Atrial Fibrillation: New Horizons

Chi-Tai Kuo, MD; Nazar Luqman1, MD; Kuo-Hung Lin, MD; Ying-Shiung Lee, MD

Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice. The understanding of the pathophysiology of AF has changed drastically during the last several decades. Recent observations have challenged the concept of the multiple circuit reentry model in favor of single focus or single circuit reentry models. Atrial electrical dysfunction provides a favorable substrate and transmembrane ionic currents are key determinants. Interest has also been generated in the role of angiotensin converting enzyme (ACE) inhibition in reversing the electrical and structural remodeling. Reverting to the sinus rhythm seems to be the best way for reverse remodeling of atria during atrial fibrillation. Antiarrhythmic drugs (AADs) are only modestly effective. Of these amiodarone seems to provide the most benefits. Drugs like verapamil and ACE inhibitors may also help as adjuvant therapies in the reverse remodeling of atria. Nonpharmacological methods have been used to control both rate and rhythm for patients with AF. Recently, there has been a surge in interest to focal ablation of atrial foci. Focal sources of AF are commonly found in pulmonary veins (PV). Ablation in pulmonary veins through identification of the earliest endocardial activation has met with variable success. Anatomical approaches have involved circumferential radiofrequency ablation of pulmonary vein ostia using novel techniques such as balloon based circumferential ultrasound ablation system and circular cryoablation catheter. Most recently the segmental approach is preferred because the myocardial fibers surrounding the PV are not continuous. Segments where musculature is present can be identified using high frequency depolarization signals recorded through multi-electrode loop catheter or even conventional catheters. (Chang Gung Med J 2003;26:712-21)

Key words: atrial fibrillation, atrial remodeling, radiofrequency ablation, pulmonary vein.

Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice. The lifetime risk of developing AF is one in four for men and one in five for women. The incidence increases with age, as does the occurrence of stroke attributed to AF. The presence of AF doubles all causes of mortality including cardiovascular mortality. The widespread occurrence and substantial morbidity and mortality rates have led many clinicians to search for methods of earlier detection and better control of AF.

PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

The understanding of the pathophysiology of AF has changed drastically during the last several decades. From the sole or multiple-circuit reentry mechanisms of the early 1950s, we have moved on to complex mechanisms and competing concepts. Previously the accepted models for AF were (Fig. 1): (1) atrial ectopic foci with rapid and spontaneous discharge; (2) single reentry circuit; (3) multiple func-
Fig. 1 Electrophysiological mechanisms of atrial fibrillation.

For the first two models, the irregularity results from interactions between high frequency wave fronts produced by a primary generator (trigger) and spatially variable refractory properties of the atrial tissue (substrate). In the multiple-circuit reentry model, the irregular atrial activity is a consequence of the primary arrhythmia mechanism. It is best described as changes in the "wavelength of reentry." In the leading circle model, the number of reexcitation waves is a simple function of the atrial size and the wavelength: decreased wavelength decreases the minimum circuit size, which increases the number of circuits that can be accommodated, which in turn favors multiple circuit reentry and tends to perpetuate AF. A new "spiral wave" theory has been proposed to explain the cardiac reentry. According to this new theory, the spiral wave perpetuates if there is sufficient excitability to support the angle of the spiral curvature. Recent work has shown that the Na⁺ blockade may terminate AF by reducing excitability and hence killing the spiral wave. This can account for the action of class I anti-arrhythmic drugs in patients with AF.

Recent observations have challenged the concept of a multiple circuit reentry model in favor of a single focus or single circuit reentry model. In experimental studies, mapping in AF points towards a primary local generator as an ectopic focus or a single small reentry circuit. The left atrial source was predominant. This may be due to the pulmonary veins musculature and/or due to ionic differences that lead to shorter refractory periods that favors reentry. There is evidence that single circuit reentry maintains AF in patients with congestive heart failure (CHF). These act as triggers and develop into AF if the substrate is ripe.

ATRIAL REMODELING IN ATRIAL FIBRILLATION

Growing clinical evidence shows that AF almost invariably occurs in a setting of atrial electrical dysfunction that provides a favorable substrate for the
arrhythmia. Rapid atrial pacing and AF leads to alteration of the atrial architecture; uneven distribution of the stretch on atrial myocytes; activation of the stretch receptors and channels, and even apoptosis that leads to irreversible damage. The electrophysiological consequences of atrial remodeling include shortening of effective refractory period (ERP), decreased rate adaptation, increased dispersion of the atrial ERP, and increased rate of atrial fibrillation. In CHF, however, conduction abnormalities and heterogeneity are important components of atrial remodeling.

**Molecular and genetic basis of remodeling**

The understanding of molecular and genetic basis for atrial fibrillation has greatly enhanced the potential to develop new therapeutic strategies. Transmembrane ionic currents at the level of ion channels are key determinants. Importantly the Ica L. that maintains a positive plateau voltage and sustains AP duration decreases within 24 hours of rapid atrial pacing and in patients with long standing AF. The outward currents Ik1 and Ikash increase in myocytes from human fibrillating hearts. Ik1 and Ikur are under strong adrenergic control and their stimulation might contribute to AF in those situations. Kv 1.5 channels are expressed functionally in human atrium but not in the ventricle which carries Ikur. Therefore, inhibiting these channels may provide a means of preventing AF without the risk of proarrhythmia.

Another important contributor to atrial remodeling, as a consequence of AF or rapid atrial pacing is the accumulation of Ca²⁺ which enters the cells through L. with each action potential. Progressive Ca²⁺ loading threatens cell viability and the cells response to minimize the impact of rate increase adaptations. Through messenger RNA encoding, the pore forming L. alpha-subunits are decreased resulting in reduced calcium channels and reduced Ca²⁺ intake. This in turn reduces the action potential duration, reduces the refractory period and promotes the induction and maintenance of AF by multiple circuit reentry. Similar ionic changes can occur in response to a variety of stresses and contribute to the milieu favoring atrial fibrillation. Hypoxia, ischemia and stretch effects may be responsible for these changes. Decreased metabolic reserve could be responsible in age related preponderance of AF. Atrial fibrillation also leads to changes in K⁺ currents but their precise role is not yet clear. Changes in connexin channel proteins that govern intercellular electrical communication have been shown but the results are inconsistent.

**Atrial remodeling in heart failure**

Unlike atrial tachycardia induced remodeling, CHF induced remodeling is different. The inward Ica is reduced only half as much as seen in atrial tachycardia remodeling. Outward Ik1 is decreased and inward sodium calcium exchange is increased. Thus, there is no reduction of action potential duration. Changes in architecture of atrial tissue leading to increased fibrosis and interference with the conduction properties is the hallmark of changes in CHF and the AF often seems to be due to single circuit reentry.

**Role of angiotensin converting enzyme in atrial fibrillation**

In patients with heart failure, ischemic heart disease, cardiomyopathy, and hypertensive heart disease where atrial angiotensin II is increased, the resulting patchy fibrosis and heterogeneity of conduction may facilitate persistence of AF after it has been triggered. Recently, interest has been generated in the role of angiotensin-converting enzyme (ACE) inhibition in reversing the electrical and structural remodeling that occurs due to increases in atrial angiotensin II in patients with conditions like heart failure, ischemic heart disease, and hypertension. In patients with AF, there is up-regulation of extracellular signal related kinase (ERK) and ACE. In experimental studies of CHF, increased atrial ACE and ERK preceded the promotion of AF. Inhibition of ACE reduced these changes. Enalapril was found in experimental animals to reduce the fibrosis and conduction abnormalities that are conducive to the perpetuation of AF.

**Genetic factors in atrial fibrillation**

Atrial fibrillation can occur in families, which suggests a genetic component. Linkage analyses have identified possible loci on chromosomes. This has the potential to provide better insight into the pathophysiology of AF and early identification of susceptible individuals. Attempts to develop transgenic mice have been partially successful and are
compatible with the notion that atrial fibrosis is an important AF promoting factor.\(^{(23)}\)

**SUCCESS IN AF MANAGEMENT**

Reverting to sinus rhythm seems to be the best way for reverse remodeling of the atria in atrial fibrillation. The earlier the procedure is performed, the better the outcome is. Studies have shown that the success rate of electrical cardioversion depends upon the duration of AF. The longer the AF duration, the higher the chance of recurrence.\(^{(24,25)}\) Results of AFFIRM trials that showed rate control was as good as rhythm control may hold true only for a select group of patients.\(^{(26,27)}\) In a large number of patients, rhythm control may still be the first option.

**Pharmacotherapy**

Most antiarrhythmic drugs (AADs) are only modestly effective in preventing or delaying the recurrence of AF, and the major use for drugs in many patients is simply the control of ventricular rate. Variable success in pharmacological cardioversion has been reported using Class IA (50%, quinidine, procainamide, disopyramide), Class IC (50-70%, flecainide, propafenone), and Class III (30-50%, sotalol, amiodarone, dofutilide, ibutilide) drugs. This success is, however, at a risk of 1 to 5% for torsades de pointes and there are various other side effects of these drugs. Maintenance of the sinus rhythm is poor using pharmacotherapy alone, which is as low as 25% at the end of the first year. It is interesting to note that even on placebo, 37% of patients with recent onset AF of <8 hours converted to sinus rhythm.\(^{(28,29)}\) Of the available antiarrhythmic drugs for control of AF, amiodarone has been shown to have the most benefits. In a recent trial the efficacy of amiodarone compared to sotalol or propafenone was significantly better. The recurrence rate of AF was only 35% in the amiodarone group compared with 63% in the sotalol or propafenone group after 16 months of treatment.\(^{(30)}\)

**Reverse remodeling of atria**

Drugs may also help as adjuvant therapy in reverse remodeling of atria. Verapamil significantly reduced the atrial ERP, the dispersion and maladaptation, and the inducibility of AF in dogs when the AF induction was not more than 24 hours.\(^{(31)}\) There was no effect on AF of more than 24 hours. In the clinical setting, however, verapamil had no significant effect on conversion of AF or the maintenance of sinus rhythm.\(^{(32)}\) Recently, interest has been generated in the role of ACE inhibition in reversing the electrical and structural remodeling that occurs due to increase in atrial angiotensin II in conditions like heart failure, ischemic heart disease, and hypertension. In experimental animals, enalapril was found to reduce the fibrosis and conduction abnormalities that are conducive to perpetuation of AF.\(^{(13,20)}\) ACE inhibitors also reduced the incidence of AF after myocardial infarction in people with left ventricular dysfunction.

**NONPHARMACOLOGICAL MANAGEMENT**

Nonpharmacological methods of management for AF have met with variable success rate because of limitations in patient selection. These have been used to control both rate and rhythm (Table 1). Recently, however, there has been a surge in interest in focal ablation of atrial foci i.e., the trigger. Therefore, this deserves discussion.

**Table 1.** Nonpharmacological Approaches to Atrial Fibrillation\(^{(43)}\)

<table>
<thead>
<tr>
<th>Method</th>
<th>Success</th>
<th>Recurrence</th>
<th>Complications</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial defibrillators</td>
<td>80%</td>
<td>-</td>
<td>minimal</td>
<td>pain with defibrillation</td>
</tr>
<tr>
<td>Focal ablation</td>
<td>50-80%</td>
<td>high</td>
<td>moderate</td>
<td>only in PAF</td>
</tr>
<tr>
<td>Atrial pacing</td>
<td>high</td>
<td>-</td>
<td>minimal</td>
<td>only SSS, vagotonic AF</td>
</tr>
<tr>
<td>Surgical Maze</td>
<td>75-90%</td>
<td>Low</td>
<td>surgical</td>
<td>with other cardiac surgery</td>
</tr>
<tr>
<td>Catheter linear ablation</td>
<td>variable</td>
<td>variable</td>
<td>moderate</td>
<td>technical, proarrhythmias</td>
</tr>
<tr>
<td>AVJ ablation</td>
<td>&gt;95%</td>
<td>low</td>
<td>low</td>
<td>pacemaker, anticoagulation</td>
</tr>
<tr>
<td>AVJ modification</td>
<td>60-85%</td>
<td>high</td>
<td>high</td>
<td>pacemaker 21%</td>
</tr>
</tbody>
</table>

**Abbreviations:** AVJ: atrioventricular junction; PAF: paroxysmal atrial fibrillation.
New insights into focal ablation

Cheung, in 1981 first showed that cardiac tissue in the sleeves around the proximal ends of the pulmonary veins generated action potential with slow spontaneous activity. Interest in focal ablation of AF has been contemplated for quite some time. However, real interest was generated only when Haissaguerre et al. demonstrated spontaneous initiation of atrial fibrillation using ectopic beat from pulmonary vein. More recently pulmonary vein activity has been shown to promote atrial remodeling and also has a role in maintaining AF. Whether pulmonary veins provide preferential zones of reentry is not clear. However, they are subjected to stretch from pulsatile blood flow that may favor ectopic activity. AF may result from rapid firing of a single focus or multiple foci. Circular movement or reentry may also occur depending upon the underlying substrate.

Focal sources of AF may be found in the right atrium, left atrium, coronary sinus, superior vena cava, vein of Marshall, or in the majority of cases (95%) within the pulmonary veins. Myocardial sleeves cover the pulmonary veins and vary from 2 to 25 mm in length and their presence can be verified by pacing from distal coronary sinus electrogram (CS) (Fig. 2). Superior pulmonary veins are covered with longer sleeves than the inferior veins. This fact explains the higher incidence of the arrhythmogenic foci from those veins. Shown here is an example of paroxysmal atrial fibrillation with the initiator at the right middle pulmonary vein. The earliest bipolar activity of ectopic beats was noted at the ablation site in eliminating all atrial premature beats. Atrial tachycardia and atrial fibrillation were no longer initiated. SVC: superior vena cava; S: spiral electrode placed at the orifice of right upper pulmonary vein; ABL: ablating catheter placed at 0.5 cm inside right middle pulmonary vein at the inferior floor; HIS: His bundle electrogram; CS: coronary sinus electrogram.

Fig. 2  Shown here is an example of paroxysmal atrial fibrillation with the initiator at right middle pulmonary vein. Spontaneous onset of ectopic beat with the earliest bipolar activity (ABL 1, 2; arrow) is noted at the right middle pulmonary vein. The pulmonary vein potential is marked by the rapid deflection preceding the other potentials. RF energy application was successful at this site in eliminating all atrial premature beats. Atrial tachycardia and atrial fibrillation were no longer initiated. SVC: superior vena cava; S: spiral electrode placed at the orifice of right upper pulmonary vein; ABL: ablating catheter placed at 0.5 cm inside right middle pulmonary vein at the inferior floor; HIS: His bundle electrogram; CS: coronary sinus electrogram.
catheter (Fig. 2). Radio frequency (RF) energy application was successful at this spot in eliminating atrial premature beats, atrial tachycardia and atrial fibrillation. Similarly atrial myocardial extension for 2 to 5 cm over the superior vena cava (SVC) has also been demonstrated using histology as well as electrophysiology. 

Focal approach

In order to eliminate foci from pulmonary veins (PV), Haissaguerre et al. introduced a focal approach in 1998. Earliest endocardial activation of premature atrial beats was mapped in pulmonary veins and ablated. This met with variable long-term success (60 to 86%) and the incidence of pulmonary artery stenosis was as high as 42%. The modest success rate and high recurrence rate may be related to (1) patient selection (2) patients had multiple foci (3) new foci emerged after ablation (4) spontaneous or inducible arrhythmia not occurring during the procedure or (5) the limited amount of energy applied in order to avoid pulmonary vein stenosis.

Anatomic approach

Ernst et alconstated that the electroanatomically-guided creation of extended radiofrequency current lesions was technically feasible only in the right atrium. In addition, procedural success in the right atrium did not suppress recurrence of idiopathic AF in the majority of patients. However, Pappone et al. introduced a new anatomic approach of circumferential radiofrequency ablation of the pulmonary vein ostia in 2000 using 3D electroanatomic LA maps. The technique involved the delivery of multiple contiguous RF applications in a circumferential fashion around the ostia of PV. The success rate was 85% at 9 months without pulmonary vein stenosis or thromboembolic complication. In the same year, Natale et al. described their first human experience with a balloon based circumferential ultrasound ablation system. Out of 15 patients, only two remained in AF at 35 weeks. There was no PV stenosis. Natale et al. used a balloon with circumferential ultrasound energy. Novel techniques for ablation are still being studied.

<table>
<thead>
<tr>
<th>Table 2. Focal Ablation inside Pulmonary Vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation characteristics</td>
</tr>
<tr>
<td>Haissaguerre, NEJM 1998</td>
</tr>
<tr>
<td>Chen, Circulation 1999</td>
</tr>
<tr>
<td>Haissaguerre, Circulation 2000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Circumferential Ablation of Pulmonary Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation characteristics</td>
</tr>
<tr>
<td>Natale, Circulation 2000</td>
</tr>
<tr>
<td>Pappone, Circulation 2000</td>
</tr>
<tr>
<td>Pappone, Circulation 2001</td>
</tr>
</tbody>
</table>

Abbreviations: W: wolts; TIA: transient ischemia attack; PV: pulmonary vein; RF: radiofrequency.

Abbreviations: AAD: antiarrhythmic drugs; PAF: paroxysmal atrial fibrillation.
developed. One such technique is circular cryoablation catheter that will reduce the chances of PV stenosis and it is also possible to deliver reverse cryolesions if the lesion is not successful.\textsuperscript{40}

\textbf{Segmental Approach}

The myocardial fibers surrounding the PV are not continuous hence there is no need to ablate the whole circumference of the PV. Segments where musculature is present can be identified using high frequency depolarization signals recorded through multi-electrode loop catheter or even conventional catheters. Once identified, these can be ablated. Usually as little as 25% of the PV circumference has such fibers and 1 to 5 applications of RF energy isolate the PV completely (Fig. 3).\textsuperscript{41} Thus, the potential arrhythmogenic veins can be identified and isolated. Even if there is no ectopy, empirical segmental isolation of the left and right superior and the left inferior PVs can be performed because these are the most common sources of arrhythmias that trigger AF.

\textbf{Conclusion}

The use of currently available anti arrhythmic drugs (AADs) to treat AF is likely to decline over the next few years specially due to proarrhythmic actions, lack of adequate arrhythmia control and due to life long use of the drug leading to issues of compliance. If improved AADs are not discovered, AF therapy might be limited to rate control and anticoagulation, limited use of amiodarone, ablation strategy and the implantable atrial defibrillator. Given the significant down-regulation of Ikur and Ica in remodeling atria, development of atrium specific drugs that upregulate or open these channels may be

<table>
<thead>
<tr>
<th>Basis for Segmental Ablation of PV \textsuperscript{40}</th>
<th>RSPV</th>
<th>LSPV</th>
<th>LIPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Musculature around PV at 10 mm from ostia</td>
<td>64+/−22</td>
<td>67+/−20</td>
<td>25+/−28</td>
</tr>
<tr>
<td>Number of segments required for ablation (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 segment</td>
<td>24</td>
<td>21</td>
<td>55</td>
</tr>
<tr>
<td>2 &amp; more</td>
<td>37</td>
<td>42</td>
<td>26</td>
</tr>
</tbody>
</table>

\textbf{Fig. 3} Anatomical and electrophysiological basis for pulmonary vein isolation.

\textbf{Ectopic Foci from PV}

103 out of 116 ectopic foci originated in Pulmonary veins.

- RSPV: 46.6%
- LSPV: 53.4%

Only few cases from inferior pulmonary veins and other areas of RA & LA
appropriate. Ikur blockade, if feasible, may be an intriguing approach because it may allow for maintenance of sinus rhythm without affecting ventricular property, thus preventing TdP. Trigger elimination through pulmonary vein isolation seems to cure focal AF in selected patients. Recent developments have opened a new horizon in this direction. Cure of atrial fibrillation has, however become a realistic goal albeit in limited number of patients and will remain a challenge for years to come.

REFERENCES

27. Van Gelder IC, Hagens VE, Bosker HA, Kigma JH,


心房颤動：新的視域
郭啓泰  Nazar Luqman¹ 林園宏 李英雄

心房顫動是臨床上最常見的心律不整。近年來對於心房顫動致病機轉的了解已有重大的改變，以往所認為的多重迴路模型機轉，已受近年來觀察提出的單一病源或單一迴路的模型機轉所挑戰。心房電位的異常造成心房顫動的誘因，而膜電位電位則為其中關鍵。而angiotensin converting enzyme inhibitor (ACEI) 轉化酶抑制劑在回復心房電位及結構變化所扮演的角色也引起大家的興趣。

將心房顫動恢復或正常異性心律似乎是回復「心房重塑」atrial remodeling 最好的方式。抗心律不整藥物的效果不盡理想，而其中amiodarone似乎是最有效的，其他的藥物如verapamil及轉化酶抑制劑 (ACEI) 對於回復心房的變化可能也有幫助。

也可以使用非藥物的方式控制心房顫動的心跳速率或者恢復正常異性心律。最近，以局部電燒的方式治療引起高度的興趣。肺靜脈是導致心房顫動常見的來源，因此在肺靜脈找出心內膜最早活化點進行電燒治療已得到不等程度的成功。另外一種電燒方式是利用特別的環狀超音波系統以及冷凝電燒方式，在肺靜脈的閉口做環狀電燒。最近研究的結果比較傾向支持前者做局部電燒，因為回繞肺靜脈的心肌纖維並非連續的，我們可以利用電生理導管辨認心肌纖維高頻電後極化的訊號，判斷心肌組織的分佈，再做片狀的電燒治療。(長庚醫誌2003;26:712-21)

關鍵字：心房顫動，心房重塑，高頻電燒治療，肺靜脈。