New Concepts in the Management of Atrial Fibrillation

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Summary

This review summarizes new developments in the pharmacologic and non-pharmacologic management of atrial fibrillation.

Key Words

Atrial fibrillation, antiarrhythmic drug therapy, stroke prevention, catheter ablation, implantable defibrillator

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. It occurs in 0.4% of the adult population and in 2 to 4% of those above 60 years of age. The prevalence rises to 17% by the age of 84 [1]. Although the causes of AF are diverse, in addition to the normal aging process hypertension and congestive heart failure (CHF) are common. The mortality of patients with AF is double that of control subjects. AF is also associated with significant morbidity including CHF, frequent and prolonged hospitalizations, and a 4 to 5 fold increase in the incidence of stroke. The quality of life of patients with AF is as impaired as that of patients with CHF.

The three major goals in the management of AF are rate control, rhythm control and stroke prevention [2]. Rate control reduces symptoms and may prevent the development or progression of CHF. Restoration and maintenance of sinus rhythm is associated with improved symptomatology too; it is uncertain, however, whether it is an effective tool to prevent thromboembolic events. In AF the only intervention to date that has been shown in multiple large scale prospective randomized trials to favorably influence outcome is anticoagulation.

The popular 3-P classification of AF helps to set the therapeutic goals. In paroxysmal atrial fibrillation there is spontaneous initiation and termination of the AF episodes. Antiarrhythmic management frequently reduces the number of paroxysms. In persistent atrial fibrillation electric or pharmacologic intervention is needed to terminate the arrhythmia. In permanent AF it is no longer possible or practical to restore and maintain a sinus mechanism. Clearly, the stakes are highest in the persistent form. A large scale NIH sponsored prospective randomized trial, the AFFIRM study will hopefully answer the question whether in addition to anticoagulation, the strategy of rate control or rhythm control is more efficacious in reducing mortality, stroke, in improving the quality of life and reducing the cost of therapy [3].

Because of the enormous impact of AF on patients' survival, well being and the cost of medical care, several aspects of the management of AF are currently undergoing intense scrutiny. This review summarizes some new concepts in the pharmacological management of AF and also gives an overview of more innovative, non-pharmacological, mostly investigational treatment modalities.

Stroke Prevention

Pharmacologic management

The absolute rate of ischemic stroke in patients with AF is critically influenced by the patient's age and by

the presence of coexistent cardiovascular disease. In patients with non-valvular AF major clinical markers of increased risk of stroke include a history of TIA or stroke, CHF or reduced left ventricular ejection fraction, hypertension, and age above 75, especially in females. Intermediate clinical markers include diabetes, thyrotoxicosis and coronary artery disease. Echocardiographic markers are left atrial enlargement, left ventricular dilatation and systolic dysfunction, mitral anular calcification, and spontaneous echo contrast. The presence of rheumatic heart disease or a prosthetic valve dramatically increases the risk of stroke. Table 1 summarizes the current recommendations for stroke prevention in AF [4]. Clearly, the vast majority of patients should be treated with warfarin. In the absence of clinical risk factors, however, especially in patients less than 65 years of age, aspirin alone may suffice. In patients without major clinical risk factors who are 65 to 75 years of age the choice between aspirin and warfarin is made based on intermediate clinical markers, echocardiographic markers, perceived bleeding risks, and patient preference. The role of transesophageal echocardiography (TEE) is debated in the management of AF. TEE is not generally required to establish the need for chronic anticoagulation. TEE is frequently used to rule out the presence of clots in the left atrial appendage (LAA) prior to cardioversion of patients with relatively recent onset AF of greater than 48 hours duration. Preliminary studies suggest that the TEE guided approach may be as safe as cardioverting patients after three or four weeks of anticoagulation.

Age (years)	Major clinical risk factor ≥ 1	No major clinical risk factor
< 65	warfarin	aspirin
65 - 75	warfarin	aspirin or warfarin
> 75	warfarin	warfarin

Table 1. Current recommendations for anticoagulation in paroxysmal and chronic atrial fibrillation and atrial flutter [4]. Major clinical risk factors for stroke in AF include rheumatic heart disease, prosthetic heart valves, a history of TIA or stroke, congestive heart failure or left ventricular systolic dysfunction, and hypertension.

Another controversial issue is anticoagulation for atrial flutter. We used to believe that atrial flutter, in contrast with AF, is not associated with significant thromboembolic risks. Newer studies suggest that in patients with clinical risk factors, the stroke risk in atrial flutter is substantial too. Most cardiologists therefore do not distinguish between AF and atrial flutter in terms of recommending anticoagulation except maybe in the category where the use of warfarin is optional.

There seem to be certain patient categories who are at an increased risk of not receiving anticoagulation. These include patients with permanent pacemakers where the underlying AF may remain unrecognized. Another category are the elderly patients who are frequently not anticoagulated because of the fear of hemorrhagic complications. Although bleeding risks do increase with advancing age, so does the risk of thromboembolism, and the consequences of the latter are usually more permanent and devastating. In elderly patients with AF therefore the relative risks of bleeding and stroke need to be carefully and individually assessed. Age in itself should not be a contraindication to anticoagulation.

Non-pharmacologic management

In AF over 90% of clots responsible for embolic events reside in the LAA. Surgical removal of the LAA (left atrial appendectomy) therefore may result in reduction of the risk of stroke. Experimental studies demonstrated that with the use of a surgical stapling device the LAA can be easily and safely removed without creating residual endocardial pockets or pouches. In a few cardiothoracic centers prophylactic left atrial appendectomy is routinely performed in patients who undergo open chest surgical procedures. It is the hope, albeit so far unproven, that this simple intervention reduces the life long risk of thromboembolism.

Therapeutic left atrial appendectomy is a more ambitious procedure. Possible candidates are patients with AF who experienced thromboembolic events despite therapeutic anticoagulation, or in whom there is an absolute contraindication to warfarin. In these patients without an independent indication for thoracotomy, the LAA can be removed with a thoracoscopic approach. Preliminary results suggest that in experienced hands and with careful patient selection this procedure can be safely performed. Left atrial appendectomy should probably not be attempted in patients with significant carotid disease, in the presence of large clots in the

LAA, in patients with advanced lung disease, and in thyrotoxicosis. The long term results of this investigational procedure are unknown.

Rate Control

As an alternative to rhythm control, rate control alone offers few advantages. These include relative safety, once a day dosing, and low cost. The downsides are more substantial and include less than optimum rate control during physical activity and mental stress, the hemodynamic disadvantage of the absence of atrial contribution to ventricular filling, and the fact that rate control almost certainly does not decrease the risk of thromboembolism. Until the AFFIRM trial [3] proves otherwise, we now believe that in the majority of patients with paroxysmal or persistent AF the rhythm control rather than the rate control strategy should be pursued. In patients with permanent AF, however, rate control becomes a crucial component of therapy.

Pharmacological management

Commonly used drugs that prolong refractoriness in the AV node include digoxin, beta adrenergic antagonists and calcium channel blockers [5]. Digoxin alone rarely results in adequate rate control. It is reasonable to use digoxin in combination with another AV nodal blocking drug in the presence of CHF. Beta blockers and both verapamil and diltiazem are more effective in controlling the ventricular response in rapid AF. These agents however have a profound negative inotropic effect and may cause hypotension.

In patients with advanced structural heart disease and AF it is sometimes impossible to control the ventricular rate even with combination treatment. An incessant rapid heart rate may initiate a vicious cycle of progressive ventricular dilatation and dysfunction resulting in further tachycardia. Another category at risk for a tachycardia induced cardiomyopathy are patients with asymptomatic AF. These patients may have rapid heart rates for several months and their first clinical presentation is that of newly diagnosed dilated cardiomyopathy with CHF. The third "high risk group" is those patients with known AF who seem to have appropriate rate control in the office setting but remain tachycardic during the activities of daily living. Table 2 summarizes the currently recommended requirements to establish adequate rate control in patients with AF. In refractory cases the addition of amiodarone sometimes results in better rate control. The typical patient in whom amiodarone should be considered is one who has severe structural heart disease, CHF, rapid AF not appropriately controlled by digoxin and diltiazem but who is not a candidate for AV junctional ablation or modification described below.

	Heart Rate	
At office visits	apical (sitting)	≤ 80 bpm
On Holter	average daily	≤ 80 bpm
	average hourly	≤ 100 bpm
Exercise Test	at 4 METs	≤ 85 % of max. predicted

Table 2. Current recommendations to establish adequate rate control in patients with atrial fibrillation. MET = metabolic equivalent.

Non-pharmacological management

Catheter ablation of the AV junction in patients with AF and poorly controlled ventricular response is a palliative intervention associated with low complication rate and excellent long term results. Patients remain in AF and therefore anticoagulation is mandatory. Because of third degree AV block a pacemaker needs to be implanted. Despite these drawbacks, a number of studies demonstrated a significant improvement in patients' quality of life, symptomatology and objective measures of left ventricular size and function including the ejection fraction and left ventricular end-systolic diameter [6]. To date there is no evidence that this technique influences survival and there has been some concern about a very small possible risk of sudden death after AV junctional ablation. Since most patients become pacemaker dependent, the long term reliability of pacing leads and pulse generators must be insured.

Recently, ablation techniques that modify AV nodal conduction without inducing complete AV block have been described [7]. The theoretical advantage of AV nodal modification compared to AV junctional ablation is that these patients may not become pacemaker dependent. AV nodal modification simply caps off the maximum ventricular response rate. Preliminary data

suggest that AV nodal modification also results in improved symptomatology and left ventricular systolic performance.

Rhythm Control

Cardioversion

About 50% of patients with new onset AF will convert spontaneously to sinus rhythm within 24 to 48 hours of presentation. Digitalis, verapamil, diltiazem and beta blockers rarely terminate AF. Pharmacologic cardioversion may be attempted with any antiarrhythmic drug used in the prevention of AF. In the United States the two most widely used intravenous agents are procainamide and ibutilide [8]. Ibutilide, this new class III antiarrhythmic drug is more efficacious than procainamide, is especially useful in patients with AF and atrial flutter of less than two weeks duration, in patients with post-surgical AF, and as pretreatment, to increase the success rate of electric cardioversion. Appropriate guidelines need to be followed to limit the incidence of ibutilide induced polymorphic ventricular tachycardia. The two most frequently used oral agents for the termination of AF are flecainide (300 mg) and propafenone (600 mg). These are most useful for patients with minimal or no structural heart disease and recent onset AF. Class IC agents are less effective in converting atrial flutter.

For patients with long standing AF and underlying structural heart disease, the success of direct current electric cardioversion is superior to pharmacologic cardioversion. Except for the risk of anesthesia, electric cardioversion is safe. In AF the usual initial energy is 200 joules, whereas for atrial flutter it is 50 or 100 joules. Higher energies should be used for patients with long standing AF or flutter, for those with severe structural heart disease, for the obese, emphysematous patients and in patients with prior thoracic surgery. Pretreatment with antiarrhythmic drugs too may increase the atrial defibrillation threshold but it also results in a lower incidence of early recurrence of the arrhythmia.

Chronic antiarrhythmic drug therapy

In paroxysmal or persistent AF the maintenance of sinus rhythm strategy offers several theoretical advantages over the strategy of pure rate control. During sinus rhythm, compared to AF, there is better physiological adaptation of the cardiovascular system to increased demand, the stroke volume is increased, and possibly, there is a reduced incidence of thromboembolism. Unfortunately, there are significant dark sides to antiarrhythmic management as well. These include the risk of proarrhythmia, an increased mortality in certain subgroups of patients, the fact that even the best antiarrhythmic agents are only partially effective, all are associated with significant side effects, they are costly, and except for amiodarone, all have a bid or tid dosing. The details of chronic antiarrhythmic drug therapy in patients with AF is beyond the scope of this review except to say that in patients without significant structural heart disease the class IC agents (flecainide, propafenon), whereas in patients with significant heart disease the class III antiarrhythmics (sotalol, amiodarone, dofetilide, azimilide) are emerging as the preferred drugs. Because of the complexities and significant risks associated with antiarrhythmic drug treatment of AF, in my view this should always be directed by a cardiologist [9].

Nonpharmacologic therapy of atrial fibrillation

Nonpharmacologic tools to treat AF include antiarrhythmic surgery, pacing, atrial defibrillation, and catheter ablation [10]. All of these interventions are investigational, some are associated with high complication rates, and the long term affects are unknown. Nevertheless, there is increasing evidence that combination or hybrid treatments of AF may result in a significant improvement of rhythm control compared to medical management alone.

Pacemaker therapy: Ventricular pacemakers are routinely used in patients with AF and slow ventricular response. It has long been recognized that in patients with the so called tachycardia-bradycardia syndrome A-V sequential pacing or atrial pacing alone is more effective than ventricular pacing in preventing episodes of AF. Studies suggest that even in patients without symptomatic bradycardia, the incidence of AF episodes can be reduced and the interval to the first AF recurrence prolonged by atrial pacing. The role of multisite atrial pacing from the right atrial appendage and the lower interatrial septum or that of biatrial pacing from the right atrial appendage and the coronary sinus are also explored. Pacemaker algorithms are developed for the rapid pace termination of new onset atrial flutter and coarse AF. Preliminary results are encouraging and suggest that especially in patients with intraatrial conduction defects and recurrent AF, pacemaker thera-

py in combination with pharmacologic management may become one of the relatively safe and effective treatment modalities.

Implantable atrial defibrillator: It has long been recognized that in AF high energy internal right atrial defibrillation has a better success rate than external cardioversion. More recently it was shown that with appropriate lead placement low energy internal cardioversion has a high success rate too, low complication rate, and it is well tolerated. This observation gave the impetus to develop implantable atrial defibrillators. It is the hope that with early recognition and prompt treatment of AF the harmful consequences of electrical remodeling that result in an increased risk of recurrent or sustained AF, and of mechanical remodeling resulting in atrial myopathy, atrial stasis and clot formation can all be prevented. These hypotheses, however, are so far unproven. Several types of implantable atrial defibrillators are undergoing clinical evaluation. The InControl Matrix atrioverter is an externally triggered stand-alone atrial defibrillator. The Medtronic Jewel-AF is a dual chamber atrial and ventricular defibrillator with complex rhythm detection and treatment algorithms. The role of implantable atrial defibrillators in the treatment strategies of AF await large scale clinical trials.

Surgical procedures: For patients with AF who cannot be managed effectively with drugs or who experienced cardiogenic embolism as a result of the arrhythmia, surgery is a therapeutic alternative for restoring sinus rhythm and AV synchrony thereby potentially limiting the risk of stroke. Several types of surgical interventions were developed for the treatment of AF of which the "maze" procedure emerged as the most effective. In the maze procedure both atrial appendages are excised and the pulmonary veins are isolated. Appropriately placed atrial incisions interrupt the conduction routes of reentrant circuits and direct the sinus impulse from the sinoatrial node to the AV node. The entire atrial myocardium except for the atrial appendages and pulmonary veins is electrically activated thereby preserving atrial transport function. The success rate of this highly invasive procedure is excellent. Ideal candidates are those patients with long standing AF who undergo open heart surgery for congenital or acquired heart disease. There have been several modifications to the original Cox-maze procedure including the use of intraoperative radiofrequency or laser photoablation instead of the surgical cuts.

Only a limited number of centers worldwide are experienced in performing the surgical maze procedure. In addition, the vast majority of patients with chronic AF do not require open heart surgery and are therefore not candidates for the surgical maze. In my view the greatest significance of the surgical maze procedure is that it established proof of concept, i.e., that AF is a potentially curable disorder [11].

"Catheter maze": Based on the success of the surgical maze, several investigators developed similar interventions with a percutaneous catheter-based technique. Long radiofrequency lesions can be placed at different right and left atrial sites either with the drag technique using conventional ablation catheters or by creating linear lesions with specially designed electrodes. The catheter maze is technically challenging, usually requires long procedure times and aggressive anticoagulation regimens, is associated with high complication rates including thromboembolism, bleeding, perforation, AV block. Extensive biatrial procedures have higher success rates but also higher complication rates compared to a purely right atrial approach. It is possible but so far unproven that more limited interventions may still result in reducing the AF burden and thus in an improved pharmacological control of AF.

Catheter ablation of focal A: For several decades the multiple wavelet theory was the leading concept explaining the pathomechanism of AF. Recently it has been shown that in a minority of patients with recurrent AF the arrhythmia is due to a focal mechanism. In these patients AF is induced by the rapid focal firing of one or more ectopic atrial foci. Mapping studies demonstrated that the majority of atrial foci reside inside the pulmonary veins, mostly the upper pulmonary veins near their orifice. The histologic substrate is a muscular sleeve extending from the atrial myocardium into the pulmonary veins. The typical patient with "focal AF" is a relatively young individual without structural heart disease who has frequent, commonly daily episodes of AF and frequent PACs in between. Several centers have recently demonstrated that in patients with focal AF the site of origin can be mapped and ablated with a high success rate. In addition to the usual complications associated with radiofrequency catheter ablation, an added complication is the risk of pulmonary vein stenosis resulting in pulmonary hypertension.

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