Mechanisms of Atrial Fibrillation: Is a Cure at Hand?

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The mechanisms of atrial fibrillation relate to the presence of random reentry involving multiple interatrial circuits. Triggers for development of atrial fibrillation include rapidly discharging atrial foci (mainly from pulmonary veins) or degeneration of atrial flutter or atrial tachycardia into fibrillation. Therapy for control of atrial fibrillation includes drugs, atrial pacing for those with sinus node dysfunction, or ablation of the atrioventricular junction. Therapeutic maneuvers for cure of atrial fibrillation include surgical or radiofrequency catheter induced linear lesions to reduce the atrial tissue and prevent the requisite number of reentrant wavelets. We need a much better understanding of basic mechanisms before a true cure is at hand. (J Am Coll Cardiol 2000;35:1687–92) © 2000 by the American College of Cardiology

Atrial fibrillation (AFib) is the most common sustained clinical cardiac arrhythmia, afflicting some 4% of people age ≥60 years (1). Recent laboratory and clinical observations have greatly enhanced our understanding of the mechanisms of this arrhythmia, and are now beginning to bear fruit in the clinical arena.

Older studies of this arrhythmia concentrated on induction by acetylcholine or vagal stimulation or use of topical aconitine application to the atrium (2,3), emphasizing a focal mechanism. Others, however, attributed AFib to reentry (4,5). The modern era of our understanding of this arrhythmia begins with the hypothesis of Moe (6), suggesting that AFib is the result of multiple atrial random reentrant waves. He showed, using a computer model, that such meandering waves could result in a sustained arrhythmia. Before this conceptual breakthrough, reentry in cardiac muscle was explained largely on the basis of fixed anatomic circuits (i.e., tachycardia rotating around an infarct scar or natural barriers).

Anatomic reentry can be described as a fixed circuit with propagation around a nonconducting barrier (7). The circuit can be divided into the depolarized area, which is called the wavelength of the tachycardia, and is determined by the average conduction velocity multiplied by the refractory period. The portion of the circuit that is not refractory is referred to as the excitatory gap. Reentry persists as long as the wavelength of the tachycardia is less than the tachycardia path length.

The next conceptual breakthrough occurred with the understanding that reentry in cardiac tissue could be functionally determined. Functional reentry does not require anatomically determined obstacles, but its initiation and persistence is dependent on basic heterogeneities of cardiac tissue. At least two mechanisms are responsible for functional reentry. Allessie et al. (8) described a leading edge type of reentry occurring in a rabbit atrium, characterized by the “tail” wave front being closely pursued by the “head” so that no excitatory gap is present. The leading edge circuit is maintained by centripetal activation, rendering the central region refractory.

Another type of functional reentry involves generation of spiral waves, which have been shown to circulate through either atrial or ventricular tissue. In spiral wave propagation, the safety margin for conduction is least at points of maximal curvature (9–11). Spiral or meandering waves may become stationary by anchoring around anatomic obstacles (i.e., pulmonary or systemic veins) and would, thus, become manifest on surface electrocardiogram (ECG) recordings as monomorphic arrhythmias (i.e., flutter). By contrast, non-stationary spiral waves would assume the typical characteristics of AFib (12,13).

Gordon Moe’s original multiple wavelet hypothesis was ultimately substantiated by Allessie et al. in both experimental as well as clinical studies. In the canine heart, for example, it was demonstrated that four to six circulating wavelets were necessary for maintenance of AFib (14). Smaller numbers of wavelets tend to coalesce and restore sinus rhythm. Several principles emerged from these observations. Maintenance of AFib depends on adequate atrial mass to encompass sufficient wavelets to perpetuate the arrhythmia. In addition, conditions that decrease atrial refractoriness (hence resulting in a decrease in tachycardia wavelength) would tend to perpetuate AFib (15). These important concepts will be revisited when we consider newer therapeutic options.
Another important concept generated by Allessie’s group is the idea that atrial fibrillation per se may act to produce both electrophysiologic and anatomic remodeling, which, apart from any preexisting structural atrial abnormalities, may result in more ready initiation as well as perpetuation of AFib. Wijffels et al. (16), for example, found that persistence of AFib produced several important electrophysiologic changes, resulting in both shortening of atrial refractoriness as well as disturbance of the normal rate responsiveness to overdrive atrial pacing. Normally, atrial overdrive pacing results in shortening of refractoriness in response to increased rate. In animals with persistent AFib who are reverted to sinus rhythm, overdrive pacing may show either no change or increased atrial refractoriness in response to overdrive pacing.

How do these concepts help to explain clinical AFib? Konnigs et al. (17) provided detailed atrial mapping in patients with the Wolff-Parkinson-White syndrome who required cardiac surgery. Atrial fibrillation was induced and recordings obtained from high density electrodes placed over the right atrium. They described three types of AFib patterns. Type I was characterized as a single dominant wave front, while type III was more akin to that predicted from the multiple wavelet hypothesis. In type III, flutter wavelets were observed to collide and extinguish, or wavelet may summate and augment conduction. Other wavelets encounter areas of block with production of “daughter” wavelets. Another type of circuit described in type III fibrillation involved waves that return to the point of origin, indicative of a leading edge circuit. Type II flutter often was found to be intermediate between the other types.

POSSIBLE EXPLANATION OF TYPE I AFIB

The close relationship between AFib and flutter was studied extensively by Waldo et al. (18,19). They showed this relationship in both the canine pericarditis model and postoperative cardiac patients (20). More recently, they showed that flutter circuits may circulate around the pulmonary veins and produce AFib with simultaneous maintenance of the originating flutter circuit. Termination of atrial fibrillation was followed by reinitiation from the original flutter circuit (21). In addition, Ikeda et al. (12) showed that meandering wave fronts had a greater tendency to become stationary when the core surrounded a larger hole (i.e., pulmonary or systemic vein). A larger hole was associated with a greater propensity for anchoring spiral waves because of a lesser angle of curvature and a greater source to sink the safety margin of conduction. Meandering waves tended, on the other hand, to detach themselves from smaller orifices because of a lesser safety margin for wave propagation around the smaller orifice.

The strong relationship between atrial flutter and fibrillation is supported by our own clinical observations that typical clockwise or counterclockwise flutter may assume atypical patterns (22,23). Atrial fibrillation may evolve from these atypical patterns and appear to result from one or more breaks in the crista terminalis (23,24). The cause of breakdown of functional barriers is not clear. Rapid atrial rates have been shown to produce alternation of atrial action potential duration (25). In ventricular muscle, these alternations may be either concordant or discordant (26). Introduction of premature complexes in ventricular rhythms showing discordant action potential duration may produce ventricular fibrillation. Similar patterns have recently been described in atrial muscle (27).

One may logically consider the pathogenesis of AFib as requiring specific triggers, a suitable substrate and modifying factors. An important trigger is the development of focal automatic atrial rhythms. Rapid rates from these foci may result in AFib by means of the mechanisms discussed above. Focal atrial tachycardia producing AFib has been verified in the clinic, and the majority of these foci originate from the pulmonary veins (28). Another trigger may result from atrial flutter (especially rapid atypical forms) as discussed above. Not only atrial flutter, but actually any supraventricular arrhythmia, may serve to trigger AFib (29,30). It is appreciated that rapid atrial rates serve to increase inhomogeneity of the refractory period and thereby increase atrial vulnerability to AFib (31). In addition, rapid rates decrease atrial wave length, and they also make the atria more vulnerable to fibrillation.

The appropriate substrate involves, first, an adequate atrial mass capable of encompassing the necessary numbers of wavelets required to maintain AFib. This explains why this arrhythmia is rarely observed in species with small atria or even in human neonates. Additional anatomic factors appear to be related to the complex architecture of the atrium, which has prominent muscle ridges (which may produce areas of anisotropic conduction) as well as the orifices of systemic and pulmonary veins. Furthermore, in patients with cardiac disease, atrial areas with heterogeneous electrophysiologic properties may act as an appropriate substrate for maintenance of atrial fibrillation.

A variety of modifying factors appear to be of importance in the initiation and maintenance of AFib. It has long been appreciated that intense vagal stimulation produces AFib in animals (32). A likely explanation appears to be related to the action of acetylcholine in shortening the atrial action potential duration, which would encourage a greater number of atrial wavelets because each wavelet would be associated with a decreased wavelength. Similar considerations apply to AFib, which may be induced by intravenous adenosine (33). The very elegant and important work from Allessie’s (16) laboratory has shown that persistent AFib
may result in modification of atrial electrophysiology as well as atrial anatomy, which may favor the perpetuation of AFib. These findings have led to the concept that AFib begets atrial fibrillation.

**TREATMENT STRATEGEMS**

Discussion of detailed management of patients with AFib is beyond the scope of this review. We will instead emphasize newer therapeutic approaches based largely on newer understanding of mechanisms.

The mainstay of current therapy for patients with AFib remains drug therapy. Atrioventricular (AV) nodal blocking agents are used primarily for rate control while antiarrhythmic agents are used to maintain sinus rhythm. The rationale for the use of antiarrhythmic drug therapy rests primarily on its ability to prolong atrial refractoriness (34). Even class IC agents, which are potent Na+ channel blockers, have been shown to exert rate-related prolongation of refractoriness (35,36). Both experimental and clinical studies have shown that the use of a calcium channel blocker attenuates both the abnormal shortening of atrial action potentials and the abnormal rate response (37). Whether use of a Ca2+ channel blocker should become standard auxiliary therapy requires further study.

Another illustration of the way recent laboratory findings impact medical therapy is the wider use of early cardioversion for treatment of patients with AFib. For patients with AFib of \( \geq 48 \) h, conventional therapy before planned direct current cardioversion was a two-to-three-week course of anticoagulant therapy. Recent prospective studies by Manning et al. (38) have shown that if the patient with AFib has a normal tranesophageal echo, then use of heparin followed by direct current external cardioversion is safe in terms of risk of systemic emboli.

**CATHETER ABLATION OR MODIFICATION OF THE AV NODE**

Catheter ablation of the AV junction was first introduced in 1982 (39) and has become an accepted treatment modality for patients with AFib who prove to be refractory to drug therapy. The advantages of AV junction ablation include ventricular rate control and improved cardiac function and quality of life (40). The chief disadvantages are initiation of a pacemaker-dependent state and continued need for anticoagulant therapy. Death after AV junction ablation has been reported, and this appears to be due in part to the relatively slow-paced rates used after ablation (41). With use of properly paced rates, the incidence of death or sudden death is identical to that of medically treated patients. More recently, attempts to modify AV nodal function in order to obviate the need for permanent pacing were introduced (42). The chief advantage of this approach is the possibility of rate control without permanent pacing. Potential problems include failure to prevent the sensation of palpitations, late onset AV block (16%) (43) and resumption of rapid AV conduction, and late deaths have been reported (43). In addition, more than one procedure may be required to achieve the desired result. Long-term rate control is achieved in almost 100% of patients after AV junctional ablation (44), as opposed to approximately 70% after AV nodal modification.

**DEVICE THERAPY**

Device therapy has been used in attempts to prevent AFib or to abort established episodes. Retrospective uncontrolled studies showed that single-site atrial pacing had a significant salutary effect, compared with ventricular pacing, in decreasing the incidence of AFib in patients with the bradycardia-tachycardia syndromes. More recent prospective controlled trials have shown conflicting data. Anderson et al. (45) showed a benefit from single-site atrial pacing, but this became manifest only after many years of follow-up. A more recent study (46) showed no benefit from atrial versus ventricular-based pacing, and the differences between studies may be the result of differences in atrial paced rates used or length of follow-up.

More recently Saksena et al. (47) have described the use of dual-site pacing in patients with sick sinus syndrome (right atrial and coronary sinus) and the impressive decreases in the incidence of AFib for those treated with atrial pacing. It should be emphasized that recurrences of AFib were the rule, and the vast majority of these patients required concomitant drug therapy. Nevertheless, dual-site pacing may ultimately prove to be a therapeutic option for patients with bradycardia-tachycardia syndrome, if confirmed by larger studies.

A unique approach to the management of AFib involves the use of the automatic internal defibrillator. This device has been extensively tested and shown to accurately detect AFib and to deliver atrial shocks without eliciting any ventricular proarhythmias (48). The chief drawbacks include painful sensations with the delivery of shocks and the necessity for three intracardiac electrodes, including right atrial and coronary sinus electrodes for sensing and shock delivery and a right ventricular sensing electrode in order to avoid delivery of atrial shocks during the ventricular-vulnerable period. The atrial defibrillator would appear to have a role in patient management, particularly for the patient with infrequent episodes who wishes to avoid emergency room visits for treatment of recurrent AFib. In addition, more rapid conversion of AFib may result in a situation in which episodes of AFib become less frequent.

In the U.S., the tendency has been for industry to package the atrial defibrillator with the ventricular defibrillator. These devices allow for atrial-based pacing and the use of sophisticated algorithms to distinguish supraventricular tachycardia (including AFib) from ventricular tachycardia and thus avoid inappropriate shocks (49). In addition, such devices can be programmed to deliver therapy and abort AFib (50). These devices allow for detailed interrogation so
that the clinician can discern the onset of AFib. For example, a recent study showed that up to 30% of episodes of AFib were preceded by bouts of atrial tachycardia (or atrial flutter) (50).

Of great interest was the finding that antitachycardia pacing or atrial burst pacing could potentially abort episodes of atrial fibrillation in over 50% of atrial tachycardia episodes (50).

TECHNIQUES DIRECTED AT CURING AFIB

Guiraudon (51) was the first to describe a procedure that created a corridor between sinus and AV nodes in patients with AFib. This ingenious procedure resulted in a regular rhythm but was essentially abandoned because atrial function was not restored (because the mass of atria were in fibrillation), and anticoagulant therapy was required. More recently, Cox et al. (52) described an innovative operation that involved multiple linear incisions over both atria (maze procedure), which proved to both restore sinus rhythm and preserve atrial function (albeit suppressed). These seminal observations sparked creation of both surgical and catheter techniques directed at curing atrial fibrillation. Other surgeons have shown that the maze procedure could be simplified with preservation of efficacy (53–55). It is still unclear whether the maze procedures are effective specifically because of the lesions created or because of nonspecific effects related to the reduction of atrial mass.

Dr. Swartz et al. (56) were the first to demonstrate that the maze procedure as described by Cox could be successfully replicated by catheter. More recent collaborative studies have also validated the concept of AFib cure using long linear atrial lesions (57). To date, the available experience suggests that left atrial lesions are necessary for the cure of most patients with AFib (58). The surgical maze procedure would appear to be most promising for those patients with atrial fibrillation who require corrective cardiac procedures (i.e., mitral valve repair). Use of the maze procedure has not gained wide general acceptance, because of the need for cardiopulmonary bypass and the associated postoperative morbidity and mortality. Similarly, the catheter maze procedures, while appealing (because it obviates the need for open-heart surgery), have been associated with serious sequelae, including cerebrovascular accidents, pulmonary hypertension owing to occlusion of the pulmonary veins and cardiac tamponade (59). It would appear that many technical problems need to be solved before widespread application of this technique can be recommended.

An exciting newer approach for cure of AFib was discovered by Haissaguerre et al. (60). They initially reported nine patients with focal tachycardia that triggered AFib. Ablation of the trigger could cure AFib. More recent studies by both Haissaguerre et al. (60) and Hsieh et al. (61) have shown that these arrhythmogenic foci are usually located in the left or right upper pulmonary veins, although successful ablation of “focal” AFib has been reported in the lower pulmonary veins or even in the right atrium. This remarkable finding has created great interest in both the electrical and anatomic relationship of the left atrium and pulmonary veins. It has been established that tongues of atrial myocardial tissue may extend for several centimeters into the pulmonary veins. These foci may discharge at very rapid rates producing AFib. In addition, these arrhythmogenic foci appear to be poorly coupled, which may allow for local reentrant arrhythmias caused by anisotropic conduction in this region. The finding of focal triggers for AFib is an important finding both conceptually and therapeutically. To date, it is still unclear how often focal tachycardias are responsible for atrial fibrillation. The incidence of long-term successful cures is uncertain. In addition, because the pulmonary veins have no Anastomosis, inadvertent occlusion of a pulmonary vein may lead to pulmonary insufficiency. The population with the highest yield for finding “focal” AFib would appear to be patients with lone atrial fibrillation who, on Holter recordings, show frequent unifocal atrial premature complexes and/or bursts of rapid atrial tachycardia that often precede the development of AFib (60,61). We do not have sufficient data to assess the risks of focal atrial ablation, and registry data from both very experienced and less experienced units are needed before making blanket recommendations.

SUMMARY

Although multiple, very significant, conceptual and practical advances have been made in both our understanding of and treatment of AFib, much more remains to be learned. The history of catheter ablation suggests that true cures occur only after more complete understanding of the tachycardia mechanism (i.e., Wolff-Parkinson-White syndrome, AV node reentrant tachycardia). I do not think that we are anywhere close to this point for patients with AFib. The contention that surgical or catheter maze procedures “cure” AFib is akin to believing that AV junctional ablation cures all supraventricular arrhythmias. I believe that AFib is a term that is used to cover a multitude of disordered atrial rhythms and that, in time, ablative procedures will be developed for specific abnormal circuits. We need to learn much more about the basic pathogenesis of this arrhythmia. Is it related to abnormalities in atrial ionic channels? Abnormalities of connexon distribution? Ischemia? Or factors unknown (62)? We need to understand the links between disordered physiology and the triggers, substrate and modifying factors. Is a cure for AFib at hand? I think not, but we are much closer today than we were five years ago.

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