



REVIEW

The progressive nature of atrial fibrillation: a rationale for early restoration and maintenance of sinus rhythm

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting young as well as elderly patients and presenting a major therapeutic challenge for clinical cardiologists. Recent research has elucidated the progressive nature of AF, including the structural and electrical remodelling that may become manifest if normal sinus rhythm is not restored, and the serious morbidities associated with long-term disease. The controversy over the merits of ventricular rate control vs. the restoration and maintenance of normal sinus rhythm in the treatment of AF has been explored in a number of large-scale, randomized clinical trials. The results of these trials suggest that whereas the two strategies may be equivalent for some patient populations, with both approaches requiring accompanying anticoagulation therapy, the restoration and maintenance of sinus rhythm provide important haemodynamic as well as subjective benefits not afforded by rate control. Although early intervention to limit the progression of this arrhythmia is hindered by the limitations of existing anti-arrhythmic therapies, it is nevertheless a critical goal.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and it tends to become more persistent and more difficult to treat over time. Recent studies have shown that this relates to alterations in the electrophysiological and contractile properties and structural architecture of the atria. These changes increase the probability of multiple coexisting atrial wavelets, which in turn set the stage for persistence of AF. Successful restoration and maintenance of sinus rhythm provide important haemodynamic as well as subjective benefits not afforded by rate control and are therefore an important goal in patients symptomatic with the arrhythmia. This is best accomplished when AF is diagnosed and treated early.¹

This article will review the epidemiology and clinical consequences, natural history, and current treatment of AF, with an emphasis on its progressive nature and the importance of early intervention. It will also show how our growing understanding of AF pathophysiology, coupled with a burgeoning body of empirical evidence gleaned from a series of landmark clinical trials, can be used to optimize treatment of this complex, and increasingly prevalent disease.

Epidemiology and clinical consequences of AF

The prevalence of AF continues to rise in Western nations. Recent research suggests that in the United States, for example, an estimated 2.3 million people have AF. The overall lifetime prevalence of the arrhythmia is approximately one in six individuals for the general population, and roughly one in four for people >40-years-old.²

AF is a major cause of morbidity and mortality, and is associated with a 1.5–1.9 relative risk of mortality and a relative risk of up to 4.5 for ischaemic stroke.^{3,4} Indeed, AF accounts for nearly 15% of all cerebral thrombo-embolic events.⁵ AF is also frequently complicated by heart failure, and the presence of both conditions may worsen the overall prognosis. The adverse haemodynamic effects of AF stem not only from the loss of atrial contraction and the rapidity and irregularity of ventricular contraction but also from the induction of tachycardia cardiomyopathy.⁶ Whether AF in the setting of heart failure is related to an increased risk of mortality is unknown at present.^{7–9}

AF causes symptoms such as palpitations, angina, dyspnoea, impaired exercise tolerance, and fatigue, and it lowers quality of life;^{10–12} it also places a significant economic burden on society.^{13,14} To make matters worse, the incidence of AF is increasing as the mean age and the prevalence of heart failure in the general population increase worldwide; associated mortality rates of patients

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with AF are also on the rise. During the past 20 years, the age-standardized death rate (per 100 000) for AF patients in the United States jumped from 27.6 to 69.8 between 1980 and 1998¹⁵—with the latter rate being nearly twice as high as for those individuals in sinus rhythm.³

AF pathophysiology and natural history

AF is a progressive disease that becomes more difficult to treat with increasing duration. This characteristic is attributed to the occurrence of electrical, contractile, and structural remodelling of the atria, which creates a fertile environment for the propagation of AF.^{16–18} Most frequently, AF occurs in the setting of underlying heart disease, which includes coronary artery disease, hypertension, valve disease, congestive heart failure, and thyroid dysfunction. In 15–30% of patients, however, no underlying disease is demonstrable; this is termed lone AF.

As AF was first recognized, its underlying aetiology has been a subject of great interest. The three primary proposed mechanisms include (i) one or more rapidly discharging, spontaneously active, atrial ectopic foci; (ii) a single re-entry circuit; and (iii) multiple functional re-entrant circuits. The multiple wavelet hypothesis, as formulated by Moe *et al.*¹⁹ and experimentally confirmed by Allesie *et al.*,^{20,21} until recently was generally accepted. Recent observations, however, have challenged this hypothesis. Optical mapping studies of AF in sheep hearts point to a primary local generator as being either an ectopic focus or a small re-entry circuit,²² implying that both concepts may, indeed, play a role in AF maintenance.

The wavelength of a cardiac impulse (the distance travelled by an impulse in one refractory period) is the product of the refractory period and conduction velocity. The stability of AF is determined by the number of wavelets simultaneously present; thus, the shorter the wavelength and the larger the atria, the more wavelets that will fit into the atria and the more stable the AF. Consequently, changes in refractory period and conduction velocity will affect the wavelength, and hence AF stability. Another important parameter affecting the vulnerability or stability of AF is inhomogeneities in electrophysiological properties: dispersion of atrial refractoriness, which is associated with conduction block, is a prerequisite for the start of re-entrant arrhythmias. AF induction may occur in the presence of (i) fibrotic and poorly conducting atria (e.g. due to haemodynamic overload, as in hypertension or heart failure); (ii) genetic disorders affecting refractory period and/or conduction velocity heterogeneously,^{23,24} or (iii) AF itself.

By shortening the atrial refractory period, reducing conduction velocity, and provoking contractile and structural remodelling, AF may set the stage for self-perpetuation (i.e. 'AF begets AF').^{16–18} These remodelling processes are seen in experimental models and have also, although not exclusively, been demonstrated in patients with AF.^{25–30} Electrical remodelling of the atria refers to changes in the atrial refractory period, including a shortening in duration and a loss of physiological rate dependence. This type of remodelling occurs rapidly (within several days) and contributes to the increased stability of AF.

Atrial contractile remodelling follows a similar time course and causes a loss of contractility that may set the stage for thrombus formation. This type of remodelling

may also lead to dilatation of the atria that can compound the persistence of AF, as a dilated atrium permits the coexistence of more wavelets than a smaller atrium and may also alter electrophysiological properties. In this respect, no uniform changes have been reported in various experimental studies, which have included different species, different models, and different degrees of severity and duration of atrial dilatation. Nevertheless, all studies demonstrated changes that supported the persistence of induced AF.^{31–34}

Structural remodelling occurs after a period of weeks to months and includes dilatation of the atria, changes in cellular structure characterized by a loss of myofibrils, accumulation of glycogen, reduction in connexin 40, changes in mitochondrial shape and size, fragmentation of the sarcoplasmic reticulum, and dispersion of nuclear chromatin, as seen with rapid atrial pacing in a healthy goat model.³⁵ These structural changes, which are indicative of a substantial deterioration of normal tissue architecture, likely promote AF. Moreover, they may be irreversible. Notably, these changes closely resemble those occurring in the setting of ischaemia-induced myocardial hibernation³⁵ and have also been observed in patients, but only after a protracted period of persistent AF.²⁹

In a study by Nattel *et al.*, dogs were subjected to rapid ventricular pacing for a period of 3 weeks. The dogs progressively developed (clinical) heart failure, and sustained AF could be induced in 10 of the 18 animals.²⁷ In contrast to the findings with rapid atrial pacing in a goat model, AF was characterized by long cycle lengths. However, discrete regions of slow conduction were found to result from changes in local expression of gap junctions or tissue fibrosis, both of which may cause increased tissue anisotropy. Although the latter alterations may promote the occurrence of AF in the setting of heart failure, they also become good candidates for the slower 'second factor' that seems to be involved in the development of permanent AF in a rapid atrial pacing model.^{16,17}

Triggers are a necessary element for the induction of AF. These include atrial ectopic foci, predominantly occurring within the sleeves of atrial tissue located in the pulmonary veins and the vena caval junctions, in addition to bradycardia and other (supra)ventricular tachycardias. Triggers may initiate re-entry if the wavelet is sufficiently short. Factors like wave front curvature and spatial and temporal organization are also relevant for the commencement of AF, because of the interaction of the propagating wave fronts with anatomical and functional obstacles, and may be considered initiators of AF. Beyond initiation, the condition of the atrial substrate can ensure the perpetuation of AF for long periods: in addition to the aforementioned electrical, contractile, and structural remodelling processes, ageing of the atria and progression of the underlying disease may contribute to the progressive nature of the arrhythmia, eventually precluding restoration and maintenance of sinus rhythm.

Triggers are thought to play the dominant role in the development of paroxysmal AF, but changes in the atrial substrate assume an increasingly important role as AF progresses to its persistent and permanent stages. A recent retrospective analysis by Al-Khatib *et al.* found that approximately 20% of patients with intermittent AF were in permanent AF after 4 years.³⁶ The most important clinical variables in predicting progression were age and whether

the patient was in AF at the time of presentation. A separate retrospective study by Kato *et al.* showed that 77% (132/171) of patients with paroxysmal AF were in permanent AF after a mean of approximately 14 years. The independent risk factors for early progression to permanent AF were ageing [hazard ratio (HR), 1.27 per 10 years], dilated left atrium (HR, 1.39 per 10 mm), myocardial infarction (HR, 2.33), and valvular disease (HR, 2.29).³⁷ Contrary to the above, in the absence of structural heart disease, paroxysmal AF does not easily seem to progress to permanent AF.^{38,39} After a first episode of paroxysmal AF many years can pass before there is a recurrence.⁴⁰ Paroxysmal AF may, though, more easily progress to permanent AF after atrioventricular junction ablation and ventricular pacing. This, however, may be due to altered haemodynamics caused by ventricular pacing.⁴¹ Thus, a different, more conservative, therapeutic approach without vigorous institution of anti-arrhythmic drugs may be adopted in this patient category.

Treatment implications

There are two basic strategies for the treatment of AF, rate and rhythm control, and each has its own benefits and drawbacks. Although rhythm control aims to restore sinus rhythm, this approach is often limited by moderate efficacy and the adverse effects of current anti-arrhythmic drugs, including the potential for dangerous pro-arrhythmia, which is especially problematic for those patients with underlying cardiovascular disease.^{42,43} A number of recent clinical trials—AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management),⁴⁴ RACE (Rate Control vs. Electrical Cardioversion),⁴⁵ PIAF (Pharmacologic Intervention in Atrial Fibrillation),⁴⁶ and STAF (Strategies of Treatment of Atrial Fibrillation)⁴⁷—failed to demonstrate the anticipated benefits of rhythm-control strategies (Table 1). In large part, however, this outcome may be due to a failure of pharmacological rhythm control. Overall, only 40–60% of the rhythm-control patients were in sinus rhythm at the end of follow-up, whereas the remainder were in AF. Thus, one of the reasons for choosing rate control is that rhythm control is often difficult to achieve in many patients. In addition, many patients are neither severely symptomatic nor suffer from AF-induced haemodynamic deterioration. The general consensus regarding the findings of these trials has been that the two strategies

are essentially equivalent with respect to the risk-benefit ratio for most AF patients, and that rate control may be preferable in many patient populations, especially those who are asymptomatic and have a low chance of successful maintenance of sinus rhythm (Table 2). However, substudies released in the wake of these four primary trials, as well as new studies conducted in recent years, have provided additional valuable insights into the question of rate vs. rhythm control.

A closer look at rate vs. rhythm control

Looking more closely at the clinical implications of establishing sinus rhythm, the RACE trial used echocardiography to evaluate atrial and ventricular remodelling in patients with and without sinus rhythm.⁴⁸ They found a significant increase in atrial size in the AF group vs. those patients in sinus rhythm, suggesting that the restoration and maintenance of sinus rhythm may provide a meaningful advantage for patients. The RACE investigators also reported that patients in sinus rhythm at the end of follow-up had better health-related quality of life as measured by the 36-Item Short Form Health Survey (SF-36), specifically in the physical functioning, physical role limitation, and vitality subscales.¹¹ Comparable quality of life findings have been reported in the CTAF (Canadian Trial of Atrial Fibrillation), PIAF, and SAFE-T (Sotalol Amiodarone Atrial Fibrillation Efficacy Trial) studies.^{12,46,49} Other recent studies have confirmed that sustained sinus rhythm is associated with improved quality of life and exercise tolerance.^{12,50}

AF may increase mortality in the general population,³ and possibly in patients with congestive heart failure (CHF).⁵¹ At present, there is no consensus as to whether AF is an independent risk factor for morbidity and mortality in CHF or just a marker of more severe disease. Some non-randomized studies and one *post hoc* analysis from the AFFIRM trial suggested that restoration of sinus rhythm is a marker for a greater likelihood of survival. In the CHF-STAT (Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy) trial, heart failure patients who converted to sinus rhythm while using amiodarone had significantly lower mortality compared with those who remained in AF.⁵² Similar results were reported in the DIAMOND (Danish Investigations of Arrhythmia and Mortality ON Dofetilide) trial, in heart failure patients with either AF or atrial flutter.⁵³ In addition,

Table 1 Potential benefits of rate- and rhythm-control strategies

Rate control	Rhythm control
<ul style="list-style-type: none"> • Easy approach • Lower costs of treatment • Fewer potential adverse treatment effects 	<ul style="list-style-type: none"> • Short-term use of anticoagulants • Fewer AF-related complaints in sinus rhythm • Improvement in left ventricular function and functional capacity • Improvement in quality of life • Prevention of heart failure • Lower mortality

Table 2 Patient populations eligible for rate versus rhythm control

Patients eligible for rhythm control All AF patients presenting for the first time Patients with symptomatic AF Patients without stroke risk factors
Patients eligible for rate control Patients with asymptomatic AF Patients in whom ECV, ablation, or arrhythmia surgery has failed Women Patients with hypertension

ECV, external cardioversion.

although the AFFIRM investigators reported no difference in mortality between those randomized to rate control and rhythm control treatments, a substudy found that the maintenance of sinus rhythm, and the use of warfarin, were associated with a lower overall risk of death (−47% and −50%, respectively).⁵⁴ After adjusting for the presence of sinus rhythm, they found that the use of anti-arrhythmic drugs increased the risk of death by 49%. The investigators speculated that if the therapeutic profile of anti-arrhythmic drugs could be improved, the maintenance of sinus rhythm might provide a survival advantage for high-risk AF patients, but till now this remains sheer speculation. Indeed, among patients who remained on oral anticoagulation in the RACE study, those who mostly were maintained in sinus rhythm under a rhythm-control strategy did not have a superior prognosis compared with those who remained in AF under a rate-control strategy.⁵⁵

Results from the PIAF, RACE, and AFFIRM trials, however, showed that AF patients remain at risk of thrombo-embolism, even when sinus rhythm is maintained, if the international normalized ratio (INR) falls outside the recommended range of 2.0–3.0.^{45,46,54} Until future studies provide other evidence, attempting to restore and maintain sinus rhythm does not replace the need for anticoagulation in high-risk patients, because of continued presence of asymptomatic AF and risk factors for thrombo-embolic complications.^{44,56}

The evidence from the trials discussed above suggests that restoration and long-term maintenance of sinus rhythm provide a variety of benefits, including an improvement in cardiac function and quality of life. Regardless of which strategy is chosen, early intervention to restore sinus rhythm and interrupt the progression of arrhythmia should improve the well being of AF patients, particularly in the younger active population with a high symptomatic burden.

Issues in AF treatment

As noted earlier, the suboptimal risk-benefit profile of current anti-arrhythmic drugs raises problems for clinicians, complicating the selection of treatments for long-term maintenance of sinus rhythm. Class IC anti-arrhythmics, such as flecainide and propafenone, are inappropriate for those with structural heart disease, as pro-arrhythmic or conduction side effects may occur in these patients. In addition, long-term use of the class III agent amiodarone, considered a first-choice treatment for AF in some countries, can cause serious non-cardiac complications.⁵⁷ As each patient has a unique underlying clinical history (age, duration of AF, underlying cardiac disease, and AF-related symptoms), treatment of AF must be individualized: one patient may benefit most from a wait-and-see approach, in the hopes that the AF may convert to sinus rhythm on its own; another may be a candidate for the immediate initiation of a class IC drug, in hospital or with use of the pill-in-the-pocket approach;⁵⁸ and yet another may best be served with acceptance of the arrhythmia.

Based on the results of the comparative trials, treatment with a goal of rate control may be recommended for those with structural heart disease, those whose condition requires a lower exposure to anti-arrhythmic drug toxicities,⁵⁷ and those with mild-to-moderate or no AF-related symptoms.⁴² The RACE study demonstrated that rate control may also be the first choice in females⁵⁹ and those with underlying

hypertension.⁶⁰ Rate control can often be achieved with use of negative chronotropic drugs. If patients remain symptomatic or if they suffer from intolerable side effects, atrioventricular node ablation in combination with pacemaker implantation (ablate-and-pace)⁶¹ may be a treatment option.⁶² The latter, however, may impair cardiac function.⁶³ Alternatively, anti-arrhythmic agents can help reduce AF-related symptoms in younger patients and in those with disabling symptoms.^{42,64} If less toxic and more effective anti-arrhythmics were available, there would be no obstacle to their more general use earlier in the course of AF. This improvement would increase the (long-term) success of early cardioversion and diminish the risk of adverse events in more severely impaired patients. It should also be noted that while other, more invasive techniques (e.g. pulmonary vein isolation) are indeed effective in treating AF, they might never be available to the majority of AF patients.^{50,65,66} Segmental and circumferential isolation of the pulmonary veins, as developed by Haïssaguerre and Pappone, respectively,^{65,66} both showed very promising results for prevention of AF in symptomatic AF patients. Haïssaguerre *et al.*⁶⁵ showed in 90 patients, mainly without structural underlying heart disease, that segmental isolation of the pulmonary veins successfully prevented AF in 71% of the patients without the use of anti-arrhythmic drugs after a follow-up of 8 ± 5 months. In more than half of the patients, however, a second or third procedure was needed to attain the final results. Complication rate was about 10% being mainly asymptomatic pulmonary vein stenosis. Pappone *et al.*⁶⁶ compared 589 patients (34% lone AF, 69% paroxysmal AF) who underwent circumferential pulmonary vein ablation with 582 patients (historical controls) who received anti-arrhythmic drugs for rhythm control. After a median follow-up of 900 days, 120 ablated patients (20%) vs. 340 pharmacologically treated patients (58%) had a recurrence of AF. All 120 unsuccessfully ablated patients underwent a second ablation procedure. Thereafter, 31 patients (26%) developed recurrent AF. At present, these therapeutic options are superior to pharmacological rhythm-control strategies, also in patients with heart failure.^{50,67} Long-term efficacy and complication rates, though, have to be awaited.

At present, rhythm-control treatment, thus, is far from ideal. In addition to the high risk of adverse events and pro-arrhythmia, anti-arrhythmic drugs are often ineffective with respect to achieving and maintaining sinus rhythm. Moreover, the management of AF becomes more difficult as the disease progresses.^{1,42,68–70} Studies of the structural effects of AF suggest that this difficulty may stem from irreversible, tachycardia-induced structural alterations in atrial myocytes, as previously discussed. Therefore, AF and the concomitant underlying disease(s) should be treated as soon as possible after its first appearance to prevent establishment of irreversible structural remodelling.⁷¹ Anti-arrhythmic drugs with a more favourable therapeutic index including ‘upstream therapy’—acting drugs like inhibitors of the renin-angiotensin system, would help achieve this objective.

A number of novel class III compounds now in development may yield some improvements in anti-arrhythmic therapy. These drugs act by blocking multiple membrane ion channels, including the three delayed potassium rectifier currents I_{Kr} , I_{Ks} , and I_{Kur} ; the transient outward current I_{to} ; and the fast sodium current I_{Na} .⁷² They have a favourable electrophysiological profile, act in remodelled atria,

appear to act predominantly in the atria, and offer a low pro-arrhythmic potential.^{73–83} Such agents may provide more powerful tools for early intervention in AF, augmenting clinicians' ability to restore sinus rhythm and halt disease progression.

In summary, the results of recent clinical trials confirm that rate control may be a reasonable conservative strategy for those patients with relatively asymptomatic AF and those with complicating cardiovascular factors. However, for symptomatic patients, restoration of sinus rhythm remains the first-choice therapy. Currently available anti-arrhythmic drugs have drawbacks for many patients. Safer and more effective pharmacological agents to restore and maintain sinus rhythm could improve the well being of AF patients. Whether these will improve prognosis remains speculative at present.

Conclusion

It has become increasingly apparent that conversion to sinus rhythm is the ideal endpoint for treatment of AF. In order to avoid complications, therapy should be started as close to diagnosis as possible: early intervention is imperative. Unfortunately, current treatment options are limited, and patients too often experience the slide from intermittent to permanent AF. The persistent and progressive nature of AF compromises patients' well being and raises their risk of serious complications and death. New strategies for safe and reliable achievement of sinus rhythm and long-term maintenance of sinus rhythm are greatly needed. It is hoped that novel class III agents currently under development may offer some improvements in this regard, allowing clinicians to intervene early in the course of AF and enhancing their ability to restore sinus rhythm and halt the progression of this serious, debilitating disease.

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