In recent years, a wealth of new information has been published on the incidence, mechanisms, consequences, and treatment of atrial fibrillation (AF) and the effect of the arrhythmia on quality of life and costs of health care. AF is the most common cardiac arrhythmia, and like prostate cancer in men, the probability of developing AF rapidly grows when a person is past 60 years of age.

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Despite all that information, our current pharmacological and nonpharmacological means to prevent or control the arrhythmia are frequently disappointing. Often, its presence has to be accepted, and measures to control the ventricular rate and to prevent thromboembolic complications have to be applied. New modes of treatment aimed at preventing the arrhythmia are therefore eagerly welcomed and investigated. In this issue of Circulation, Pappone et al describe such a new therapeutic approach in a selected group of patients with AF that uses a transcutaneous catheter technique directed at controlling the mechanism of the arrhythmia. What do we know about AF mechanisms, and does that knowledge help us in selecting a curative approach?

**Mechanism(s) of AF**

Many years ago, Moe postulated that AF was based on multiple-reentrant wavelets occurring in random order in the atrium. That theory was subsequently confirmed by mapping atrial activation during AF in animal and human hearts. Fibrotic changes in the atria occurring with aging and atrial dilatation secondary to increased stiffness of the ventricular wall or valvular disease, ischemia, and infiltrative diseases will facilitate the development of a substrate for those multiple-reentrant wavelets. Cox et al realized that such a mechanism for AF opened new therapeutic possibilities and developed the maze operation. When several linear incisions were made in both atria, the multiple-reentrant wavelets were no longer possible, and AF disappeared. The results of the maze operation were a stimulus for cardiologists to perform a similar procedure using linear ablation in both atria by transcutaneous catheter techniques. Such an approach also resulted in prevention of AF, but it is still hampered by technical problems and the possibility of serious complications, such as cerebrovascular accidents, cardiac tamponade, and loss of atrial rhythm and atrial function.

It was also shown that a large reentrant wave in the right atrium may become unstable, giving rise to secondary smaller wavelets resulting in AF. Pharmacological therapy in those patients restored the large reentrant (flutter) wave, and catheter ablation of the right atrial isthmus resulted in prevention of AF, but pharmacological therapy had to be continued. More recently, pioneering work by Haissaguerre and coworkers showed that a rapidly firing focus in or close to the pulmonary veins could also be the cause of the arrhythmia in patients suffering from paroxysmal AF. That was subsequently confirmed and expanded by other investigators and led to radiofrequency catheter ablation of these foci.

**Why the Pulmonary Vein?**

The muscular wall of the left atrium may extend up to a few centimeters around the pulmonary veins, more so in the superior than in the inferior pulmonary veins. There may be marked differences in diameter, wall thickness, and the extension of cardiac tissue in and around the pulmonary vein (sleeve length). Embryologists argue about the role of the sinus venosus segment of the heart in the development of the pulmonary veins. It has been shown that node-like cells are present in the myocardium that encircles the pulmonary veins. In the guinea pig, pacemaker activity in this area has been demonstrated. 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 pulmonary vein. Although these findings suggest the possibility of pacemaker activity in or around the pulmonary veins, 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. Nevertheless, Haissaguerre et al and Chen et al clearly showed by mapping studies that rapidly firing foci can be identified in and around the pulmonary veins and that ablation of the focus may lead to disappearance of paroxysmal AF.

**Hype or Hope?**

Cardiac arrhythmologists and industry enthusiastically welcomed this new approach of pulmonary vein ablation to treat patients with paroxysmal AF. After the initial experience showing the possibility of eradicating the mechanism of the arrhythmia, however, it became clear that it was a long-lasting procedure with possible complications, such as pulmonary vein stenosis, thromboembolism, air embolism, hemopericardium, and possible damage to such adjacent
extracardiac structures as bronchioles, the right pulmonary artery, and lung tissue. Also, the outcome was not always successful, and paroxysmal AF recurred. This has resulted in enormous activity to overcome these obstacles. What are some of the problems? First is the localization of the ectopic foci, which are most commonly found in the superior pulmonary veins and are characterized by a sharp electrogram, which may or may not be conducted to the atrium. A rapidly firing focus conducted to the atrium may be the mechanism for paroxysmal AF, but 1 or 2 pulmonary vein ectopic beats may also initiate AF in case of an additional substrate in the left or right atrium. Localization of the pulmonary veins can be echocardiographically guided. Potentials from the pulmonary veins have to be differentiated from those of the ligament of Marshall and the right atrium, which can also be foci of paroxysmal AF. Identification of the site(s) of origin in the different pulmonary veins can be helped by use of multielectrode catheters or electroanatomic mapping systems and will, we hope, be facilitated in the future by the development of QRS-T removal algorithms clearly exposing the polarity of the premature P wave and therefore the site of origin of this beat. Unfortunately, ectopic activity in the pulmonary vein may not be present during the electrophysiological study, even when provocative pharmacological or pacing procedures are performed.

Second, what is the best energy source for ablation? Currently, most experience is with heat with radiofrequency (RF) energy. Studies are ongoing on the appropriate RF power, heat limits, pulsed versus continuous RF energy delivery, and the use of irrigated-tip RF ablation. The purpose is to produce a lesion that is homogenous, not producing irreversible pulmonary vein narrowing, and not damaging to adjacent extracardiac structures. These considerations have led to the development of other energy sources, such as ultrasound delivered through a balloon in the pulmonary vein, laser, and cryoablation. More knowledge is needed concerning the histopathological consequences of these approaches. Advantages and disadvantages of the different techniques have to be analyzed, preferably in comparative studies.

Third, much activity is going on in the development of the appropriate shape of the catheter at the site where the energy has to be delivered. The purpose of ablation is to eliminate the high-frequency pulmonary vein potential and the creation of bidirectional block in the pulmonary vein. To prevent ectopic pulmonary vein activity from entering the left atrium, a circular lesion in or (probably better!) around the orifice of the pulmonary vein seems a logical approach, assuming that no pulmonary vein stenosis occurs. Pappone et al1 found such an approach rewarding in preventing recurrences of AF in their patients. However, the time required to make circular lesions with the current catheter makes this a less attractive procedure. Obviously, technical developments have to occur to speed up localization and isolation or eradication of ectopic activity.

Last, what are the long-term results of pulmonary vein ablation in AF? As pointed out by Haissaguerre et al2 and Chen et al,3 the short-term results of pulmonary vein ablation are promising in patients with paroxysmal AF, but uncertainty exists about long-term results with regard to arrhythmia recurrence. Also, the best way to evaluate the possible development of pulmonary vein stenosis needs to be established: echocardiography, MRI, or angiography. Ectopic activity may arise in ≥1 pulmonary vein, and that was the reason for Pappone et al1 to isolate each pulmonary vein by creating circumferential RF lesions around their ostia. With that approach, 22 of 26 patients were free of AF >9±3 months after the procedure. Half of the patients without AF were still on antiarrhythmic drugs. Interestingly, similar results of the ablation procedure were obtained in patients with paroxysmal AF and with persistent AF, raising the question about reversibility of electrophysiological changes in the atrium induced by AF. As pointed out by Allessie and coworkers (Wijffels et al15) in the animal heart and confirmed by other investigators in the human heart, AF induces electrophysiological and morphological changes in the atria favoring recurrence and maintenance of the arrhythmia. It is unknown up to what time point in the natural history of AF those changes are still reversible and the patient can be helped by removal of the initiating trigger.

In conclusion, dissatisfaction with pharmacological therapy resulted in growing interest in nonpharmacological treatment of AF, including His-bundle ablation and pacing, preventive atrial pacing, the implantable atrial defibrillator, and linear biatrial catheter ablation. Pulmonary vein ablation is an interesting and exciting new approach to AF, resulting in much hype among electrophysiologists and industry. However, at this point in time, it is a long-lasting procedure not without risk, with uncertainty about long-term outcome and the proper selection of patients and restricted to selected centers.

The hope is that technical refinements and close follow-up, preferably by use of a worldwide registry, will lead to better understanding of who might profit from such a procedure. Even then, it probably will be of help in only a small portion of our AF patients. AF is a disease that occurs progressively with aging, primarily because of increasing fibrosis of the heart, with 1% of the muscle being replaced each year by fibrous tissue when we are past 50 years of age. In the future, one would like to have more generally applicable therapies, like those aimed at the prevention of fibrosis or the availability of antiarrhythmic agents binding only to atrial tissue. It is obvious, though, that it will be quite a while before we can take this last big hurdle in treating supraventricular tachycardias.16

References


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