

Rate control versus rhythm control – Decision making

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The present review examines the data and presents recommendations concerning the selection of rate-control or rhythm-control strategies, as opposed to the selection of specific therapies for rate control or rhythm control. There are several trials completed and others in progress that address issues surrounding the comparison of the two strategies, primarily using pharmacological therapies. The main results and some subanalyses of these trials are briefly reviewed. Gaps in the available data are identified. On the basis of the data, there is no clear advantage of one strategy over the other, although each seems to have potential advantages in different subsets of patients. Accordingly, the main recommendations are that either approach is acceptable, and that selection of a rhythm-management strategy should be individualized. This recommendation is based on a primarily pharmacological approach because that is currently the most common form of therapy used for rhythm management and because the evidence base is composed of comparisons of drug therapies. A number of clinical factors are identified to help individualize therapy and, included in these, is patient preference. It is also recommended that treating physicians be prepared to cross over from one strategy to another or change to non-pharmacological therapies when treatment goals are not achieved or adverse effects prevail.

Key Words: *Atrial fibrillation; Rate control; Rhythm control; Rhythm management*

RECOMMENDATIONS

The following recommendations apply to recurrent atrial fibrillation (AF) outside the setting of reversible causes. Anti-coagulation therapy should be used according to the subsequent sections of the present supplement, regardless of whether a rate control or rhythm control approach is used. The recommendations are based on a primarily pharmacological approach.

Class I

- 1) There is no evidence that rhythm control or rate control is superior to the other, and both are recommended as acceptable initial approaches, with the exception of permanent AF, for which rate control is recommended (level of evidence A).

Class IIa

- 1) The choice of rate control or rhythm control for initial therapy should be individualized and is determined by a number of factors (Table 1) such as classification of AF and degree of symptoms (level of evidence C).

Maîtrise de la fréquence cardiaque ou maîtrise du rythme cardiaque? Voilà la question

Le présent article passe en revue des données et présente des recommandations sur le choix de la stratégie entre la maîtrise de la fréquence cardiaque et la maîtrise du rythme cardiaque, par opposition à un choix de traitements particuliers pour la maîtrise de la fréquence cardiaque ou pour la maîtrise du rythme cardiaque. Plusieurs essais sont déjà terminés et d'autres sont en cours sur la comparaison de ces deux stratégies de traitement, principalement médicamenteuses. Nous faisons un bref survol des principaux résultats et de certaines analyses secondaires de ces essais. Nous relevons également certaines lacunes dans les données existantes. D'après les éléments recueillis, aucune stratégie ne semble vraiment supérieure à l'autre, même si chacune semble avoir des avantages potentiels dans des sous-groupes différents de patients. Par conséquent, les principales recommandations sont que les deux approches sont valables et que la stratégie de traitement du rythme devrait être individualisée. La recommandation repose sur une approche essentiellement médicamenteuse parce qu'il s'agit là de la forme la plus courante de traitement des troubles du rythme et que la base de données se compose de comparaisons de traitements médicamenteux. Un certain nombre de facteurs cliniques peuvent aider à individualiser le traitement, notamment la préférence du patient. Il est également recommandé que les médecins traitants soient disposés à passer d'une stratégie de traitement à l'autre ou à une stratégie de traitement non médicamenteux lorsque les objectifs visés ne sont pas atteints ou que les effets indésirables l'emportent sur les bienfaits recherchés.

Class IIb

- 1) Crossover to the alternative strategy, return to the initial strategy and nonpharmacological therapies should be considered when therapy fails due to adverse effects or failure to improve symptoms (level of evidence C).

ORIGIN OF THE RATE VERSUS RHYTHM QUESTION

There are two accepted general strategies for arrhythmia management in AF. The first is to control the heart rate without any specific attempt to restore and maintain sinus rhythm (rate control strategy). The second is to restore and attempt to maintain sinus rhythm, including repeated cardioversion for recurrences (rhythm control strategy). Of note, rhythm management, however accomplished, is accompanied by a concurrent strategy for the reduction of thromboembolism risk. Antithrombotic therapy usually consists of permanent anti-coagulation therapy for high-risk patients, acetylsalicylic acid or no therapy for low-risk patients, and episodic anticoagulation

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TABLE 1
Rate control versus rhythm control

Favours rate control	Favours rhythm control
Persistent atrial fibrillation	Paroxysmal atrial fibrillation
Recurrent atrial fibrillation	First episode of atrial fibrillation
Less symptomatic	More symptomatic
≥65 years of age	<65 years of age
Hypertension	No hypertension
No history of congestive heart failure	History of congestive heart failure
Previous antiarrhythmic drug failure	No previous antiarrhythmic drug failure
Patient preference	Patient preference

therapy for cardioversion in all patients, which will be further discussed in the present supplement (see Talajic and Roy, pages 19B-25B, and Connolly and Gillis, pages 71B-73B).

Historically, the rate control approach came first with the introduction of digitalis glycosides over 200 years ago. However, with the advent of effective antiarrhythmic drugs and electrical cardioversion almost 50 years ago, rhythm control became preferred by physicians based on a logical but unproven rationale (better relief of symptoms; reduced risk of thromboembolism and need for anticoagulation therapy; lower risk of death; increased functional capacity; better quality of life; better ventricular function; etc). However, approximately 15 years ago, the primary status of the rhythm control strategy began to be questioned.

The basis for questioning the primacy of the rhythm control strategy was twofold. First, the major therapeutic modality for heart rhythm control in AF was antiarrhythmic drugs, and these drugs were found to have poor efficacy (1) and a significant potential for toxicity, including death (2,3). Second, the major morbidity attributable to AF was due to thromboembolism, and antithrombotic therapy had a clear evidence base in the reduction of this problem (4). The juxtaposition of these two points led many to question whether the rhythm control strategy and selective anticoagulation therapy should indeed be the primary approach to AF arrhythmia management compared with the heart rate control strategy and anticoagulation therapy (5). This has also led to several recent randomized trials, some of which have been completed.

REVIEW OF CURRENT AND PENDING TRIALS WITH RESPECT TO THE FORMULATION OF GUIDELINES

There have been five major trials that have been completed and published concerning the rate versus rhythm question (6), and two more are in progress (7,8). The findings of the published trials have been summarized in a recent review (6). Briefly, these trials have not demonstrated any major advantage of the rhythm control strategy and have elevated the rate control strategy to the status of a primary therapy that is at least equivalent to the rhythm control strategy. With respect to the primary and secondary endpoints in these trials, two of the trials (9,10) that administered a six-minute walk test found that there was a small advantage (approximately 10% difference in distance walked; unblinded evaluation) favouring the rhythm control strategy. This difference might be more clinically significant in highly symptomatic patients. However, in all of the other important measures of morbidity or mortality,

there was either no difference between the two strategies, or the trend actually favoured the rate control strategy. Adverse drug effects and hospitalization (important determinants of cost) were more frequent in the rhythm control strategy. Furthermore, the need for continued antithrombotic therapy in high-risk patients despite the apparent maintenance of sinus rhythm was underscored. However, when formulating guidelines, it is helpful to delve a little deeper into the results of these trials.

Which AF patients were enrolled in the trials?

The first issue requiring examination involves the characteristics of the patients enrolled in these trials because the results cannot be generalized to patients that were not enrolled or were enrolled in small numbers. Close examination of patient characteristics in the major trials leads to several observations that have a direct impact on the interpretation of these trials in the context of clinical guidelines. For example, the patients enrolled in the completed trials were largely elderly patients with recurrent, persistent AF who had risk factors for stroke. Few had severely impaired systolic function and advanced congestive heart failure. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (11) was the only one of these trials that allowed enrollment of patients following their first episode of AF. Thirty-six per cent of the patients enrolled in AFFIRM were enrolled after their first documented episode of AF, but these patients were highly selected and far from typical of all patients who have had a first documented episode of AF (12). Indeed, the AFFIRM investigators were instructed only to enroll such patients when they thought there was a high risk of recurrence of AF. In registries of patients who presented with their first documented episode of AF, particularly lone AF or paroxysmal AF, one of the key observations was that in many such patients, it may be months or years before AF recurs (13,14). Thus, one might argue that the addition of long-term antiarrhythmic therapy to optimal therapy for underlying problems such as hypertension should not be undertaken until AF is recurrent. The results of the rate versus rhythm control trials clearly apply only to patients with recurrent AF or those with a high likelihood of recurrence. Because there is no accepted method to quantify symptoms of AF, and because the enrolling physicians had to think that a patient was eligible for both strategies (due to the bias that highly symptomatic patients require rhythm control), it can also be surmised that an unknown but probably low proportion of patients in four of the trials had disabling symptoms during AF. One trial was an exception to the other four. The Paroxysmal Atrial Fibrillation 2 (PAF 2) trial enrolled only patients with highly symptomatic paroxysmal AF who had failed medical therapy. All patients had an atrioventricular junction ablation and permanent pacemaker implantation and then were randomly assigned to receive or not receive antiarrhythmic drug therapy (15).

How were patients in these trials managed?

The second issue requiring examination involves the types of therapy that were used in these trials because the results cannot be generalized to include therapies that were infrequently used. Rhythm control was largely attempted with antiarrhythmic drugs and amiodarone was the drug most commonly used, often after failure of other antiarrhythmic drugs. Only a handful of patients were treated with newer, nonpharmacological therapies.

Drug therapy was also the main means of controlling heart rate, and only approximately 5% of those randomly assigned to this approach went on to have atrioventricular junction ablation and a permanent pacemaker. Again, PAF 2 was an exception in this regard because all of the patients enrolled had an atrioventricular junction ablation and pacemaker (15). Thus, the results of the trials apply most specifically to AF arrhythmia management with drug therapy.

Information from additional analyses

There are some ancillary analyses that are also pertinent to the present discussion. The first is the analysis of the prespecified subgroups in AFFIRM with respect to the primary endpoint of total mortality. In this analysis (16), two subgroups showed a clear advantage in favour of the rate control strategy – those 65 years of age or older and those without a history of congestive heart failure. In the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial (17), the subgroups that showed a clear advantage for the rate control strategy with respect to their composite primary endpoint were women and those with a history of hypertension. A subgroup analysis on the basis of age and history of heart failure was not presented for RACE. Those same trends (rate control favourable in women and hypertensive patients) were also seen in AFFIRM but were not found to be significant. In AFFIRM, however, the analysis was confined to mortality, which was only one element of the composite endpoint used in RACE.

A second analysis of AFFIRM that is pertinent to the present discussion is an analysis of the reasons for abandonment of either of the two strategies (18). In this analysis, a duration of AF longer than two days was associated with failure (crossover to rate control) of the rhythm control strategy and conversely associated with successful rate control. These analyses are primarily hypothesis-generating in nature, but they do suggest that there are groups who may do better with one approach compared with the other, and underscore the point that a single approach for all patients is probably inappropriate.

REVIEW OF EXISTING GUIDELINES

Over the years, a number of organizations, including the Canadian Cardiovascular Society, have formulated guidelines concerning the treatment of patients with AF. As evidence continues to accumulate, each guideline supersedes the preceding edition. With respect to current guidelines of major organizations to be considered in the present discussion of rate control versus rhythm control, there are two – those of the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) (19) and those of the American Academy of Family Practice/American College of Physicians (AAFP/ACP) (20).

The ACC/AHA/ESC guidelines were published before the publication of the results of the major rate control versus rhythm control trials. There is only brief mention of the rate control versus rhythm control issue in the ACC/AHA/ESC guidelines (19). In the context of the ACC/AHA/ESC guidelines and the rate control versus rhythm control issue, AF is subdivided into “first documented episode”, “recurrent paroxysmal” and “recurrent persistent” categories. In all cases, however, the recommendation is that the rhythm control strategy is the preferred initial approach for patients presenting with ‘disabling symptoms’ during AF. The problem with this

of course, is that no definition of ‘disabling symptoms’ is provided and, as mentioned previously, there is no widely accepted schema for the quantification of the symptoms of AF. Therefore, the decision about what constitutes ‘disabling symptoms’ is left entirely to the judgment of the treating physician.

The AAFP/ACP guidelines were published after the results of the major trials of rate control versus rhythm control were available. This set of guidelines was aimed at newly detected AF in the primary care setting. The AAFP/ACP guidelines recommend rate control (and anticoagulation therapy) for the majority of such patients, with rhythm control as a secondary option on the basis of special considerations, such as patient symptoms, exercise tolerance and patient preference. However, the observation that some types of AF may not recur for years after the first episode (13,14) suggests that decisions about rate control versus rhythm control may be deferred until the problem is recurrent. The restoration of sinus rhythm without specific maintenance therapy other than optimal treatment of any underlying cardiac condition may be preferable for the first episode. Another advantage of restoring sinus rhythm with the first episode is that it allows the practitioner to make an assessment of symptoms during AF by asking the patient to compare symptoms before and after the restoration of sinus rhythm. In those who have an insidious and apparently asymptomatic onset of their AF, it is not uncommon for the patient to retrospectively recognize that they were quite symptomatic. Recall that symptoms during AF play a major role in determining which approach will be used.

GAPS IN THE AVAILABLE DATA

One major deficiency in the available data is the examination of the rate control versus rhythm control question in other subsets of patients that are commonly plagued by AF. Patients with reduced systolic function and congestive heart failure are one such group, and they are being investigated in an ongoing trial (7). The largest remaining populations in which AF is commonly encountered are the subset of patients with AF and isolated diastolic dysfunction and the subset of patients with paroxysmal AF, but who are otherwise healthy. The other deficiency in the available database is the examination of this question using some of the more recent, nonpharmacological therapies. This type of study has a number of methodological issues that need to be resolved before they can provide reliable, unbiased data. The other major trial in progress (8) is currently evaluating different drugs than those used in the European and North American studies; nevertheless, it is still primarily an evaluation of drug therapies.

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