Atrial Fibrillation: New Horizons

Chi-Tai Kuo, MD; Nazar Luqman[1], 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.(1) 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.(1) 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-

This article has been presented in part at the 2nd National Medical Convention, Brunei Darussalam on 20th-22nd September 2002.

From the Division of Cardiology, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan; [1]Dr. Nazar Luqman was a visiting cardiologist from RIPAS Hospital, Bander Seri Begawan, Brunei Darussalam.

Received: May 21, 2003; Accepted: Jul. 3, 2003

Address for correspondence: Dr. Chi-Tai Kuo, Division of Cardiology, Chang Gung Memorial Hospital. 5, Fu-Shin Street, Kweishan, Taoyuan, Taiwan 333. Tel.: 886-3-3281200 ext. 8162; Fax: 886-3-3271192; E-mail: chitai@adm.cgmh.org.tw

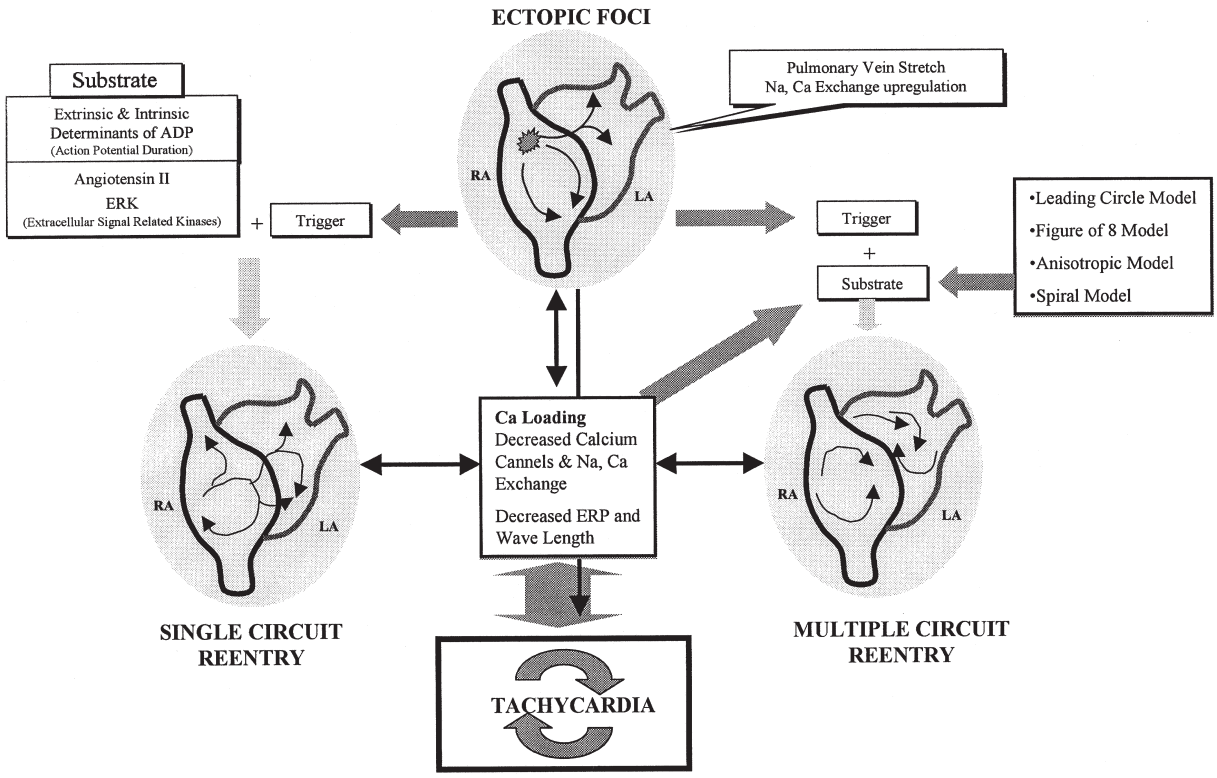


Fig. 1 Electrophysiological mechanisms of atrial fibrillation.

tional reentrant circuits.

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.[2,3] 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.[4] 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.[5] 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.[6,7] There is evidence that single circuit reentry maintains AF in patients with congestive heart failure (CHF).[8,9] 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.[10] 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".[11] In CHF, however, conduction abnormalities and heterogeneity are important components of atrial remodeling.[12,13]

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 Ik_{ach} increase in myocytes from human fibrillating hearts.[14,15] Iks and Ikur are under strong adrenergic control[16] 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 Ca^{2+} which enters the cells through I_{ca} with each action potential.[2] Progressive Ca^{2+} loading threatens cell viability and the cells response to minimize the impact of rate increase adaptations. Through messenger RNA encoding, the pore forming I_{ca} alpha-subunits are decreased resulting in reduced calcium channels and reduced Ca^{2+} 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.[3] 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.[17]

Atrial remodeling in heart failure

Unlike atrial tachycardia induced remodeling, CHF induced remodeling is different. The inward I_{ca} is reduced only half as much as seen in atrial tachycardia remodeling. Outward Iks is decreased and inward sodium calcium exchange is increased. Thus, there is no reduction of action potential duration.[18] 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.[19]

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.[12,13] 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.[13,20]

Genetic factors in atrial fibrillation

Atrial fibrillation can occur in families, which suggests a genetic component.[21] Linkage analyses have identified possible loci on chromosomes.[10,22] 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]

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

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.[33] 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.[34] More recently pulmonary vein activity has been shown to promote atrial remodeling and also has a role in maintaining AF.[35] 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.[2]

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.[2,34-36] 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

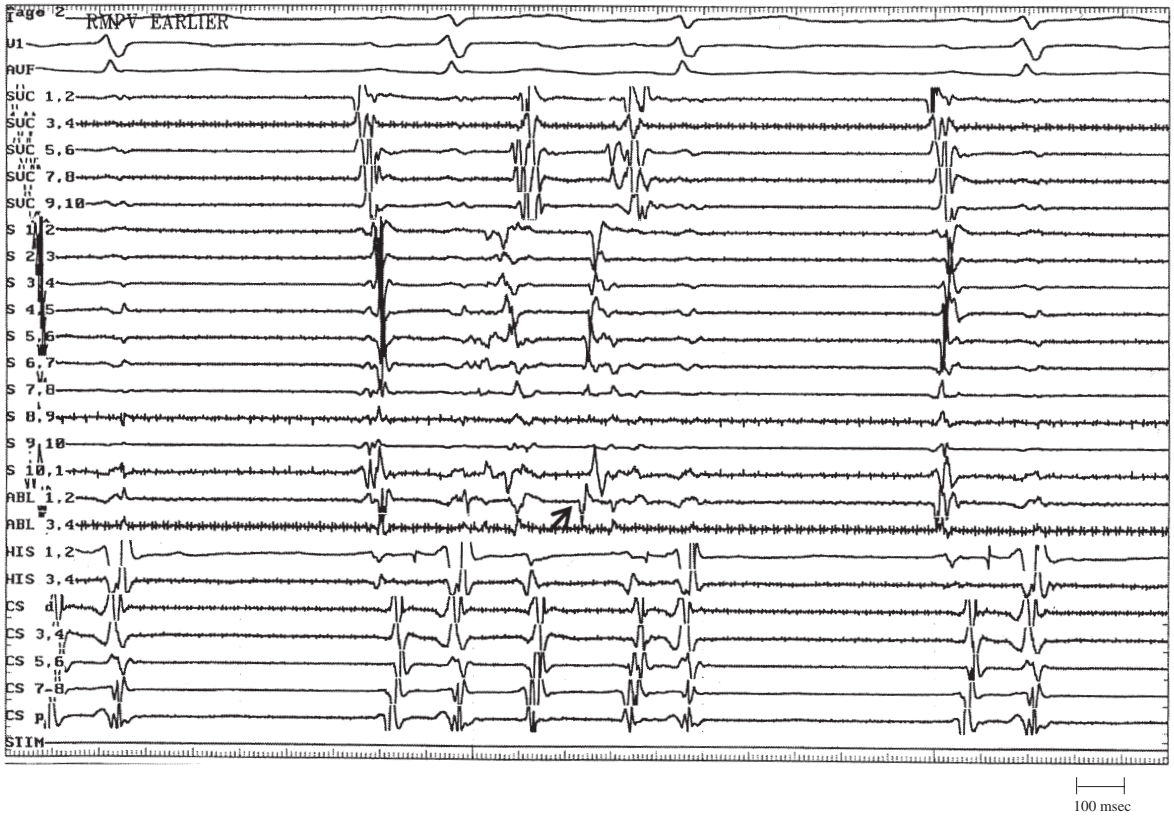


Fig. 2 Shown here is an example of paroxysmal atrial fibrillation with the initiator at right middle pulmonary vein. Spontaneous onset of ectopic beat with the earliest bipolar activity (ABL 1, 2; arrow) is noted at the right middle pulmonary vein. The pulmonary vein potential is marked by the rapid 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.

Table 2. Focal Ablation inside Pulmonary Vein [34,41,44]

	Ablation characteristics	No. of pts and foci	Results	Complications
Haissaguere, NEJM 1998 [34]	50 degree C, 30-60 seconds, 25-30W	41 pts, 65 foci	62% success (8m), 75% need a 2nd or 3rd session	pericardial effusion ≥ 4%, TIA ≤ 2%, PV stenosis ≤ 2%
Chen, Circulation 1999 [41]	60 degree C, 20-40 seconds	79 pts, 103 foci,	86% success (6±2m), 75% success (8m), 7% need 2nd session	42% focal PV stenosis
Haissaguere, Circulation 2000 [44]	50 degree C, 25-50W	90 pts, 197 foci,	71% success (8±5m), 93%, 73%, 55% success for 1, 2, ≥ 3 foci	6% PV stenosis (esp. with RF power > 45W)

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

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.[36]

Focal approach

In order to eliminate foci from pulmonary veins (PV), Haissaguerre et al. introduced a focal approach in 1998[34](Table 2). 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%.[25,35] The modest success rate and high recurrence rate may be related to the (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 al.[37] demonstrated 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.[38] introduced a new anatomic approach of circumferential radiofrequency ablation of the pulmonary vein ostia in 2000 using 3D electroanatomic LA maps (Table 3). 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± 6 weeks. There was no PV stenosis. Natale et al. used a balloon with circumferential ultrasound energy.[39] Novel techniques for ablation are still being

Table 3. Circumferential Ablation of Pulmonary Veins [38,39,42]

	Ablation characteristics	No. of pts and foci	Results	Complications
Natale, Circulation 2000 [39]	ultrasound ablation >55 C, 2 minutes	15 pts 12 foci 4(1-29) lesions	67% success (35±6 weeks)	embolic stroke phrenic nerve partial paralysis coronary spasm
Pappone, Circulation 2000 [38]	"CARTO" 3D LA map 60 degree C, 50 W procedure time 290±58 min.	26 pts (14 PAF) 118±16RFAND pulses	62% success (23% on AADs) 9±3months	1 hemopericardium, 2 mild pericardial effusion
Pappone, Circulation 2001 [42]	60 degree C 15-30 seconds procedure time 148±26 min.	251 pts (PAF 179), 980 lesions	85% success (PAF), 68% (permanent AF) 10.1±4.5 months	cardiac tamponade 0.8%

Abbreviations: AAD: antiarrhythmic drugs; PAF: paroxysmal atrial fibrillation.

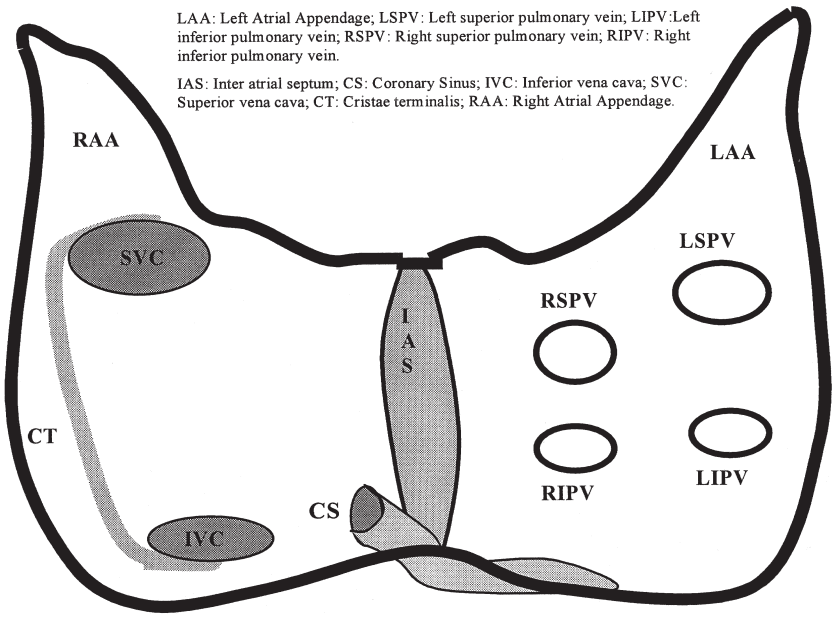
developed. One such technique is circular cryoablation catheter that will reduce the chances of PV stenosis and it is also possible to deliver reverse cryolesions if the lesion is not successful.[40]

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).[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.

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



Ectopic Foci from PV

103 out of 116 ecopic foci originated in Pulmonary veins.

RSPV: 46.6%

LSPV: 53.4%

Only few cases from inferior pulmonary veins and other areas of RA & LA [25]

Basis for Segmental Ablation of PV [40]	RSPV	LSPV	LIPV
% Musculature around PV at 10 mm from ostia	64+/-22	67+/-20	25+/-28
Number of segments required for ablation (%)			
1 segment	24	21	55
2 & more	37	42	26

Fig. 3 Anatomical and electrophysiological basis for pulmonary vein isolation.

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

1. Wang TJ, Larson M., Lloyd-Jones DM, Leip EP, Levy D, Vasan RS. The lifetime risk of atrial fibrillation: the Framingham Study. Circulation 2002;106(II):456.
2. Allessie MA, Bonke FIM, Schopman FJG. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 1977;41:9-18.
3. Rensma PL, Allessie MA, Lammers WJ, Bonke FI, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res 1988;62:395-410.
4. Garrey WE. Auricular fibrillation. Physiol Rev 1924;4: 215-50.
5. Cox JL, Ad N. New surgical and catheter based modifications of the Maze procedure. Semin Thorac Cardiovasc Surg 2000;12:68-73.
6. Fenelon G, Wijns W, Andries E, Brugada P. Tachycardiomyopathy: mechanisms and clinical implications. PACE 1996;19:95-106.
7. Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. Stroke 2001;32:803-8.
8. Nattel S. Experimental evidence for proarrhythmic mechanisms of antiarrhythmic drugs. Cardiovasc Res 1998;37: 567-77.
9. Nattel S. Newer developments in the management of atrial fibrillation. Am Heart J 1995; 130:1094-106.
10. Aime-Sempe C, FolliguetbT, Rucker-Martin C, Krajewska M, Krajewski S, Heimburger M, Aubier M, Reed JC, Mercadier JJ, Hatem SN. Myocardial cell death in fibrillating and dilated human atria. J Am Coll Cardiology 1999;34:1577-86.
11. Gray RA, Pertsov AM, Jalife J. Spatial and temporal organization during cardiac fibrillation. Nature 1998; 392:75-8.
12. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs. Atrial remodeling of a different sort. Circulation 1999;100:87-95.
13. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, Nattel S. 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.
14. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res 1997;81:512-25.
15. Bosh RF, Zeng X, Grammar JB, Popovic K, Mewis C, Kuhlamp V. Ionic mechanisms of electrical remodeling in human atrial fibrillation. Cardiovasc Res 1999;44:121-31.
16. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. Am Heart J 1964;67:200-20.
17. Mandapati R, Skanes AC, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. Circulation 2000; 101:194-9.
18. Mansour M, Mandapati R, Berenfeld O, Chen J, Samie FH, Jalife J. Left-to-right gradient of atrial frequencies during acute atrial fibrillation in the isolated sheep heart. Circulation 2001;103:2631-6.
19. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995;91:1588-95.
20. Madrid AH, Bueno MG, Rebollo JMG, Marin I, Pena G, Bernal E, Rodriguez A, Cano L, Cano JM, Cabeza P, Moro C. 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.
21. Brugada R, Tapscott T, Czernuszewicz GZ, Marian AJ, Mont L, Brugada J, Iglesias A, Girona J, Domingo A, Bachinski L, Robert R. Identification of a genetic locus for familial atrial fibrillation. N Engl J Med 1997;336: 905-11.
22. Li D, Zhang L, Kneller J, Nattel S. Ionic mechanism of repolarization differences between canine right and left atrium. Circ Res 2001;88:1168-75.
23. Derakhchan K, Li D, Courtemanche M, Smith B, Brouillette J, Page PL, Nattel S. Method for simultaneous epicardial and endocardial mapping of the in vivo canine heart: application to atrial conduction properties and arrhythmia mechanisms. J Cardiovasc Electrophysiol 2001;12:548-55.
24. Wijffels MCEF, Kirchhof CJHJ, Dolland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. Circulation 1995;92:1954-68.
25. Hobbs WJC, Fynn S, Todd MB, Wolfsons P, Galloway M, Garratt CJ. Reversal of atrial electrical modeling after cardioversion of persistent atrial fibrillation in humans. Circulation 2000;101:1145-51.
26. The Atrial Fibrillation Follow-up Investigation (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
27. Van Gelder IC, Hagens VE, Bosker HA, Kigma JH,

Kamp O, Kigma T, Said SA, Darmanata JI, Tieleman AJM, Tijssen JGP, Crijns HJGM. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. Engl J Med 2002;347:1834-40.
28. Nattel S, Wang Z, Pelletier LC, Carrier M, Meere C, Cartier R. Termination of atrial fibrillation with drugs. Atrial and Ventricular Fibrillation: Mechanisms and Device Therapy, 1997. Futura Publishing Co, NY: 199-213.
29. Nattel S, Hadjis T, Talajik M. The treatment of atrial fibrillation: an evaluation of drug therapy, electrical modalities and therapeutic considerations. Drugs 1994;48:345-71.
30. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagn P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. N Engl J Med 2000;342:913-20.
31. Lee SH, Yue WC, Cheng JJ, Hung CR, Ding YA, Chang MS, Chen SA. Effect of Verapamil on long-term tachycardia-induced atrial electrical remodeling. Circulation 2000; 101:200-6.
32. Tieleman RG, DeLangen CDJ, Van Gelder IC, de Kam PJ, Grandjean J, Bel KJ, Wijffels MCEF, Allessie MA, Crijns HJGM. Verapamil reduced Tachycardia induced electrical remodeling of the atria. Circulation 1997;95: 1945-53.
33. Jais P, Haissaguerre M, Shah DC, Chouairi S, Hocini M, Clementy J. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 1997;95: 572-6.
34. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Mouroux AL, Metayer PL, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-66.
35. Shah DC, Haissaguerre M, Jais P. Catheter ablation of pulmonary vein foci for atrial fibrillation. Thorac Cardiovasc Surg 1999;47(Suppl):352-6.
36. Tsai CF, Tai CT, Hsieh MH, Lin WS, Yu WC, Ueng KC, Ding YA, Chang MS, Chen SA. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava. electrophysiological characteristics and results of radiofrequency ablation. Circulation 2000;102:67-74.
37. Ernst S, Schluter M, Ouyang F, Khanedani A, Cappato R, Hebe J, Volkmer M, Antz M, Kuck KH. Modification of the substrate for maintenance of idiopathic human atrial fibrillation: efficacy of radiofrequency ablation using Nonfluoroscopic catheter guidance. Circulation 1999; 100:2085-2092.
38. Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G, Salvati A, Dicandia C, Mazzone P, Santinelli V, Gulletta S, Chierchia S. Circumferential radiofrequency ablation of pulmonary vein ostia. Circulation 2000;102:2619-28.
39. Natale A, Pisano E, Shewchik J, Bash D, Fanelli R, Potenza D, Santarelli P, Schwei R, White R, Saliba W, Kanagaratnam L, Tchou P, Lesh M. First human experience with pulmonary vein isolation using a through-the-balloon circumferential ultrasound ablation system for recurrent atrial fibrillation. Circulation 2000;102:1879-82.
40. Skanes AC, Klein GJ, Krahn AD, Yee R. Initial experience with a novel circular cryoablation catheter for pulmonary vein isolation. Circulation 2002;106(SuppII): 633.
41. Haissaguerre M, Jais P., Shah DC, Garrigue S, Takahashi A, Lavergne T, Hocini M, Peng JT, Roudaut R, Clementy J. Electrophysiological endpoint for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation 2000;101:1409-17.
42. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, Salvati A, Dicandia C, Calabro MP, Mazzone P, Ficarra E, Gioia CD, Gulletta S, Nardi S, Santinelli V, Benussi S, Alfieri O. Atrial electroanatomical remodeling after circumferential radiofrequency pulmonary vein ablation. Efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. Circulation 2001;104:2539-44.
43. Scheinman MM, Morady F. Nonpharmacological approaches to atrial fibrillation. Circulation 2001;103: 2120-5.
44. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, Hsu SU, Ding AN, Chang MS. Initiation of Atrial Fibrillation by Ectopic Beats Originating From the Pulmonary Veins: Electrophysiological Characteristics, Pharmacological Responses, and Effects of Radiofrequency Ablation. Circulation 100:1879-86.

心房顫動：新的視域

郭啓泰 Nazar Luqman[1] 林圀宏 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，以往所認爲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。心房電位的異常是造成心房顫動的誘因，而膜離子電位則爲其中關鍵。而angiotensin converting enzyme inhibitor (ACEI) 轉化脢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。

將心房顫動恢復成正常竇性心律似乎是回復「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及轉化脢抑制劑 (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度或者恢復成正常竇性心律。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的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，在肺靜脈的開口做環狀電燒。最近研究的結果比較傾向支持前者做局部電燒，因爲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識心肌纖維高頻去極化的訊號，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。

長庚紀念醫院 台北院區 內科部 第一心臟內科；[1]Dr. Nazar Luqman客座心臟內科醫師 RIPAS Hospital, Bander Seri Begawan, 汶萊
受文日期：民國92年5月21日；接受刊載：民國92年7月3日。
索取抽印本處：郭啓泰醫師，長庚紀念醫院 內科部 第一心臟內科。桃園縣333龜山鄉復興街5號。Tel: (03)3281200 轉8162; Fax: (03)3271192; E-mail: chitai@adm.cgmh.org.tw