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Atrial Fibrillation: A Review of Mechanism, Etiology, and Therapy

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Summary: The prevalence of elderly individuals in the populations of developed countries is increasing rapidly, and atrial fibrillation (AF) is quite common in these elderly patients: currently, 11% of the U.S. population is between the ages of 65 and 85 years; 70% of people with AF are between the ages of 65 and 85 years. AF causes symptoms secondary to hemodynamic derangements that are the result of increased ventricular response and loss of atrial booster function. AF can lead to reversible impairment of left ventricular function, cardiac chamber dilatation, clinical heart failure, and thromboembolic events. AF requires treatment in order to prevent these potential complications. Type Ia, Ic, and III antiarrhythmics are capable of converting AF to normal sinus rhythm (NSR). Amiodarone has the greatest efficacy and safety for converting AF and maintaining NSR while digoxin and verapamil are ineffective in restoring NSR. Quinidine, flecainide, disopyramide, and sotalol have also been shown to maintain NSR after conversion of AF. Proarrhythmia is a definite concern with the latter four agents. Alternative therapy for AF includes anticoagulation with warfarin or aspirin for the prevention of thromboembolic events, and a variety of agents to control the ventricular response. All medications used to treat AF carry significant risks in the elderly, whether from proarrhythmia, overdosing because of compliance errors, or hemorrhage secondary to anticoagulation. Treatment of AF must be based on a careful risk–benefit evaluation. The physician must know the capability of the particular patient as well as drug mechanisms and effects in the elderly. The decision to convert patients from AF to NSR or to leave the patient in AF and control the ventricular response represents a complex intellectual challenge. Factors favoring one or the other of these two clinical strategies are discussed. Multicenter clinical trials, for example, the Atrial Fibrillation Follow-up Investigation Rhythm Management (AFFIRM) trial, are currently underway to assess various clinical strategies for maintenance of NSR following conversion from AF. Amiodarone is one of the drugs under investigation.

Key words: atrial fibrillation, torsade de pointes, proarrhythmia, thromboembolism, tachyarrhythmia, atrial pacing

Introduction

Atrial fibrillation (AF) is the cardiac arrhythmia most frequently encountered in clinical practice. The prevalence of AF is definitely related to age. Feinberg *et al.*[1] estimated that, based on the recent U.S. census, there are 2.2 million persons with AF, with a median age of 75 years, in the United States. The prevalence of AF was found to be 2.3% in persons >40 years of age and 5.9% in those >65 years of age. Feinberg reported that 70% of those with AF were between the ages of 65 and 85 years.

Atrial fibrillation is associated with a doubling of mortality regardless of underlying cardiac pathology. The risk of thromboembolic events is markedly increased, perhaps as much as 17.7 times greater, in patients with AF than in the general public.[2]

Of the Veterans Administration's (VA) 2.9 million patients in 1995, 38% were >65 years of age, while 40% of the VA's outpatient clinic visits were made by persons ≥65 years.[3] The VA estimates that by the year 2010 the number of patients who will be ≥85 years will increase by 400%. This aging population automatically will increase the prevalence of AF in VA hospitals and clinics. In 1991, the United States spent a total of $738 billion on health care.[4] Between 1985 and 1990, Nattel[5] found that patients with AF spent an average of 5 days in hospital at a cost of $4,800/hospital stay, representing approxi-

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mately one billion dollars annually. It is therefore obvious that AF is a prevalent and expensive cardiac arrhythmia with potentially serious complications. Is converting AF to normal sinus rhythm (NSR) coupled with attempting to maintain NSR after conversion, a reasonable goal worth the risks of therapy?

To begin to answer this question, the physician must assess the patient's hemodynamic status and identify the origin of AF, while trying to prevent complications, especially thromboembolism. The physician must determine the best drug therapy with the least side effects capable of converting AF to NSR, consider nonpharmacologic strategies (DC cardioversion, radiofrequency catheter ablation, pacing, etc.) if drugs are unsuccessful, and evaluate the need for drug therapy with attendant side effects aimed at preventing the recurrence of AF after cardioversion.

Etiology/Associated Symptoms of Atrial Fibrillation

Lok and Lau[6] found in their 1993 review of 291 cases of AF presenting to a regional emergency room that the most common presenting symptoms were palpitation (42.3%), dyspnea (38.1%), and heart failure (22%). In addition, they noted that chest pain was not an uncommon finding.

Furthermore, the same authors noted that the most frequently associated etiologies of AF were hypertension and hypertensive heart disease (28.9%), atherosclerotic cardiovascular disease (24.7%), and rheumatic heart disease (17.5%), as well as mitral valve disease and cardiomyopathy. Enlarged left atrial (LA) diameter has also been said to play an important role in the etiology of AF and in the physicians' ability to cardiovert and maintain NSR. Brodsky *et al.*[7] found that patients with moderate LA enlargement (45–60 mm) could be maintained in NSR with antiarrhythmic medication after cardioversion, but patients with markedly dilated LA (>60 mm) were unlikely to maintain NSR.

In one study, the following noncardiac conditions were also associated with AF: pulmonary disease (18.6%), diabetes mellitus (12.7%), and thyrotoxicosis (5.2%).[6] Mandel[8] found major predisposing factors to AF in patients without overt heart disease to be hypertension, diabetes mellitus, left ventricular hypertrophy by electrocardiographic (ECG) criteria, and nonspecific ECG repolarization abnormalities. Diabetes and hypertension carried the greatest risk for developing AF. High consumption of alcohol is a known cause of cardiomyopathy, but excessive alcohol ingestion by itself can result in isolated AF without evidence of myocardial disease.[2]

Classification of Atrial Fibrillation

Atrial fibrillation has been classified in a number of different ways by various authorities. Acute AF is present for 24–48 h, carries a high chance of successful conversion and maintenance of NSR, and is associated with a low incidence of thromboembolic events. Chronic AF is persistent, can be paroxysmal, or may be sustained. Chronic AF usually requires thromboembolic prophylaxis, that is, treatment with anticoagulants, and is more difficult to convert and maintain in NSR. Alpert *et al.*[9] identified 35% of AF presentations as paroxysmal (PAF). PAF, as defined by Alpert, entails "recurrent episodes of PAF with or without underlying etiology or precipitating cause." Other studies have reported the frequency of PAF or so-called lone AF (AF in the absence of structural heart disease) to be between 1 and 30% of patients with AF. Because of the lack of a standardized definition of "lone" AF, it is better to identify the presence and significance of associated risk factors when deciding on a treatment regime.

Multiple episodes of PAF frequently precede the onset of chronic or persistent AF. Allessie *et al.*[10] reported experiments in chronically instrumented goats that revealed marked electrophysiologic changes in the atrium during the first days after the onset of AF. These changes favored induction and perpetuation of AF. Allessie suggested that these electrophysiologic changes may be due to chronic shortening of atrial refractoriness during fibrillation based on changes in composition of the ion channels responsible for atrial repolarization. With acute AF, these electrophysiologic changes reverse within several days after conversion to NSR. Therefore, early treatment of acute AF with maintenance of NSR may prevent the onset of chronic AF due to electrophysiologic remodeling.

Mechanism of Atrial Fibrillation

Patients with AF do not belong to a homogeneous population. As already noted, many different factors contribute to this complex arrhythmia producing direct clinical and therapeutic consequences. The currently accepted theory for the mechanism of AF involves random waves of intra-atrial reentry with multiple macroreentrant circuits moving from one area of the atrial muscle to another.[11] This mechanism produces an ECG pattern with an undulating baseline without discernable P waves. The ventricular response to this atrial activity is irregularly irregular depending on the refractory period and conductivity of the AV node.

The chaotic atrial contractions of AF result in a 20–30% decline in stroke volume and cardiac output in normal individuals and a greater decrease of output in patients with heart disease.[9] The fall in stroke volume and cardiac output is the result of a decrease in the volume of blood arriving in the left ventricle during diastole due to the asynchronous atrial contractions and loss of the atrial booster function or "kick."

Tachyarrhythmias such as AF are often related to the action of the autonomic nervous system. Coumel *et al.*[12] reported that the parasympathetic (vagal) and sympathetic nerve terminals are anatomically close to each other in heart muscle and thus are affected by each other. The functional response to cholinergic (vagal) stimulation occurs within milliseconds, while the response to adrenergic (sympathetic) stimulation takes seconds. According to Coumel *et al.*, this temporal difference has important clinical implications for heart rate variability. Diseased atrial muscle may react differently than normal atrial muscle fibers with increased sensitivity to adren-

ergic stimulation. Coumel *et al.* state that "there is a predominance of vagal influence in the normal atria...vagal withdrawal is an early characteristic of diseased hearts that even precedes the increase of sympathetic drive."[12] Therefore, either the parasympathetic or the sympathetic portion of the autonomic nervous system may produce arrhythmias via the vagal limb in normal atria and the sympathetic limb in diseased atria. In actual practice, in patients with acute AF, this condition is more likely to have been vagally induced, while patients with structural heart disease tend to have sustained attacks mediated by a sympathetic nervous mechanism.[12]

The rapid ventricular response in AF is due to asynchronous atrial contractions and can lead to palpitations, syncope, angina, and/or left ventricular dysfunction. According to Sopher and Camm,[13] AF can be associated with reversible impairment of ventricular function, cardiac chamber enlargement, heart failure, and thromboembolic events.

Morbidity of Untreated or Sustained Atrial Fibrillation

Morbidity from AF is related to the effects of sustained rapid, irregular heart rate, decreased ventricular preload, and atrial thrombosis. Excessive ventricular rate may lead to hypotension, pulmonary congestion, angina pectoris, and anxiety in susceptible individuals. Rapid ventricular rate in patients with PAF and sick sinus syndrome can result in syncopal episodes due to prolonged periods of ventricular asystole or severe bradycardia that follows cessation of the tachyarrhythmia.[14, 15] The loss of synchronized atrial contraction, the so-called "atrial kick," can compromise cardiac output and produce fatigue. Systemic embolization from atrial stasis is the most devastating complication and will be addressed separately (see below).

Complications are more common in patients with advanced age, prior history of congestive heart failure, a history of smoking, echocardiographic evidence of enlarged left atrial diameter (>40 mm), and recent myocardial infarction.[16]

Thromboembolic Events/Anticoagulation

Atrial fibrillation is an important cause of stroke in an aging population. The Framingham Study found that the risk of stroke rose from 1.5% in the age group of 50–59 years to 23.5% in persons >80 years.[17] The risk of stroke varies depending on age and preexisting structural heart disease. In a recent study, patients <60 years and without hypertension or cardiovascular disease had a very low incidence of stroke.[18] This same study noted that patients <60 years, without diabetes, hypertension, or transient ischemic attacks (TIAs) had an annual stroke rate of only 1%.[18]

Patients >75 years of age with at least one risk factor (diabetes, hypertension, prior TIA/stroke) have an annual stroke rate of 8.1%.[18] The European Atrial Fibrillation Trial noted an annual stroke rate of 12% in patients with AF and TIA.[19]

A major dilemma for the treatment of AF and stroke prevention is to decide the balance between individuals at greatest risk for stroke compared with those who are at greatest risk for hemorrhagic complications of therapy. The elderly have both an increased rate of AF and stroke. It seems reasonable, therefore, to provide anticoagulation for elderly patients without an increased risk of intracranial hemorrhage from falls, dementia, or uncontrolled hypertension. It is of paramount importance to monitor the intensity of anticoagulation in all patients, especially the elderly, as well as to control blood presure. Concomitant medications, for example, over-the-counter medications such as nonsteroidal anti-inflammatory agents, aspirin, and cimetidine can have a marked effect on warfarin anticoagulation and thereby increase the risk of hemorrhage.

Avoiding the complication of thromboembolic events in patients with AF requires intervention by the physician based on risk stratification. When comparing treatment with the anticoagulant warfarin, or the antiplatelet agent aspirin, the European Atrial Fibrillation Trial found that oral anticoagulation reduced the annual rate of primary events (major intracranial hemorrhage) from 17 to 8% and the risk of strokes from 12 to 4%.[19] In the same trial, aspirin decreased the risk of a primary event from 19 to 15% and the risk of stroke from 12 to 10%.

Laupacis *et al.* recommend that long-term anticoagulant therapy (INR 2.0 to 3.0) be strongly considered for all patients with AF >65 years of age, and for patients <65 years with the following risk factors: previous TIA or stroke, hypertension, diabetes, heart failure, clinical coronary artery disease, mitral stenosis, prosthetic heart valves, or thyrotoxicosis.[20] Patients who either decline anticoagulation or are poor candidates for any reason should be given aspirin 325 mg/day.[20] Laupacis *et al.* felt that patients <65 years without risk factors for stroke could be treated with aspirin only or with no antithrombotic therapy.

For patients between the ages of 65 and 75 years without risk factors, the use of antithrombotic therapy must be negotiated between patient and physician based on risk assessment, side effects, and convenience.[20]

In patients >75 years of age, oral anticoagulation is recommended because of the high prevalence of stroke; however, this must be weighed against the increased risk of cerebral hemorrhage. Anticoagulation at the lower end of the therapeutic range (INR 2.0–3.0) might be appropriate in this age group.[20]

Finally, it was recommended by the Fourth ACCP Conference on Antithrombotic Therapy that patients with AF for more than 2 days be anticoagulated (INR 2.0–3.0) for 3 weeks prior to elective cardioversion and that anticoagulation be continued until sinus rhythm has been maintained for 4 weeks.[20]

Goals of Therapy for Atrial Fibrillation

The immediate cause of symptoms when AF develops usually is the rapid, irregular heart rate. The primary goal of

therapy, therefore, is to control ventricular response, prevent arterial emboli, and to convert the patient to NSR, if possible, leading to resolution of symptoms. Control of the ventricular response can be accomplished by three classes of medications used alone or in combination: beta blockers such as propranolol, atenolol, or metoprolol; the calcium-channel blockers verapamil and diltiazem, and/or digoxin.[21] Restoration of sinus rhythm can be achieved by direct-current cardioversion or traditional antiarrhythmic drug (classes 1A, 1C, III) therapy. Successful cardioversion is more likely to occur if AF has been present for < 12 months with minimal left atrial enlargement.[22] The second goal of therapy is to prevent the recurrence of AF. Treatment options vary depending on the presenting symptoms of the patient and the experience of the physician.

Maintenance of Normal Sinus Rhythm after Conversion of Atrial Fibrillation

Patients cardioverted from AF to NSR have a decreased chance of maintaining NSR unless they receive antiarrhythmic drug therapy. In six comparative studies comparing no drug therapy or placebo to active drug therapy after cardioversion, the overall percentage of patients in NSR after 1 year was 29% without antiarrhythmic drug therapy.[11] Treatment with quinidine, flecainide, or disopyramide increased that percentage to 49%; sotalol has been found to have efficacy similar to quinidine;[11] amiodarone had greater efficacy in maintaining NSR 1 year after conversion of AF. Of the patients studied, 31% maintained NSR after 1 year with amiodarone therapy.[11]

Maintaining NSR offers hemodynamic benefits through maintenance of the "atrial kick," thus improving ventricular performance. However, maintenance of NSR with type I or type III antiarrhythmic agents is not without risks. All of these drugs carry proarrhythmic and drug-related morbidity mediated by early afterdepolarizations for drugs that delay repolarization, or by blockade of sodium channels allowing the development of electrical reentry.[11,23,24] Currently, multicenter randomized trials, such as the AFFIRM trial, are underway to compare the risk–benefit ratio of maintaining NSR versus controlling ventricular rate and chronically anticoagulating patients in AF.[25]

In patients with AF, maintenance of NSR is desirable to eliminate symptoms, improve functional capacity, and reduce the risk of thromboembolic complications. Multiple factors need to be considered in deciding between rate control versus conversion of AF to NSR (Table I). Factors that favor conversion of AF to NSR with antiarrhythmic drug therapy to maintain NSR include LA size < 50 mm, duration of AF < 1 year, increased symptoms of congestive heart failure or fatigue with AF, younger, more active patients, and/or contraindications to chronic anticoagulation. Most patients deserve at least one attempt at conversion of AF to NSR with drug therapy to maintain NSR; however, multiple clinical factors must be taken into account in deciding a course of action.

TABLE I Conversion of atrial fibrillation to normal sinus rhythm versus rate control: Factors to be considered

Factors favoring conversion of AF to NSR and antiarrhythmic drug therapy to maintain NSR
1. Symptoms of CHF or fatigue increase when NSR is not present
2. LVH or markedly decreased LV function: AF usually associated with increased symptoms
3. LA size < 50 mm
4. Duration of AF < 1 year
5. Younger, more active patients
6. Presence of PAF
7. Contraindication to chronic anticoagulation
Factors favoring maintenance of AF with pharmacologic rate control
1. No deterioration in symptomatic status with AF when heart rate is controlled
2. Normal or near normal LV function
3. LA size > 50 mm
4. Duration of AF > 1 year
5. Older, less active patients
6. Sustained AF
7. No contradications to anticoagulation
8. Failure to maintain NSR despite cardioversion and adequate antiarrhythmic drug therapy

Abbreviations: AF = atrial fibrillation, NSR = normal sinus rhythm, CHF = congestive heart failure, LVH = left ventricular hypertrophy, LA = left atrial, LV = left ventricular, PAF = paroxysmal atrial fibrillation.

Rate Control as a Goal in Place of Conversion to Normal Sinus Rhythm (Table I)

Maintenance of sinus rhythm may not be possible despite medical therapy, or the risk of therapy may be too great; for example, compromised left ventricular function increases the risk of proarrhythmia with antiarrhythmic drug therapy, thereby favoring rate control as the treatment of choice. Factors that favor maintaining AF with pharmacologic control include LA size > 50 mm; AF of > 1 year's duration; older, less active patient; no contraindication to anticoagulation; and/or prior failure to maintain NSR after conversion from AF (Table I). Adequate rate control can minimize both hemodynamic consequences and symptoms associated with excessive heart rate. Anticoagulation for thromboembolic prophylaxis and rate control medication are increasingly popular therapeutic strategies. Drugs that control rate include digoxin, calcium-channel blockers, and beta blockers.

Treatment Strategies

Direct-Current Cardioversion of Atrial Fibrillation to Normal Sinus Rhythm (Table II)

Direct-current (DC) cardioversion is the most rapid and effective method for restoring NSR in a patient in whom AF is

TABLE II Procedures and antiarrhythmic agents used to control atrial fibrillation

Direct-current (DC) cardioversion of AF to NSR

Dose: Delivery of the direct current charge must be synchronized with the R wave of the ECG to prevent discharge during the vulnerable period of the ventricles, thus avoiding ventricular fibrillation.

Mechanism: Direct current delivered in a transthoracic manner to the heart results in generalized cardiac depolarization, abolishing disordered conduction. During the systole that follows, the SA node is allowed to resumed its role as cardiac pacemaker.

Adverse reactions: Those associated with anesthesia, ventricular fibrillation, thromboembolic events (see anticoagulation), and minimal myocardial damage.

Digoxin

Dose (adult): Digitalizing; 0.75–1.5 mg p.o. (divided doses); maintenance: 0.125–0.5 mg/day.

Mechanism: Increases influx of calcium ions by inhibition of sodium and potassium ATPase pump; this increase in intracellular calcium results in positive inotropic effect; decreases conduction through atrial and AV nodal tissue.

Adverse reaction: Anorexia, nausea, vomiting, lethargy, blurred vision, halos, green or yellow vision, flashing lights. Conduction abnormalities: sinus bradycardia, SA node block, AV node block, atrial or nodal ectopic beats, ventricular irritability, atrial tachycardia with AV block.

Drug interactions: Decreased effect/levels: antacids (magnesium, aluminum), cholestyramine, colestipol, kaolin. Increased levels: amiodarone, nifedipine, quinidine, quinine, verapamil.

Class Ia antiarrhythmic agents

Quinidine

Dose: p.o. (sulfate) 200–400 mg every 4-6 h; (gluconate) 324–648 mg every 8-12 h.

Mechanism: Depresses phase 0 of the action potential, decreases myocardial excitability and conduction velocity by decreasing sodium influx during depolarization and potassium efflux during repolarization, reduces calcium transport across cell membranes.

Adverse reaction: GI symptoms (nausea, diarrhea), cinchonism, hepatic granulomas and necrosis, thrombocytopenic purpura, heart block, respiratory distress, hypotension. ECG: absence of P waves; prolongation of QRS, PR, and QT intervals.

Drug interactions: Decreased serum concentrations with phenobarbital, phenytoin, and rifampin; increased serum concentrations with verapamil, amiodarone, alkalinizing agents, and cimetidine. Increases plasma concentration of digoxin.

Procainamide

Dose: Loading: IV 20 mg/min (up to 17 mg/kg) infusion over 25–30 min; maintenance: 50–100 mg/kg/day in divided doses.

Mechanism: Decreases myocardial excitability and conduction velocity by increasing the electrical stimulation threshold of the ventricles, His-Purkinje system, and through direct cardiac effect.

Adverse reactions: SLE-like syndrome, confusion, GI symptoms, hemolytic anemia, neutropenia, arthralgia, rash. Overdose associated with widening QRS and torsade des pointes.

Drug interactions: Increased plasma levels with cimetidine, ranitidine, beta blockers, and amiodarone.

Disopyramide

Dose: < 50 kg: 400 mg/24 h; > 50 kg: 600 mg/24 h.

Mechanism: Decreases myocardial excitability and conduction velocity, reduces disparity in refractoriness between normal and infarcted myocardium; possesses anticholinergic, peripheral vasoconstrictive, and negative inotropic effects.

Adverse reactions: Urinary retention and hesitancy, chest pain, CHF; hypotension, muscle weakness, stomach pain, bloating, blurred vision, hypokalemia. ECG: widening QRS, prolongation of QT interval.

Drug interactions: Decreased effect: phenytoin, phenobarbital, rifampin. Decreases levels of quinidine. Increased serum concentration with erythromycin and quinidine; increases serum level of digoxin.

Class Ic antiarrhythmic agents

Flecainide

Dose: 100–400 mg daily.

Mechanism: Slows conduction in cardiac tissue by altering transport of ions across cell membranes causing prolongation of refractory periods; decreases rate of rise of the action potential without affecting its duration.

Adverse reactions: Dizziness, headaches, dyspnea, bradycardia, CHF, alopecia, blood dyscrasis, new-onset ventricular tachycardia or fibrillation, heart block, heart failure. ECG: prolongs PR and QRS.

Drug interactions: Increased plasma concentration of digoxin and propranolol. Increased effect with cimetidine, amiodarone, smoking, high-dose anatacids, sodium bicarbonate, verapamil.

Propafenone

Dose: Initially 150 mg every 8 h, increase every 3–4 days, if necessary; maintenance: 150–300 mg every 8 h.

Mechanism: Blocks the fast inward sodium current and slows the rate of increase of the action potential; prolongs conduction and refractoriness in all areas of the myocardium, with slightly more effect on intraventricular conduction.

Adverse reactions: Dizziness, dry mouth, drowsiness, AV block, conduction disturbances, GI symptoms, CHF, new or worsened arrhythmias, abnormal speech and dreams.

Drug interactions: Decreased levels with rifampin. Increased levels with cimetidine, quinidine, and beta blockers. Increases levels of warfarin, cyclosporine, digoxin, and beta blockers.

(continued)

TABLE II Procedures and antiarrhythmic agents used to control atrial fibrillation *(continued)*

Type II antiarrhythmic agents
Propranolol (typical beta blocker)
Dose: 10–80 mg every 6-8 h.
Mechanism: Competitively blocks response to beta-1 and beta-2 adrenergic stimulation.
Adverse reactions: Bradycardia, impotence, mental depression, skin rash, wheezing, CHF, reduced peripheral circulation, impaired myocardial contractility, nightmares, hypoglycemia, hyperglycemia, worsening of AV conduction disturbances.
Drug interactions: Decreased effect with phenobarbital, rifampin. Increased toxicity with cimetidine, flecainide, hydralazine, propafenone, and quinidine.
Type III antiarrhythmic agents
Amiodarone
Dose: Loading 800–1600 mg/day for 1–3 weeks; maintenance: 100–400 mg/day.
Mechanism: Inhibits adrenergic stimulation, prolongs the action potential and refractory period in myocardial tissue; decreases AV conduction and sinus node function.
Adverse reactions: Ataxia, nausea, vomiting, pulmonary fibrosis, interstitial pneumonitis/alveolitis, abnormal liver function tests, hyper- or hypothyroidism, insomnia, cardiac arrhythmias, sinus bradycardia, heart block, hypotension. ECG: prolongation of QRS, QT and PR intervals.
Recommendation: All patients on amiodarone need periodic ECG, liver function tests, thyroid function tests, and chest x-rays.
Drug interactions: Increased serum levels and toxicity of digoxin, flecainide, procainamide, quinidine, warfarin, and phenytoin. Decreased serum levels with cholestyramine.
Sotalol
Dose: 80 mg b.i.d. (may be increased to 240–320 mg/day).
Mechanism: Possess both β1- and β2-receptor blocking activity as well as blocking potassium channels resulting in prolonged repolarization.
Adverse reactions: Bradycardia, torsade de pointes, mental depression, decreased sexual activity, breathing difficulties, CHF, reduced peripheral circulation, GI complaints, severe hypotension, hypoglycemia. Warning: Use with caution in patients with CHF, hypokalemia, hypomagnesemia, sick-sinus syndrome; abrupt withdrawal may result in life-threatening arrhythmias. Monitor serum magnesium, potassium, ECG.
Drug interactions: Decreased effect/level with coadministration of aluminum- and/or magnesium-containing antacids.
Ibutilide (experimental drug)
Dose: IV: 1 mg over 10 min in patients weighing > 60 kg. In patients weighing < 60 kg, the dose should be adjusted to 0.01 mg/kg. The dose can be repeated once after 10 min if needed.
Mechanism: Prolongs repolarization by increasing the slow inward sodium current and by blocking the delayed rectifier current in both atrium and ventricles.
Adverse reactions: Heart block and heart failure; 3–8% of patients treated with ibutilide developed torsade de pointes. Ibutilide is teratogenic in rats.
Drug interactions: Avoid use with other drugs that affect cardiac conduction and the nonsedating antihistamines terfenadine (Seldane®) and astemizole (Hismanal®).
Type IV antiarrhythmic agents
Verapamil
Dose: Supraventricular arrhythmias: 5–10 mg IV slow push, may repeat with 10 mg in 15–30 min if patient tolerates initial dose.
Mechanism: Inhibits calcium ion from entering the "slow channels" or select voltage-gated areas of vascular smooth muscle and myocardium during depolarization; produces a relaxation of coronary vascular smooth muscle and coronary vasodilation; slows automaticity and conduction of AV node.
Adverse reactions: Skin rash, bradycardia, heart block, CHF, hypotension, peripheral edema.
Drug interactions: Decreased serum concentrations of phenobarbital, phenytoin, sulfinpyrazone, and rifampin. Increased serum concentrations of digoxin, quinidine, carbamazepine, and cyclosporine. Increased toxicity with rifampin and cimetidine.
Diltiazem
Dose: Bolus with 0.25 mg/kg over 2 min, may repeat dose in 15 min, if necessary; continuous infusion of 5–15 mg/h for up to 24 h.
Mechanism: Same as verapamil.
Adverse reactions: Similar to verapamil.

Abbreviations: AF = atrial fibrillation, NSR = normal sinus rhythm, ECG = electrocardiogram, SA = sinoatrial, ATPase = adenosine triphosphatase, AV = atrioventricular, p.o. = orally, GI = gastrointestinal, IV = intravenous, SLE = systemic lupus erythematosus, CHF = congestive heart failure, b.i.d. = twice a day.

causing instability, that is, hypotension, angina, or heart failure. This therapy was introduced in 1962 by Lown and is the mainstay of cardioversion from AF to NSR.[26] It can be used electively in an outpatient setting. Chronicity of AF, left atrial diameter, and the presence of mitral stenosis are important variables in predicting the outcome of DC cardioversion.[11] Left atrial size < 50 mm or duration of AF of < 1 year have been considered to have positive predictive value for mainte-

nance of NSR. It is interesting that the electrocardiographic F wave amplitude has shown little correlation in predicting long-term maintenance of NSR after conversion from AF.[27, 28] According to Van Gelder, the most important variables related to the success or failure of DC cardioversion are the duration of AF and the patient's age.[29] In some patients, in whom DC cardioversion fails initially, the procedure can be successful during a second attempt after administration of a class I or III antiarrhythmic drug.[22]

Pharmacologic Therapies

Digoxin (Table II): Digoxin, originally employed as an herbal remedy, has stood the test of time. It is still the most widely prescribed medication to control ventricular response during AF. Digoxin acts directly on atrial tissue and the atrioventricular (AV) node; however, its main effect is mediated by the autonomic nervous system. In the resting, digitalized patient, vagal influences on the AV node are enhanced and, as a result of these effects, the ventricular rate is slowed.[30] The effect of vagal stimulation on the atrium is more complex. Vagal stimulation shortens the atrial refractory period and increases dispersion of refractoriness; this result is the opposite of digoxin's direct effect on atrial tissue.[30] Because the predominant effect of digoxin on the AV node is mediated by enhanced vagal tone, its beneficial effect on resting heart rate is not always maintained during exertion, a period of vagal withdrawal. Vagal withdrawal during exertion can result in tachycardia, dyspnea, and fatigue during normal daily activities. Therefore, digoxin may need to be coupled with a beta blocker or a calcium-channel blocker, such as diltiazem or verapamil (directly slows AV nodal conduction), to control the ventricular response during exertion.

Despite the belief that digoxin restores NSR in patients with recent-onset AF, investigation does not support this claim. Falk and Leavitt noted that in the absence of congestive heart failure, digoxin does not act as an antiarrhythmic drug in the atrium.[11, 30] In a double-blind, randomized, placebo-controlled study in patients with recent-onset AF unassociated with congestive heart failure, no benefit was observed for digoxin compared with placebo for conversion of AF to NSR.[31]

Class Ia Antiarrhythmic Agents (Table II)

Quinidine: Quinidine constitutes the traditional preventive treatment for paroxysmal AF.[32–34] It has been widely used to prevent the recurrence of AF after successful conversion to NSR. Pritchett reported that patients treated with lower and hence safer doses of quinidine avoided the prolonged QT syndrome. However, the success rate for cardioversion was only 60%.[22] Torsade de pointes is the probable cause of "quinidine syncope." This potentially fatal arrhythmia can occur even with low serum concentrations of quinidine or even after a single dose.[23, 35–37]

Recently, a meta-analysis of investigations employing quinidine to maintain sinus rhythm found increased mortality in patients receiving this antiarrhythmic agent compared with placebo. These data coupled with comparable results from the CAST investigation have markedly decreased clinician enthusiasm for quinidine therapy to maintain NSR.[24, 38, 39]

Procainamide: Intravenous (IV) procainamide is widely used to restore NSR in patients with recent onset AF. The advantage of IV procainamide over DC cardioversion is that procainamide does not require anesthesia and may help to maintain NSR after conversion. However, procainamide is less successful in converting AF to NSR than DC cardioversion. Procainamide can be given with greater safety than quinidine; however, it is associated with provocation of torsade.[40, 41] Procainamide can be given intravenously with greater safety than quinidine.

Disopyramide: Disopyramide has been widely used for long-term maintenance of NSR following cardioversion from AF, but caution must be exercised in employing this agent with its attendant proarrhythmic potential. Morady *et al.*[42, 43] noted that in 80% of published reports of disopyramide-induced malignant ventricular arrhythmias, ventricular tachycardia or ventricular fibrillation occurred within 1 month of starting therapy. Torsade de pointes is a definite risk associated with disopyramide therapy.[44]

Class Ic Antiarrhythmic Agents (Table II)

Flecainide and propafenone: These two agents are efficacious in the chemical conversion of AF to NSR.[11] They are also effective in preventing the recurrence of AF to NSR once NSR has been reestablished. These drugs are generally well tolerated. The use-dependent effect of these agents results in increasing degrees of fast-channel blockade as stimulation rates are increased.[45] This phenomenon can result in a marked QRS widening at rapid ventricular rates.[46] Flecainide has more potent proarrhythmic effects than propafenone and should be used with great caution, if at all, in patients with compromised left ventricular function.[11] Flecainide should be reserved for patients with refractory, symptomatic AF and normal left ventricular function.

Propafenone also prolongs the action potential duration, slows intra-atrial, AV nodal, and His-Purkinje conduction, and prolongs atrial and ventricular refractory periods. Repique *et al.* believe that propafenone appears to have fewer serious side effects and is better tolerated than type Ia antiarrhythmic agents.[11]

Type II Antiarrhythmic Agents (Table II)

Beta blockers: These agents have modest efficacy for either chemical cardioversion of AF or prophylactic maintenance of NSR. Beta blockers also have proven efficacy in controlling the ventricular response in AF both at rest and with exertion (sympathetic block). Because beta blockers oppose the effect of adrenergic stimulation, they are of least value when adren-

ergic tone is low and are most efficacious in situations where enhanced sympathetic tone is present.[12] The combination of digoxin and beta blockers is sometimes successful in converting AF to NSR.[11] Some patients have adrenergically mediated PAF. Beta-blocker therapy often decreases or abolishes PAF in these individuals.

Type III Antiarrhythmic Agents (Table II)

Amiodarone: Amiodarone has powerful antiarrhythmic effects. It is effective in refractory AF when other agents have failed to maintain NSR. It is also effective in preventing the recurrence of AF after DC cardioversion.[11,34] In nonrandomized trials of amiodarone for AF refractory to conventional agents, amiodarone has been successful in maintaining NSR in 53–79% of patients during a mean follow-up of 15–27 months.[47] Middlekauff *et al.* reported intolerable side effects that included pulmonary toxicity in the range of 1–12%, but noted extremely low proarrhythmic effects even in the face of severe left ventricular dysfunction.[47] In another review, Hohnloser *et al.* reported that of 2,878 patients treated with amiodarone only 57 had a proarrhythmic event, resulting in an overall incidence of 2%. Torsade de pointes was noted in only one third of these patients, giving an overall incidence of torsade of 0.7%.[48]

Sotalol: Sotalol is an agent which combines the electrophysiologic features of a beta blocker (type II antiarrhythmic) with those of a type III antiarrhythmic agent. Sotalol is highly effective against supraventricular and ventricular arrhythmias and is frequently used to prevent episodes of PAF and to maintain NSR following cardioversion from AF.[49] Torsade is a potential complication of sotalol therapy.

Ibutilide: Ibutilide is a Class III antiarrhythmic agent currently undergoing extensive clinical trials. It lengthens the effective refractory period in both the atrium and ventricle while having limited effect on the conduction in normal cardiac tissue.[50]

Ibutilide appears to be effective in the pharmacologic conversion of recent-onset AF. Results from a recent prospective nonrandomized trial comparing procainamide with ibutilide for rapid conversion of AF and atrial flutter showed ibutilide to be superior for conversion of AF to NSR. Unlike procainamide, ibutilide did not produce hypotension or ventricular proarrhythmia during the infusion.[51] Successful conversion of AF to NSR with ibutilide appears to be dose-dependent: 12% conversion rate with an ibutilide dose of 0.005 mg/kg and 46% conversion rate with a dose of 0.025 mg/kg. Ellenbogen *et al.* reported that the success rate of conversion to NSR with ibutilide was not affected by the concomitant use of calcium-channel blockers, digoxin, or beta blockers.[51]

Type IV Antiarrhythmic Agents (Table II)

Verapamil and diltiazem: Repique *et al.* state that both sinus nodal and AV nodal depolarization are calcium-dependent processes and that diltiazem and verapamil decrease the amplitude of sinoatrial and AV nodal action potentials.[11] Prolonging the AV nodal refractory period decreases the ventricular response in AF.

Both diltiazem and verapamil control ventricular response at rest and during exertion and are thus superior to digoxin.[33] Calcium-channel blockers can be used alone or in combination with digoxin to control ventricular response. Both beta blockers and verapamil have negative inotropic and chronotropic effects and therefore should rarely be used together.[11]

Complications due to Pharmacologic Therapies

Proarrhythmia (Table III)

Proarrhythmia refers to drugs that have the potential to provoke a new arrhythmia or worsen a preexisting arrhythmia. Patients with AF may be at greater risk for proarrhythmia because of the association of AF with underlying heart disease. Pharmacologic treatment aimed at controlling AF may adversely affect the ventricular electrophysiologic milieu, allowing the emergence of a new or worsened atrial or ventricular arrhythmia. The Cardiac Arrhythmia Suppression Trial (CAST I) and CAST II studies of the early 1990s noted that antiarrhythmic drugs have the potential to exacerbate rather than suppress arrhythmias.[52,53]

Torsade de Pointes

Polymorphic ventricular tachycardia (QRS axis wraps around the isoelectric baseline) associated with QT prolongation is one of the most common proarrhythmias associated with therapy for AF.[23]

Most antiarrhythmic agents can cause torsade de pointes; however, torsade is most frequently associated with Type Ia antiarrhythmics such as quinidine, procainamide, and disopyramide which cause QT interval prolongation. Quinidine-induced torsade de pointes can occur within 48 h of starting this agent although some patients receive treatment for over a year before the onset of torsade.[35] Several risk factors are associated with the development of torsade, specifically low serum potassium, excessive bradycardia, and low serum magnesium. Based on the clinical experience of Falk, it was estimated that torsade has an annual occurrence rate of 1.5% in patients receiving antiarrhythmic agents.[36]

The development of torsade after conversion of AF to NSR probably is related to the decrease in ventricular response rate. Bradycardia may be associated with the abnormal cellular phenomenon of early repolarization which may favor the development of torsade.[37] For example, the beta-blocking effects of sotalol may result in torsade, in part due to the induced bradycardia. It is therefore of paramount importance to monitor serum electrolytes in patients who are receiving type I antiarrhythmic agents. Torsade is less likely to develop in patients who maintain normokalemia.

TABLE III Proarrhythmic effects of medications used to treat atrial fibrillation

Adverse effect	Drug	Mechanism
Torsade de pointes	Quinidine, disopyramide, procainamide, sotalol, ibutilide	QT prolongation, aggravated by hypokalemia, bradycardia, decreased magnesium
Ventricular tachycardia/fibrillation	Almost any antiarrhythmic medication	Probably a function of underlying ventricular disease: decreased ventricular function increases the likelihood of this complication
Drug-induced increased ventricular response	Type Ia and Ic agents	Ventricular response is determined by the refractory period of AV node, concealed conduction within the node, autonomic tone; vagolytic effects of drugs
Prolongation of AF	Calcium-channel blockers	May be due to increased sympathetic tone secondary to vasodilation
High-degree AV block	Digoxin, type Ia or Ic agents (quinidine procainamide, flecainide, propafenone, diltiazem, verapamil	Decreased conduction through AV node
Increased duration of AF	Digoxin, verapamil, diltiazem, beta blockers	Increased parasympathetic tone

Abbreviations: AF = atrial fibrillation, AV = atrioventricular.

Drug-Induced Increased Ventricular Response

The ventricular response to AF is determined by the refractory period of the AV node, the degree of concealed conduction within the node, and autonomic tone. Alteration of any of these factors by antiarrhythmic agents can increase the ventricular response rate. Quinidine-induced ventricular rate increase in patients with AF has been known for a long time; this phenomenon can be countered by the co-administration of digoxin. Increased ventricular response following quinidine or procainamide administration is the result of vagolytic properties of these agents.

Type Ic agents, as noted above, are used to terminate recent-onset AF or to maintain NSR after conversion. Type Ic agents can result in marked QRS widening at rapid ventricular rates, for example, atrial flutter with 1:1 conduction. Falk noted that the overall incidence of transformation of AF to atrial flutter with 1:1 conduction is in the range of 3.5–5%.[36]

Prolongation of Atrial Fibrillation

The calcium-channel blockers diltiazem and verapamil are used to control the ventricular rate in AF; however, they have also been noted to prolong episodes of paroxysmal AF.[36] This effect may be due to an increase in sympathetic tone caused by the vasodilatory effects of these calcium-channel blockers.

High-Degree Atrioventricular Block

Drugs that decrease conduction through the AV node, such as digoxin, type Ia, and Ic antiarrhythmics, have a propensity to produce AV block which can be severe at times, leading to symptomatic bradycardia.

Increased Duration of Atrial Fibrillation

Digoxin, verapamil, diltiazem, and beta blockers can either cause a marked bradycardia or increase parasympathetic tone leading to prolongation of episodes of AF. These drugs can also aggravate sick sinus syndrome, thereby leading to an increased tendency toward development of AF.[36]

Nonpharmacologic Strategies for Treating Atrial Fibrillation

Nonpharmacologic therapies include DC cardioversion (discussed earlier), cardiac pacing, radiofrequency (RF) catheter ablation, antiarrhythmic surgery, and internal atrial defibrillation. Many of these procedures remain experimental but point to future modalities for the management of recalcitrant AF.

Radiofrequency Catheter Ablation

Patients with AF refractory to drug therapy have been treated with RF ablation which interrupts conduction in the AV node.[54–57] A consequence of RF AV nodal ablation is the development of third-degree AV block requiring permanent pacemaker therapy. The need for permanent pacing can be diminished if RF ablation is targeted to the posterior or midseptal right atrium, thereby modifying AV nodal conduction and decreasing the ventricular response.[54]

In a procedure resembling the surgical "maze" operation (see below), Haissaguerre *et al.* employed a 14-polar catheter to make linear lesions in the right atrium with successful long-term termination of AF in one patient.[56]

Atrial Pacing

Atrial pacing may be useful in patients with tachy-brady syndrome who manifest paroxysmal AF.[21] Atrial fibrillation may develop during episodes of bradycardia which allow fibrillation to develop. Permanent AV sequential pacing is felt by some authorities to prevent episodes of PAF by abolishing periods of atrial asystole. In a very select group of patients, rapid atrial pacing can induce chronic self-sustaining AF which can then be controlled with digoxin, beta blockers, or calcium-channel blockers.[57]

Surgery for Atrial Fibrillation

Patients who cannot be managed medically or who have recurrent cardiogenic embolism as a result of AF may require interventional therapy. The "maze" procedure attempts to abolish AF by channeling atrial electrical activation between multiple incisions made and repaired in both the right and left atrium.[21,57,58] The goal of this treatment is to limit the amount of electrically involved atrial muscle so that the chaotic rhythm cannot develop or sustain itself. This procedure requires open chest cardiothoracic surgery with the complications and risks attendant on that type of major surgery.

Internal Atrial Defibrillation by Implantable Device

Internal atrial defibrillation has been evaluated for over two decades.[57] Patients who may benefit have infrequent, symptomatic, long-lasting attacks despite maximal drug therapy.

Conclusion

Populations in most developed countries are experiencing significant increases in elderly individuals, leading to a situation where AF will become even more prevalent than it is today. Currently, 11% of the U.S. population is between the ages of 65 and 85 years; 70% of patients with AF are between the ages of 65 and 85 years.

Atrial fibrillation generally causes symptoms secondary to hemodynamic derangements which are the result of increased ventricular response and loss of atrial booster function. It is associated with reversible impairment of left ventricular function, cardiac chamber dilation—the clinical syndrome of heart failure—and thromboembolic events. Atrial fibrillation requires treatment to prevent these alterations in cardiac function from becoming permanent and/or to minimize symptoms.

Type Ia and Ic antiarrhythmics are capable of converting AF to NSR. Amiodarone has the greatest efficacy and safety for converting AF and maintaining NSR, while digoxin and verapamil are ineffective in restoring NSR. Quinidine, flecainide, disopyramide, and sotalol have also been shown to maintain NSR after conversion of AF. These latter agents carry a significant risk of malignant proarrhythmia.

Alternative therapy for AF includes anticoagulation with warfarin or aspirin for the prevention of thromboembolic events and a variety of agents to control ventricular response rate during AF. All medications used to treat AF carry significant risks in the elderly, whether from proarrhythmia, overdosing because of drug errors, or hemorrhage secondary to anticoagulation. Treatment of AF must be based on a careful risk–benefit evaluation. The physician must know the capability of his/her patients as well as drug mechanisms and effects in the elderly.

The decision to convert patients from AF to NSR or to control the ventricular response and maintain AF represents a complex intellectual challenge. Factors favoring one or the other of these two clinical strategies are listed in Table I.

Multicenter drug trials, such as AFFRIM, are currently underway to assess various drug therapies for the maintenance of NSR after conversion from AF. Amiodarone is one of the drugs under investigation. The results of these trials will be extremely important in determining the future management of AF.

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