Approaches to restoring and maintaining normal sinus rhythm

DAVID O. MARTIN, MD, MPH; WALID SALIBA, MD; PATRICK M. McCARTHY, MD; A. MARC GILLINOV, MD; WILLIAM BELDEN, MD; NASSIR F. MARROUCHE, MD; AND ANDREA NATALE, MD

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-

From the Department of Cardiovascular Medicine (D.O.M., W.S., W.B., N.F.M., and A.N.), the Department of Thoracic and Cardiovascular Surgery and the Kaufman Center for Heart Failure (P.M.M. and A.M.G.), and the Center for Atrial Fibrillation (P.M.M., A.M.G., W.B., N.F.M., and A.N.), The Cleveland Clinic Foundation, Cleveland, Ohio.

Address: Send correspondence to designated section author at: Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195. *Section I:* David Martin, MD, Mail Code F15, martind3@ccf.org; *Section II:* Walid Saliba, MD, Mail Code F15, salibaw@ccf.org; *Section III:* Patrick McCarthy, MD, Mail Code F25, mccartp@ccf.org; *Section IV:* Andrea Natale, MD, Mail Code F15, natalea@ccf.org.

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.

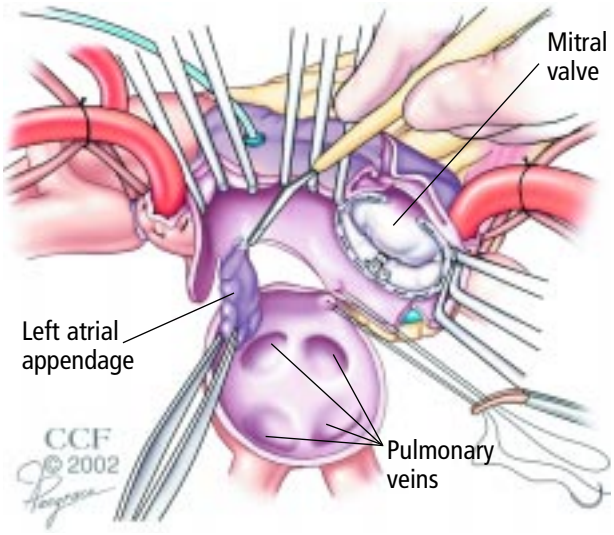

Figure 1. Left-side incisions for the classic maze procedure:
- **Encircle all four pulmonary veins**
- **Excise the left atrial appendage**
- **Extend to the mitral annulus with cryolesions placed at the annulus and on the coronary sinus.**

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

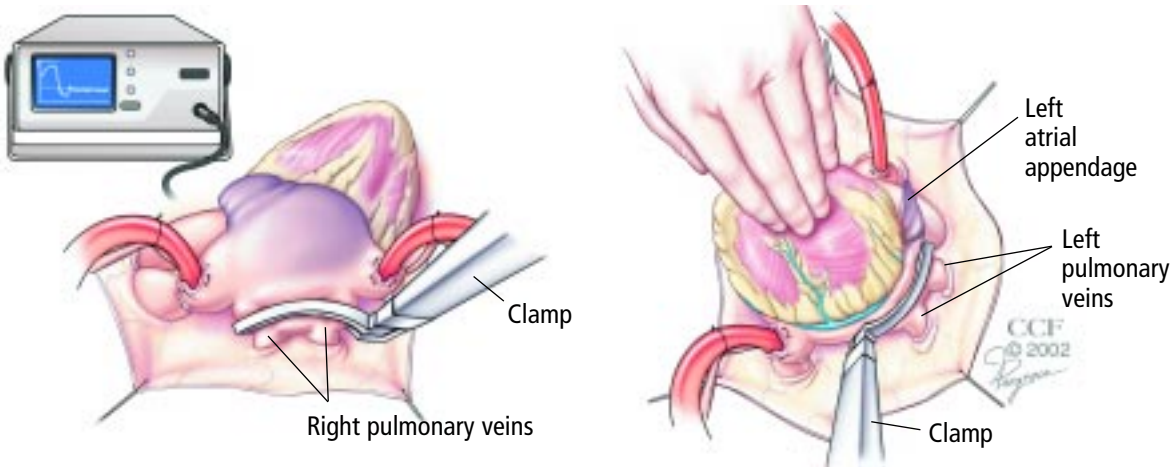

Figure 2. The AtriCure bipolar radiofrequency clamp is placed on the left atrium (not directly on the pulmonary veins) to electrically isolate the site of atrial fibrillation initiation from the pulmonary veins. The illustration on the left shows electrical isolation of the right pulmonary veins. The 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.

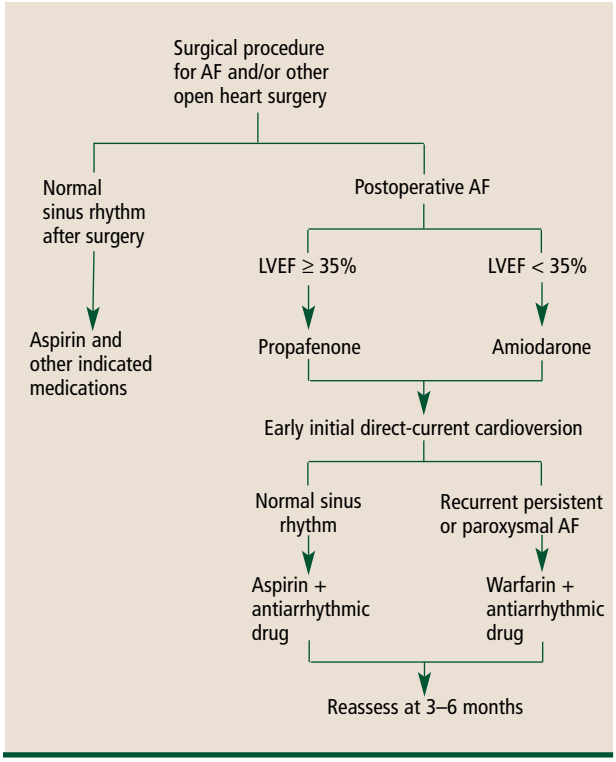

Figure 3. Algorithm for the postoperative management of patients undergoing surgery for atrial fibrillation (AF). LVEF = left ventricular ejection fraction

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

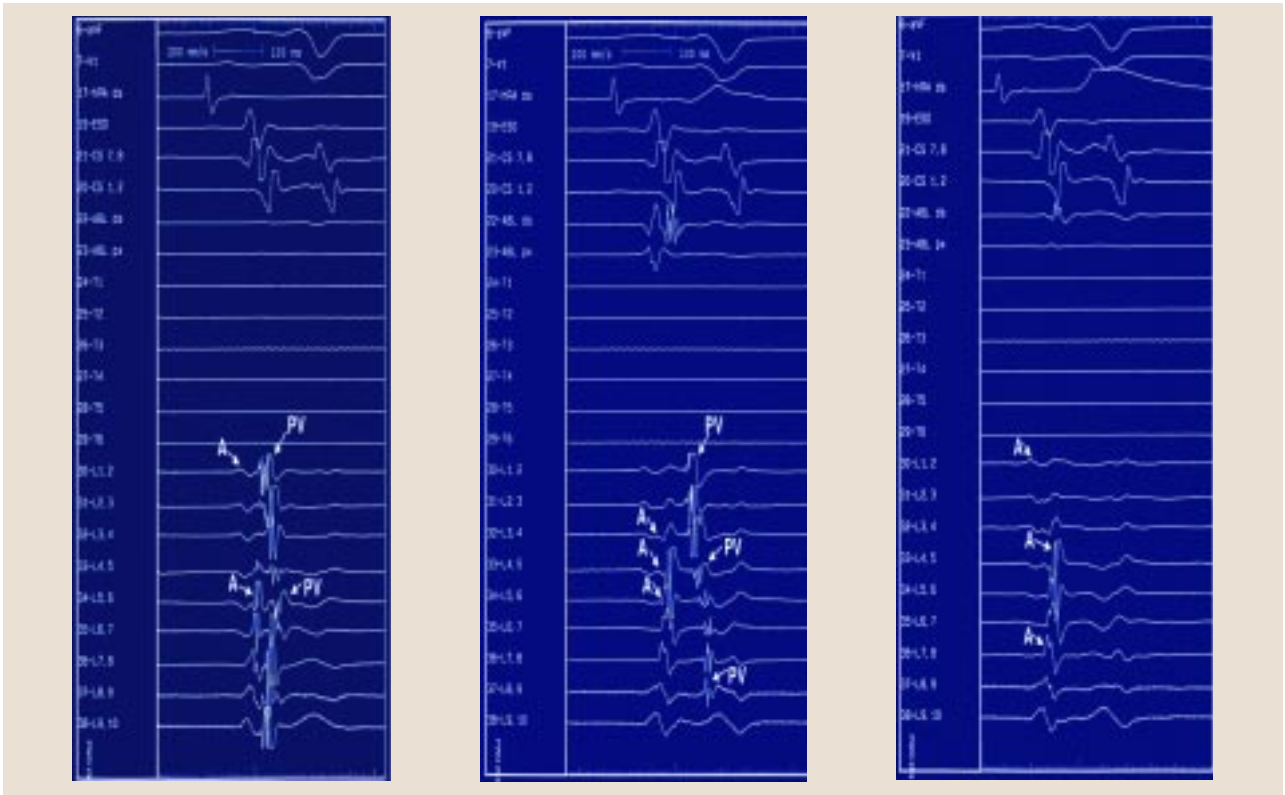

Figure 4. Left upper pulmonary vein (PV) electrograms (from $L_{1–2}$ to $L_{9–10}$) and far-field atrial potential (A) electrograms in a patient with atrial fibrillation. *Left panel:* Before ablation, PV electrograms occur early in segments $L_{1–2}$ and $L_{9–10}$. *Middle panel:* After delivery of 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

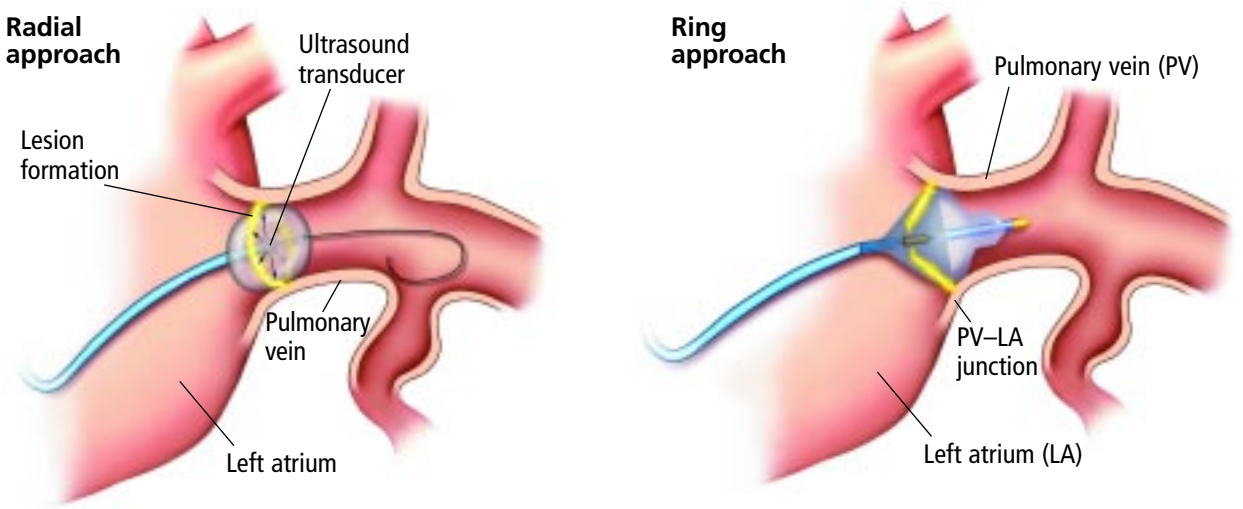

Figure 5. In the "radial" approach *(left)*, ultrasound energy is delivered through a saline-filled balloon. A balloon-tipped catheter is inflated within the pulmonary vein (PV). Energy is then delivered perpendicularly from the ultrasound transducer, forming a circular lesion that electrically isolates 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.

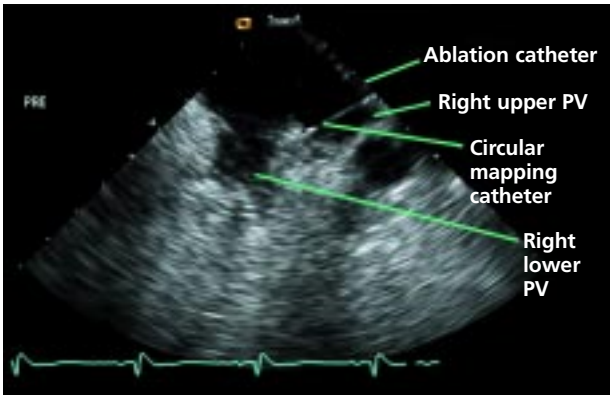

Figure 6. A phased-array intracardiac echocardiogram used to guide pulmonary vein (PV) isolation. Here the right upper and right lower PVs are visible. The circular mapping catheter is placed at the ostium of the right upper PV.

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.

REFERENCES

1. **Roy D, Talajic M, Dorian P, et al.** Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atril Fibrillation Investigators. N Engl J Med 2000; 342:913–920.
2. **Stanton M.** Class I antiarrhythmic drugs. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology: From Cell to Bedside. 3rd ed. Philadelphia: WB Saunders; 2000:890–903.
3. **Coplen SE, Antman EM, Berlin JA, et al.** Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis. Circulation 1990; 82:1106–1116.
4. **The Cardiac Arrhythmia Suppression Trial (CAST) Investigators.** Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321:406–412.
5. **Nattel S.** Class III drugs. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology: From Cell to Bedside. 3rd ed. Philadelphia: WB Saunders; 2000:921–932.
6. **Waldo AL, Camm AJ, deRuyter H, et al.** Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. Lancet 1996; 348:7–12.
7. **Singh S, Zoble RG, Yellen L, et al.** Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. Circulation 2000; 102:2385–2390.
8. **Greenbaum R, Campbell TJ, Channer KS, et al.** Conversion of atrial fibrillation and maintenance of sinus rhythm by dofetilide: the EMERALD study. Circulation 1998; 98(suppl I):I-633. Abstract.
9. **Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al.** Dofetilide in patients with congestive heart failure and left ventricular dysfunction. DIAMOND Study Group. N Engl J Med 1999; 341:857–865.
10. **Kober L, Bloch-Thomsen PE, Moller M, et al.** Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. Lancet 2000; 356:2052–2058.
11. **Stambler BS, Wood MA, Ellenbogen KA, et al.** Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. Circulation 1996; 94:1613–1621.
12. **Lamas GA, Lee KL, Sweeney MO, et al, for the MODE Selection Trial.** Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002; 346:1854–1862.
13. **Skanes AC, Krahn AD, Yee R, et al.** Progression to chronic atrial fibrillation after pacing: the Canadian Trial of Physiologic Pacing. CTOPP Investigators. J Am Coll Cardiol 2001; 38:167–172.
14. **Gillis AM, Kerr CR.** Whither physiologic pacing? Implications of CTOPP. Pacing Clin Electrophysiol 2000; 23:1193–1196.
15. **Gillis AM, Wyse DG, Connolly SJ, et al.** Atrial pacing periablation for prevention of paroxysmal atrial fibrillation. Circulation 1999; 99:2553–2558.
16. **Gillis AM, Connolly SJ, Lacombe P, et al.** Randomized crossover comparison of DDDR versus VDD pacing after atrioventricular junction ablation for prevention of atrial fibrillation. The PA (3) study investigators. Circulation 2000; 102:736–741.
17. Hotline Sessions of the 23rd European Congress of Cardiology. Eur Heart J 2001; 22:2033–2037.
18. **Padeletti L, Purerfellner H, Adler S, et al.** Atrial septal lead placement and atrial pacing algorithms for prevention of paroxysmal atrial fibrillation: ASPECT study results. Pacing Clin Electrophysiol 2002; 25(4 Pt II):687. Abstract 659.
19. **Bailin SJ, Adler S, Giudici M.** Prevention of chronic atrial fibrillation by pacing in the region of Bachmann's bundle: results of a multicenter randomized trial. J Cardiovasc Electrophysiol 2001; 12:912–917.
20. **Kale M, Bennett DH.** Atrial septal pacing in the prevention of paroxysmal atrial fibrillation refractory to antiarrhythmic drugs. Int J Cardiol 2002; 82:167–175.
21. **El Allaf D, et al.** Low atrial septum pacing and dynamic atrial overdrive to lower AF burden. Europace 2001; 2(suppl):B38. Abstract.
22. **Saksena S, Prakash A, Ziegler P, et al.** Improved suppression of recurrent atrial fibrillation with dual-site right atrial pacing and antiarrhythmic drug therapy. J Am Coll Cardiol 2002; 40:1140–1152.
23. **Ramdat Misier AR, Beukema WP, Oude Luttikhuis HA, et al.** Multisite atrial pacing: an option for atrial fibrillation prevention? Preliminary results of the Dutch dual-site right atrial pacing for prevention of atrial fibrillation study. Am J Cardiol 2000; 86(9 Suppl 1);K20–K24.
24. **Mirza I, James S, Holt P.** Biatrial pacing for paroxysmal atrial fibrillation: a randomized prospective study into the suppression of paroxysmal atrial fibrillation using biatrial pacing. J Am Coll Cardiol 2002; 40:457–463.
25. **Padeletti L, Pieragnoli P, Ciapetti C, et al.** Randomized crossover comparison of right atrial appendage pacing versus interatrial septum pacing for prevention of paroxysmal atrial fibrillation in patients with sinus bradycardia. Am Heart J 2001; 142:1047–1055.
26. **Israel CW, Hugl B, Unterberg C, et al, for the AT500 Verification Study.** Pace-termination and pacing for prevention of atrial tachyarrhythmias: results from a multicenter study with an implantable device for atrial therapy. J Cardiovasc Electrophysiol 2001; 12:1121–1128.
27. **Carlson MD, Gold MR, Ip J, et al.** Dynamic atrial overdrive pacing decreases symptomatic atrial arrhythmia burden in patients with sinus node dysfunction. Circulation 2001; 104(suppl):II-383. Abstract 1825.
28. **Lee MA, Weachter R, Pollak S, et al.** Can preventive and antitachycardia pacing reduce the frequency and burden of atrial tach-

yarrhythmias? The ATTEST study results. Pacing Clin Electrophysiol 2002; 25(4 Pt II):541. Abstract 74.
29. **Seidl K, Cazeau S, Gaita F, et al.** Dual-site pacing vs mono-site pacing in prevention of atrial fibrillation. Pacing Clin Electrophysiol 2002; 24(4 Pt II):568. Abstract 184.
30. **Vollmann D, Moeller C, Stevens J, et al.** Automatic 50-Hz burst pacing for the termination of atrial fibrillation: manual success analysis in patients with intermittent atrial tachyarrhythmias in a novel dual-chamber ICD. Circulation 2001; 104(suppl II):II-384. Abstract 1829.
31. **Daoud EG, Timmermans C, Fellows C, et al.** Initial clinical experience with ambulatory use of an implantable atrial defibrillator for conversion of atrial fibrillation. Circulation 2000; 102:1407–1413.
32. **Wood MA, Brown-Mahoney C, Kay GN, et al.** Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. Circulation 2000; 101:1138–1144.
33. **Ozcan C, Jahangir A, Friedman PA, et al.** Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. N Engl J Med 2001; 344:1043–1051.
34. **Cox JL, Ad N, Palazzo T, et al.** Current status of the Maze procedure for the treatment of atrial fibrillation. Semin Thorac Cardiovasc Surg 2000; 12:15–19.
35. **McCarthy PM, Gillinov AM, Castle L, et al.** The Cox–Maze procedure: the Cleveland Clinic experience. Semin Thorac Cardiovasc Surg 2000; 12:25–29.
36. **Lonnerholm S, Blomstrom P, Nilsson L, et al.** Effects of the Maze operation on health-related quality of life in patients with atrial fibrillation. Circulation 2000; 101:2607–2611.
37. **Cox JL, Ad N, Palazzo T.** Impact of the Maze procedure on the stroke rate in patients with atrial fibrillation. J Thorac Cardiovasc Surg 1999; 118:833–840.
38. **Gillinov AM, Pettersson G, Rice TW.** Esophageal injury during radiofrequency ablation for atrial fibrillation. J Thorac Cardiovasc Surg 2001; 122:1239–1240.
39. **Schaff HV, Dearani JA, Daly RC, et al.** Cox-Maze procedure for atrial fibrillation: Mayo Clinic experience. Semin Thorac Cardiovasc Surg 2000; 12:25–29.
40. **Arcidi JM Jr, Doty DB, Millar RC.** The Maze procedure: the LDS Hospital experience. Semin Thorac Cardiovasc Surg 2000; 12:38–43.
41. **Haisaguerre M, Jais P, Shah DC, et al.** Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998; 339:659–666.
42. **Gillinov AM, McCarthy PM.** Atricure bipolar radiofrequency clamp for intraoperative ablation of atrial fibrillation. Ann Thorac Surg 2002; 74:2165–2168.
43. **Quader MA, McCarthy PM, Gillinov AM, et al.** Does preoperative atrial fibrillation reduce survival after coronary artery bypass grafting? Ann Thorac Surg. In press.
44. **Prasad SM, Maniar HS, Schuessler RB, et al.** Chronic transmural atrial ablation by using bipolar radiofrequency energy on the beating heart. J Thorac Cardiovasc Surg 2002; 124:708–713.
45. **Haissaguerre M, Jais P, Shah DC, et al.** Right and left atrial radiofrequency catheter therapy of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 1996; 7:1132–1144.
46. **Ernst S, Schluter M, Ouyang F, et al.** Modification of the substrate for maintenance of idiopathic human atrial fibrillation: efficacy of radiofrequency ablation using nonfluoroscopic catheter guidance. Circulation 1999; 100:2085–2092.
47. **Shah DC, Haissaguerre M, Jais P.** Current perspectives on curative catheter ablation of atrial fibrillation. Heart 2002; 87:6–8.
48. **Chen SA, Tai CT, Tsai CF, et al.** Radiofrequency catheter ablation of atrial fibrillation initiated by pulmonary vein ectopic beats. J Cardiovasc Electrophysiol 2000; 11:218–227.
49. **Haissaguerre M, Jais P, Shah DC, et al.** Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation 2000; 101:1409–1417.
50. **Marrouche NF, Martin DO, Wazni O, et al.** Phased-array intracardiac echocardiography monitoring during pulmonary vein isolation in patients with atrial fibrillation: impact on outcome and complications. Circulation 2003; 107:2710–2716.
51. **Marrouche NF, Dresing T, Cole C, et al.** Circular mapping and ablation of the pulmonary vein for treatment of atrial fibrillation: impact of different catheter technologies. J Am Coll Cardiol 2002; 40:464–474.
52. **Ng FS, Camm AJ.** Catheter ablation of atrial fibrillation. Clin Cardiol 2002; 25:384–394.
53. **Kanagaratnam L, Tomassoni G, Schweikert R, et al.** Empirical pulmonary vein isolation in patients with chronic atrial fibrillation using a three-dimensional nonfluoroscopic mapping system: long-term follow-up. Pacing Clin Electrophysiol 2001; 24:1774–1779.
54. **Pappone C, Oreto G, Rosanio S, et al.** Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation. Circulation 2001; 104:2539–2544.
55. **Natale A, Pisano E, Shewchik J, et al.** First human experience with pulmonary vein isolation using a through-the-balloon circumferential ultrasound ablation system for recurrent atrial fibrillation. Circulation 2000; 102:1879–1882.
56. **Saliba W, Wilber D, Packer D, et al.** Circumferential ultrasound ablation for pulmonary vein isolation: analysis of acute and chronic failures. J Cardiovasc Electrophysiol 2002; 13:957–961.
57. **Cooper JM, Epstein LM.** Use of intracardiac echocardiography to guide ablation of atrial fibrillation. Circulation 2001; 104:3010–3013.
58. **Chen MS, Marrouche N, et al.** Pulmonary vein isolation for treatment of atrial fibrillation in patients with impaired systolic function. Presented at: annual meeting of the American College of Cardiology; March 2002; Atlanta. Abstract.
59. **Chen SA, Hsieh MH, Tai CT, et al.** Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation 1999; 100:1879–1886.
60. **Gerstenfeld EP, Guerra P, Sparks PB, et al.** Clinical outcome after radiofrequency catheter ablation of focal atrial fibrillation triggers. J Cardiovasc Electrophysiol 2001; 12:900–908.
61. **Sanders P, Morton JB, Deen VR, et al.** Immediate and long-term results of radiofrequency ablation of pulmonary vein ectopy for cure of paroxysmal atrial fibrillation using a focal approach. Intern Med J 2002; 32:202–207.
62. **Pappone C, Rosanio S, Oreto G, et al.** Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. Circulation 2000; 102:2619–2628.
63. **Haissaguerre M, Shah DC, Jais P, et al.** Electrophysiological breakthroughs from the left atrium to the pulmonary veins. Circulation 2000; 102:2463–2465.
64. **Oral H, Knight BP, Tada H, et al.** Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation 2002; 105:1077–1081.
65. **Mangrum JM, Mounsey JP, Kok LC, et al.** Intracardiac echocardiography-guided, anatomically based radiofrequency ablation of focal atrial fibrillation originating from pulmonary veins. J Am Coll Cardiol 2002; 39:1964–1972.
66. **Oral H, Knight BP, Ozaydin M, et al.** Segmental ostial ablation to isolate the pulmonary veins during atrial fibrillation: feasibility and mechanistic insights. Circulation 2002; 106:1256–1262.
67. **Macle L, Jais P, Weerasooriya R, et al.** Irrigated-tip catheter ablation of pulmonary veins for treatment of atrial fibrillation. J Cardiovasc Electrophysiol 2002; 13:1067–1073.
68. **Deisenhofer I, Schneider MA, Bohlen-Knauf M, et al.** Circumferential mapping and electric isolation of pulmonary veins in patients with atrial fibrillation. Am J Cardiol 2003; 91:159–163.
69. **Robbins IM, Colvin EV, Doyle TP, et al.** Pulmonary vein stenosis after catheter ablation of atrial fibrillation. Circulation 1998; 98:1769–1775.
70. **Yu W, Hsu T, Tai C, et al.** Acquired pulmonary vein stenosis after radiofrequency catheter ablation of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2001; 12:887–892.
71. **Wu RC, Brinker JA, Yuh DD, et al.** Circular mapping catheter entrapment in the mitral valve apparatus: a previously unrecognized complication of focal atrial fibrillation ablation. J Cardiovasc Electrophysiol 2002; 13:819–821.