

Evolution of non-pharmacological curative therapy for atrial fibrillation Where do we stand today?

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Abstract

The present review aims at giving a comprehensive synthesis regarding not only the epidemiological aspects but also the evolution, over the last decades, of the curative surgical and catheter-based ablative treatments for atrial fibrillation (AF), with particular emphasis on the experience of Milan working group which has always been committed to the on-going and fascinating therapeutic challenges inherent in this type of cardiac arrhythmia.

After discussing the surgical treatment of AF we report the rationale basis of current pulmonary vein (PV) ablation techniques. In particular, we report on circumferential PV ablation, an intellectually appealing strategy, aimed at creation of RF lesions around each PV ostia using a non-fluoroscopic electro-geometric mapping system to reconstruct the anatomy of venous-atrial junction, allowing to tailor number and size of lesions to the complex morphology of the PV-LA junction in each patient. This purely anatomic approach not only disconnects PVs (as demonstrated by elimination of PV ostial potentials and absence of discrete electrical activity inside the lesion during pacing outside the ablation line), but also, like surgery, reduces the “electrically active” atrial tissue, involving substantial parts of the posterior LA wall, with a profound atrial electroanatomic remodeling, as expressed by voltage abatement (<0.1 mV) inside and around the encircled areas.

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1. Introduction

Over the last few years we have witnessed a rapid evolution such as never before in our views on the mechanism and treatment of atrial fibrillation (AF), which remains among the most vexing varieties of supraventricular arrhythmias that confront electrophysiologists. As a result of the extraordinary growth in all fields of knowledge regarding AF in the past decade, it is often difficult for the practising electrophysiologist to integrate in routine clinical practice new knowledge and a proposed investigational approach.

The present review aims at giving a personal and comprehensive synthesis regarding not only the epidemiological aspects but also the evolution, over the last decades, of the curative surgical and catheter-based ablative treatments for AF, with particular emphasis on the experience of my working group which has always been committed to the on-going and fascinating therapeutic challenges inherent in this type of cardiac arrhythmia.

2. Epidemiology

AF is the commonest sustained cardiac arrhythmia. According to a recent US study, AF affects 1 in 25

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adults, 60 years or older and nearly 1 in 10 adults, 80 years or older. Due to symptoms and the current risk of ischemic stroke in elderly patients, this type of arrhythmia is a source of considerable concern, and its impact is likely to be amplified as the number of individuals affected by AF increases nearly 2.5-fold over the next 50 years [1–3]. It is therefore easy to guess what the economic repercussions on national health systems around the world will be. In fact, AF patients require frequent clinical visits to modify medications and to monitor anticoagulation. This arrhythmia is also associated with an increased number of emergency room visits, hospitalization and numerous procedures [4]. Even when compared with patients matched for age and presence of cardiovascular disease, AF patients have medical costs that are ~\$2500 more per year [4]. Finally, AF is associated with a doubling of mortality in both sexes, which remains above 1.5-fold after adjustment for comorbidity [5]. Increased mortality is mainly due to cerebrovascular events, progressive ventricular dysfunction, and increased coronary mortality. One can therefore see how imperative it is to promote coordinated efforts on behalf of cardiologists, electrophysiologists, neurologists and primary-care providers in order to meet the increasing challenge of stroke prevention and rhythm management in the ever-growing AF population.

3. Drug therapy to maintain sinus rhythm

To date, most therapy has been directed at either preventing recurrences or controlling the symptoms of AF using antiarrhythmic drugs or electrical cardioversion. The latter has demonstrated a high success rate of as much as 86–94%, but only 23% of the patients remain in sinus rhythm after 1 year and 16% after 2 years: sinus rhythm can thus be restored in a substantial proportion of patients by direct current shock, but the rates of relapses are high [6–9]. Nevertheless, antiarrhythmics have approximately doubled the percentage of patients remaining in sinus rhythm up to 1 year after cardioversion, although causing a significant increase in annual mortality rates, from 3 to 7% [10,11]. Recently, amiodarone as compared to propafenone or sotalol has been shown to be effective in maintaining sinus rhythm in 50 to

80% of cases at 1–3 years after atrial fibrillation onset, but the rate of unwanted side effects is remarkable [9].

At present, however, it is still difficult to maintain a safe and successful sinus rhythm using current available drug therapy, despite the continuous introduction on the market of new agents having an increasingly selective mechanism. The relative ineffectiveness of pharmacologic approaches to AF, the risks of antiarrhythmic treatment particularly due to proarrhythmic effects and the growing recognition of deleterious AF health effects have contributed to the search for curative methods designed to fully restore sinus rhythm control over the atrium [12,13].

4. Surgical therapy for AF

In 1914, Garrey et al. first demonstrated that a ‘critical mass’ of atrial tissue was required to sustain fibrillation by showing that any atrial piece ceases fibrillating when cut small enough [14]. Moe’s studies, later confirmed by Allesie et al. and largely accepted at that time, showed the existence of multiple wavelets in AF [15,16]. The persistence of arrhythmia depended on the average number of wavelets present in the atria. This number in turn is determined both by atrial tissue mass and the wavelength of the atrial impulse. These electrophysiological concepts led to the development of surgical techniques designed to restore sinus rhythm in patients affected by AF.

The first such technique was termed the ‘corridor operation’: the atrial free walls were surgically isolated from the septum maintaining the connection between the sinus and the atrioventricular nodes via the remaining corridor [17]. Therefore, the atrial kick was lost and the cardiac hemodynamics were not restored to normal. Thus, the corridor procedure corrected only one of the detrimental sequelae associated to AF, i.e. the irregular ventricular rhythm similar to catheter ablation of His’ bundle and implantation of a permanent pacemaker. Subsequent surgical approaches were more specifically designed to eliminate AF. The objective of the atriotomies (the Maze, proposed by Cox et al., and its variants) was, in fact, to reduce the ‘critical mass’ and to modify the arrhythmogenic substrate by interrupting all possible

macroreentrant circuits responsible for AF with suture lines of conduction block placed sufficiently close to each other in a labyrinth pattern [18,19].

The surgical Maze procedure, initially attempted for lone AF, has been refined and is currently performed in association with mitral valve repair or coronary artery bypass, with a success rate of 74–90% at 2 to 3 years postoperatively. Regardless of the proposed modifications, surgical therapy for AF suffers from some considerable drawbacks. The chief disadvantage among these is that this procedure requires open thoracotomy with all its attendant risks and complications. Although incidence is low, perioperative stroke, myocardial infarction, and even death have been reported in association with this procedure whose complexity means that it cannot be routinely recommended for all patients affected by AF [12,13,18,19]. For these reasons, the Maze procedure can be utilized only in selected patients requiring surgery for concomitant cardiac conditions.

5. Catheter-based Maze procedure: ablating substrate for maintenance of AF

The results of the Maze operation acted as a stimulus for electrophysiologists to perform a similar procedure using linear radiofrequency (RF) ablations in both atria by transcutaneous catheter techniques. Linear lesions were placed to divide the atrial anatomy. Ablation lines were always connected to at least one block region to prevent the occurrence of a new reentrant circuit around the line. The block region was a valve annulus, vessel insertion or previous ablation line. Ablation was initially limited to the right atrium because the risks, mostly thromboembolic accidents, pericardial effusion or valve damage, were considered fewer than in the left atrium (LA). However, in spite of being a safe technique, ablation in the right atrium alone provided limited success, nearly 33% [20]. Because sustained common right atrial flutter and monomorphic atrial tachycardias triggering AF occurred in many patients after ablation in the right atrium alone, multiple ablation sessions were required.

The need to also extend lesions to the LA, initially considered by electrophysiologists as a prohibited chamber due to the high risk associated with trans-

septal puncture and potential thromboembolic complications, clearly emerged. The fact that this chamber plays a crucial role in AF genesis was demonstrated by mapping studies in mitral valve patients affected by chronic AF, suggesting a general tendency for reentrant circuits or ectopic foci to be present in the LA posterior wall but not in the right atrium and based on the assumption that the LA acts as an electrical driving chamber and should therefore be the target for Maze surgery and transcatheter ablation [21,22]. With regard to this, we demonstrated for the first time 3 years ago how, in patients affected by paroxysmal AF, the LA approach alone was safe, with no thromboembolic events [23]. In addition, it also proved capable of restoring long-term sinus rhythm in 60% of patients. This success rate was obtained through the creation of a long line encircling the PVs to compartmentalize the LA.

Furthermore, our experience was also innovative because a 3D electroanatomical nonfluoroscopic mapping system was used for the first time. This system permitted a significant reduction in fluoroscopy time and an overall decrease in procedural time, whilst simultaneously providing the stimulus to find out new electroanatomical criteria that could be used to stratify AF risk recurrence and, at the same time, validate lesions' completeness.

6. PV origin of AF: ablating triggers for initiation of AF

As pointed out above, our experience, on a par with the surgical one, proved to be eminently empirical. However, at that time, the need for pure electrophysiologists to have more convincing proof of why the LA is so important for ablation to be successful was palpable.

This issue was solved when the Bordeaux School, guided by Haissaguerre, demonstrated the focal origin of AF, setting the theoretical basis for a paradigm shift in AF treatment [24,25]. In his mapping studies, the author showed that a rapidly firing focus in or close to the PVs could be the cause of arrhythmia in patients suffering from paroxysmal AF. This critical observation shed light on the important interplay between substrate and trigger in AF pathophysiology. Although fascinating from a

practical point of view, on account of being able to suppress AF with discrete RF energy applications within the PVs, the focal approach immediately showed considerable limitations. After 8 ± 6 months of follow-up, the success rate was 62%, not dissimilar from the former linear ablation we obtained in the LA [25]. The early experience with the focal ablation of PV arrhythmias indicated that the recurrence rate was high and the success rate only modest, even in experienced laboratories. Despite the high acute success rate, the feasibility of this technique was indeed limited by the difficulty in mapping the focus if the patient was in AF or had no consistent firing; the frequent existence of multiple foci causing high recurrence rates; the appearance of new foci after the procedure and an incidence of PV narrowing as high as 42% [26].

Despite these limiting aspects, the noteworthy observation made by Haissaguerre et al. that AF can, at times, be cured by focal application of RF therapy has energized electrophysiology and industry, turned therapeutic dogma on its head, and mobilized hosts of Internet-savvy arrhythmia sufferers. It has also revealed how our understanding of AF has come full circle. In fact, studies on morphology and electrical activity of the myocardial sleeves that connect the LA to PVs, appear more and more frequently, even today, in the most prestigious cardiology journals.

7. PV–LA junction: the ‘critical region’

The anatomical and electrophysiological features of the PV–LA junction are able to explain many aspects of the AF pathogenesis. The LA muscular wall may extend up to a few centimetres through myocardial fibers of working phenotype, in a circular, spiral or oblique direction into the PVs, more in the superior than in the inferior veins [27,28]. There may be marked differences in diameter, wall thickness, and extension of cardiac tissue in and around the PV (sleeve length), with gaps of fibrous tissue. Additionally, the highly variable myocardial architecture in PVs, the complex mesh-like arrangement, stretch, and increase in fibrosis may produce greater non-uniform anisotropic properties. Fibrotic changes, more frequent in the elderly, may cause conduction block, causing reentry, and slow conduction. Abundant

nerves and ganglions of the autonomic system are present at the venoatrial junction; ablation targeting this region could alter the sympathetic and vagal neural regulatory mechanisms involved in the AF onset.

Embryologists argue about the role of the sinus venosus segment of the heart in PV development. It has been shown that node-like cells are present in the myocardium that encircle the PVs. Pacemaker activity in this area has been demonstrated in guinea pigs. More recently, Blom et al., using HNK-1 immunohistochemistry to delineate the development of the cardiac conduction system in the human embryo, found transient HNK-1 antigen expression in the myocardium around the common PV [29]. Although these findings suggest the possibility of pacemaker activity in or around the PVs, the question arises as to why it stays dormant for such a long time in the human heart and why that ectopic activity becomes manifest in a limited number of patients.

Proposed mechanisms for generation of abnormal focus activity include increased automaticity and triggered activity (abnormal electrophysiology generating extra depolarizations of cells), or very small reentrant circuits between small number of cells.

8. PV isolation: mapping- and electroanatomically-guided strategies

Understanding and overcoming the limitations of the focal PV ablative approach has incited electrophysiologists to experiment with new catheter-based strategies for AF.

The Bordeaux School and ours, both unaware of each other’s respective research work, published at a distance of only 1 week and in the same journal, two alternative studies proposing two different approaches to AF treatment [30,31]. In his study, Haissaguerre et al. described the results of PV segmental isolation guided by circumferential mapping data obtained by using a steerable circular catheter, 15 or 20 mm in diameter, equipped with 10 1-mm electrodes (i.e. 10 bipoles) in a loop made of shape-retaining material (Lasso) orthogonal to the shaft. The hypothesis was that, although PV muscle covers a large extent of the PV ostial perimeter, there are specific breakthrough(s)

from the LA that allow ostial PV disconnection with minimal ablation. Muscle activation was never circumferentially synchronous in the PVs during sinus rhythm, indicating preferential breakthrough(s) into the vein. The LA–PV breakthrough was inferred from the mapping data showing sequential activation of the PV perimeter. After assessment of perimetric distribution and activation sequence of PV potentials, ostial ablation was performed at segments showing earliest activation, with the end-point of PV disconnection. The extent of perimetric ablation was thus less than the actual muscle coverage, thereby minimizing the risk of PV stenosis. Even though the success rate was 73%, 44% of patients suffered from a recurrence of AF after only a 4-month follow-up meaning that multiple ablation sessions were necessary for most of them due to unmasked foci from the ostial edge or atrial tissue [30].

However, the main limitation of this approach is the improper alignment of the mapping catheter with the notoriously irregular geometry of the PVs making interpretation of the recorded electrograms challenging. Furthermore, catheter ‘drift’ may mislead the operator regarding ostial position. Finally, this technique may not be applicable to RF ablation outside the PV ostia, which may require complete circumferential lesions to produce distal disconnection.

To circumvent these limitations, we proposed a purely anatomic approach in which circumferential RF lesions are created using 3D electroanatomical guidance at nearly 5 mm around the ostia of each PV, with the aim of disconnecting these veins from the LA whilst reducing the risk of PV stenosis [31]. There is an important distinction between Haissaguerre’s approach and ours, owing to the fact that an approach aimed at eliminating arrhythmogenic triggers or critical connections between substrate and trigger, irrespective of ongoing trigger activity, appears to yield greater success. An anatomically-based procedure eliminates the need for mapping spontaneous or induced arrhythmias and would be effective in preventing recurrent AF caused by multiple PV foci, even if new foci may emerge at some future time.

An additional advantage of our technique is that the lesion can be tailored to the varying PV–LA junction features, unlike novel circumferential ablation catheters with a prefixed size and design, which

are difficult to accommodate in ostia having larger diameters, eccentric shape, or a complex proximal PV branching pattern. This approach also appears more feasible than LA compartmentalization through a single long line encircling the PVs altogether and connected to the mitral annulus. The overall success rate of our approach was nearly 85%. Interestingly, similar success rates were obtained either in patients with paroxysmal (86%) or permanent AF (83%), thereby raising the question about the reversibility of AF-induced electrophysiological changes in the atrium.

As pointed out by Alessie et al., in the animal heart and, as confirmed by other investigators, in the human heart as well, AF induces electrophysiological and morphological changes in the atria thus favoring recurrence and maintenance of arrhythmia [32]. Thus, our anatomy-based RF lesions may have altered AF arrhythmogenic substrate (*maintenance’s substrate*) beyond preventing the egress of impulses arising from the arrhythmogenic PVs (*initiating substrate*). Publication of our innovative therapeutic proposal for the cure of AF was accompanied by an Editorial by Wellens questioning some aspects related to safety, long-term results and the repeatability of our approach in other laboratories [33]. From a point of view of safety, we demonstrated that in a large cohort of patients (251, of whom 179 were affected by paroxysmal AF and 72 by permanent AF), our approach is safe with major complications (cardiac tamponade) occurring in only 0.8% of patients, with no thromboembolic event or PV stenosis [34]. With regard to long-term results, after a 1-year follow-up, freedom from AF was 80% overall, 86% for paroxysmal AF and 68% for permanent AF, with a minority of them on drugs [34]. As far as the repeatability of our approach is concerned, we are fully aware that this represents a considerable problem. Many of our daily efforts are dedicated to teaching this technique to an ever-increasing number of electrophysiologists who visit our laboratories from all over the world. The quantitative analysis of electroanatomical voltage maps has provided important results with a view to obtaining a pathophysiological explanation of the success of our approach (Fig. 1).

We have in fact demonstrated that there is no relation between lesion completeness (defined by a

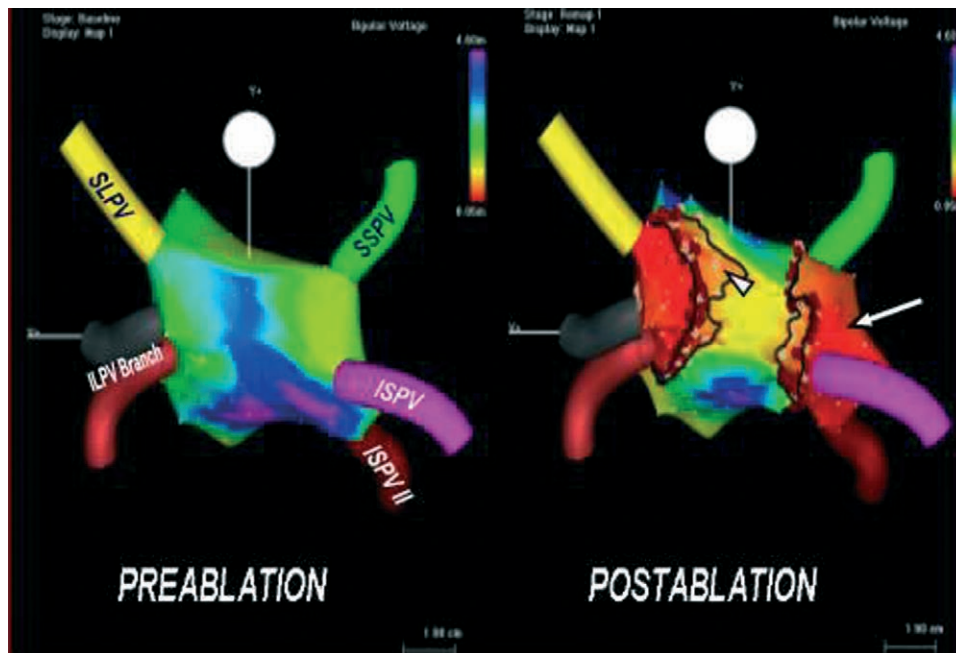


Fig. 1. Voltage maps of the left atrium, posteroanterior view (left, pre-ablation; right, post-ablation), depicting peak-to-peak bipolar electrogram amplitude. Red represents lowest voltage and purple, highest voltage. Claret red spheres represent radiofrequency lesions. Post-ablation areas within and around the ablation lines, involving to some extent the left atrial posterior wall, show low-amplitude electrograms. This purely anatomic approach yields a profound atrial electroanatomic remodeling, as expressed by the voltage abatement (bipolar amplitude ≤ 0.05 mV) inside the encircled areas (arrow) and around them (< 0.1 mV) involving, to some extent, the left atrial posterior wall (arrow head). LSPV, left superior pulmonary vein; LIPV, left inferior PV; RSPV, right superior PV; RIPV, right inferior PV.

bipolar amplitude < 0.1 mV inside the lesion) and clinical outcome whilst the amount of the post-RF low voltage encircled area, related to the overall LA surface, is higher in patients without recurrence and thus can be considered the only predictive criterion for successful ablation. However, another important observation that could cause us to reassess what may be considered the optimal end-point for effective disarticulation of PVs from the LA, is that the voltage abatement obtained inside the circular lesions is correlated to the disappearance of PV potentials and abolition of type-A AF (defined by others as PV tachycardia). Thus, this finding suggests that with our approach it is possible to obtain PV isolation in a very simple manner without the need for long or tedious mapping studies. Therefore, the absence of correlation between clinical outcome and lesions' completeness indicates that isolation of PV foci may not be the sole mechanism responsible for AF cure: it is likely that ablation, when effective, results in a profound atrial 'electroanatomical remodeling' involving, to some extent, the LA posterior wall to the point that the substrate for AF maintenance is no

longer present [34]. Ablation targeting the area surrounding the PV ostia is able to interrupt connections between the sleeves of myocardial fibers in the PVs and atrial myocardium, making unsuitable reentry pathways, destroying focal driving rotors responsible for AF maintenance and/or exerting a denervation effect. With regard to the latter, the heart rate variability analysis demonstrated a post-ablation shift of sympathovagal balance toward parasympathetic predominance, thus suggesting the destruction of some structures, such as endocardial nerve terminals and/or Marshall's ligament, involved in autonomic regulation [34–36]. Furthermore, the term 'electroanatomical remodeling' coined by us also derives from the fact that circumferential PV ablation, when effective, determines a significant reduction in LA size and improvement in its transport function during follow-up [34].

9. Current surgical approaches to AF

All this new recent information about AF genesis

and the experience of electrophysiologists, in terms of a sort of serendipity, have inspired modifications and simplifications of the surgical approach, just as the first surgical procedures for the cure of AF stimulated the development of catheter-based AF treatment. In fact, from the typical Maze operation, characterized by an extensive use of right and LA incisions, there was a progressive shift towards limited intraoperative cryoablation of the LA posterior wall alone with the latter being associated, as reported by Sueda et al., with the disappearance of chronic AF in 78% of mitral valve patients and recovery of LA contractility in 71% [22]. Additionally, the ablative experiences of electrophysiologists have influenced the techniques for AF treatment used by heart surgeons consisting at present in encircling the PVs by means of RF energy delivered from the epicardium. Thanks to this approach it is possible to restore sinus rhythm in about 80% of chronic AF patients affected by mitral valve disease [37]. Compared with intraoperative endocardial ablation, the epicardial approach is less time-consuming and easier to perform; furthermore, the contiguous nature of the lesions applied can be validated under direct vision. Additionally, since the heat source is on the epicardial surface, the risk of ablation-related thromboembolism is virtually null, and the loss of contraction is limited to a negligible area of the atrial wall. However, a potential limitation of this technique is the possibility of creating nontransmural lesions, thereby increasing the risk of proarrhythmic reentrant circuits. Moreover, the possibility of complete AF ablation from the epicardium has paved the way for beating AF heart surgery, first performed by Melo and co-workers, and for minimal invasive surgical approaches [38–40].

10. Future directions

For future optimal curative ablation therapy for AF, some problems still remain to be solved. Firstly, it is necessary to find a more effective imaging system able to visualize the PV–LA junction in the most precise possible way. This should allow visualization of the catheter in order not only to ensure contact with targeted tissue and assess the pathological effects of ablation in atrial myocardium but also to provide quantitative data to stratify the procedural

and clinical success. Secondly, it is important to perfect current catheter technology in order to improve co-axial movement of the tip, not only to perform effective lesions in an area, i.e. the PV–LA junction, whose morphology is so complex, but also to reduce procedural times. Thirdly, it is advisable to test other forms of energy such as saline-irrigated or cooled RF energy, microwave energy, or cryoablation which are promising in terms of reducing the risk of charring, thromboembolism, and pulmonary hypertension.

In conclusion, we think that we are at the dawn of a new era in which the majority of patients with AF may be managed with catheter-based therapy, thus eliminating the need for life-long and daily doses of drugs. Appropriate randomized controlled trials will offer the prospect of a changing treatment focus in the next decade with much less emphasis on controlling and combating AF, and a greater focus on cure.

References

- [1] Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults. *J Am Med Assoc* 2001;285:2370–5.
- [2] Stewart S, Hart CL, Hole DJ, McMurray JJV. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart* 2001;86:516–21.
- [3] Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med* 1998;158:229–34.
- [4] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983–8.
- [5] Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946–52.
- [6] Sopher SM, Camm AJ. Atrial fibrillation. Maintenance of sinus rhythm versus rate control. *Am J Cardiol* 1996;77:24A–37A.
- [7] Pritchett ELC. Management of atrial fibrillation. *N Engl J Med* 1992;326:1264–71.
- [8] Jung F, DiMarco JP. Treatment strategies for atrial fibrillation. *Am J Med* 1998;104:272–86.
- [9] Falk RH. Atrial fibrillation. *N Engl J Med* 2001;344:1067–78.
- [10] Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990;82:1106–16.
- [11] Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. *J Am Coll Cardiol* 1992;20:527–32.
- [12] Guerra PG, Lesh MD. The role of nonpharmacologic therapies for the treatment of atrial fibrillation. *J Cardiovasc Electrophysiol* 1999;10:450–60.
- [13] Scheinman MM, Morady F. Non-pharmacologic approaches to atrial fibrillation. *Circulation* 2001;103:2120–5.

- [14] Garrey WE. The nature of fibrillatory contraction of the heart: its relation to tissue mass and form. *Am J Physiol* 1914;33:397.
- [15] Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn Ther* 1962;140:183–8.
- [16] Allesie MA, Rensma P, Lammers WJ et al. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. *Circ Res* 1988;62:395–410.
- [17] Guiraudon GM, Campbell CS, Jones DL et al. Combined sino-atrial node atrio-ventricular node isolation: a surgical alternative to his bundle ablation in patients with atrial fibrillation. *Circulation* 1985;72:III220, Abstract.
- [18] Cox JL, Sundt TM. The surgical management of atrial fibrillation. *Annu Rev Med* 1997;48:511–23.
- [19] Sundt TM, Camillo CJ, Cox JL. The maze procedure for cure of atrial fibrillation. *Cardiol Clin* 1997;15:739–48.
- [20] Haissaguerre M, Jais P, Shah DC et al. Right and left atrial radiofrequency catheter therapy of paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 1996;7:1132–44.
- [21] Harada A, Sasaki K, Fukushima T et al. Atrial activation during chronic atrial fibrillation in patients with isolated mitral valve disease. *Ann Thorac Surg* 1996;61:104–12.
- [22] Sueda T, Nagata H, Orihashi K et al. Efficacy of a simple left atrial procedure for chronic atrial fibrillation in mitral valve operations. *Ann Thorac Surg* 1997;63:1070–5.
- [23] Pappone C, Oreto G, Lamberti F et al. Catheter ablation of paroxysmal atrial fibrillation using a 3D mapping system. *Circulation* 1999;100:1203–8.
- [24] Jais P, Haissaguerre M, Shah DC et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation* 1997;95:572–6.
- [25] Haissaguerre M, Jais P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–66.
- [26] Chen SA, Hsieh MH, Tai CT et al. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins. *Circulation* 1999;100:1879–86.
- [27] Nathan H, Eliakim M. The junction between the left atrium and the pulmonary veins. *Circulation* 1966;34:412.
- [28] Ho SY, Cabrera JA, Tran VH, Farrè J, Anderson RH, Sanchez-Quintana D. Architecture of the pulmonary veins: relevance to radiofrequency ablation. *Heart* 2001;86:265–70.
- [29] Blom NA, Gittenberger-de Groot AC, DeRuiter MC et al. Development of the cardiac conduction tissue in human embryos using HNK-1 antigen expression: possible relevance for understanding of abnormal atrial automaticity. *Circulation* 1999;99:800–6.
- [30] Haissaguerre M, Shah DC, Jais P et al. Electrophysiological breakthroughs from the left atrium to the pulmonary veins. *Circulation* 2000;102:2463–5.
- [31] Pappone C, Rosanio S, Oreto G et al. Circumferential radiofrequency ablation of pulmonary vein ostia. *Circulation* 2000;102:2619–28.
- [32] Allesie MA, Boyden PA, Camm J et al. Pathophysiology and prevention of atrial fibrillation. *Circulation* 2001;103:769–77.
- [33] Wellens HJJ. Pulmonary vein ablation in atrial fibrillation. Hype or hope? *Circulation* 2000;102:2562–4.
- [34] Pappone C, Oreto G, Rosanio S et al. Atrial electrophysiological remodeling after circumferential radiofrequency pulmonary vein ablation. *Circulation* 2001;104:2539–44.
- [35] Doshi RN, Wu TJ, Yashima M et al. Relation between ligament of Marshall and adrenergic atrial tachyarrhythmia. *Circulation* 1999;100:876–83.
- [36] Wu TJ, Ong JJC, Chang CM et al. Pulmonary veins and ligament of Marshall as sources of rapid activations in a canine model of sustained atrial fibrillation. *Circulation* 2001;103:1157–63.
- [37] Benussi S, Pappone C, Nascimbene S et al. A simple way to treat chronic atrial fibrillation during mitral valve surgery: the epicardial radiofrequency approach. *Eur J Cardio-Thorac Surg* 2000;17:524–9.
- [38] Melo J, Adragao P, Neves J et al. Surgery for atrial fibrillation using radiofrequency catheter ablation: assessment of results at one year. *Eur J Cardio-Thorac Surg* 1999;15:851–5.
- [39] Melo J, Adragao P, Neves J et al. Endocardial and epicardial radiofrequency ablation in the treatment of atrial fibrillation with a new intra-operative device. *Eur J Cardio-Thorac Surg* 2000;18:182–6.
- [40] Lee R, Nitta T, Schuessler RB, Johnson DC, Boineau JP, Cox JL. The closet heart maze: a nonbypass surgical technique. *Ann Thorac Surg* 1999;67:1696–702.