

# Role of Atrial Remodeling in Patients with Atrial Fibrillation

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Atrial fibrillation (AF) maintenance is promoted by an atrial substrate that is suitable for the initiation and continuation of the re-entering wavelets. During the first week of AF, the atrial substrate is modified by electrical remodeling, with shortening of the atrial refractoriness and slowing of the conduction velocity. Structural remodeling is the so-called “second factor” that facilitates the maintenance of AF in the following months. The ultrastructural changes result in an inhomogeneous conduction and electrical uncoupling, and the enlarged atrium is able to accommodate more circulating wavefronts that stabilize the AF. Reversal of the electrical remodeling develops within 1 week after the restoration of AF to sinus rhythm. However, reverse structural remodeling develops more slowly and may be just partially reversible. The substrate properties during AF recurrences after undergoing catheter ablation are more complex and need to be clarified in future studies. [J Chin Med Assoc 2007;70(8):303–309]

**Key Words:** atrial fibrillation, remodeling, substrate, voltage

## Introduction

It is generally believed that atrial premature complexes are one of the triggers that could initiate atrial fibrillation (AF).<sup>1,2</sup> These triggers mainly reside in the sleeves of the atrial tissue within the pulmonary veins (PVs) or vena caval junctions.<sup>1–4</sup> The natural history of AF is characterized by a progression from paroxysmal to persistent and then to permanent AF over time. Since the coordinated atrial activity is replaced with disorganized rapid excitations, the possibility of the conversion and maintenance of sinus rhythm decreases as the duration of AF increases.<sup>5</sup> This pathophysiologic adaptation to fibrillatory conduction has been termed remodeling. The concepts of tachycardia-induced atrial electrical and structural remodeling have since then been investigated. In this review article, we will focus on substrate remodeling from electrophysiologic and anatomic points of view, and examine the possibility of reverse remodeling after the elimination of AF.

## Electrical Remodeling of the Atrium During AF

### *Evidence from animal studies*

Wijffels et al postulated the concept of “AF begets AF” to explain why atrial pacing for 2–3 weeks led to sustained AF in healthy goats in 1995.<sup>6</sup> Marked shortening of the atrial refractoriness (–45%) and a reversion of the normal rate adaptation of the refractory periods were demonstrated after 24 hours to 2 weeks of electrically maintained AF. Morillo et al also demonstrated a minimal reduction of 15% in the atrial refractory period, together with a decrease in the atrial conduction velocity, after sustained rapid atrial pacing (up to 400 bpm) in a canine model.<sup>7</sup> There was a significantly shorter AF cycle length in the left atrium compared with the right atrium, especially over the left atrial posterior wall. After 6 weeks of continuous rapid atrial pacing, sustained AF (> 15 minutes) was induced in 82% of the dogs. Similar results were also observed by Elvan et al<sup>8</sup>

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and Gaspo et al<sup>9</sup> in chronic atrial-paced (6 weeks) dogs. Since the wavelength is the product of the refractoriness and conduction velocity, the results lead to a shorter atrial wavelength. It results more easily in the formation of reentry in small regions of intra-atrial conduction block and the perpetuation of AF.

### *Mechanisms of electrical remodeling*

The mechanisms for these phenomena are due to ionic remodeling and atrial ultrastructural changes.

1. Ionic remodeling:  $\text{Ca}^{2+}$  enters the cells through L-type  $\text{Ca}^{2+}$  current ( $I_{\text{CaL}}$ ) with each action potential. Therefore, during AF, rapid atrial rate increases cellular  $\text{Ca}^{2+}$  loading and threatens cell viability. The cells may respond to the  $\text{Ca}^{2+}$  load insult by some defense mechanisms to minimize the  $\text{Ca}^{2+}$  overload.<sup>10</sup> Yue et al provided evidence from chronic paced dogs that the densities of the  $I_{\text{CaL}}$  and transient outward current ( $I_{\text{to}}$ ) became progressively reduced with the prolongation of rapid atrial pacing; also, the action potential duration (APD) and APD adaptation to the rate were decreased.<sup>11</sup> A significant reduction in the  $\text{Na}^+$  current ( $I_{\text{Na}}$ ) density was also reported by Gaspo et al in a dog model.<sup>12</sup> Yue et al further proved that downregulation of the mRNA concentrations of the  $\alpha_1\text{C}$  subunit of the L-type  $\text{Ca}^{2+}$  channels,  $\text{Kv}4.3$ , and  $\alpha$  subunit of the cardiac  $\text{Na}^+$  channel genes occurred in chronic pacing dogs.<sup>13</sup> The decrease in the  $I_{\text{CaL}}$  seems to be responsible for the shortening of the APD, the reduction in  $I_{\text{Na}}$  might be contributing to the decrease in the conduction velocity, and the decrease in  $I_{\text{to}}$  is considered to result in a loss of the physiologic rate adaptation of the action potential.
2. Ultrastructural changes: marked changes in the atrial ultrastructure have been documented by Mary-Rabine et al, where a portion of the atrial myocytes displayed a loss of myofilaments and had clusters of accumulated glycogen and lysosomal degeneration in patients with atrial arrhythmias.<sup>14</sup> Morillo et al also characterized an increase in the mitochondrial size and number, and disruption in the sarcoplasmic reticulum, in a canine model.<sup>7</sup> These changes may result in an inhomogeneous conduction and electrical uncoupling, which in turn may facilitate the maintenance of AF.

### *Clinical studies and voltage mapping*

The changes in electrical remodeling are similar in humans. Yu et al showed that in patients with chronic AF, the atrial effective refractory period was significantly

shortened, the rate adaptation response became impaired, especially in the distal coronary sinus, and the conduction properties of the atria became depressed.<sup>15</sup> In addition, with the evolving techniques following the development of electroanatomic mapping systems, we are able to evaluate the substrate properties in the human atrium. Voltage mapping studies revealed regions of contiguous reduction in the electrogram voltage representing diseased myocardium.<sup>16</sup> In our laboratory, Higa et al demonstrated that focal atrial tachycardia may arise from low voltage zones (LVZs) or border zones around the LVZ in 79% of atrial tachycardia patients.<sup>17</sup> Lin et al also reported a reduction in mean voltage in patients with atrial tachyarrhythmias as compared to those with atrioventricular nodal reentrant tachycardia.<sup>18</sup> The voltage further became reduced with shorter pacing cycle lengths in patients with atrial flutter and AF. LVZ and scarring were independent predictors of long-term recurrence of AF after PV isolation.<sup>19</sup> The substrate properties of the activation and cycle-length dependent voltage reduction may be related to the development of atrial flutter and AF.

### **Structural Remodeling of the Atrium During AF**

It has been shown that the atrial tissue develops structural abnormalities, which can be identified on gross evaluation (by atrial enlargement) and microscopic examination (by ultrastructural changes) after periods of AF.<sup>7,20</sup> The ultrastructural and molecular changes (see the descriptions in the previous paragraph) together with atrial stretch are associated with morphologic remodeling in patients with AF. Atrial enlargement due to structural remodeling in patients with AF is also well-established.

#### *AF and left atrial enlargement: a chicken-egg relationship*

As early as 1914, it has been proposed that there is a relationship between the atrial tissue mass and AF.<sup>21</sup> The work by Henry et al led to the observation that AF is rare (3%) when the left atrial dimension is below 44 mm, but is common (54%) when this dimension exceeds 40 mm.<sup>22</sup> The data suggest that left atrial size is an important factor in the development of AF. A large clinical trial identified atrial dilatation as an independent risk factor for the development of AF.<sup>23</sup> The risk elevates 1.4 times per 5-mm increase in left atrial size. In addition, from Moe and Abildskov's multiple wavelets hypothesis, a critical number of wandering

wavelets is needed for the perpetuation of AF. The enlarged atrium is therefore needed to be able to accommodate more circulating wavefronts, and then stabilizing AF.<sup>24</sup>

Left atrial enlargement may also act as a consequence of arrhythmia. It is prominent in patients with persistent AF, but is seldom observed in patients with paroxysmal AF.<sup>25</sup> In patients with structural heart disease, the diseased left atrium further dilated after the development of AF.<sup>22</sup> In patients without structural heart disease (lone AF), Suarez et al found that the left atrial dimension also increased by 15% over the baseline measurement during a mean follow-up of 6.2 years in a retrospective study.<sup>26</sup> Sanfilippo et al followed AF patients with no detectable cardiac disease and reported a significantly increasing left atrial size, from 45 to 64 cm<sup>3</sup> within 20 months.<sup>27</sup> Increasing left atrial pressure and wall stress with decreasing chamber distensibility might be the mechanisms of the atrial enlargement as a consequence of AF. Moreover, during AF, the loss of the atrial kick component of ventricular filling is known to be approximately 20%. The constant venous return to the left atrium makes the mean atrial pressure increase in order to maintain ventricular filling, and is then followed by atrial enlargement.

## Electrical and Structural Remodeling Go Hand in Hand

Both electrical and structural remodeling may involve the genesis of atrial tachyarrhythmias. Boyden et al studied the feline heart with primary myocardial disease.<sup>28</sup> Changes in transmembrane action potentials were found in the dilated atria. There were pronounced structural abnormalities, such as interstitial fibrosis, cellular hypertrophy and degeneration, and thickened basement membranes in the diseased atria. The electrical remodeling developed within hours to days, and the structural remodeling was a much slower process.

### *Electrical remodeling starts on the first day of AF*

Electrical remodeling develops more quickly than structural remodeling. As in Wijffels et al's goat model, a reduction in the refractory period was observed after 6 hours of sustained high-rate pacing, and the remodeling was complete within 3–5 days.<sup>6</sup> Gaspo et al also claimed near-maximal changes in the refractoriness within 7 days in a rapid pacing dog model.<sup>9</sup> However, the conduction velocity was found to be moderately decreased after 6 weeks of rapid pacing. Goette et al further reported that a reduction in the refractory

period occurred during the first 30 minutes of the onset of rapid atrial pacing in dogs.<sup>29</sup> Even then, AF could not be perpetuated without an alteration in the atrial structure.

### *Structural remodeling acts as a second factor for AF maintenance*

The time course of the changes in atrial refractoriness did not run parallel with the increase in the persistence of AF in Wijffels et al's study. The AF cycle length reached a steady state within 3–5 days, but it often took an additional 1–2 weeks for AF to become persistent.<sup>6</sup> Structural remodeling is the so-called "second factor" that plays an important role in the maintenance of AF. Electrical remodeling occurs earlier within days, and structural remodeling is a much slower process, which may continue for several months.

In pacing-induced AF goats, the first sign of ultra-structural changes occurred during the first week of AF with the presentation of a homogeneous chromatin distribution and a decrease in the myocardial protein cardiotin (dedifferentiation). An increased myolysis and glycogen accumulation developed in 8 weeks. After 16 weeks of AF, 42% of the myocytes were affected by myolysis.<sup>30</sup> The amount of connective tissue in the atrium did not change after 4 months of AF. Tissue anisotropy may result in inhomogeneous conduction and may be responsible for the slow conduction and reentry which stabilizes AF. However, to the best of our knowledge, no studies to date have looked at the association of AF and left atrial enlargement in a temporal fashion in a large cohort. An enlarged left atrium in AF patients was observed in previous studies 20–24 months after the persistence of AF.<sup>25–27</sup>

Therefore, both electrical and structural remodeling can create a substrate for AF. The shortening of the action potential results in a smaller intra-atrial circuit, and the enhanced tissue anisotropy generates a local conduction delay. In addition, the larger atrium harbors more wavelets. This positive feedback between the remodeling and AF renders the arrhythmia everlasting.

## Complex Atrial Substrate Properties in Patients Receiving Therapy for AF

Catheter ablation of PVs has become an effective treatment for patients with AF after the pioneering work of Haissaguerre et al<sup>1</sup> and Chen et al.<sup>2</sup> Around 60–80% of patients can be AF-free without any antiarrhythmic drugs after the PV isolation procedure. It is anticipated that reverse remodeling of the atrial substrate might occur in patients after the restoration of sinus

**Table 1.** Structural remodeling of the left atrium and pulmonary veins after catheter ablation of atrial fibrillation

Reference (year)	Patients, n	Diagnostic tools (n)	Arrhythmia type (n)	AF duration, yr	Ablation sites	Follow-up, mo	AF recurrence, n (%)	Atrial/PV remodeling	
								No recurrence group	Recurrence group
Lemola et al <sup>37</sup> (2004)	41	CT (41)	PAF*/PeAF†, 25/16	5 ± 3	4 PVs + MI + posterior LA	4 ± 2	3 (7)	LA volume ↓ 15% <sup>§</sup> PV ostial area ↓ 10% <sup>§</sup>	LA volume ↓ ↑ PV ostial area ↓ ↑
Beukema et al <sup>42</sup> (2005)	105	TTE (105)	PAF/PeAF, 52/53	6.0 ± 5.1/ 7.6 ± 6.0 (PAF/PeAF)	4 PVs ± MI ± posterior LA ± CTI	6	23 (22)	LAD ↓ 7.4% <sup>§</sup> (PAF) ↓ 9.1% <sup>§</sup> (PeAF)	LAD ↓ ↑ (PAF) ↑ 8.9% <sup>§</sup> (PeAF)
Tsao et al <sup>38</sup> (2005)	45	MRI (45)	PAF, 45		4 PVs	21 ± 11	10 (22)	LA volume ↓ 7.9% <sup>  </sup> PV ostial area ↓ 9.1–10%*	LA volume ↑ 28% <sup>§</sup> PV ostial area ↓ ↑
Reant et al <sup>41</sup> (2005)	48	TTE (48)	PAF/CAF†, 37/11	6.1 ± 5.6/ 12 ± 8.8 (PAF/PeAF)	4 PVs + CTI ± MI ± LA roof	11	13 (27)	LA area ↓ 19%* (PAF), ↓ 24% <sup>  </sup> (CAF)	LA area ↓ 5% <sup>  </sup> (PAF), ↓ 7% (CAF)
Verma et al <sup>39</sup> (2006)	67	CT (26), TEE (41)	PAF/PeAF, 40/27	5.8 ± 5.1	4 PVs + SVC	6	0 (0)	LA area ↓ 11% <sup>§</sup> (CT) LA volume ↓ 15% <sup>§</sup> (CT)	N/A
Chang et al <sup>40</sup> (2007)	40	MRI (40)	PAF, 40	N/A	4 PVs	20 ± 11	10 (25)	LAA orifice area ↓ 12.5% <sup>§</sup> LAA neck area ↓ 16.8% <sup>§</sup> LAA length ↓ 8.7% <sup>§</sup>	LAA orifice area ↑ 14.4% <sup>  </sup> LAA neck area ↑ 17.4% <sup>  </sup> LAA length ↑ 6.0% <sup>  </sup>

\*PAF is defined as recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days; †PeAF is defined as AF that is sustained beyond 7 days or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion; ‡CAF includes PeAF and permanent AF (AF in which cardioversion has either failed or not been attempted); §p ≤ 0.05; ||p ≤ 0.01; ¶p ≤ 0.001; ¶¶p ≤ 0.0001; AF = atrial fibrillation; CT = computed tomography; TTE = transthoracic echocardiography; MRI = magnetic resonance imaging; TEE = transesophageal echocardiography; PAF = paroxysmal atrial fibrillation; PeAF = persistent atrial fibrillation; CAF = chronic atrial fibrillation; PV = pulmonary vein; MI = mitral isthmus; LA = left atrium; CTI = cavotricuspid isthmus; SVC = superior vena cava; LAD = left atrial appendage; LAA = left atrial appendage; N/A = not available; ↑ = increase in the parameter compared to value before catheter ablation; ↓ = decrease in the parameter compared to value before catheter ablation; ↓↑ = no significant change compared to value before catheter ablation.

rhythm. However, recurrence of AF still remains a prevalent issue after PV isolation. The atrial substrate turns into a more complex entity after the therapeutic intervention.

#### *Electrical properties after the therapy for AF*

Wijffels et al observed a restoration of all electrophysiologic changes within 1 week after sinus rhythm was restored.<sup>6</sup> Lee et al further demonstrated the recovery of the shortened atrial refractoriness during 48-hour measurements, and the recovery was slower in the left atrium than in the right atrium or Bachmann's bundle.<sup>31</sup> In humans, Yu et al identified that the electrical remodeling of the atrium reversed completely within 4 days of the resumption of sinus rhythm.<sup>15</sup> Raitt et al observed a different rate of recovery between the coronary sinus ostium and distal coronary sinus within 1 week after cardioversion.<sup>32</sup> The transient dispersion of the refractoriness may increase the risk for early recurrence of AF. Therefore, recurrence of AF occurs mostly within 3–5 days after restoration of sinus rhythm.

However, in patients with recurrence of AF after prior successful PV isolation, the features of the atrial substrate become more complex. Lo et al discovered a progressive remodeling of the atrial substrate with a decreasing left atrial voltage in patients with recurrence of PV-AF.<sup>33</sup> In addition, increasing LVZ areas were also demonstrated. Mesas et al observed lower voltages over the left atrial posterior wall and mitral isthmus during recurrent AF.<sup>34</sup> Whether progressive atrial remodeling is the cause or consequence during the recurrence of AF remains obscure, and further investigation is needed.

#### *Reversibility of the atrial structure after the therapy for AF*

There are conflicting results regarding the reversibility of the atrial structure. No reverse remodeling of atrial structure was observed 2 weeks after cardioversion of AF in dogs in the study by Everett et al.<sup>35</sup> Ausma et al studied goats with restoration to sinus rhythm up to 4 months.<sup>36</sup> However, the structural abnormalities were still present 4 months post-AF, although to a lesser extent. The number of myocytes with severe myolysis had normalized 4 months post-AF, whereas myocytes with mild myolysis were still significantly increased. Therefore, the topic of structural changes after recurrent AF becomes more intricate.

Several studies have shown decreases in left atrial volume (–8% to –15%), left atrial appendage orifice area (–12.5%) and PV ostial area (–10%) 6–21 months after successful ablation of AF.<sup>37–40</sup> However, the structural changes in patients during recurrence exhibited

controversial results in different studies. Reant et al reported that the left atrial area decreased by 5–7% during the recurrence of AF (11 months after the first ablation procedure).<sup>41</sup> On the contrary, Tsao et al<sup>38</sup> demonstrated a 28% increase in the left atrial volume, and Chang et al<sup>40</sup> showed a 14% increase in the left atrial appendage orifice area during recurrence (21 months after the first ablation procedure). Lemola et al<sup>37</sup> and Beukema et al<sup>42</sup> did not observe any left atrial structural changes during recurrence (4–6 months after the first ablation procedure). A summary is shown in Table 1. The structural remodeling was not consistent with the progressive electrical remodeling in patients with recurrent AF. Since structural remodeling is a slower process than electrical remodeling, it may be the cause of the lack of an immediate response following AF recurrence. The timing of the left atrial image sampling and effect of atrial scarring after catheter ablation may also have an important effect on the inconsistent results of structural remodeling. These issues need to be clarified in future studies.

### Future Perspectives

From experimental and clinical studies, it appears that electrical and structural remodeling play important roles in the genesis and maintenance of AF. Understanding the mechanisms and processes of electrical and structural remodeling during AF will make the treatment of AF more efficient. Electrical remodeling develops more rapidly and reverses the process within a short time (3–5 days) after the restoration of sinus rhythm. Structural remodeling acts as a second factor of the perpetuation of AF and alters the substrate in a much slower process. The reversibility of the structural changes also takes at least several months, and may be just partially reversible. During AF recurrence after catheter ablation, the atrial substrate is more complex. The progressive reduction in the left atrial voltage with discordant changes in the left atrial size points out the perplexity of the atrial substrate in patients with recurrent AF. Therefore, more research is encouraged to specify this subject.

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