THE CLEVELAND CLINIC FOUNDATION

CLEVELAND CLINIC JOURNAL OF MEDICINE

MANAGING ATRIAL FIBRILLATION:
FOCUS ON NONPHARMACOLOGIC STRATEGIES

SUPPLEMENT EDITOR:
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THE CLEVELAND CLINIC

SUPPLEMENT 3 TO VOLUME 70
JULY 2003

SPECIAL ISSUE

CLEVELAND CLINIC JOURNAL OF MEDICINE

Supplement 3 to Volume 70, July 2003

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This publication is supported by an unrestricted educational grant from St. Jude Medical, Inc.

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*Dr. Mills has indicated that he has no commercial affiliations or interests that pose a potential conflict of interest with his role as editor of this supplement. For disclosures from individual authors, see the first page of their respective articles.

The *Cleveland Clinic Journal of Medicine* (ISSN 0891-1150) is published 12 times yearly by The Cleveland Clinic Foundation.

Subscription rates: U.S. and possessions: personal $98; institutional $124; single copy/back issue $16. Foreign: $124; single copy/back issue $16. Institutional (multiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Postmaster address changes: Cleveland Clinic Journal of Medicine, NA32, 9500 Euclid Avenue, Cleveland, OH 44195. Subscription orders, editorial, reprint, and production offices (same address): phone (216) 444-2661; fax (216) 444-9385; e-mail ccjm@ccf.org; World Wide Web address: http://www.ccjm.org

Printed in USA.

Beyond drugs alone: Pacing, ablation, and surgery for atrial fibrillation

Cardiologists in every subspecialty area deal with patients who experience atrial fibrillation. An aging population, the prevalence of hypertension, and the emergence of heart failure as the final common pathway of heart disease in the modern era guarantee that atrial fibrillation will only expand as a clinical problem.

In this era of increasing fragmentation in cardiology, we must struggle to incorporate up-to-date information into our management decisions. With the growth of electrophysiology and heart failure management as subspecialty disciplines, general cardiologists, imaging specialists, and invasive cardiologists stand to benefit from a description of state-of-the-art approaches to atrial fibrillation.

Nondrug approaches promise major impact

In this supplement, I have brought together a group of experts to review current concepts of atrial fibrillation, with an emphasis on nonpharmacologic management. The focus on nondrug approaches reflects in part a reluctance to add to the polypharmacy required in heart failure management, and in part an intuition that nondrug approaches will have a major impact on management, as they do in ventricular arrhythmia.

Why atrial fibrillation now?

In view of two recent trials[1,2] showing no advantage to rhythm control over rate control as a management strategy, some may wonder why we have chosen to revisit atrial fibrillation management. Although the trial data were helpful in tempering enthusiasm for restoration of sinus rhythm in all patients, atrial fibrillation results in:

- Increased risk of cardioembolic stroke
- Loss of appropriate rate control
- Alterations in diastolic filling
- Unpleasant symptoms in many patients.

In selected patients, one or more of these facets of atrial fibrillation pathophysiology will drive the management strategy toward rhythm control.

Management is still a work in progress

This supplement describes a work in progress, not a finished product. We have not solved the problems of atrial fibrillation, but we have gone a long way toward asking the right questions. For some patients, the techniques described here can result in long-term restoration of normal sinus rhythm; for others, a decision for rate control and anticoagulation may be the best option available today. What's important is that *options now do exist*. And when options exist, we must know how to make well-informed recommendations to our patients.

As a clinical cardiologist, I have appreciated the opportunity to edit this supplement. I invited contributions from colleagues who put together the key pieces in the jigsaw puzzle that shows the overall picture of atrial fibrillation. We journey from the basic science to pharmacology, pacing, the electrophysiology laboratory and radiofrequency ablation, and the operating room to look at all the management options we can bring to bear.

Ultimately, the test for each of us is to select the best strategy for managing atrial fibrillation in the context of each individual patient. To do that well, we must keep up to date. I hope that this collaborative effort helps.

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Basic mechanisms of atrial fibrillation

DAVID R. VAN WAGONER, PHD

By its electrocardiographic inscription, atrial fibrillation (AF) is an easily recognized arrhythmia, yet it remains one of the most vexing arrhythmias to treat. The challenge stems partly from the fact that the common electrocardiographic features mask significant differences in the mechanisms and etiologies of AF in different patients. Differences in etiology suggest that treatment strategies may need to target the underlying arrhythmic mechanisms. This review briefly discusses the mechanisms and pathophysiology of AF.

TYPES AND PROGRESSION OF ATRIAL FIBRILLATION

In a minority of patients, AF exists in the absence of structural heart disease or other apparent risk factors (lone AF). Inflammatory mechanisms have been proposed as initiators of the arrhythmia in these patients.[1]

In its most common form, AF is a degenerative disease that primarily affects older people, often in association with other conditions, including hypertension, valve disease, diabetes, or lung disease. The clinical course of AF frequently progresses from transient and self-terminating episodes (paroxysmal AF) to episodes of longer duration, sometimes becoming persistent (not converting to sinus rhythm without intervention or cardioversion) or permanent (persistent despite cardioversion). Progression from paroxysmal to permanent AF involves changes in the individual atrial myocytes (eg, myolysis, hypertrophy, changes in ion channel density or distribution) and structural changes to the chamber (eg, dilatation, increased fibrosis, fatty infiltration).

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This article was supported by a grant from the National Institutes of Health (NIH RO1 HL-65412).

Disclosure: The author has indicated that he has no commercial affiliations or interests that pose a potential conflict of interest with this article.

WHAT HAPPENS DURING ATRIAL FIBRILLATION

In its essence, AF is a manifestation of multiple simultaneous waves of electrical activation in the atria. The normal uniform electrical and contractile activation of the atria from the sinoatrial node to the atrioventricular (AV) node is replaced by an apparently chaotic pattern of simultaneous electrical activation at multiple sites with continuously changing, wandering pathways. Intra-atrial activations can be recorded as irregular, rapid depolarizations at rates that often exceed 300 to 400 beats per minute. The asynchrony may be due to the appearance of secondary (ectopic) pacemaker activity and/or to areas of slow conduction that facilitate the persistence of reentrant activity. Ectopic pacemaker activity may be caused by sinoatrial node dysfunction, increased vagal tone, increased sympathetic tone, or cytosolic Ca^{2+} overload.

Mechanically, this rapid, disordered atrial activation results in a loss of coordinated atrial contraction. Irregular electrical inputs to the AV node and the His-Purkinje system lead to irregular ventricular contractions. Clinically, symptoms related to AF may be due to rapid or irregular conduction to the ventricles, leading to rapid ventricular rates and irregularity of ventricular rhythm.

Loss of atrial contractility and loss of AV synchrony also may be hemodynamically detrimental. In normal subjects, loss of atrial "kick" may reduce cardiac stroke output by 20% to 30%.[2] The atrial contribution to cardiac output may be even higher in patients with heart disease. For example, loss of atrial contraction in patients with significant left ventricular diastolic dysfunction or aortic stenosis

may lead to significant symptoms, including heart failure.

ECTOPIC ACTIVITY AS AN INITIATOR OF ATRIAL FIBRILLATION

Recent studies have highlighted the importance of initiating triggers in the pathogenesis of AF, particularly in patients with lone AF. These studies have shown that ectopic activity that can trigger AF frequently arises in the region of the pulmonary veins entering the left atria.[3] Cellular mechanisms underlying this focal ectopic activation are still poorly understood.

Recognition of these initiating triggers has focused much clinical attention on electrically isolating the pulmonary veins from the remainder of the left atrium. This has been done either noninvasively using endocardial ablation[4] or via open heart surgery using the maze procedure and its variants.[5]

The pulmonary veins are a primary location for entry of vagal nerves into the left atrium.[6,7] Depending on the branches stimulated, vagal activity can cause slowing of the heart rate, slowing of AV nodal conduction, or heterogeneous shortening of atrial action potentials; these effects result from activation of the muscarinic potassium channels that are present at high density in atrial and nodal myocytes.[8] In canine models, vagal stimulation alone is sufficient to sustain AF as long as the stimulation is maintained.[9]

Patients with "vagal AF" are typically young and athletic and have high parasympathetic tone and slow basal heart rates. These patients are quite distinct from the majority of older, sicker AF patients, and require different medical management (eg, beta-blockers are contraindicated).

THE MULTIPLE WAVELET HYPOTHESIS

A "multiple wavelet hypothesis" may help to explain how AF is maintained after initiation. Under this hypothesis, AF is sustained by the propagation of multiple reentrant circuits.[10] Continuously changing, wandering pathways are determined by the local refractoriness, excitability, and conduction properties of atrial tissue. This hypothesis has been supported by electrophysiologic mapping studies in animals and humans demonstrating the presence of multiple reentrant wavelets.[11,12] The initiation and perpetuation of AF may depend on increasing atrial size and decreasing reentrant circuit wavelength, the product of conduction velocity and atrial refractory period, conditions that would support more reentrant wavelets.[13] Therefore, structural enlargement of the atria (whether directly by AF-induced hypertrophy, or indirectly as a result of underlying valvular disease) can predispose to AF persistence by allowing more reentrant circuits to sustain in the atria. Also, small reentrant circuits from shortened tissue refractoriness may enhance vulnerability to atrial tachyarrhythmias.

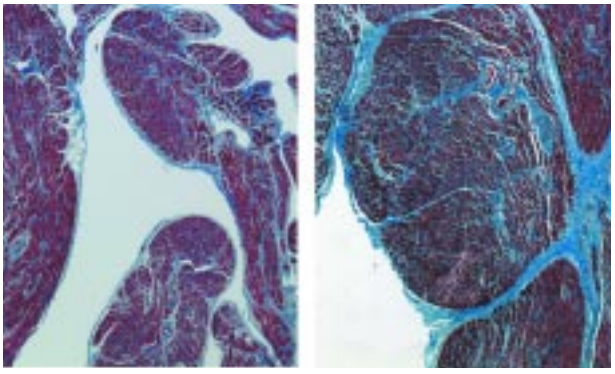

Figure 1. Right atrial appendage specimens from a 72-year-old patient in normal sinus rhythm (left) and from a 73-year-old patient with persistent atrial fibrillation undergoing maze surgery and mitral valve repair (right) (Masson trichrome stain). Fibrosis, shown in blue, is evident in both specimens, but interstitial fibrosis is clearly increased in the atrial appendage of the patient with atrial fibrillation.

THE DUAL SUBSTRATE CONCEPT

Thus, the mechanism of AF may be seen as having two substrates—one for initiation and one for maintenance. The substrate for sources initiating AF and the substrate for maintenance of AF likely underlie the spectrum of disease seen in AF and may explain its varied clinical presentation.[14] Early manifestations may include frequent atrial ectopy, often initiating from a single focal source, which may progress to repetitive bursts of atrial tachycardia and then paroxysms of AF. These paroxysms may become more frequent, longer, or even persistent as electrophysiologic and structural remodeling occur. Factors that may promote remodeling include atrial stretch, calcium overload, left ventricular hypertrophy, ventricular dysfunction, valve disease, autonomic tone, inflammation, and oxidative stress. Whether interventions directed at these factors can prevent or reverse remodeling has not yet been well studied.

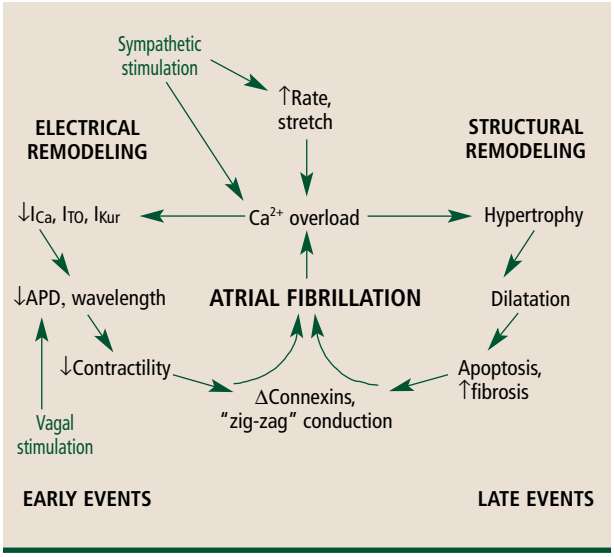

Figure 2. Schematic of the interacting remodeling pathways that underlie the progressive electrophysiologic, contractile, and structural abnormalities associated with atrial fibrillation. APD = action potential duration; I_{Ca} = inward calcium current; I_{TO} and I_{Kur} = repolarizing potassium currents. Adapted from reference 28 with permission from Elsevier.

ELECTROPHYSIOLOGIC REMODELING IS RAPID AND REVERSIBLE

Cellular electrophysiologic changes are the earliest adaptation of the atria to fibrillation or high-rate activity that contributes to the maintenance of AF. Using the burst-pacing model of AF in goats, Wijffels et al[15] showed that, in the presence of maintained fibrillation, the atrial effective refractory period (aERP) was reproducibly and rapidly attenuated, with much of the effect being evident within 24 hours of AF. Reversal of the electrophysiologic remodeling followed a time course similar to that of its onset. The effects of 5 days of AF were fully reversed within a 2-day recovery period.[16]

Action potentials in atrial myocytes reflect the integrated activity of all ion channels in the cell membrane. Electrophysiologic studies have shown that several common electrophysiologic changes underlie the abbreviated ERP accompanying both experimental tachycardia models and human AF. These include reductions in the density of repolarizing potassium currents and of the inward calcium current.[17] The net abbreviation of the ERP reflects a greater impact of AF on the inward calcium current than on the repolarizing currents. In experimental studies, the reduction in the inward calcium current is strongly implicated in the loss of contractility that accompanies AF, and both the loss and the recovery of mechanical function are well correlated with ERP recovery.[18]

SLOW CONDUCTION AND FIBROSIS AS A SUBSTRATE FOR ATRIAL FIBRILLATION

The cellular electrophysiologic changes in the atria are too rapid and too reversible to fully explain the increased persistence of AF. In the persistently fibrillating aged or failing heart, the amount of fibrosis between atrial muscle bundles is increased. This fibrosis is associated with broadening of the P wave on the electrocardiogram and impaired ("zig-zag") conduction within the atria.[19] Thus, in the presence of an initiating ectopic beat, it is easy to understand how more fibrotic atria would be more likely to sustain AF. In patients undergoing cardiac surgery, the extent of fibrosis in the right atrial appendage correlates positively with patient age and with the occurrence of AF after surgery[19] **(Figure 1)**.

Fibrosis is a long-term response to injury. In canine models, atrial fibrosis is increased following the induction of heart failure by ventricular pacing but not following rapid atrial pacing.[20] In the heart failure model, fibrosis primarily increases the heterogeneity of conduction, with little change in the cellular electrophysiologic properties of the atrial myocytes. Pretreatment of experimental animals with an ACE inhibitor attenuated, but did not prevent, the increase in atrial fibrosis.[21] It is therefore uncertain whether atrial fibrosis, once developed, can be reversed. This poses a major challenge to the pharmacologic management of AF in older patients.

PATHOLOGIC MECHANISMS IN ATRIAL FIBRILLATION–INDUCED REMODELING

AF is a high-rate rhythm that significantly increases energy utilization. Mechanisms implicated in the long-term structural and electrophysiologic remodeling processes include activation of cellular proteases (eg, calpains[22,23]), activation of Ca^{2+}-dependent kinases or phosphatases, and increased oxidative stress,[24] resulting from altered mitochondrial function and/or inflammatory mechanisms.[25] It is likely that all of these mechanisms and perhaps several more are involved in atrial remodeling. Further studies are needed to identify which, if any, of these mechanisms are effective targets for pharmacologic intervention.

CONCLUSIONS AND IMPLICATIONS

AF is a complex, multifactorial disease **(Figure 2)**. The underlying etiology is likely different in different patient subpopulations. However, electrophysiologic remodeling is commonly observed and is an early contributing factor to the persistence of the arrhythmia. Structural remodeling (at both the subcellular and tissue levels) is also frequently present and contributes to the altered tissue substrate that promotes AF maintenance.[26] Whereas experimental studies suggest that the electrophysiologic changes in AF are quite reversible, the structural changes are much slower and more difficult to reverse.[27] Available drug therapies for AF based on ion channel blockade have had limited efficacy. It will be of great interest to see whether more mechanistically based therapies, device-based therapies, or some combination of the two can improve outcomes for patients with this vexing arrhythmia.

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Current clinical issues in atrial fibrillation

MINA K. CHUNG, MD

Because atrial fibrillation (AF) affects a heterogeneous clinical population, applying evidence-based approaches to individual patients with AF remains a challenge. The mainstays of therapy include pharmacologic rate control and antiarrhythmic therapy, cardioversion, and antithromboembolic management. Nonpharmacologic therapies, including ablation, devices, and surgical approaches, are now increasingly used and, in some cases, potentially curative. This article surveys the clinical challenges posed by AF and broadly assesses current and evolving treatment strategies to manage them.

MAGNITUDE OF THE PROBLEM

AF is the most common sustained arrhythmia seen in clinical practice. **Table 1** presents a basic classification of the common types of AF.

The prevalence of AF is estimated at 0.4% of the general population; an estimated 2.2 million Americans have paroxysmal or persistent AF.[1,2] The Framingham Heart Study reported a 0.1% annual incidence of AF, which translates to more than 160,000 new US cases per year.[3]

The prevalence of AF increases with age;[1] age-specific prevalence rates are as follows:[1,2,4–6]

- 0.2% in the population aged 25 to 34 years
- less than 1% in the population under age 60
- 2% to 5% in the population over age 60
- 6% to 10% in the population over age 80.

In light of these findings, AF will be a growing clinical challenge as the US population ages **(Figure 1)**.[7]

AF is often associated with other cardiovascular diseases, most commonly hypertension and ischemic heart disease. Other predisposing conditions and factors are listed in **Table 2**. Factors that can predispose to AF in a normal heart include high adrenergic states, alcohol, stress, certain drugs (especially sympathomimetics), excessive caffeine, hypoxia, hypokalemia, hypoglycemia, and systemic infection. The incidence of AF is particularly high, 20% to 40%, after cardiac surgery.[8]

CLINICAL CONSEQUENCES OF ATRIAL FIBRILLATION

Mortality. Though not usually considered a life-threatening arrhythmia, AF is associated with a 1.5-fold to twofold increase in total and cardiovascular mortality, based on Framingham Heart Study data.[9,10] Factors that may increase mortality in patients with AF include advanced age, mitral stenosis, aortic valve disease, coronary artery disease, hypertension, and congestive heart failure. Acute myocardial infarction and congestive heart failure are each associated with higher mortality if AF is present.

Stroke and thromboembolic events are both associated with AF and are among its most clinically important consequences.[11] AF is one of the most potent risk factors for stroke in the elderly[3] and is the most common cause of cardiogenic stroke. It also carries a significant risk for silent cerebral infarction.[12] The risk of stroke in patients with nonvalvular AF increases with age, concomitant cardiovascular disease, and other risk factors for stroke.[13] Patients with nonvalvular AF show an approximately twofold to sixfold increase in the risk of stroke, with an incidence of 3% to 5% per year.[2,11,14] In the presence of rheumatic heart disease, chronic AF is associated with a 17-fold increase in the risk of stroke.[15] The Framingham Heart Study reported an annual stroke rate of 4.2%[15] and showed that the relative risk of stroke was significantly increased in the

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Disclosure: The author has indicated that she has no commercial affiliations or interests that pose a potential conflict of interest with this article.

TABLE 1
Basic classification of the types of atrial fibrillation (AF)

Lone AF occurs in the absence of cardiac or other conditions predisposing to AF
Acute AF generally refers to AF lasting less than 48 hours
Paroxysmal AF generally is characterized by recurrent, transient episodes that revert to sinus rhythm spontaneously or with treatment
Persistent AF does not convert to sinus rhythm without intervention or cardioversion
Permanent AF is persistent despite cardioversion

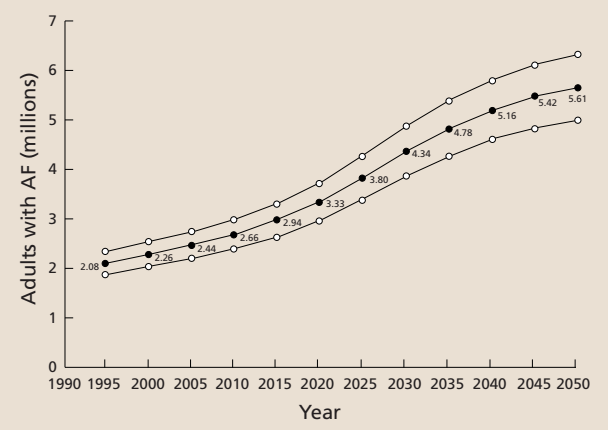

Figure 1. Projected number of adults with atrial fibrillation in the United States, 1995 to 2050. Upper and lower curves represent the upper and lower projections based on sensitivity analysis. Reprinted from reference 7 with permission.

presence of AF, congestive heart failure, coronary artery disease, and hypertension; the increase in the presence of AF was nearly fivefold.[11]

At the same time, the risk of stroke is low in patients with AF who are younger than age 60 and do not have hypertension or cardiovascular disease. A meta-analysis of five major primary prevention trials for stroke in patients with AF[13] estimated the incidence of stroke to be approximately 1% per year in those younger than age 65 without hypertension, diabetes, or prior stroke or transient ischemic attack. The incidence of stroke in patients who are older, have risk factors for stroke, or have concomitant cardiovascular disease is approximately 3% to 5% per year. Patients older than age 75 who have risk factors for stroke are at particularly high risk (8% incidence per year). Furthermore, stroke development tends to cluster at the onset of AF.[16,17]

Tachycardia-induced cardiomyopathy. Persistent rapid rates in patients with AF can lead to tachycardia-mediated cardiomyopathy with left ventricular dysfunction and congestive heart failure.[18,19] The cardiomyopathy may be reversible with ventricular rate control or regularization of the rhythm.[18,19] This may be achievable with medical rate control, atrioventricular node ablation, or restoration of sinus rhythm. An atrial cardiomyopathy can also result from structural remodeling during AF, leading to an increase in atrial size.[20]

Symptoms and hemodynamics. AF may cause symptoms as a result of rapid ventricular rates, irregularity of ventricular rhythm, or loss of atrioventricular synchrony. Symptoms may include functional capacity limitations, palpitations, fatigue, dyspnea, angina, and congestive heart failure.

RHYTHM VS RATE CONTROL AFTER AFFIRM

The concept of substrates supporting reentry and their susceptibility to structural and electrical remodeling (see the review by Van Wagoner earlier in this supplement) provides a theoretical rationale for a rhythm-control approach to restoring and maintaining sinus rhythm in AF. Class IA and III antiarrhythmic drugs have been used to prolong atrial refractory periods with the goal of limiting atrial reentrant circuits. Class IC agents, which are sodium channel blockers, slow conduction and may promote blocking of reentrant circuits. Verapamil has been studied as a calcium channel blocker that may abrogate the shortening of atrial refractory periods, potentially by preventing the calcium overload that may underlie early atrial electrical remodeling. Earlier conversion of AF to sinus rhythm may be more successful in avoiding the electrical and structural remodeling of the atria that may predispose to recurrent and persistent AF. In addition, maintenance of sinus rhythm may help to reverse electrical and structural remodeling.

It remains controversial, however, whether a rhythm-control approach to maintain sinus rhythm is clinically superior to a strategy of ventricular rate control. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM),[21] the largest of several randomized trials comparing these two approaches, no survival benefit or improvement in quality of life was achieved with a rhythm-control approach. Whether the theoretical advan-

TABLE 2
Conditions and factors that can predispose to atrial fibrillation

Hypertension	Wolff-Parkinson-White syndrome
Ischemic heart disease	Pericarditis
Advanced age	Pulmonary embolism
Rheumatic heart disease*	Thyrotoxicosis
Nonrheumatic valve disease	Chronic lung disease
Cardiomyopathies	Neoplastic disease
Congestive heart failure	Diabetes
Congenital heart disease	Postoperative state
Sick sinus syndrome/ degenerative conduction system disease	

*Especially mitral valve disease

tages of avoiding or reversing structural or electrical remodeling justifies a rhythm-control strategy in some patients remains to be established, given the higher risk of adverse drug effects with this approach.

The results of AFFIRM and other recent randomized trials comparing rate control with rhythm control have prompted a redefinition of the types of patients who are appropriate candidates for these respective approaches. It is worth noting that patients who were highly symptomatic with rate-control therapy may not have been enrolled in AFFIRM. Patients with persistently symptomatic, new, or first-onset AF may be good candidates for rhythm control, as may younger patients, in whom avoiding remodeling might be advantageous over the long term. These patients might also be current or future candidates for newer curative procedures.

■ RATE CONTROL: DRUGS VS ATRIOVENTRICULAR JUNCTION ABLATION

The mainstays of a rate-control strategy for AF have been anticoagulation and pharmacologic treatment with beta-adrenergic blockers, calcium channel blockers, and digoxin. For patients with rapid rates refractory to these agents, atrioventricular junction ablation or modification with implantation of a permanent pacemaker has successfully improved symptoms, quality of life, and left ventricular dysfunction caused by tachycardia-mediated cardiomyopathy.[22,23] The disadvantage is that patients become pacemaker-dependent.

Early reports of an increased risk of late sudden death, primarily after early procedures using direct-current ablation, have not been confirmed in recent studies with radiofrequency ablation.[24] Nevertheless, recent studies have suggested a possible increase in heart failure and mortality in patients with implantable cardioverter defibrillators receiving right ventricular pacing.[25] Long-term follow-up studies of patients undergoing atrioventricular junction ablation are warranted to determine outcomes and whether left or biventricular pacing may be preferable or superior in these patients.

■ SELECTING DRUGS FOR RHYTHM CONTROL

When treating an individual patient, the decision between rhythm control and rate control often involves complex analyses of the risks and benefits of maintaining sinus rhythm. The safe and effective maintenance of sinus rhythm is an ongoing challenge in patients electing a rhythm-control approach. Patients may remain symptomatic in AF despite rate control and therefore may try a rhythm-control approach with its potential for more complete symptom relief and hemodynamic improvement. However, even with antiarrhythmic therapy, approximately one half of patients develop recurrent AF after cardioversion to sinus rhythm, and recent studies raise concern over the potential for increased mortality and proarrhythmic potential when antiarrhythmic drugs are used.

The decision to use an antiarrhythmic drug should be influenced by the frequency and duration of the AF, the symptoms involved, the reversibility of the arrhythmia, and the presence or absence of structural heart disease.[2,26] The risk of side effects, including organ toxicity and proarrhythmia, also should be weighed against the benefit and efficacy rates of the drugs.[2,26]

For example, amiodarone is an effective antiarrhythmic drug for AF and has a low proarrhythmic potential. However, long-term use may not be suitable for some patients, particularly younger patients, because of its risk of long-term organ toxicity. Nevertheless, amiodarone may be the first-line choice in patients with severe structural heart disease, regardless of patient age.

Inpatient initiation of some antiarrhythmic drugs may be advisable, particularly those that predispose to QT prolongation, proarrhythmia, or bradycardia, or for patients with risk factors for these effects.

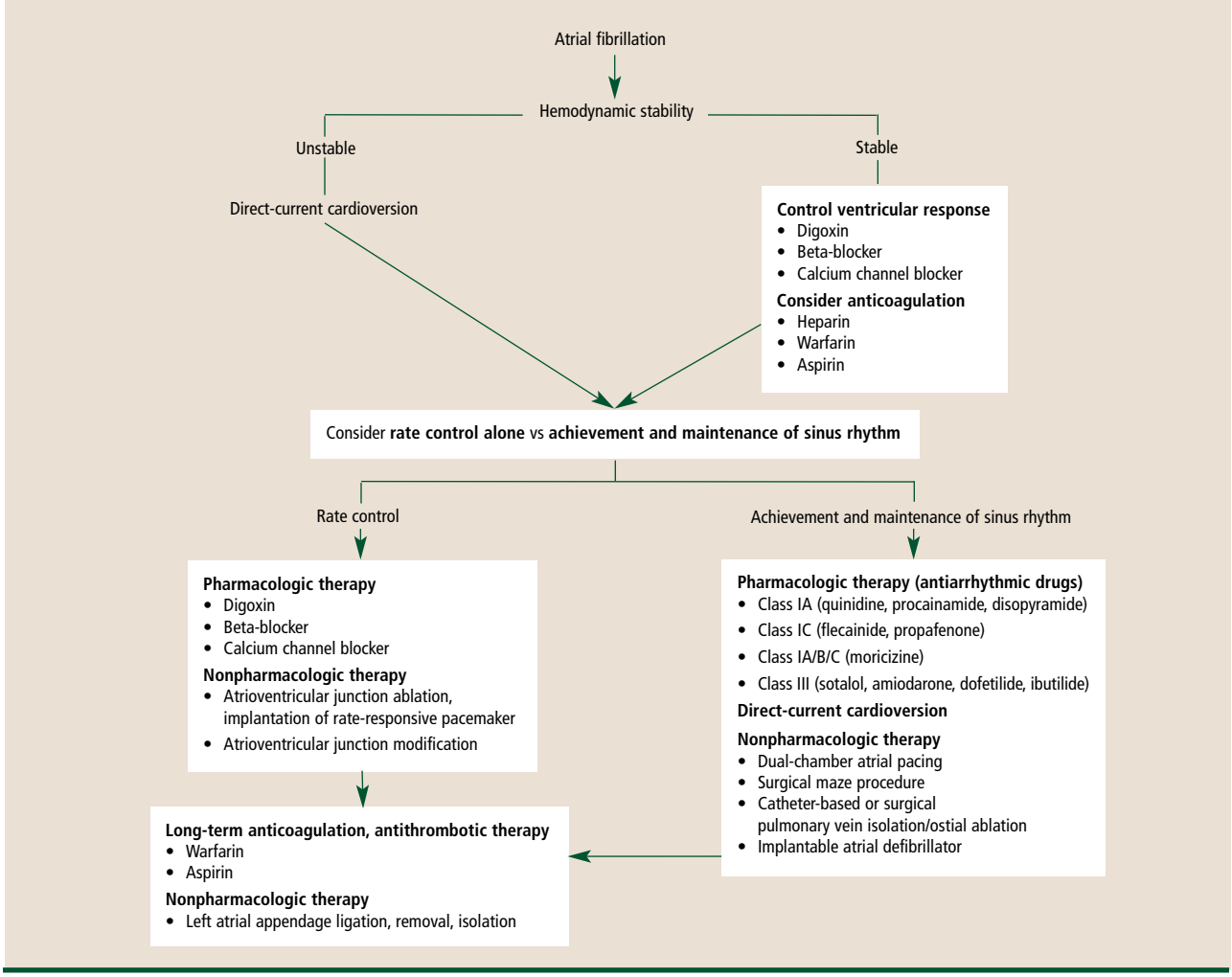

Figure 2. General algorithm for the management of atrial fibrillation.

When AF is treated medically, recurrences are expected (50% at 6 to 36 months) but are generally not life-threatening. Because total suppression of AF episodes may risk drug toxicity, quality-of-life improvement may be a reasonable goal for guiding therapy.

■ THROMBOEMBOLIC RISK: LIFELONG MANAGEMENT NEEDED

Several studies have established warfarin's efficacy in reducing the risk of stroke and thromboembolism in patients with AF and risk factors for stroke. Although treatment with warfarin before cardioversion and for about 4 weeks afterward has been a common practice, AFFIRM and other recent trials have shown that thromboembolic risk is not reduced by a rhythm-control strategy with apparent maintenance of sinus rhythm. AFFIRM showed no reduction in thromboembolism with rhythm control over rate control,[21] and the Rate Control vs Electrical Cardioversion (RACE) for Persistent Atrial Fibrillation study[27] found a higher incidence of thromboembolism with rhythm control than with rate control. In both studies most events occurred after anticoagulation had been stopped or when it was subtherapeutic.

These findings underscore the importance of continued anticoagulation, even in the context of a rhythm-control strategy with apparent achievement and maintenance of sinus rhythm. Moreover, the only intervention or therapy that has been shown to improve survival in patients with AF has been the use of warfarin. The Atrial Fibrillation Investigators reported a 33% relative reduction in mortality with

warfarin compared with control therapy in a combined analysis of five randomized trials.[13] New antithrombotic agents that might be effective substitutes for warfarin are being studied (eg, in the Stroke Prevention by Oral Thrombin Inhibitor in Atrial Fibrillation [SPORTIF] trial and others).

■ ASSESSING THE VALUE OF ABLATIVE APPROACHES

The recognition of triggering foci that initiate AF has led to surgical and catheter-based ablative approaches that allow AF to be cured in some patients. These two types of procedures are the most promising and exciting approaches to AF management to emerge over the past several years.

The surgical maze procedure has been used with a high degree of success, and newer related approaches are now employing cryoablation or innovative methods to deliver radiofrequency or microwave energy to isolate the pulmonary vein ostia. Surgical approaches also may be combined with left atrial appendage removal or ligation.

Catheter-based ablation has been directed toward isolating pulmonary vein ostial or superior vena cava sources and has been associated with long-term success rates of 49% to 86%.[28–31] Limitations of current methods include a high rate of recurrence, leading to a need for repeat procedures, and the risk of symptomatic pulmonary vein stenosis from ablation within the pulmonary vein (~2% to 5% risk).[32] The latter has led to the use of intracardiac ultrasound and ring-type electrode catheters to isolate pulmonary vein ostia by applying ablation energy to the left atrial side rather than inside the pulmonary vein ostia. Circumferential ablation methods using alternative delivery techniques or energy sources (eg, ultrasound, microwave, or laser energy; cryoablation) are under investigation, as are novel imaging and navigation methods. The success of applying catheter-based ablation to the spectrum of AF patients is not yet defined, but the procedure has been used with success even in patients with chronic persistent AF.

The favorable efficacy and improving complication rates of surgical and catheter-based ablative procedures have made these potentially curative strategies a hopeful treatment option for many patients with refractory symptomatic AF. Whether and when the benefits of these procedures outweigh the risks are questions that arise more and more often in the management of individual patients. Whether to proceed with current ablative methods or await future advances, albeit at an older age, is a decision that faces many patients today. As technological advances further improve efficacy and safety, both the surgical and catheter-based procedures will likely become viable options for more patients.

■ SUMMARY AND IMPLICATIONS

Treatment of patients with AF should aim to reduce the risk of AF-related mortality and morbidity, including thromboembolic events, symptoms, and hemodynamic effects, and to ameliorate the effects of structural and electrical remodeling induced by the arrhythmia. Both rate-control and rhythm-control strategies are reasonable primary approaches. For some patients, cure of AF may be possible via catheter-based or surgical ablation techniques. Evidence-based selection of a strategy from the palette of treatment choices **(Figure 2)** requires an understanding of each patient's presentation and individual needs and of the risks and benefits of each option. Broadly applicable interventions to reduce the mortality associated with AF remain elusive, but reduction in thromboembolic risk with warfarin may contribute to improved prognosis.

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Approaches to restoring and maintaining normal sinus rhythm

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I. Pharmacologic management: Often insufficient, but still first-line

David O. Martin, MD, MPH

The primary strategies in managing patients with atrial fibrillation (AF) are rate control, termination of the arrhythmia, and prevention of recurrences and thromboembolic events. Although there have been great advances in nonpharmacologic therapies to achieve these aims, drug therapy remains first-line treatment for patients with AF. This review briefly profiles the drugs most commonly used for rhythm control in AF, concluding with general recommendations for their use.

DRUG CLASSIFICATION, GENERAL ISSUES

Antiarrhythmic drugs used to treat AF may be classified in a number of ways, but the most widely used is the modified Vaughan Williams classification, which is outlined in **Table 1**. The class II and IV antiarrhythmic drugs, along with digoxin, are useful for controlling the ventricular response rate during AF, whereas the class I and III drugs are useful for terminating AF and for maintaining sinus rhythm.

Class I agents are sodium channel blockers, whereas class III agents are generally potassium channel blockers. Class IA agents prolong conduction and repolarization, whereas class IC agents only prolong conduction and have little effect on repolarization. Class III agents prolong action potential duration. Moricizine, usually categorized as a class IC agent, has been used to treat AF but has not been well studied for this indication and will not be discussed here.

Prevention of AF recurrence at 1 year averages about 50% for all the class I and class III antiarrhythmic drugs except amiodarone, which prevents recurrence at 1 year in about 65% of patients.[1] Despite this modest efficacy advantage, amiodarone also has the greatest potential for end-organ damage and is therefore not the drug of first choice in all patients with AF.

Indeed, safety and efficacy are together the most important considerations in selecting drugs for treating AF, followed by cost, convenience of dosing to enhance patient adherence, safety of outpatient initiation, drug metabolism, and drug–drug interactions.

CLASS IA ANTIARRHYTHMICS

Quinidine

Actions. First described in 1848, quinidine is the oldest membrane-active antiarrhythmic drug. It is the *d*-isomer of quinine, and both are found in the bark of the cinchona tree.

Quinidine is effective for both acute cardioversion and maintenance of sinus rhythm. It affects depolarization by blocking sodium channels and repolarization by blocking potassium channels. Its net electro-

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Disclosures: Drs. Martin, Saliba, Belden, Marrouche, and Natale have indicated that they have no commercial affiliations or interests that pose a potential conflict of interest with this article. Dr. McCarthy has indicated that he is a consultant to the AtriCure and Epicor Medical corporations. Dr. Gillinov has indicated that he is a consultant to the AtriCure, Edwards Lifesciences, and Medtronic corporations.

physiologic effect results from a complex interaction of actions on various inward and outward currents. By blocking muscarinic receptors, quinidine also acts as a vagolytic. Because this vagolytic effect can enhance conduction through the atrioventricular (AV) node, the ventricular response rate during AF may increase. This underscores the importance of beginning treatment with an AV nodal blocking agent in most cases.

Safety. Quinidine is associated with a higher rate of side effects compared with newer antiarrhythmic drugs. Abdominal cramping and diarrhea occur in one third of patients.[2] Cinchonism (decreased hearing, tinnitus, and blurred vision) is also reported. Because quinidine can be proarrhythmic and cause torsades de pointes, it should be initiated in the hospital with continuous electrocardiographic monitoring. A meta-analysis of six randomized trials of quinidine for the treatment of AF suggested an increased mortality rate (2.9%) in patients receiving the drug compared with patients receiving placebo (0.9%).[3]

Role. Because other antiarrhythmic drugs have similar efficacy with fewer side effects, quinidine is not a first-line agent for the treatment of AF.

Procainamide

Actions. Procainamide entered clinical use in 1951. Its electrophysiologic effects are similar to those of quinidine, although it has little effect on the parasympathetic nervous system. The drug is metabolized in the liver to the active metabolite *N*-acetylprocainamide, which has class III antiarrhythmic activity.

Safety. Gastrointestinal side effects occur in 25% of procainamide recipients and are dose-related. Antinuclear antibodies form in approximately 80% of patients, most of whom serologically convert in the first few months of therapy. Lupus develops in 30% of patients who use the drug on a long-term basis.[2]

Torsades de pointes also may occur, so continuous monitoring should accompany drug initiation. Dosage adjustments are required for patients with renal or hepatic dysfunction or with heart failure.

Role. Because of its side effects, procainamide is not a first-line agent for the treatment of AF.

Disopyramide

Actions. Disopyramide was approved for use in the United States in 1977. Like quinidine, disopyramide is vagolytic. It is a potent negative inotrope and should be avoided in patients with systolic dysfunction. Conversely, in patients with diastolic dysfunction, ventricular performance may improve with this drug.

TABLE 1
Antiarrhythmic drugs used to treat atrial fibrillation

Class IA agents
Disopyramide (Norpace and others)
Procainamide (Procanbid and others)
Quinidine (Quinidex and others)

Class IC agents
Flecainide (Tambocor)
Propafenone (Rythmol)
Moricizine (Ethmozine)

Class II agents
Beta-blockers (eg, metoprolol)

Class III agents
Amiodarone (Cordarone and others)
Dofetilide (Tikosyn)
Ibutilide (Corvert)
Sotalol (Betapace AF)

Class IV agents
Calcium channel blockers (eg, verapamil, diltiazem)

Safety. Anticholinergic side effects occur in one third of patients and include dry mouth, blurred vision, constipation, and urinary retention.[2] Like other drugs that prolong repolarization, disopyramide may induce torsades de pointes in some patients. Dosing adjustments may be required in patients with hepatic or renal dysfunction.

Role. Like the other class IA agents, disopyramide is not a first-line agent for patients with AF, owing to its side-effect profile.

■ CLASS IC ANTIARRHYTHMICS

Flecainide

Actions. Flecainide was introduced in the United States in 1985 and was approved for treating supraventricular arrhythmias in 1991. It is useful for the acute termination of AF and for maintenance of sinus rhythm. Prolongation of atrial refractoriness is probably the mechanism by which it terminates AF. Like disopyramide, flecainide has negative inotropic effects and should be avoided in patients with severe left ventricular dysfunction or a history of heart failure.

Safety and role. Although side effects are uncommon, central nervous system adverse reactions include blurred vision, headache, and ataxia.[2] Because flecainide was associated with increased mortality in the Cardiac Arrhythmia Suppression Trial,[4] it should be avoided in patients with coronary artery disease. However, in patients with structurally normal hearts, flecainide is both safe and effective and

can be recommended as first-line therapy.

Dosing. A single 300-mg oral loading dose can successfully convert recent-onset AF. Flecainide can be started at a dosage of 50 mg every 12 hours and increased by 50 mg per dose every 3 to 5 days, to a maximum of 200 mg every 12 hours. The QRS duration should be monitored before each dosage adjustment, and it is safest not to allow the duration to increase more than 20% over baseline. We typically initiate flecainide therapy on an outpatient basis. Generally, an AV nodal blocker should be given with flecainide to prevent 1:1 conduction if slow atrial flutter ("IC flutter") should occur.

Propafenone

Actions. Propafenone was approved for use in the United States in 1989. It has electrophysiologic properties similar to those of flecainide. Unlike flecainide, it demonstrates nonselective beta-adrenergic blocking as well as a mild calcium channel blocking effect. Propafenone has a negative inotropic effect that is less pronounced than that of disopyramide or flecainide.

Safety. Nausea, dizziness, and a metallic taste are the most common side effects. Blurred vision, paresthesias, constipation, elevated liver enzyme levels, and conduction abnormalities also may occur.[2]

Role and dosing. In patients with structurally normal hearts, propafenone is safe and effective and can be recommended as first-line therapy. A single 600-mg oral loading dose can successfully convert recent-onset AF. The dosage for long-term use is 150 to 300 mg every 8 hours. We generally initiate propafenone on an outpatient basis.

■ CLASS III ANTIARRHYTHMICS

Sotalol

Actions. Sotalol was approved in the United States in 1992 for ventricular arrhythmias and in 2000 for AF (Betapace AF). It is a racemic mixture of *d*- and *l*-isomers and has both class III and beta-blocking actions. Almost all of its beta-blocking activity resides in the *l*-isomer. In contrast to the antiarrhythmic drugs discussed so far, sotalol exhibits reverse use-dependent behavior (ie, its pharmacologic effects are greater at lower heart rates). It is eliminated largely unchanged in the urine. The dosage should be reduced in patients with renal dysfunction.[5]

Sotalol is ineffective in terminating AF but is effective in preventing AF recurrences. Although *d*-sotalol was associated with increased mortality in patients with coronary artery disease in the Survival with Oral *d*-Sotalol (SWORD) trial,[6] the racemic mixture has been found safe in patients with coronary artery disease.

Safety and role. Sotalol is generally well tolerated. Its main side effects stem from its beta-blocking properties (eg, bronchopasm). Sotalol may also cause torsades de pointes, particularly in patients with hypokalemia or renal failure. Because of the risk of proarrhythmia, sotalol therapy should be started in the hospital setting. Sotalol is a first-line agent for the treatment of AF in patients with a normal or near-normal (≥40%) left ventricular ejection fraction.

Dofetilide

Actions. Dofetilide is the most recently approved antiarrhythmic drug (1999) and is among the most rigorously studied. The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D)[7] and the European and Australian Multicenter Evaluative Research on Atrial Fibrillation (EMERALD)[8] studies found dofetilide to be superior to placebo (SAFIRE-D) and to low-dose sotalol (EMERALD) in converting patients with persistent AF to sinus rhythm. In the two Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) trials,[9,10] one involving patients with heart failure and one involving patients with recent myocardial infarction and left ventricular dysfunction, dofetilide demonstrated efficacy in restoring sinus rhythm and had a neutral effect on mortality. These trials showed that, when appropriately used, dofetilide is safe and efficacious in patients with ischemic or nonischemic cardiomyopathy.

Dofetilide increases action potential duration in the atria and ventricles, though this effect is more pronounced in the atria. Its mechanism of action is blockade of the cardiac ion channel carrying the rapid component of the delayed rectified potassium current. Dofetilide has no effect on sodium channels (class I effect), beta-adrenergic receptors, or alpha-adrenergic receptors.

Safety. Like all class III antiarrhythmics, dofetilide increases the QT interval and may cause torsades de pointes. This risk is minimized by adjusting the dose according to the patient's creatinine clearance and closely monitoring the patient in the hospital during drug initiation. Other than the increased risk of proarrhythmia, dofetilide's reported side effects were similar to those reported with placebo.

A number of important drug–drug interactions must be considered when using dofetilide. It should

not be used with verapamil, cimetidine, trimethoprim, ketoconazole, thiazide diuretics, phenothiazines, tricyclic antidepressants, and some macrolide antibiotics.

Role. Dofetilide is a first-line agent for treating AF in patients with structural heart disease. Physicians must receive special education in order to prescribe dofetilide; details on how to become a prescriber are available at *www.tikosyn.com*.

Ibutilide

Actions. Introduced in 1996, ibutilide is an injectable agent approved for the acute termination of atrial flutter and AF. Unlike other class III agents, it prolongs action potential duration by enhancing a slow inward sodium current rather than by blocking outward potassium currents. It is usually given as a 10-minute intravenous infusion, with an initial dose of 1 mg followed by a second dose of 0.5 to 1 mg if needed.

Safety. Ibutilide's most significant potential adverse effect is torsades de pointes, which has been reported in about 8% of patients.[11] Continuous monitoring is necessary for rapid detection and appropriate treatment of ibutilide-induced proarrhythmia.

Role. Ibutilide is not useful for chronic therapy but is a first-line agent for the pharmacologic cardioversion of AF. In addition to this role, ibutilide lowers the defibrillation threshold for AF and can be used in combination with electrical cardioversion when electrical cardioversion alone has failed.

Amiodarone

Actions. Amiodarone was developed as an antianginal drug but was later found to have antiarrhythmic properties and was introduced in 1986. It is generally categorized as a class III antiarrhythmic, though it has properties of all four classes. Amiodarone has unique pharmacokinetics. It is highly lipid-soluble, and because a long time is required for adequate loading to saturate body lipids, drug levels build up slowly with repeated doses. Plus, the very large lipid stores act as a massive drug reservoir when treatment is stopped, resulting in a very long elimination half-life (about 50 days).[5]

Safety. Amiodarone is associated with a variety of adverse effects, including pulmonary fibrosis, corneal microdeposits, skin photosensitivity, gray-blue skin discoloration, and reversible liver enzyme abnormalities. Central nervous system side effects are relatively common and include anxiety, tremor, headaches, and peripheral neuropathy.[5] Hypothyroidism also is relatively common. Although QT prolongation occurs often, torsades de pointes is uncommon.

Role. Other than dofetilide, amiodarone is the only antiarrhythmic that has been found safe and effective in patients with moderate to severe left ventricular dysfunction. Like dofetilide, amiodarone is a first-line agent for patients with AF and structural heart disease. It also is useful for patients with renal disease. Because of its potential for organ toxicity, we generally reserve amiodarone as a second- or third-line agent for other types of patients with AF.

■ SUMMARY AND RECOMMENDATIONS

For patients with AF and structurally normal hearts, the class IC agents, flecainide and propafenone, are first-line choices for maintaining sinus rhythm. Sotalol and dofetilide are also effective for this patient population. Because of its potential for organ toxicity, amiodarone should be reserved as a third-line option for these patients.

For patients with coronary artery disease and a left ventricular ejection fraction of 40% or greater, sotalol and dofetilide are first-line agents. For patients with an ejection fraction less than 40%, dofetilide and amiodarone are the drugs of choice.

Because the class IA agents are not as well tolerated as the class IC and III drugs, they should be reserved as third-line agents for patients with AF.

Although many patients with AF can be managed with drug therapy alone, many others continue to have symptoms related to AF despite optimal drug therapy. For these latter patients, nonpharmacologic therapies—the focus of the rest of this article—should be considered.

II. Pacing and devices: Progress toward a preventive role

Walid Saliba, MD

While permanent pacing is required for patients with AF who have symptomatic bradycardia, the concept of pacing for the primary prevention of AF is new. New pacing algorithms, biatrial and dual-site atrial pacing, and site-specific pacing have all been studied as substrate modulators to prevent recurrent AF. Other studies have assessed the use of pacing algorithms and device-based internal cardioversion for early termination of AF. This review briefly surveys the use of pacing to reduce the recurrence of

AF, focusing on progress to date, remaining questions and clinical challenges, and the potential roles of pacing in the overall management of AF.

■ RATIONALE FOR PACING IN ATRIAL FIBRILLATION

As detailed earlier in this supplement, several electrophysiologic mechanisms are thought to initiate and perpetuate AF. Early studies noted that AF episodes were initiated by a premature atrial contraction or were bradycardia-dependent following a long short cycle. Thus, pacing can potentially treat AF in a number of ways. Controlling the atrial rate may prevent the arrhythmogenic consequences of bradycardia-induced dispersion of atrial refractoriness, and overdrive suppression of premature atrial complexes (PACs) may prevent initiation of the arrhythmia. Furthermore, multisite pacing and pacing at nonconventional sites may improve intra-atrial conduction delays, correct atrial asynchrony, and reduce abnormal activation caused by conduction blocks. This may result in "resynchronization" of atrial activation and more homogeneous refractoriness throughout the atria, which would prevent reentry and make the atrial substrate less conducive to sustaining AF. In addition, maintenance of AV synchrony with atrial pacing may reduce the detrimental hemodynamic effects induced by ventricular pacing, which can lead to stretch-induced changes in atrial refractoriness and thus predispose to AF.

■ PACING TO PREVENT ATRIAL FIBRILLATION

Importance of pacing mode

Several studies have shown the benefit of atrial, or dual-chamber, pacing over single-chamber, or ventricular, pacing for the prevention of chronic AF in patients with sick sinus syndrome. In the Mode Selection Trial (MOST),[12] 2,010 patients with sick sinus syndrome were randomized to either dual-chamber pacing (with a DDDR pacemaker) or ventricular pacing (with a VVIR pacemaker). Over a median follow-up of 3 years, AF developed in 24% of the study population, and 22% of these patients progressed to chronic AF. Dual-chamber pacing was associated with a lower rate of progression to chronic AF as compared with ventricular pacing (15.2% vs 26.7%; hazard ratio 0.44).

Similarly, patients undergoing pacemaker placement, regardless of the initial indication, are more likely to remain free of AF if they receive a physiologic (AAI/DDD) pacemaker rather than a ventricular pacemaker. In the Canadian Trial of Physiologic Pacing (CTOPP),[13] 2,568 patients undergoing initial pacemaker implant were randomized to a VVIR device or a DDDR device. Over a mean follow-up of 3 years, physiologic pacing (DDDR) was associated with a 27% relative reduction in the risk of chronic AF compared with ventricular pacing (2.8% per year vs 3.8% per year). Notably, this advantage with physiologic pacing was not apparent until 2 years after implantation, and follow-up to 7 years has shown that this incremental benefit continues to increase. Patients with an intrinsic heart rate less than 60 beats per minute (bpm) were the most likely to benefit from physiologic pacing for the prevention of chronic AF.[14]

This raises the question of whether atrial pacing prevents chronic AF in patients without a bradycardia indication for pacing. The first phase of the Atrial Pacing Periablation for Paroxysmal Atrial Fibrillation (PA-3) study[15] randomized 97 patients to either no pacing (DDI mode at a rate of 30 bpm) or atrial pacing with DDI mode at 70 bpm for 12 weeks prior to AV node ablation for paroxysmal AF. The study found no significant difference between the two groups in overall AF burden or in the time to first AF occurrence. Furthermore, following AV node ablation (second phase of the PA-3 study),[16] the AF burden increased over time, with no difference according to whether patients were randomized to atrial pacing (DDDR mode) or to no atrial pacing (VDD mode).

Similarly, phase 2 of the Atrial Fibrillation Therapy (AFT) study[17] examined the effects of DDD pacing at 70 and 85 bpm, with or without rate response, versus "support" pacing (DDD pacing at 40 bpm) in patients with paroxysmal AF. There was no significant difference between patients in the various rate groups in terms of mean AF burden, AF recurrence, or mean duration of sinus rhythm between episodes.

In summary, it remains unclear whether fixed conventional atrial pacing can prevent the development of chronic AF, and it is not wholly clear whether the difference in AF rates between atrial and ventricular pacing is due to an antiarrhythmic effect on the part of atrial pacing or perhaps a proarrhythmic effect on the part of ventricular pacing.

Site-specific pacing

A number of trials have studied pacing at specific sites for the prevention of AF, but most have been small and had short follow-up periods. The rationale for

site-specific pacing is to reduce the duration of atrial activation by targeting pacing to sites along the septum at interatrial connections, such as the coronary sinus os inferiorly or the Bachmann bundle superiorly.

The Atrial Septal Pacing Efficacy Clinical Trial (ASPECT)[18] showed that a septal lead position reduces interatrial conduction time; pacing near the coronary sinus ostium (posterior to the triangle of Koch) was superior to pacing at the midseptum position in shortening P-wave duration. In a randomized trial by Bailin et al,[19] pacing in the area of the Bachmann bundle (high interatrial septum) was associated with a significant reduction in the development of chronic AF compared with pacing from the right atrial appendage. Similarly, Kale et al[20] showed that atrial septal pacing in conjunction with antiarrhythmic drug therapy resulted in a complete or marked subjective improvement in symptoms in 68% of patients with AF previously refractory to antiarrhythmic drugs. Objective data supported these findings, showing that paroxysmal AF was prevented in 60% of the study's patients. These data are encouraging, but larger studies are needed.

Ultimately, it may prove more beneficial to combine septal pacing with other pacing modalities, such as biatrial or dual-site atrial pacing, or with algorithms for AF suppression in the newer generation of pacemakers. For instance, El Allaf et al[21] showed that combining pacing in the low atrial septum with an algorithm for dynamic atrial overdrive reduced the AF burden by 82.2% in a group of 30 patients.

Dual-site or biatrial pacing

Dual-site right atrial pacing and biatrial pacing have produced modest beneficial effects. The Dual-Site Atrial Pacing to Prevent Atrial Fibrillation (DAPPAF) study[22] compared dual-site right atrial pacing, single-site right atrial pacing, and support pacing modalities for AF prevention. Dual-site pacing showed incremental benefit over single-site pacing, and this benefit was derived almost exclusively among the subgroup of patients receiving antiarrhythmic drugs. Among these patients, dual-site pacing reduced the risk of AF recurrence and prolonged the time to first recurrence compared with single-site pacing. A full 72% to 80% of patients who received dual-site pacing and antiarrhythmic drug therapy were free from AF recurrence at 6 months,[22] which compares favorably with the 30% to 60% rates historically reported with antiarrhythmic drug therapy alone.

Thus, dual-site right atrial pacing appears to potentially confer an additional AF-suppressing benefit as part of "hybrid" therapy in patients already on antiarrhythmic drugs. However, a small study by Ramdat Misier et al[23] showed only a modest improvement with biatrial pacing over single-site atrial pacing (high right atrium) in terms of the AF-free duration and time to first AF recurrence, even among patients who were also receiving antiarrhythmic drugs.

Attempts at atrial resynchronization with biatrial pacing, with or without overdrive suppression algorithms, have also been studied, with variable success. Mirza et al[24] reported a significant reduction in AF episodes with biatrial pacing among 16 of 19 patients studied. The optimal lead sites were at the high right atrium and distal coronary sinus, and simultaneous pacing conferred no benefit over sequential (interatrial delay) pacing.

Suppressive pacing algorithms

As the beneficial effects of atrial pacing have come to be recognized, investigators have evaluated the characteristics and effectiveness of various atrial pacing algorithms to prevent AF recurrence. Individual components of these algorithms can generally be assigned to the following groups:

- Dynamic rate overdrive pacing
- Pacing for prevention of short long cycles (post-PAC pacing)
- Overdrive suppression of ectopic activity after atrial premature beats
- Prevention of early reinitiation of AF after sinus conversion
- Prevention of AF following exercise
- Circadian rhythm variation.

Various algorithms incorporating combinations of these components have been evaluated for AF prevention in a number of clinical trials. **Table 2** summarizes eight of these studies.[17,18,25–29]

Overall, two of the studies showed beneficial responses to atrial pacing algorithms. In phase 3 of the Atrial Fibrillation Therapy (AFT) trial,[17] the mean AF burden decreased by 30.4% with all algorithms programmed "on," and the duration of sinus rhythm increased from 23 to 59 days. In the Atrial Dynamic Overdrive Pacing Trial (ADOPT-A),[27] the mean AF burden was reduced by 25% with the algorithm turned on. There also was a 63% reduction in the number of cardioversions and a 60% reduction in the mean number of AF episodes among patients with the algorithm turned on. However, 45% of patients demonstrated a benefit from standard DDDR pacing

TABLE 2
Selected trials of algorithm-based pacing to prevent atrial fibrillation

Study/ investigators	No. pts	Study design	Pacing mode/site	Pacing algorithm(s)	Length of follow-up	Reduction in AF burden
Padeletti et al[25]	46	R, P, CO	DDDR; IAS or RAA	CAP on vs off	6 months	Not significant
AT500[26]	325	L, P	DDDR	3 algorithms* on + ATP	3 months	Not significant
ADOPT-A[27]	288	R, P	DDDR 60 bpm	DAO on vs off	6 months	25%
AFT (phase 3)[17]	92	R, P	DDD 70 bpm	4 algorithms† on vs off	2 months	30%
ASPECT[18]	294	R, P, CO	DDDR; IAS or RAA	3 algorithms* on vs off	6 months	Not significant
ATTEST[28]	370	R, P	DDDR	3 algorithms* on vs off ± ATP	3 months	Not significant
PIPAF 2[29]	44	R, P, CO	Dual-site DDD 70 bpm	SRO on vs off	6 months	Not significant
PIPAF 4[29]	47	R, P, CO	DDDR 70 bpm	SRO on vs off	6 months	Not significant

* Atrial preference pacing, atrial rate stabilization, and postmode switch overdrive pacing

† Premature atrial complex (PAC) suppression, postexercise response, atrial overdrive pacing, and post-PAC response

ATP = atrial antitachycardia pacing; **bpm** = beats per minute; **CAP** = consistent atrial pacing; **CO** = crossover; **DAO** = dynamic atrial overdrive; **IAS** = interatrial septum; **L** = longitudinal; **P** = prospective; **R** = randomized; **RAA** = right atrial appendage; **SRO** = sinus rhythm overdrive

without the need for any special algorithm.

Looking at the current data, it appears that AF-suppression algorithms may play an adjunctive role in managing paroxysmal AF in selected patients who require pacing for standard indications, such as sick sinus syndrome. These patients stand to benefit from reductions in both symptoms and costs associated with paroxysmal AF. Variations in the populations studied, differences in the pacing protocols, and a lack of uniform end points likely account for the variable results from the studies to date. It has been postulated that at least 90% atrial pacing is probably needed for any pacing protocol to be effective. Whether this is true remains to be proven.

■ PACING TO TERMINATE ATRIAL TACHYARRHYTHMIA

Since it has been suggested that AF begets AF, one can postulate that early termination of atrial tachyarrhythmia (AT; ie, AF and atrial flutter) with antitachycardia pacing or through cardioversion with an implantable cardioverter-defibrillator may prevent or delay the development of chronic AF.

Antitachycardia pacing therapy

The Atrial Therapy Efficacy and Safety Trial (ATTEST)[28] included 370 patients with primary bradycardia pacing indications as well as paroxysmal AT/AF. Patients were randomized to antitachycardia pacing plus AF-suppressive pacing or to no therapy. Among 85 patients in the "on" group, 41% of the 15,789 AF episodes were classified by the device as having a "successful termination." Nevertheless, there was no significant reduction in the AF burden (median minutes of AF per day) or AF frequency (median AF episodes per month) between the two groups over the relatively short follow-up period (3 months). However, patients in the "on" group experienced fewer long episodes of AF. This suggests that a subgroup of patients in this population might benefit from such therapy, especially with longer follow-up.

Vollmann et al[30] found that 50-Hz atrial burst pacing with a dual-chamber implantable cardioverter defibrillator (GEM III AT, Medtronic, Minneapolis) resulted in termination of only 2.4% of the device-defined AF episodes. Notably, spontaneous termination occurred anyway in 91% of the episodes. In some cases, secondary termination related to 50-Hz burst pacing was observed: conversion of AF into a more organized AT enabled antitachycardia pacing termination or vice versa, with conversion of antitachycardia pacing–resistant atrial flutter into AF that would terminate spontaneously within 2 minutes of the delivered therapy. Whether this success was related to spontaneous termination or to the effectiveness of the delivered therapy is debatable.

Overall, it appears that antitachycardia pacing does not terminate AF but may reduce AF in some patients by virtue of its effect on AT. The efficacy of antitachycardia pacing for terminating AT depends on the AT cycle length, so a hybrid approach that includes antitachycardia pacing in conjunction

with class I and III antiarrhythmic drug therapy to slow the AT rate or convert AF into AT might be important. However, the success rate may be lower than the reported device-defined "success" rates, since most episodes terminate spontaneously.

Internal cardioversion

Internal cardioversion is an effective means for early conversion of AF into sinus rhythm, and is now possible using stand-alone atrial defibrillators (Metrix, InControl, Redmond, WA) or in conjunction with ventricular defibrillators (Jewel AF, Medtronic, Minneapolis). The latter device includes tiered atrial therapy in addition to atrial conversion. In a study involving the Metrix device,[31] 105 patients with recurrent, drug-refractory AF received Metrix implants, with the shock coils situated in the right atrium and distal coronary sinus. Shock efficacy was 90% over a 1-year follow-up, with an average of 1.6 shocks delivered per episode. Successful therapy was associated with high satisfaction and only moderate discomfort. However, there was only modest evidence that early cardioversion from AF resulted in subsequent lengthening of the period of sinus rhythm.

■ 'ABLATE AND PACE' FOR SYMPTOM RELIEF

In about 10% of patients with recurrent or persistent AF, symptom relief and ventricular rate control with medical therapy remain problematic. In these patients, AV junction ablation with pacemaker placement is usually the only remaining option.

This "ablate and pace" approach has been accepted largely on the basis of small uncontrolled trials with diverse clinical outcome measures. A meta-analysis[32] of 21 such studies comprised 1,181 patients and 19 clinical outcome measures, including symptoms, quality-of-life scores, exercise function, cardiac performance, health care utilization, and drug utilization. The analysis showed significant improvement in 18 of the 19 measures examined. These results are consistent with findings from Ozcan et al,[33] who studied 350 patients with AF who underwent AV junction ablation and pacemaker placement and compared them with 229 historical controls with AF who were treated with antiarrhythmic drugs. They found no difference in long-term mortality between the two groups over 6 years of follow-up, suggesting that the "ablate and pace" approach appears to be safe and effective in this patient population. However, there is still an ongoing risk of thromboembolism, along with the resulting lifelong pacemaker dependency.

Ventricular rate regularization also has been studied as a means for symptom relief in patients with AF, although small preliminary trials have found an inconsistent effect on ventricular function and quality of life. It may be that the potential improvement in ventricular function is offset by the potential detrimental effect of increased frequency of right ventricular pacing. Overall, it appears that rate control is more important than rate stabilization in terms of symptom relief and cardiac performance (ejection fraction). In patients in whom AV junction ablation is planned, placement of a pacemaker and an initial trial of ventricular rate regularization can be considered. If there is a suitable response, the patient may not need AV junction ablation; if not, nothing is lost and ablation can still be performed.

■ CONCLUSIONS

Device-based therapy involving specific sites of stimulation combined with overdrive pacing algorithms shows promise for reducing the incidence of paroxysmal AF and delaying the development of persistent AF. Still, debate continues over valid end points in AF trials, and future comparative analyses of pacing devices and other therapies for AF will require a clearer separation between mathematically defined and clinically defined measures.

Interventions that do not show significant benefits in the short term might potentially confer benefit over longer follow-up, especially when combined with other therapies. Hybrid therapy that combines two or more treatment modalities for AF—antiarrhythmic drugs, various atrial pacing protocols, multiple-site or site-specific pacing, and even ablation—offers the physician a wide range of options for attempting to maintain normal sinus rhythm. However, because of the progression of the disease process in the atria, these interventions are often only temporary.

AF-suppression algorithms are likely to become an integral and essential component of future pacing devices. Whether or not pacing has a primary therapeutic role in patients who do not require a pacemaker for symptomatic bradycardia remains the object of future research. However, for patients who require a pacemaker for standard indications and who are at risk for AF, a device with an AF-suppression algorithm offers another welcome therapeutic option. In the final analysis, the various modalities of atrial pacing can prevent AF at some times and in some patients.

III. Surgical approaches: At the 'tipping point'

Patrick M. McCarthy, MD, and A. Marc Gillinov, MD

Cardiac surgeons confront the problem of AF in two types of patients:

- Those with a history of AF who are scheduled to undergo a cardiac operation
- Those with symptomatic lone AF in whom medical therapy and catheter ablation have failed.

Surgery has been a treatment option for AF since the clinical introduction of the Cox maze procedure, considered the "gold standard" curative approach to AF, more than 13 years ago. Since then, the maze procedure has been associated with a low risk of perioperative morbidity and mortality, and recent reports document late freedom from AF in 90% to 98% of patients, a less than 1% risk of thromboembolic events, and excellent quality of life.[34–37] Nevertheless, the maze procedure has not been widely adopted because it is complex, unfamiliar to most cardiac surgeons, and difficult to add to other complex surgical procedures (such as reoperations, multiple valve procedures, and operations in patients with poor ventricular function). **Figure 1** provides a snapshot and very general description of the procedure.

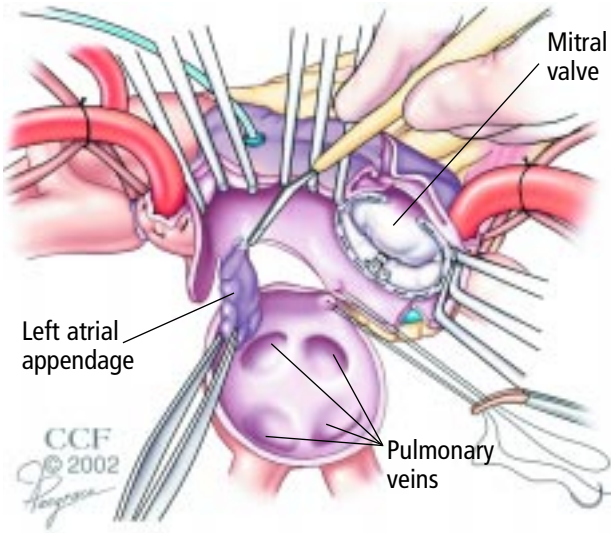

Figure 1. Left-side incisions for the classic maze procedure:
- **Encircle all four pulmonary veins**
- **Excise the left atrial appendage**
- **Extend to the mitral annulus with cryolesions placed at the annulus and on the coronary sinus.**

The left atrial incisions electrically isolate all four pulmonary veins, reduce the size of the left atrium, and eliminate the potential macro reentry circuits that maintain atrial fibrillation. Right atrial lesions are also typically performed as part of the maze procedure.

Despite this lack of wide adoption, surgery for AF has reached a "tipping point" with the convergence of new technologies, improved understanding of the pathogenesis of AF, and development of minimally invasive cardiac surgical techniques. This is reflected in the broader application of surgical procedures for AF. For instance, at the Cleveland Clinic the maze procedure was performed in about 20 patients each year during the 1990s, generally in patients with chronic AF undergoing mitral valve repair and occasionally as an isolated procedure in patients with lone AF. In 2002, however, the maze procedure or a more limited operation for AF was performed in more than 300 patients at the Cleveland Clinic. This represented about 9% of all patients undergoing cardiac surgery at our institution. These 300-plus patients included some with lone AF; some with a history of AF who needed valve surgery, coronary artery bypass grafting, or myectomy for hypertrophic obstructive cardiomyopathy; and a few with poor ventricular function or who were undergoing complex reoperations.

■ THE CLEVELAND CLINIC EXPERIENCE

Because data from large series of patients undergoing open heart surgery for AF are limited, we have reviewed the Cleveland Clinic experience.

The maze procedure was first performed at the Cleveland Clinic in 1991 and was performed 312 times through the end of 2001. In 2001 (the most recent year for which complete data are available), patients at our institution underwent the maze procedure in a variety of clinical settings, as detailed below:

- 37% of maze procedures were for lone AF
- 27% were in conjunction with mitral valve repair
- 11% were in conjunction with mitral valve replacement
- 11% were in conjunction with coronary artery bypass graft surgery
- 14% were in conjunction with other procedures, including myectomy for hypertrophic obstructive cardiomyopathy.

The operative mortality was 1.9%, and in only 1 patient was death related to the surgical procedure.[38] Late stroke or systemic thromboembolism was rare, occurring in only 0.9% of patients. As with all car-

Intraoperative pulmonary vein isolation: A practical alternative to maze

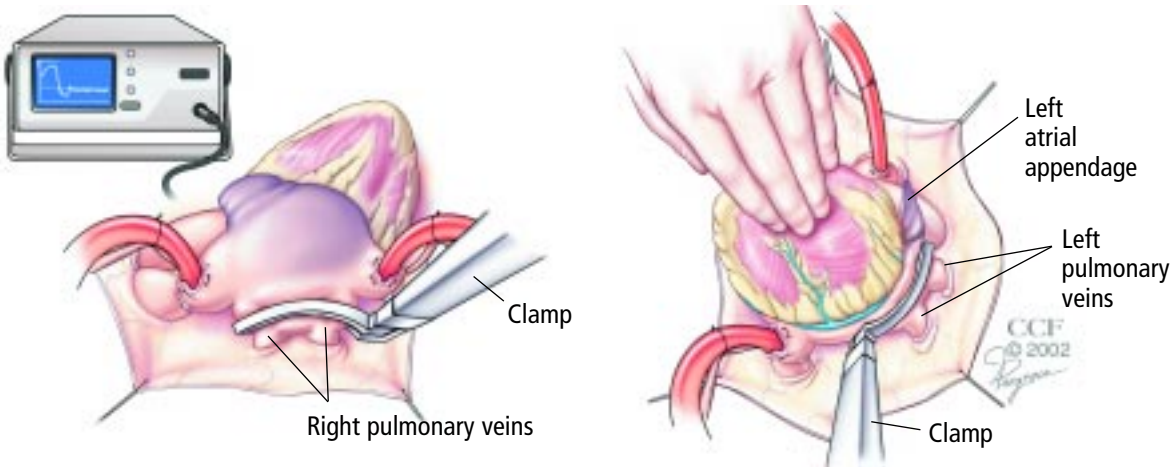

Figure 2. The AtriCure bipolar radiofrequency clamp is placed on the left atrium (not directly on the pulmonary veins) to electrically isolate the site of atrial fibrillation initiation from the pulmonary veins. The illustration on the left shows electrical isolation of the right pulmonary veins. The illustration on the right shows electrical isolation of the left pulmonary veins, with the left atrial appendage stapled closed. This procedure can be performed with or without cardiopulmonary bypass, and new technologies allow it to be performed with minimally invasive incisions. Reprinted from reference 42 with permission from the Society of Thoracic Surgeons.

diac operations, perioperative AF was common and occurred in more than 40% of patients (see "Postoperative Management" below for treatment of patients with perioperative AF; patients without perioperative AF receive no antiarrhythmic drug). Freedom from AF more than 6 months after surgery has been achieved in 97% of patients with lone AF and in approximately 95% of patients with AF who underwent mitral valve surgery.

The Cleveland Clinic results with the maze procedure are similar to those in the literature, including greater than 90% efficacy in treating AF, a less than 1% risk for late strokes, and improved quality of life.[34,36,37,39,40]

Intraoperative pulmonary vein isolation. Identification of the pulmonary veins as an important initiating site for AF,[41] coupled with the success of pulmonary vein isolation in selected patients, opened up the possibility of AF surgery in more patients. We began using intraoperative pulmonary vein isolation in 1999, typically with left atrial appendage exclusion, for patients with preoperative AF undergoing complex surgery and for patients who are elderly or have extensive comorbidities. By the end of 2001, 28 patients had undergone pulmonary vein isolation in conjunction with a variety of other cardiac operations, with no operative mortality and with 86% of patients free from AF during a mean follow-up of 6 months.

The lesions involved in pulmonary vein isolation are far less complex than the complete maze lesions, and a bipolar radiofrequency clamp released in November 2001 makes it fast, simple, and practical to create these lesions **(Figure 2)**.[42]

POSTOPERATIVE MANAGEMENT

We use propafenone (which lengthens the atrial refractory period) in patients who develop postoperative AF and who have a left ventricular ejection fraction of 35% or greater **(Figure 3)**. For patients with postoperative AF and an ejection fraction less than 35%, we begin amiodarone. Patients with normal sinus rhythm after the operation who do not have other indications for warfarin (such as mechanical valves) receive aspirin. If an individual patient has recurrent perioperative episodes of AF, warfarin is used. Patients are encouraged to have close follow-up with their physician for periodic electrocardiograms during the first 3 months after returning to the community. If a patient has no further episodes of AF, antiarrhythmic therapy is gradually withdrawn and stopped in 6 months. Warfarin is also withdrawn at 6 months if AF does not return.

CURRENT, FUTURE SURGICAL APPROACHES

Patients with AF before coronary artery bypass graft surgery are at higher risk for perioperative morbidity and mortality. In a recent analysis from our institution, we found that AF itself was a risk factor that increased early and late mortality, even after accounting for other variables in the patients with AF, such as increased age and poor left ventricular function.[43] As a result, we now believe that all cardiac surgery patients who have a history of AF should receive surgical therapy for AF as an adjunct to their operation. This may include the classic maze procedure or pulmonary vein isolation with excision of the left atrial appendage.

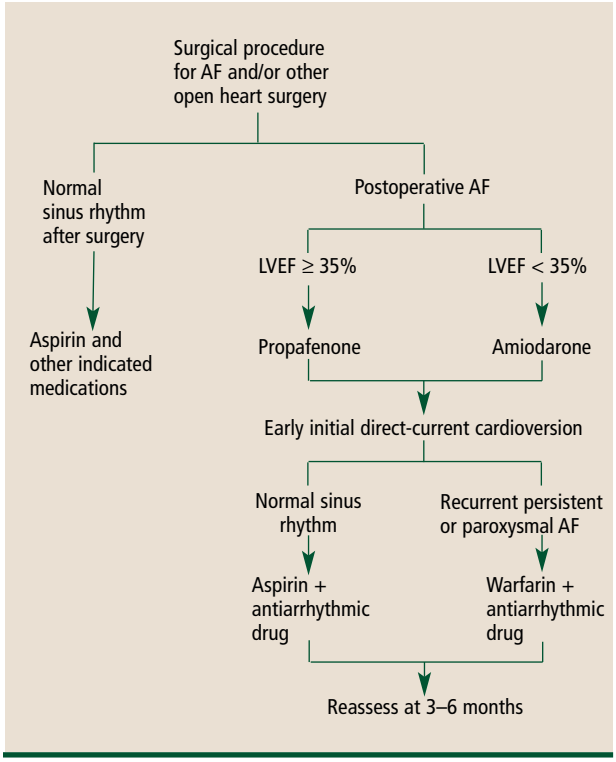

Figure 3. Algorithm for the postoperative management of patients undergoing surgery for atrial fibrillation (AF). LVEF = left ventricular ejection fraction

A variety of new technologies are available for creating atrial lesions, either as part of the maze procedure or for pulmonary vein isolation. These include unipolar and bipolar radiofrequency systems, microwave energy, ultrasound energy, lasers, and cryothermy. Our largest experience has been with bipolar radiofrequency ablation because its lesions are created quickly and are transmural. Whereas the classic cut-and-sew maze procedure adds 45 minutes onto cardiopulmonary bypass surgery, pulmonary vein isolation with bipolar radiofrequency energy adds only 5 to 10 minutes and can be performed on a beating heart.[42,44]

Several factors have brought surgery for AF to the tipping point and led to a much wider potential application:

- Remarkably positive late results with the maze procedure for restoring sinus rhythm and preventing strokes
- The introduction of minimally invasive cardiac surgery and new ablation technologies
- Recognition of the importance of the pulmonary vein in the pathogenesis of AF.

Currently, patients with lone AF who are highly symptomatic or who have a history of emboli are frequently undergoing the maze procedure. The operative mortality for this group at our institution is 0%. In many of these patients surgery is performed using minimally invasive techniques. New technologies and surgical approaches now in development or in early clinical use will allow endoscopic isolation of the pulmonary vein with left atrial appendage closure. The goal of these new technologies and procedures is a quick, low-risk operation with a very short hospital stay. While these simpler procedures may not be quite as effective as the gold standard of the maze procedure, they should be safe and at least as effective as percutaneous pulmonary vein isolation.

IV. Catheter ablation: A less invasive path to potential cure

William Belden, MD, Nassir F. Marrouche, MD, and Andrea Natale, MD

High rates of successful surgical cure of AF with the maze procedure encouraged the development of catheter-based ablation techniques designed to achieve the same success in a less invasive way.[45] The goal of both techniques is to create linear lesions in the atria, rendering the atrial tissue incapable of supporting the intra-atrial reentry necessary for the maintenance of AF. Although catheter-based maze procedures showed great promise initially, subsequent experience has been disappointing.[46] These procedures are technically demanding, time-consuming, and associated with high morbidity and complication rates. Moreover, gaps in the linear lesions were found to actually be proarrhythmic, giving rise to flutter circuits.[47]

However, experience with the catheter-based maze technique led to observations that have opened the door to effective and practical catheter-based cures for AF. Seminal work by Haissaguerre et al[41] (and confirmed by Chen et al[48]) showed that the majority of AF is initiated by ectopic foci found primarily in the pulmonary veins (PVs). While attempting catheter-based maze procedures in the left atrium, these researchers observed bursts of activity that initiated episodes of AF. Mapping of this ectopic activi-

ty localized it to sleeves of atrial tissue that invest the proximal portions of the PVs. The researchers also showed that catheter-based ablation of these ectopic foci could eradicate episodes of AF.

These findings ushered in an exciting era in AF therapy, offering the promise of a true cure for AF. In the 4 years since, two primary strategies for the ablation of PV foci have emerged:

- Electrically guided focal ablation of PV triggers
- Electrical isolation of the PV from the left atrium by way of either segmental or circumferential lesions at the PV ostium.

FOCAL ABLATION

Haissaguerre et al[41] and Chen et al[48] initially targeted individual arrhythmogenic foci within the PVs for ablation. Discharges from PVs, regardless of whether they initiate AF, are mapped with catheters in the left atrium. These discharges are identified in the mapping catheter tracing as sharp high-frequency potentials referred to as pulmonary vein potentials (PVPs).[49] These are distinct from lower-frequency potentials in the tracing, which represent activation of atrial tissue adjacent to the PV.

This focal approach has significant drawbacks. First, firing of the PVPs is required for identification and ablation of the arrhythmogenic focus. Stimulation with high-dose isoproterenol is often required to induce sufficient ectopy to allow accurate mapping; this can lead to induction of AF, requiring multiple cardioversions during the procedure. Additionally, multiple ablations are typically required within the PV to eradicate the focus, which lengthens procedure time. Finally, high rates of PV stenosis have been reported with the focal ablation technique.[50]

CIRCUMFERENTIAL PULMONARY VEIN ISOLATION

In response to the difficulties of focal ablation, an alternate strategy has been developed that seeks to electrically isolate the PV from the atrial tissue. Two approaches to isolation have evolved:

- One targets for isolation only the PVs that manifest arrhythmogenic foci, for an approach that is both electrically and anatomically guided.
- The other relies strictly on anatomy and *empirically* isolates each PV without regard for ectopic beats.

The goal in each case is to create entrance block to the PV. Multipolar circular catheters have been developed that facilitate identification of the electrical connections that are present at the junction of the atrium and the PV, and radiofrequency energy is applied in a circumferential fashion until entrance block is achieved **(Figure 4)**. In some PVs, relatively narrow bands of atrial tissue, identified by early activation on the circular catheter, often provide the sole electrical conduit between the atrium and the PV, and targeting these bands can isolate the vein with fewer ablations.

Circumferential PV isolation provides advantages over focal ablation, including a simplified procedure that can be completed without inducing AF, a shorter procedure time, and a lower incidence of PV stenosis.[51,52]

ABLATION STRATEGIES, CATHETER TECHNOLOGIES

Circumferential PV isolation is achieved primarily by one of three strategies:

- Use of electroanatomic mapping to guide delivery of radiofrequency energy
- Delivery of ultrasound energy (or energy from alternative sources) through a saline-filled, balloon-tipped catheter
- Use of circular mapping to guide delivery of radiofrequency energy.

Electroanatomic mapping uses a magnetic field to map a cardiac chamber and the precise location of an ablation catheter within it. The location of the catheter is integrated with voltage or activation data to create a three-dimensional picture of the cardiac chamber. The system is an effective aid in ablation of both atrial and ventricular arrhythmias and is well suited to mapping the anatomy and activations around PVs.

Unfortunately, results of trials using electroanatomic mapping have shown variable success. In a study of 71 patients, Kanagaratnam et al[53] reported a 21% success rate (sinus rhythm without use of antiarrhythmic drugs) after 29 ± 8 months of follow-up, a 17% incidence of severe PV stenosis (>70% narrowing), and a 20% incidence of left atrial flutter. However, Pappone et al[54] reported a much higher success rate **(Table 3)** with no PV stenosis using a similar approach.

Application of ultrasound energy through a saline-filled balloon **(Figure 5**, left panel**)** promises to avoid some of the limitations of focal ablation and to depend less on operator expertise than do other types of circumferential ablation. Our institution has reported moderate success with this anatomically guided approach in small series.[55,56] In the series with

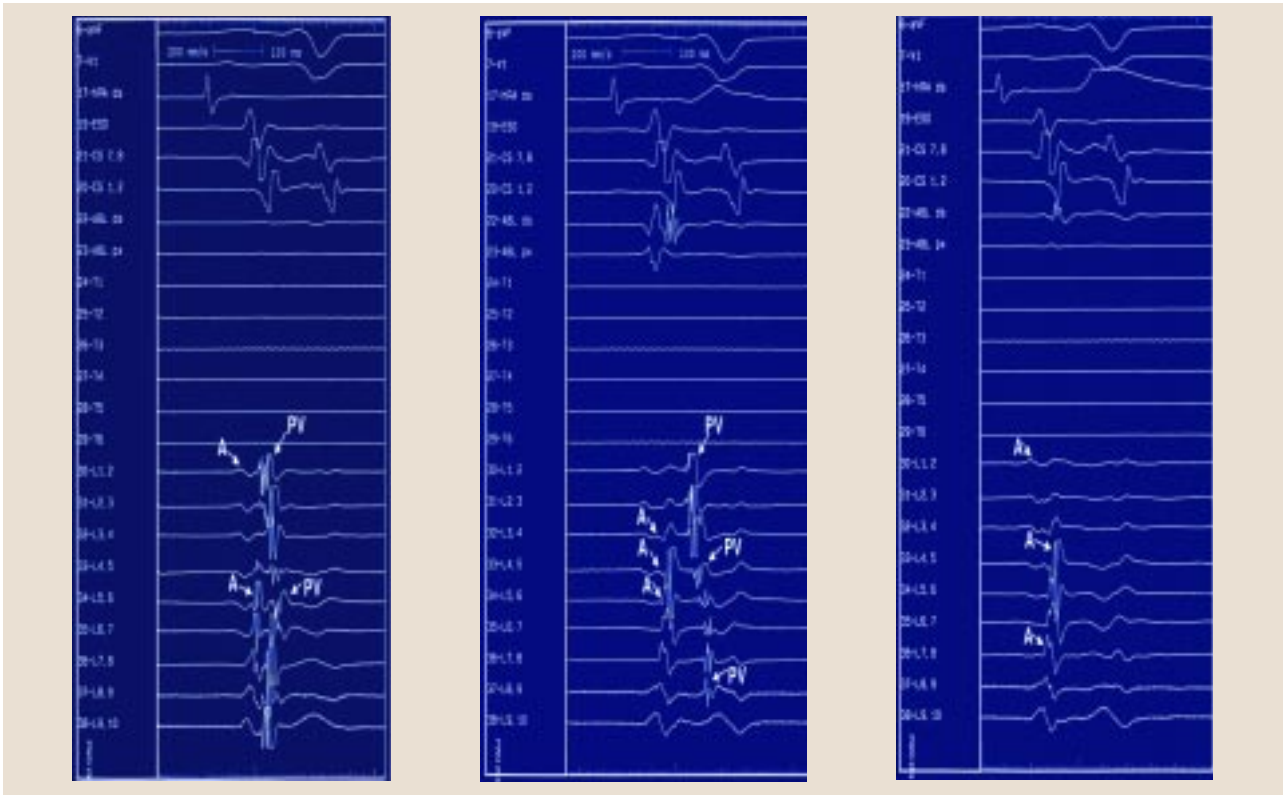

Figure 4. Left upper pulmonary vein (PV) electrograms (from $L_{1–2}$ to $L_{9–10}$) and far-field atrial potential (A) electrograms in a patient with atrial fibrillation. *Left panel:* Before ablation, PV electrograms occur early in segments $L_{1–2}$ and $L_{9–10}$. *Middle panel:* After delivery of radiofrequency energy at segment $L_{1–2}$, there is prolongation of activation into the PV. *Right panel:* Limited ablation at segments $L_{1–2}$ and $L_{9–10}$ results in isolation of the PV, with abolition of all PV electrograms.

the longer follow-up (mean of 22 months),[56] sinus rhythm was maintained in about 39% of patients and there was a single case of PV stenosis **(Table 3)**.

This limited success is likely related to the initial catheter design, reflecting ineffective energy delivery to the PV as a result of anatomic mismatch between the balloon and the highly variable PV ostia. Newer balloon systems using a variety of energy sources will soon enter clinical trials. Most of these systems have moved away from the initial concept of "radial" energy delivery and are based on the "ring" approach illustrated in the right panel of **Figure 5**.

The technique that has produced the highest success rates with the lowest complication rates is the empiric circumferential PV isolation technique described above. In a study from our institution, Marrouche et al[51] evaluated the effect of various ablation strategies and catheter technologies on the ability to cure AF. Among the 211 patients studied, the first 21 were treated with isolation distal to the PV–left atrial junction and showed disappointing results. Success was achieved in only 29% of these patients, and severe PV stenosis (> 70% narrowing by CT scan) occurred in 4%. Circumferential ablation at the ostium was performed in all nonresponding patients in this group and in the remainder of the study population. Three different ablation catheters were used: 4-mm, 8-mm, and cooled-tip. As shown in **Table 3**, the 8-mm and cooled-tip catheters were associated with higher success rates, lower complication rates, and shorter procedure times.

VALUE OF INTRACARDIAC ECHOCARDIOGRAPHY IN GUIDING ABLATION

Ultrasound technology has progressed rapidly over the past several years and is fast becoming an essential tool for many electrophysiologic procedures, including ablation for AF.[57] Phased-array echo catheters now provide high-resolution, real-time images of intracardiac structures and present Doppler imaging in a wedge-shaped image sector similar to that of standard echocardiographic modalities. The echo catheter is positioned in the right atrium.

Intracardiac echocardiography (ICE) is vastly superior to fluoroscopy. Studies have consistently found distinct advantages of ultrasonographic guidance at each step of ablation for AF.[57] These include:

- Real-time imaging of the highly variable PV ostial anatomy
- Confirmation of correct catheter position at the PV ostium **(Figure 6)**, a critical step for avoiding ablations deep in the PV (thus reducing the risk of PV stenosis)

TABLE 3
Summary of large published series of catheter-based ablation for atrial fibrillation

Study	Technique	Imaging	No. PVs targeted	No. pts	% Cured	Complications (no. or %)	Follow-up (months)	Length of procedure
Haissaguerre, 1996[45]	Maze	F	NA	45	22	Atrial flutter (19), hemopericardium (1)	11 ± 4	248 ± 79 min
Haissaguerre, 1998[41]	FA	F	Active	45	62	None	8 ± 6	NA
Chen, 1999[59]	FA	F	Active	79	86	PV stenosis (42%), CVA (2), hemothorax (1), hemopericardium (1)	6 ± 2	90 ± 32 min
Gerstenfeld, 2001[60]	FA, CA	F	Active	71	23	PV stenosis (8.3%)	60 ± 33	7.5 ± 2 hr
Sanders, 2002[61]	FA	F	Active	51	30	PV stenosis (1)	11 ± 8	NA
Natale, 2000[55]	CA	F, US	2 superior + LIPV	15	60	CVA (1)	7 ± 2	224 ± 89 min
Saliba, 2002[56]	CA	F, US	2 superior + active	33	39	CVA (1), PV stenosis (1)	29 ± 6	224 ± 89 min
Pappone, 2000[62]	CA	F, C	4	26	62	None	9 ± 3	370 ± 58 min
Pappone, 2001[54]	CA	F, C	4	251	75	Tamponade (2)	10 ± 4.5	148 ± 26 min
Haissaguerre, 2000[49]	CA	F	Active	90	71	PV stenosis	8 ± 5	278 ± 154 min
Haissaguerre, 2000[63]	CA	F	Active	70	73	None	4 ± 5	206 ± 49 min
Kanagaratnam, 2001[53]	CA	F, C	2 superior + active	71	21	Flutter (20%), PV stenosis (17%)	29 ± 8	365 ± 77 min
Oral, 2002[64]	CA	F	2 superior, 1 inferior	70	70 parox, 22 persist	Retinal embolus (1)	5	NA
Mangrum, 2002[65]	CA	F, ICE	Active	56	66	CVA (3), tamponade (1)	13 ± 7	243 ± 75 min
Oral, 2002[66]	CA	F	2–3	40	85	None	148 ± 87 days	277 ± 59 min
Macle, 2002[67]	CA	F	4	136	66	None	8 ± 5	188 ± 54 min
Marrouche, 2002[51]	FA	F	Active	21	29	PV stenosis (3)	11 ± 3	5.4 ± 3 hr
	CA	F, 4mm	4	47	79	PV stenosis (1), CVA (1)	10 ± 3	5.5 ± 3 hr
		F, 8mm	4	21	100	None	8 ± 4	3 ± 1 hr
		F, cooled	4	122	85	PV stenosis (1), CVA (1), tamponade (2)	4 ± 2	4 ± 1 hr
Marrouche, 2003[50]	CA	F	4	56	80	PV stenosis (3), embolic event (2)	417 ± 145 days	250 ± 66 min
		F, ICE	4	107	83	PV stenosis (2), embolic event (3)	417 ± 145 days	190 ± 48 min
		F, ICE, MB	4	152	90	None	417 ± 145 days	185 ± 65 min
Chen, 2002[58] (substudy, EF < 45%)	CA	F, ICE, MB	4	30	70	Pulmonary edema (3%), CVA (3%)	12 ± 5	NA
Deisenhofer, 2003[68]	CA	F	3	75	51	PV stenosis (6)	230 ± 133 days	353 ± 143 min

C = CARTO mapping; **CA** = circumferential ablation; **cooled** = catheter with cooled tip; **CVA** = cerebrovascular accident; **EF** = ejection fraction; **F** = fluoroscopy; **FA** = focal ablation; **LIPV** = left inferior pulmonary vein; **ICE** = intracardiac echocardiography; **MB** = microbubbles; **NA** = not available; **parox** = paroxysmal atrial fibrillation; **persist** = persistent atrial fibrillation; **PV** = pulmonary vein; **US** = balloon-tipped ultrasound catheter; **4mm** = catheter with 4-mm tip; **8mm** = catheter with 8-mm tip

Two approaches to energy delivery in catheter ablation

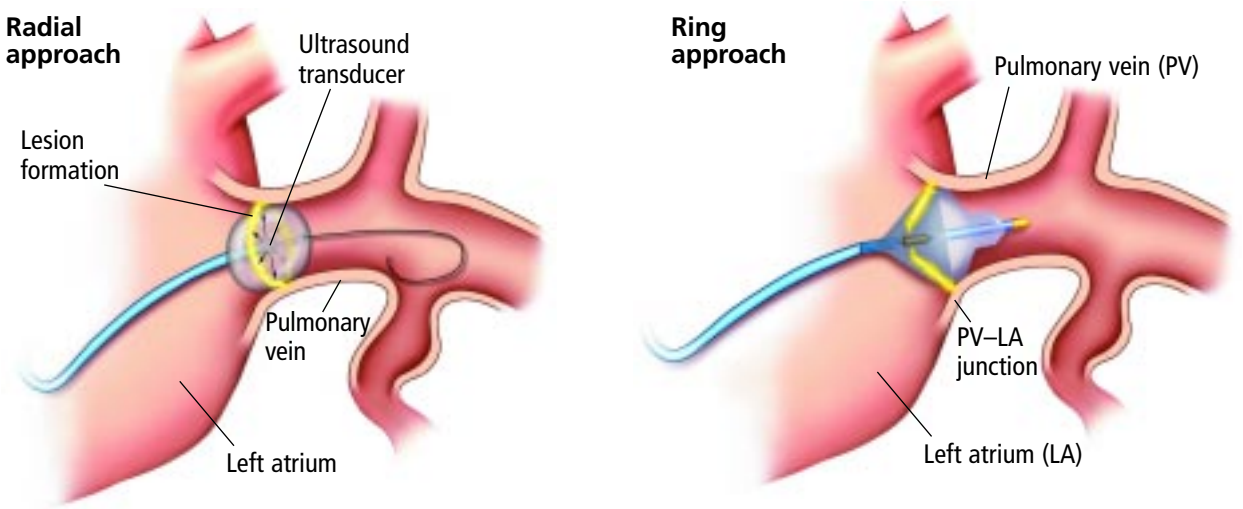

Figure 5. In the "radial" approach *(left)*, ultrasound energy is delivered through a saline-filled balloon. A balloon-tipped catheter is inflated within the pulmonary vein (PV). Energy is then delivered perpendicularly from the ultrasound transducer, forming a circular lesion that electrically isolates the the ectopic focus that is causing atrial fibrillation (AF). Because this system cannot be deployed in the "funnel" portion of the PV, a considerable amount of PV-related tissue is left intact, which can result in AF recurrence. In contrast, with the "ring" approach *(right)*, a balloon-tipped catheter is inflated in front of the PV ostium. Energy is then delivered forward, targeting the PV–left atrial junction and forming a circumferential lesion around the PV ostium. This approach makes it possible to incorporate the antrum of the PV–left atrial junction in the lesion.

- Recognition of PV stenosis when it occurs
- Visualization of clot formation during ablation
- Identification of proper electrode–tissue contact
- Early detection of pericardial effusions
- Visualization of the intra-atrial septum during the transseptal puncture required for all PV ablations.

ICE enhances energy titration

Delivery of excessive energy during ablation is associated with an increased incidence of PV stenosis.[49] During fluoroscopically guided radiofrequency ablation, only temperature, power, and impedance are monitored. Energy delivery is stopped either after a predetermined time or when elevated ablation catheter impedance levels are noted, indicating excessive tissue heating that results in endocardial surface disruption.

ICE has revolutionized radiofrequency ablation through visualization of tissue changes and microbubble formation during the procedure. Microbubble formation is a two-stage process. Initially, scattered microbubbles are seen that are reflective of "early" overheating (type 1 microbubbles) and should prompt downward power titration. When this process cannot be stabilized or made to subside, it progresses to brisk generation of microbubbles (type 2 microbubbles), which signals impending impedance rise. Proper energy titration under ICE guidance involves increasing energy delivery until type 1 microbubbles are seen and stopping energy delivery at the first sign of type 2 microbubble formation. Unlike standard monitoring of radiofrequency ablation, ICE enables the operator to avoid type 2 microbubbles and therefore avoid the tissue damage and attendant complications (PV stenosis, perforation, pericardial effusion, stroke) that stem from impedance rise.

Encouraging outcomes with ICE-guided ablation

We recently reported results on the impact of ICE monitoring in 315 patients who underwent PV isolation with circumferential mapping.[50] In this retrospective analysis, we divided patients into three treatment groups:

- In group 1, standard fluoroscopic guidance was used
- In group 2, ICE guided catheter placement
- In group 3, ICE was used to assess catheter position and to aid titration of radiofrequency energy based on microbubble formation.

At a mean follow-up of 417 ± 145 days, AF had recurred in 19.6% of patients in group 1, 16.8% of those in group 2, and 9.8% of those in group 3. Moreover, no cases of severe PV stenosis or embolic events occurred in group 3 **(Table 3)**.[50]

In a subset of 125 patients, angiographic localization of the PV ostium was compared with localization using ICE. The angiographic localization correlated with the ICE localization in only 15% of patients. Furthermore, ICE showed that angiography-based placement of the circular catheter was inaccurate (deeper into the PV than the true PV–left atrial junction) in nearly 85% of these patients.

This use of ICE to assess catheter position and guide energy titration was effective even in a subset

of 30 patients with left ventricular systolic dysfunction (defined as an ejection fraction < 45%).[58] As **Table 3** shows, the success rate was lower in this subpopulation (70% vs 87%). However, the difference was attributed to the significantly larger size of the PV ostia in these patients with impaired systolic function (average PV diameter of 2.2 cm vs 1.4 cm) rather than to non-PV origin of AF. Indeed, even in this subpopulation recurrence was associated with conduction recovery between the PVs and the left atrium, and a second procedure appeared to be curative in most patients.

■ OUTCOMES: WHAT WE KNOW SO FAR

Discussing outcomes following AF ablation is challenging, owing to the wide variety of techniques and technologies currently used and to the relatively small study populations. **Table 3** summarizes the results of many of the largest series to date.[41,45,49–51,53–56,58–68] In these series, success reflects cure without antiarrhythmic drugs after one or more procedures. We draw the following conclusions from these data:

- If properly performed, catheter ablation of arrhythmogenic foci in PVs is a highly effective and safe cure for AF in most patients.
- Empiric circumferential isolation performed under ICE guidance at the ostia of all four PVs and the superior vena cava right atrial junction achieves higher success rates with fewer complications, fewer repeat procedures, and reduced procedure times compared with other ablation strategies.
- Left ventricular systolic dysfunction and large PV ostia appear to be the only patient characteristics that have an adverse effect on success.
- The catheter technology can have an important effect on the procedure's success, as can operator skill and experience.

■ PV STENOSIS, OTHER COMPLICATIONS

PV stenosis is a well-recognized complication of ablation for AF.[69,70] Severe PV stenosis (>70% narrowing) is associated with multiple symptoms, including dyspnea on exertion, persistent cough, hemoptysis, chest pain, and lung consolidation. A high index of suspicion for PV stenosis is necessary in patients undergoing ablation, since these complaints are mostly nonspecific and misdiagnosis is common. Mild to moderate stenosis is usually clinically silent and does not appear to change the pulmonary circulation.

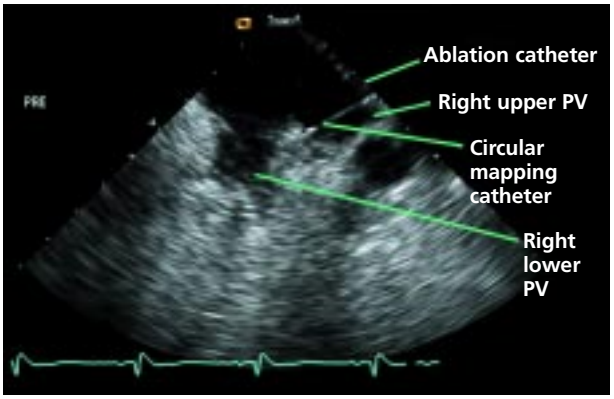

Figure 6. A phased-array intracardiac echocardiogram used to guide pulmonary vein (PV) isolation. Here the right upper and right lower PVs are visible. The circular mapping catheter is placed at the ostium of the right upper PV.

Reported rates of PV stenosis in patients undergoing ablation for AF range from 0% to 42%[70] using a wide variety of diagnostic tools, including magnetic resonance imaging, computed tomography (CT), transesophageal echocardiography, and ICE. Strategies to minimize the risk of severe stenosis include:

- Ostial ablation vs ablation deep in the PV
- Careful energy titration
- Minimization of the number of ablations per PV
- Use of alternative energy sources.

At our institution, a high-resolution CT scan is performed on each patient 3 months after the ablation procedure. If clinically silent narrowing is present, CT scanning is repeated to exclude progression of narrowing. When severe stenosis with symptoms is identified, patients are referred for PV angioplasty.

Other complications have been reported, including cerebrovascular accident, cardiac perforation, pericardial effusion, tamponade, phrenic nerve palsy, and circular catheter entrapment in the mitral valve apparatus with subsequent chordal disruption.[71] The incidence of these complications is relatively low but must be weighed against the benefits of the procedure.

■ WHO IS A CANDIDATE FOR ABLATION?

Patients should be considered for PV isolation if they have symptomatic, drug-refractory AF. When performed by experienced operators and by extending ablation to the antrum proximal to the "tubelike" portion of the PVs, the procedure is safe and effective regardless of the patient's age and left atrial size.

Patients who have cardiovascular syndromes requiring cardiac surgery should be considered for perioperative PV isolation or the maze procedure. In rare cases, PV firing is associated with non-PV foci, which usually requires a different procedural strategy supported by sophisticated mapping systems.

The only group that does not appear to respond to PV isolation are patients with diffuse preexisting atrial myopathy that results in electrically silent or low-amplitude-electrogram areas in the left atrium. This finding is usually recognized only at the time of the initial procedure but can be predicted by the absence of left atrial mechanical function before ablation.

Ultimately, patients should be selected for ablation on a case-by-case basis, weighing risks and benefits.

CONCLUSIONS

Recognition of the role of arrhythmogenic foci in the PVs in initiating AF has dramatically altered the management of this common arrhythmia. Although still under development, catheter-based ablation procedures that cure AF are a reality. Currently, the highest success rates and lowest complication rates appear to be achieved with empiric circumferential isolation of all four PV ostia and the superior vena cava using ICE guidance to titrate energy delivery through large-tipped catheters. Future technological refinements that enable anatomic isolation of the PVs with less dependence on operator skill and experience may allow catheter-based ablation to become the dominant strategy for treating AF.

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Managing chronic atrial fibrillation:
Strategies to control symptoms and prevent embolism

DAVID O. MARTIN, MD, MPH

Even though atrial fibrillation (AF) is the most common sustained cardiac arrhythmia seen in clinical practice, no consensus has been reached on how best to manage it. However, by focusing management on two goals—controlling patient symptoms and preventing systemic embolism—clinicians can make rational therapy choices for individual patients with AF. This review briefly surveys strategies to achieve these goals, along with related issues in the management of chronic AF.

ESSENTIALS OF THE EVALUATION

Recent guidelines on AF management from the American College of Cardiology, American Heart Association, and European Society of Cardiology (ACC/AHA/ESC)[1] outline the principles for assessing patients with known or suspected AF. At minimum, the clinician should:

- Take a history and conduct a physical examination with an eye toward defining the nature of symptoms and detecting underlying heart disease or other reversible conditions, such as hyperthyroidism or excessive alcohol consumption
- Obtain an electrocardiogram to verify AF, exclude prior myocardial infarction, assess ventricular rate, and measure the QRS and QT intervals if antiarrhythmic drug therapy is considered
- Order a chest radiograph when the clinical findings suggest a pulmonary abnormality
- Obtain an echocardiogram to assess valvular heart disease, right and left atrial size, left ventricular size and function, right ventricular pressure (pulmonary hypertension), and pericardial disease
- Order blood tests of thyroid function for patients with a first episode of AF, if the ventricular rate is difficult to control, or when AF recurs soon after cardioversion.

Additional useful testing

The following tests may also be useful in selected patients:

- Exercise testing, to assess rate control during AF, to exclude exercise-induced AF, and to exclude ischemia before treatment with type IC antiarrhythmic drugs
- Holter monitoring, to assess ventricular rate control during normal activity
- Transesophageal echocardiography, to identify left atrial thrombus and to guide cardioversion.

Once a thorough evaluation is completed, the physician is better prepared to achieve the two main goals in managing patients with AF: symptom control and prevention of systemic embolism.

SELECTING A STRATEGY FOR SYMPTOM CONTROL

Symptom control can be achieved with a strategy of rhythm control, in which the goal is to restore and maintain sinus rhythm, or a strategy of rate control, in which the goal is to control the ventricular rate during AF. Recent clinical trials have shown that both approaches are acceptable as initial strategies in most patients with AF.[2,3]

Restoring sinus rhythm

The standard approaches for converting AF to sinus rhythm are direct-current cardioversion and pharmacologic cardioversion using class IA, IC, or III antiarrhythmic drugs. Electrical cardioversion is indicated in hemodynamically unstable patients. In stable patients, either electrical or pharmacologic

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Disclosure: The author has indicated that he has no commercial affiliations or interests that pose a potential conflict of interest with this article.

cardioversion may be tried, although at our institution we generally prefer electrical cardioversion because of its higher efficacy.

Maintaining sinus rhythm

Drug therapy. Only about 25% of patients who undergo cardioversion remain in sinus rhythm for more than 1 year without antiarrhythmic drug therapy. Treatment with an antiarrhythmic drug increases this proportion to approximately 50%.[1]

As detailed in the preceding article in this supplement, class IA, IC, and III antiarrhythmic drugs are useful for maintaining sinus rhythm. Briefly, for patients with no (or minimal) heart disease, flecainide, propafenone, and sotalol are first-line agents, with dofetilide and amiodarone as second-line options.[1] We generally avoid amiodarone in patients without structural heart disease because of its potential for toxicity with long-term use.

For patients with left ventricular dysfunction, dofetilide and amiodarone are the drugs of choice. For patients with coronary artery disease, sotalol is the drug of choice if left ventricular function is relatively preserved, whereas dofetilide and amiodarone are preferred if there is moderate or severe left ventricular dysfunction.[1]

We generally do not use class IA antiarrhythmic drugs because they are less well tolerated and have no greater efficacy than the class IC and III agents.

Notably, recurrence of AF does not necessarily mean drug failure. In fact, for most patients with AF, antiarrhythmic drugs should be viewed as tools for delaying the recurrence of AF rather than for preventing AF altogether. It is perfectly acceptable to have AF recurrences on antiarrhythmic drug therapy so long as recurrence rates are tolerable to the patient and conversion to sinus rhythm (either spontaneous or elective) occurs in a timely manner.

Nondrug therapies. Because antiarrhythmic drug therapy is often ineffective, many patients may need to be switched to a rate-control strategy or to nonpharmacologic therapies for restoring and maintaining sinus rhythm. As detailed in the preceding article, nonpharmacologic approaches include catheter ablation to isolate the pulmonary veins,[4,5] the surgical maze procedure or related operations,[6,7] and implantation of an atrial defibrillator.[8] Additionally, for patients with AF who require pacemaker implantation, the physician can choose a pacemaker with pacing algorithms that help prevent AF.[9,10]

Because of the risk of procedure-related stroke and pulmonary vein stenosis, we generally reserve catheter-based pulmonary vein isolation for patients with symptomatic AF refractory to multiple antiarrhythmic drugs. For patients with AF undergoing open heart surgery for another reason (eg, valve repair or replacement), a concurrent maze-type procedure should be considered.[11] In the occasional patient, implantation of an atrial defibrillator can enhance patient autonomy and satisfaction by allowing the patient to initiate his or her own defibrillation.

Rate control

The ventricular rate may be controlled during AF by giving medications that slow atrioventricular nodal conduction. Such agents work by one of three main physiologic mechanisms:

- Calcium channel blockade (with verapamil or diltiazem)
- Reduction of sympathetic tone (with beta-blockers)
- Enhancement of parasympathetic tone (with a vagotonic drug such as digoxin).

In patients with preserved left ventricular function, rate control can generally be achieved with a beta-blocker, a calcium channel blocker, or both. In patients with reduced left ventricular function, a beta-blocker, digoxin, or both should be used for rate control. Amiodarone may also be used as a rate-controlling drug in patients with left ventricular dysfunction.

If pharmacologic rate control fails because of symptoms or side effects, consider nonpharmacologic rate control or switching to a rhythm-control strategy. The primary nonpharmacologic method of ventricular rate control is to ablate the atrioventricular node and implant a permanent pacemaker.[12] Although this approach is aggressive, it is generally quite effective in enhancing quality of life.[13]

Rhythm control vs rate control

Until recently, rhythm control was preferred over rate control for patients presenting with their first few episodes of AF. Because AF was associated with increased mortality and stroke rates, it was natural to assume that restoring sinus rhythm would not only reduce symptoms but also reduce the risk of death and stroke. However, the recent Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)[2] demonstrated that embolic events occur with equal frequency regardless of whether a rate-control or rhythm-control strategy is used. Moreover, the study found a trend toward reduced mortality with rate control as opposed to rhythm control (haz-

TABLE 1
Risk-based recommendations for anticoagulation in patients with chronic atrial fibrillation

Patient features	Antithrombotic therapy
Age < 60 years; no heart disease (lone atrial fibrillation)	Aspirin (325 mg/day) or no therapy
Age < 60 years; heart disease but no risk factors for stroke*	Aspirin (325 mg/day)
Age ≥ 60 years; no risk factors for stroke*	Aspirin (325 mg/day)
Age ≥ 60 years with diabetes or coronary artery disease	Warfarin (INR 2–3); adding aspirin 81–162 mg/day optional
Age ≥ 75 years	Warfarin (INR ~2)
Heart failure or LVEF ≤ 35%	Warfarin (INR 2–3)
Thyrotoxicosis	Warfarin (INR 2–3)
Hypertension	Warfarin (INR 2–3)
Rheumatic heart disease (mitral stenosis)	Warfarin (INR 2.5–3.5 or higher may be appropriate)
Prosthetic heart valves	Warfarin (INR 2.5–3.5 or higher may be appropriate)
Persistent atrial thrombus on TEE	Warfarin (INR 2.5–3.5 or higher may be appropriate)

* Risk factors for stroke are heart failure, LVEF ≤35%, and hypertension.
INR = international normalized ratio; **LVEF** = left ventricular ejection fraction; **TEE** = transesophageal echocardiography

ard ratio 0.87). There was no difference between the two strategies in patients' quality of life or functional status. Similar findings were reported in the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial.[3] Both studies showed that embolic events occur most often after warfarin therapy is stopped or when the international normalized ratio is subtherapeutic. Thus, both rate control and rhythm control are acceptable approaches and both generally require anticoagulation.

■ PROGRESS IN PREVENTING EMBOLISM

The incidence of systemic embolism is about 5% per year in patients with chronic AF who are not receiving an anticoagulant.[14] The risk of stroke increases dramatically with advanced age. Other risk factors for stroke include diabetes, hypertension, previous stroke, and left ventricular dysfunction. The recent ACC/AHA/ESC guidelines[1] lay out recommendations for the use of aspirin or warfarin to minimize embolic risk in patients with chronic AF **(Table 1)**.

Transesophageal echocardiography

The ACC/AHA/ESC guidelines recommend that nonhospitalized patients who have been in AF for more than 48 hours receive 3 to 4 weeks of warfarin therapy before and after cardioversion.[1] The recommended target international normalized ratio is 2.5 (range 2 to 3). Transesophageal echocardiography (TEE)-guided cardioversion is an alternative approach that can preclude the need for prolonged anticoagulant therapy before cardioversion; if TEE reveals no atrial thrombus, cardioversion can be performed safely after only a short period of anticoagulation. If TEE reveals a thrombus, the patient should receive anticoagulant therapy for at least 3 weeks before cardioversion is performed. Whether a repeat TEE is required to confirm thrombus dissolution remains controversial.

The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial[15] compared a TEE-guided cardioversion strategy with a conventional cardioversion strategy in 1,222 patients with AF. The study found no difference between the strategies in systemic embolic events, and TEE-guided cardioversion was associated with a lower incidence of hemorrhagic events (2.9% vs 5.5%) and a higher incidence of successful restoration of sinus rhythm (71% vs 65%). The TEE-guided approach may be especially useful in patients who need to be hospitalized or who have an increased risk of bleeding during prolonged anticoagulation with warfarin.

Left atrial appendage occlusion, ligation

The left atrial appendage (LAA) is the source of a large majority of the emboli associated with AF. For this reason, LAA occlusion devices are being developed that can be implanted in the cardiac catheterization laboratory to seal the LAA in patients with chronic AF in whom anticoagulation is contraindicated.[16] Additionally, patients with AF undergoing open heart surgery can have their LAA ligated to prevent thrombus formation within the appendage. Whether LAA occlusion or ligation eliminates the need for anticoagulation requires further study.

■ INDICATIONS FOR HOSPITALIZATION

Many patients with first-detected AF are admitted to the hospital. A common reason for admission is to "rule out" acute myocardial infarction. However, AF is rarely the sole manifestation of an acute coronary event, and there is no reason to admit patients for this condition unless there are other clinical grounds for suspecting an ischemic event, such as anginal chest pain or an electrocardiogram showing an acute infarct or ischemia.[17] Patients whose clinical status is uncomplicated and who are at low risk for coronary ischemia can generally be managed in the emergency room or observational unit.

■ CONCLUSIONS

Although AF can pose frustrating clinical challenges, virtually all patients with this arrhythmia can be managed successfully if the full arsenal of treatment options is available. The risk of systemic embolism can be minimized by following established anticoagulation guidelines. As a general rule, these guidelines should be followed regardless of whether a strategy of rate control or rhythm control is used. For most patients with recurrent AF, pharmacologic rate control may be tried as initial therapy. If this does not effectively control symptoms, then pharmacologic rhythm control may be tried. If this too proves ineffective, then a nonpharmacologic intervention should be considered, such as pulmonary vein isolation or atrioventricular node ablation with pacemaker implantation. As these and other nonpharmacologic therapies for AF steadily advance, we can expect that they will be used earlier and earlier in the management of patients with AF.

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