Mechanism of promotion of atrial fibrillation (AF). Ach, acetylcholine; Ang II, angiotensin II; SAC, stretch activated channel; PV, pulmonary vein; ERP, effective refractory period; Erk, extracellular signal-regulated kinase.

some forms of AF was initially suggested by the high incidences (25–40%) of AF after cardiac surgery. Activation of the complement system and release of proinflammatory cytokines occur after cardiac surgery, suggesting the presence of an intense inflammatory process. The production of CRP, a prototypic marker of inflammation, is driven by the proinflammatory cytokines interleukin (IL)-1, tumor necrosis factor- α , and IL-6²⁹ Bruins et al reported that IL-6 levels rise markedly, peaking 6 h after surgery³⁰ A second peak of CRP elevation comes on the second postoperative day, and

the complement-CRP complexes peak on the second or third postoperative day. The incidence of atrial arrhythmias similarly peaks 2–3 days after surgery. It was demonstrated by Page et al in a canine sterile pericarditis model that the peak of AF induction comes on the second postoperative day³¹ Mapping studies during AF in the sterile pericarditis model have shown that multiple unstable re-entrant circuits are critical for maintaining AF³² In this model, we have demonstrated that elevated CRP was associated with sustained AF³³

Atrial structural remodeling might occur from inflammatory stressors. The anatomic substrate of electrical atrial instability has been investigated in vivo using both surgical and atrial biopsy approaches. Basso et al reported a 50% incidence of isolated atrial myocarditis in fatal Wolff–Parkinson–White cases³⁴ This finding supports the hypothesis that atrial inflammatory foci might act as a trigger of paroxysmal AF. Notably, the possibility of an isolated arrhythmogenic atrial myocarditis was put forward by Fromer et al³⁵ who studied 2 cases of drug-refractory ectopic atrial tachycardia; surgically resected tissue showed focal myocarditis at endomyocardial biopsy being associated with a minor elevation of antibodies against echovirus in 1 case. In the canine pericarditis model, we showed that active perimyocarditis, which consisted of patchy inflammatory infiltrate with lipid degeneration, occurred in dogs with sustained AF and was confined to the atrial myocardium³³ Thus, inflammatory changes might contribute to atrial structural remodeling and increase the propensity for AF to persist.

Statin and AF

It is conceivable that the prevention of AF with elevated CRP might be improved by using anti-inflammatory agents or other CRP-lowering drugs. Recent studies have shown that it is possible to modulate CRP levels with pharmacological interventions, including HMG-CoA reductase inhibitor (statin) drugs.^{36–38} Statin reduces cardiovascular risk, the mechanism of which might include diminished arterial inflammation, as suggested by a reduction in levels of CRP in serum that appear to be independent of a reduction in low-density lipoprotein-cholesterol levels.^{39,40} Thus, modalities targeting inflammation and reducing proinflammatory cytokines and CRP levels could be a potential additional strategy in the prevention of cardiovascular disease. Ridker et al⁴¹ demonstrated that patients who have increased CRP levels (increased inflammation) gain a greater benefit from pravastatin therapy⁴¹ and that median CRP levels were reduced to 17.4% in the group that received pravastatin.³⁶ Furthermore, Jialal et al showed that treatment with atorvastatin also results in a significant reduction in CRP levels (mean percent reduction in CRP levels: 28.3%).⁴⁰ Therefore, it is conceivable that the prevention of AF with elevated CRP might be improved by the use of statins. We documented that atorvastatin prevented the promotion of atrial electrophysiological and structural changes resulting from inflammation in the canine sterile pericarditis model (Figs 3,4).³³ Thus, atorvastatin could attenuate the substrate of AF by inhibiting inflammation.

Although we proved that atorvastatin did prevent the maintenance of AF in the canine sterile pericarditis model, these results could not be extrapolated to other animal AF models or non-postoperative AF patients. However, Chung et al demonstrated that CRP was also elevated in patients with lone AF in the absence of structural heart disease when compared with the control subjects.²⁸ Moreover, inflammatory changes have also been reported in patients with non-postoperative AF. In a series of 12 patients with drug-refractory paroxysmal AF, which was studied by using an atrial endomyocardial biopsy, Frustaci et al found isolated atrial lymphocytic myocarditis in 66% of the cases.⁴² The cause-effect relationship between myocarditis and AF was further supported by the absence of AF recurrence in patients treated with steroids. Thus, recent data suggest that in a certain population of patients with lone paroxysmal AF, this could be caused by isolated atrial myocarditis. Therefore, anti-inflammatory agents or CRP-lowering drugs such as statins might improve the prevention of AF.

The pleiotropic effects of statins might be largely mediated by nitric oxide,⁴³ which can induce cardioprotection. It has been demonstrated that statins can attenuate oxidant-induced mitochondrial dysfunction in cardiac myocytes⁴⁴ and downregulate the activity of small G proteins in cardiomyocytes and, therefore, influence surrogate markers of cardiac dysfunction such as the atrial natriuretic factor and myosin light chain-2.⁴⁵ These additional effects of statins might be involved in their antiarrhythmic activity. However, it has been reported that pacing-induced AERP shortening and AF promotion were unaffected by vitamin C or vitamins C and E in a dog model.⁴⁶ In addition, the result of a recent clinical study has shown that the use of statins in patients with lone AF was associated with a decrease in the recurrence of AF after successful cardioversion.⁴⁷ Thus, statins might constitute a novel therapeutic approach for the prevention of AF.

Clinical Evidences

AF is a common arrhythmia in patients with heart failure, and we often experience difficulties in controlling drug-induced negative inotropic and proarrhythmic effects, especially in patients with left ventricular dysfunction. Recent clinical trials have reported that ACEI and ARB reduce the incidence of new-onset AF in patients with left ventricular dysfunction and congestive heart failure.^{5,48–52} In addition to this suppression of new-onset AF, the AFFIRM study demonstrated that ACEI treatment suppresses AF relapse in patients with congestive heart failure who had been randomized to rhythm control.⁵³ Van Den Berg et al showed that an ACEI, lisinopril, decreased the recurrence of AF after cardioversion in patients with congestive heart failure.⁵⁴ Furthermore, Madrid et al reported that patients who had been treated with amiodarone plus the ARB, irbesartan, had a lower rate of AF recurrence after electrical cardioversion of persistent AF (>7 days) compared with the patients treated with amiodarone alone.⁵⁵ Ueng et al also demonstrated that the addition of the ACEI, enalapril, to amiodarone decreased AF relapse after cardioversion in patients with persistent AF (>3 months).⁵⁶ Zaman et al showed that long-term ACEI therapy significantly decreased the duration of signal-averaged P-wave 1 year after successful electrical cardioversion in patients with persistent AF, which suggests amelioration of the arrhythmogenic substrate.⁵⁷ Based on these results, angiotensin II inhibition might help reverse the AF-induced arrhythmogenic remodeling in favor of subsequent long-term maintenance of sinus rhythm after cardioversion of persistent AF. These previous clinical trials demonstrated that treatment with an ACEI or ARB had beneficial effects in AF patients with cardiac risk factors.^{5,48–52,57}

Upstream Therapy for AF

In Fig 5, the mechanism of promotion of AF is summarized. There are multiple factors for etiology of AF, including stretch, autonomic imbalance, hyperthyroidism, and inflammation. Of several factors for AF, stretch and inflammation increase the angiotensin II level, which induces calcium over load and a triggered activity, before initiating AF. Whereas angiotensin II activates the Erk cascade through the AT₁R, inducing interstitial fibrosis of the atria, before promoting slow conduction. Short atrial refractoriness and slow conduction set a stage for multiple re-entry, before maintaining AF. Antiarrhythmic drugs, which are considered downstream therapy, can suppress the ectopic focal activities and re-entrant excitations, but cannot prevent the structural substrate development. In contrast, ACEI and ARB can prevent the promotion of AF by suppressing the development of structural remodeling, and therefore, might constitute an upstream therapy for preventing AF promotion.

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