

2004 Canadian Cardiovascular Society Consensus Conference: Atrial Fibrillation

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BACKGROUND AND CONSENSUS PROCESS

Atrial fibrillation (AF) affects approximately 200,000 to 250,000 Canadians and is associated with many common clinical conditions such as aging, thromboembolism, hypertension, valvular heart disease and heart failure. In Canada, AF is likewise responsible for substantial morbidity and increased mortality. Increased mortality rates are mainly due to strokes, with AF being a major independent risk factor (up to 15% of all strokes are due to AF). Even still, the clinical impact of AF is probably underestimated because this arrhythmia is frequently asymptomatic and can be the unrecognized cause of complications such as precipitated heart failure or stroke. Consequently, AF places a tremendous burden on our health care resources. Therefore, the management of AF is complex and has far-ranging implications that make it an important challenge for treating physicians.

WHY UPDATE THE AF CONSENSUS CONFERENCE?

AF was the topic of the 1994 Consensus Conference of the Canadian Cardiovascular Society (CCS). The subsequent

publication of the Consensus in the January 1996 issue of *The Canadian Journal of Cardiology* provided the first North American recommendations regarding the management of AF (1). At the time, however, the Chair of the Consensus initiative, Charles R Kerr, indicated in his introductory remarks that many of the recommendations were based on clinical judgement with little firm scientific evidence.

In the intervening decade, much of our knowledge about the management of AF has been solidified or modified by the enormous amount of research being performed on this disease. Unfortunately, many issues remain for which there is little or no scientific evidence to guide clinical practice. Other organizations have reported practice guidelines on AF, the most recent and comprehensive of which was from the 2001 American College of Cardiology/American Heart Association/European Society of Cardiology Board Task Force (2), but the CCS thought it worthwhile to revisit the topic for two important reasons. First, since the publication of the 2001 Task Force report, a number of major randomized clinical trials on the subject have been completed, and as will be evident in the ensuing papers, Canadian physicians, researchers, nurses and patients

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have been at the forefront of these studies. Second, Canadian practices for dealing with AF differ somewhat from those of our American and European counterparts, particularly in areas such as antiarrhythmic drug use, health care access and costs.

The present Consensus Conference was developed to incorporate these new data and to update AF practice recommendations in the context of Canadian standards of practice and the Canadian health care system.

ORGANIZATION OF THE CONSENSUS

Following a recommendation of the CCS Consensus Conference Committee, the cochairs were appointed by council in June 2003 and, subsequently, they identified the 16 clinical and scientific experts of the primary panel. Major areas of interest were selected and assigned to the experts on the panel. The primary panelists prepared documents that were circulated, and recommendations were then debated, revised and voted on during a face-to-face meeting in February 2004. A secondary panel of physicians, cardiologists and arrhythmia experts reviewed the manuscripts during the spring of 2004. Following these revisions, the documents were then reviewed by the entire CCS membership through e-mails and postings on the CCS Web site. The final text and recommendations were presented at the Annual Meeting of the Canadian Cardiovascular Congress in Calgary, Alberta, in October 2004.

RECOMMENDATIONS AND RULES OF EVIDENCE

Recommendations are expressed in the standard American College of Cardiology/American Heart Association/European Society of Cardiology Board format:

Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence

and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: The weight of evidence or opinion is in favour of the procedure or treatment.

Class IIb: Usefulness/efficacy is less well established by evidence or opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.

Evidence supporting the recommendations is ranked as:

A (highest): When the data were derived from multiple randomized clinical trials involving a large number of individuals.

B (intermediate): When the data were derived from a limited number of randomized trials, nonrandomized studies or observational registries.

C (lowest): When the primary basis for the recommendation was expert consensus.

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These recommendations reflect emerging clinical and scientific advances as of the date issued and are subject to change. These consensus conference statements are intended to assist practitioners in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The information is not to be construed as dictating an exclusive course of treatment or procedure to be followed and variations may be appropriate. Each cardiovascular specialist must exercise his or her own professional judgment in determining the proper course of action in each patient's differing circumstances. The CCS assumes no responsibility or liability arising from any error or omission in or from the use of any information contained herein.

Etiology and initial investigation

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AC Skanes, P Dorian. Etiology and initial investigation. *Can J Cardiol* 2005;21(Suppl B):11B-14B.

The initial evaluation of a patient with atrial fibrillation should include a comprehensive review of historical factors, a physical examination and initial investigations. This evaluation has many important purposes, including the development of a therapeutic strategy for symptom relief, the assessment and management of thromboembolic risks, and the identification of underlying etiology. This evaluation should also review management of risk factors for overall cardiovascular morbidity and the treatment of atrial fibrillation. Baseline history, appropriate laboratory tests, and 12-lead electrocardiogram and echocardiography results should be obtained in all patients to identify the potential etiology and other comorbidities, and to stratify for risk of stroke.

Key Words: Ablation; Arrhythmia; Atrial fibrillation; Cardioversion; Electrophysiology

L'étiologie et l'exploration initiale de la fibrillation auriculaire

L'évaluation initiale de la fibrillation auriculaire (FA) devrait comprendre une anamnèse complète des antécédents, un examen physique et une première série d'examen. L'évaluation vise trois objectifs importants : élaborer une stratégie de traitement pour atténuer les symptômes, évaluer et traiter le risque de thrombo-embolie et rechercher la cause sous-jacente. L'évaluation devrait également tenir compte des facteurs de risque de l'ensemble des maladies cardiovasculaires et de leur traitement. Enfin, il faudrait procéder à une anamnèse de départ, à des examens de laboratoire appropriés ainsi qu'à une électrocardiographie à 12 dérivations et à une échocardiographie chez tous les patients atteints de FA pour rechercher la cause possible et l'existence d'autres maladies concomitantes et pour évaluer le risque d'accident vasculaire cérébral.

RECOMMENDATIONS

Class I

- 1) Baseline history, appropriate laboratory tests, 12-lead electrocardiogram (ECG) and echocardiography should be obtained in all patients to identify potential etiology and other comorbidities, and to stratify for risk of stroke. Details are highlighted in Tables 1 and 2 (level of evidence C).
- 2) Underlying causes or precipitating factors including underlying hypertension should be identified, eliminated or treated (level of evidence C).

Class IIa

- 1) Other ancillary tests should be considered under specific circumstances. Details are highlighted in Table 1 (level of evidence C).

INITIAL EVALUATION

The initial evaluation of a patient with atrial fibrillation (AF) should include a comprehensive review of historical factors, a physical examination and initial investigations. This evaluation has many important purposes including developing a therapeutic strategy for symptom relief, assessing and managing thromboembolic risks, and identifying underlying etiology.

This evaluation should also review management of risk factors for overall cardiovascular morbidity and its treatment.

It is incumbent upon the physician to document AF in at least one ECG lead. A perception of 'rapid irregular palpitations' may be reported during a multitude of rhythms including atrial tachycardia or atrial flutter with variable ventricular response, and occasionally during sinus tachycardia with or without ectopic beats. The approach to treatment and the thromboembolic risks differ significantly for these alternate rhythms.

The predominant pattern of AF should be determined:

The following points are based on references 1 and 2.

- First detected AF;
- Paroxysmal: AF is self-terminating within seven days of recognized onset;
- Persistent: AF is not self-terminating within seven days or is terminated electrically or pharmacologically; or
- Permanent: AF in which cardioversion has failed or in which clinical judgment has led to a decision not to pursue cardioversion.

One may not be able to identify the pattern of AF at the time of initial presentation and the pattern may change over time. An assessment of the severity of symptoms and impact on

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TABLE 1
Initial investigation of atrial fibrillation (AF)

Routine investigation
History and physical examination
Establish pattern (first detected, paroxysmal, persistent, permanent)
Establish severity including impact on quality of life
Identify potential etiology
Consider hypertension, alcohol abuse, thyroid disease and sleep apnea
Determine underlying thromboembolic risk
Develop a treatment strategy based on clinical risk factors
Evaluate likelihood of other arrhythmia – PSVT/atrial flutter
Document prior pharmacological therapies aimed at rhythm and rate control, including effectiveness and adverse effects
Twelve-lead electrocardiogram
Document presence of AF
Assess for left atrial abnormality/left ventricular hypertrophy/conduction disease/pre-excitation/sinus node disease
Assess for myocardial infarction
Measure baseline intervals (eg, QT interval) that may be affected by pharmacological therapy
Transthoracic echocardiography
Assess for chamber size and ventricular function
Assess valvular function
Assess for hypertrophy
Complete blood count, electrolytes, renal function
Thyroid function
Additional investigations of potential value
Chest radiography
When two-dimensional echocardiography is unavailable or difficult to obtain
If specific pulmonary abnormalities are anticipated
Ambulatory electrocardiogram monitoring
This includes 24 h Holter monitor, event recorder or loop monitor
Document arrhythmia and establish symptom-rhythm correlation – AF or alternative contributing arrhythmia (PSVT/flutter)
Assess rate control with activity during AF
Assess for bradycardia that may limit the use of specific rate- or rhythm-controlling agents
Help determine pattern if unclear from history
Treadmill exercise test
Only in those who have an intermediate or high risk for coronary disease
To evaluate rate control
Transesophageal echocardiography
Assess left atrial size
Rule out left atrial thrombus
Facilitate direct current cardioversion (with respect to stroke risk)
Investigate specific underlying etiological factors, especially left ventricular hypertrophy associated with hypertension
Electrophysiological study
Documented or suspected underlying PSVT
Consider atrial flutter ablation in those where this forms a substantial part of the symptom burden

PSVT Paroxysmal supraventricular tachycardia

quality of life should be performed. Symptoms associated with AF are highly variable, with some patients being truly asymptomatic and others having highly disruptive symptoms. The impact of these symptoms on lifestyle as well as a record of emergency room visits, hospital admissions and cardioversions should be made.

TABLE 2
Etiology of atrial fibrillation (AF)

Cardiovascular causes
Hypertension
Valvular disease
Coronary artery disease with prior myocardial infarction
Cardiomyopathy
Dilated
Hypertrophic
Restrictive
Pericardial disease
Electrical/senescence
Bradycardia-tachycardia (sick sinus) syndrome
Frequent/prolonged episodes of AF may cause electrical and structural remodelling of the atria, promoting further AF
Genetic/familial
Postoperative
Congenital heart disease
Noncardiovascular causes
Autonomically mediated (vagal)
Toxin – eg, alcohol
Endocrine – eg, thyroid disease
Pulmonary disease – chronic obstructive pulmonary disease, pneumonia, sleep apnea
Neurological – usually associated with myopathic muscle diseases
Idiopathic
Occult hypertension
Occult genetic causes

Symptoms at the termination of paroxysms should be sought and, if present, a symptom-rhythm correlation should be made using an ambulatory ECG (Holter, event recorder or loop recorder) if possible. Patients with tachycardia-bradycardia (sick sinus) syndrome often have sinus pauses, especially at the termination of AF. Symptomatic pauses may require pacing. Asymptomatic pauses may limit the use of rate- or rhythm-controlling agents in these patients.

Both paroxysmal supraventricular tachycardia (PSVT) and atrial flutter can cause a tachycardia-induced tachycardia and degenerate into AF. Successful ablation of the underlying PSVT can eliminate both the supraventricular tachycardia and the associated AF (3-6). Therefore, it is important to elicit and investigate any history of regular palpitation. This can be further explored by ambulatory ECG recording during symptoms, especially at the onset.

The underlying etiology and associated factors should also be determined. Specifically, efforts should be made to determine 'potentially reversible' causes such as excessive alcohol consumption that can trigger AF. Likewise alcohol withdrawal – the 'holiday heart syndrome' is also recognized as a potential trigger. Thyroid disease can be a potentially reversible and important cause of underlying AF. This may be particularly difficult to diagnose in the elderly. Hypertension is likely the most common cause of AF. Careful blood pressure assessment and investigation for underlying hypertension should be undertaken. It is incumbent upon the physician to make careful blood pressure determinations as outlined by the Canadian Hypertension Society for the diagnosis of underlying hypertension (7,8). AF may be the first presentation of an otherwise untreated

hypertensive patient. It is important to note that home blood pressure and 24 h blood pressure monitoring devices are greatly influenced by the variable rate during AF and, therefore, are not useful during this condition. Nonetheless, during sinus rhythm, these devices may add to the diagnostic yield of hypertension (see Canadian Hypertension Society Guidelines [7,8]). Other clues to an underlying etiology of hypertension include the presence of left ventricular hypertrophy detected using ECG or echocardiography.

Coronary artery disease with prior myocardial infarction and valvular disease are obvious etiologies of AF. Moreover, the left ventricular function will influence choices of therapy for both rate control and rhythm control. Some patients have a strong family history of AF, which may have a genetic basis in these cases (9).

Screening evaluation for obstructive and nonobstructive sleep apnea should be performed and investigation considered if suspected. Obstructive sleep apnea may be associated with obesity and hypertension, and may lead to AF. Moreover, management of the obstructive sleep apnea may facilitate control of hypertension and underlying AF. While not well investigated, it is likely that wide swings in autonomic tone associated with sleep apnea may facilitate development of AF in these patients. Holter monitoring for nocturnal bradycardia may be a useful screening test in these patients. In some patients, a formal sleep study may be required. Other forms of pulmonary disease, (eg, chronic obstructive pulmonary disease) are associated with AF. Investigations such as chest x-ray and pulmonary function tests should be performed as appropriate.

It is also important at the initial evaluation to determine thromboembolic risk in each patient. Large clinical trials have determined clinical risk factors for stroke associated with AF (10-14). Recommendations for anticoagulation therapy use these clinical risk factors to determine the use of acetylsalicylic acid versus warfarin therapy (see the American College of Chest Physicians recommendations for anticoagulation therapy in AF [Connolly and Gillis, pages 71B-73B]). It is important to highlight that these recommendations do not distinguish between patterns of AF. Paroxysmal AF in large clinical trials results in a similar risk for stroke as persistent or permanent AF (15).

It is important to document which rhythm- and rate-controlling agents have been used and discontinued in the past and the reason for discontinuation, such as perceived inefficacy or adverse effects.

The physical findings suggestive of AF include an irregular pulse (that may or may not be rapid in rate), an irregular jugular venous pulse and variation in the loudness of the first heart sound. Confirmation using ECG should be made if possible. The ventricular response during AF and the associated blood pressure should be noted (see above). The physical examination may also uncover associated valvular disease, myocardial disease or congestive heart failure.

A number of routine investigations are warranted in all patients presenting with a history of AF (Table 1). An ECG is useful both in sinus rhythm and AF. Evidence of left atrial enlargement, left ventricular hypertrophy, pre-excitation, underlying conduction disease or clues as to the underlying etiology of AF should be sought. A transthoracic echocardiogram should be performed in all patients. This will evaluate left ventricular function, which is useful for determination of specific therapies for rate control and antiarrhythmic drugs. Left atrial size should be noted, as well as any evidence of left atrial or left

atrial appendage thrombus; however, this is rarely observed with the transthoracic echocardiogram. Depending on practice patterns, prompt echocardiography may not be easily attained. Under these circumstances, a posteroanterior and lateral chest x-ray may replace the echocardiography to screen for cardiomegaly or left atrial enlargement. Otherwise, chest x-ray should not be routinely performed unless a specific underlying diagnosis is sought.

Routine bloodwork should be performed. Specifically, a complete blood count should be performed at least once. Urea and creatinine should be performed as a screen for renal function. This will influence choices and dose of drugs as well as potentially highlight end-organ damage of hypertension or adverse effects of other cardiovascular drugs. In the case of a history of excessive ethanol use, liver enzymes should be determined. A lipid profile is recommended in most patients as part of an overall assessment of cardiovascular risk. Thyroid function is not routinely measured due to cost. However, in elderly patients or those with clinical suspicion of hyperthyroidism, thyroid function should be measured. The yield of routine screening is likely to be low. Nonetheless, the impact of untreated hyperthyroidism can be significant and hyperthyroidism is frequently occult and difficult to diagnose from clinical presentation in the elderly population (16).

Ambulatory ECG monitoring is not routinely performed but has a number of important purposes. Holter monitoring, transient event recordings or loop recordings may document the underlying AF. It is also useful in an attempt to uncover PSVT or atrial flutter contributing to the AF (see above). Holter monitoring is very useful for assessment of rate control during activities of daily living and exercise. It may be also uncover associated bradycardia either caused by pharmacological agents or associated tachycardia-bradycardia (sick sinus) syndrome. It may be useful to determine the pattern of AF in minimally symptomatic patients who are unable to determine whether intervening sinus rhythm occurs. Such determination may have influence on plans for antiarrhythmic agents and direct current cardioversion.

The routine use of treadmill exercise testing is not recommended. It is best reserved for assessment of underlying functional capacity in patients during persistent or permanent AF as well as determination of the adequacy of rate control with exercise. Because myocardial ischemia is a rare cause of AF, treadmill exercise testing is not routinely recommended for patients without a history of ischemic symptoms. Patients who present with AF and associated chest pain may require assessment for underlying ischemic disease. Likewise, routine cardiac troponin evaluations should not be performed in patients with acute presentation of AF in whom there is a low likelihood of underlying ischemic disease.

Transesophageal echocardiography is not routinely required. It has become part of a useful strategy to rule out the presence of left atrial appendage thrombus and to facilitate direct current cardioversion in selected clinical scenarios (17-19).

Electrophysiological studies should be considered in patients with idiopathic AF at a young age, especially in those with documented regular supraventricular tachycardias or a history suggesting an underlying supraventricular tachycardia (ie, a history of regular palpitations preceding irregular palpitations). Underlying PSVT, due to accessory pathway-mediated tachycardia, AV node re-entry tachycardia or focal atrial

tachycardia, both inside and outside of the pulmonary veins, may cause AF as a tachycardia-induced tachycardia. Successful ablation of such PSVTs may also eliminate AF in young patients with these substrates (3-6). In addition, electrophysiological study and catheter ablation of underlying atrial flutter should be considered when atrial flutter forms a substantial part of the symptom burden. The best results occur when atrial flutter is the predominant or sole rhythm disturbance. A more thorough discussion of this topic is presented in Guerra and Skanes, pages 31B-34B, and Simpson et al, pages 67B-70B.

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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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Drug therapy for termination of atrial fibrillation and maintenance of sinus rhythm

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M Talajic, D Roy. Drug therapy for termination of atrial fibrillation and maintenance of sinus rhythm. *Can J Cardiol* 2005;21(Suppl B):19B-25B.

Antiarrhythmic drug therapy to maintain sinus rhythm has not been demonstrated in randomized clinical trials to improve prognosis or prevent thromboembolic complications in patients with atrial fibrillation (AF). Therefore, drug therapy to restore and maintain sinus rhythm should be limited to those patients who have a greater symptomatic burden of AF. Patients with AF may be completely unaware of their arrhythmia or may present with palpitations, poor exercise tolerance or symptoms of congestive heart failure. In general, younger patients with paroxysmal arrhythmia and patients with decreased left ventricular compliance tend to be more symptomatic. The present article outlines the mechanisms of action of antiarrhythmic drugs in AF. Drugs that are recommended and frequently used to convert AF and maintain sinus rhythm are reviewed, and the toxicity of antiarrhythmic drug toxicity is discussed.

Key Words: *Antiarrhythmic agents; Arrhythmia; Atrial fibrillation; Cardioversion; Drugs*

RECOMMENDATIONS

Conversion of atrial fibrillation

Class I

- 1) Electrical or pharmacological conversion should be considered in patients with atrial fibrillation (AF) who are hemodynamically stable (level of evidence C).
- 2) Immediate conversion to sinus rhythm is recommended in patients with AF who are hemodynamically unstable. Electrical cardioversion is more effective and is preferred over pharmacological conversion in these patients (level of evidence C).

Class IIA

- 1) Rate control with anticoagulation therapy alone is acceptable while awaiting spontaneous conversion in patients with AF of less than 48 h duration (level of evidence B).
- 2) Pharmacological agents may be used to accelerate conversion of AF in patients with AF of less than 48 h duration (level of evidence B). See Table 1 for drug recommendations.
- 3) Antiarrhythmic drugs may be used to pretreat patients before electrical cardioversion (to decrease early recurrence of AF and to enhance cardioversion efficacy) (level of evidence B).

La pharmacothérapie de la suppression de la fibrillation auriculaire et du maintien du rythme sinusal

Les antiarythmiques utilisés pour maintenir le rythme sinusal n'ont pas montré, dans des essais cliniques menés avec hasardisation, leur efficacité à améliorer le pronostic ou à prévenir les complications thromboemboliques chez les patients atteints de fibrillation auriculaire (FA). La pharmacothérapie visant à rétablir et à maintenir le rythme sinusal devrait donc être limitée aux patients qui manifestent le plus de symptômes. Dans certains cas, la FA peut être complètement asymptomatique, tandis que, dans d'autres, elle peut causer des palpitations, une faible tolérance à l'effort et même des symptômes d'insuffisance cardiaque. En général, les jeunes qui présentent de l'arythmie paroxystique et les patients qui ont une diminution de la compliance ventriculaire gauche ont tendance à présenter davantage de symptômes. Le présent article donne un aperçu des mécanismes d'action des antiarythmiques utilisés dans le traitement de la FA. Nous passerons en revue les médicaments recommandés et souvent prescrits pour réduire la FA et maintenir le rythme sinusal et nous traiterons également de la toxicité des antiarythmiques.

Class IIB

- 1) Blockade of the angiotensin-renin system may be considered in combination with amiodarone before electrical cardioversion to decrease the recurrence rate of AF (level of evidence B).

Maintenance of sinus rhythm in patients with AF

Class I

- 1) Oral antiarrhythmic drugs may be used in patients with recurrent AF in whom long-term maintenance of sinus rhythm is desired and in whom a reversible cause of AF is not identified (level of evidence B).
- 2) The choice of an antiarrhythmic drug should be based on the safety profile of the different agents, taking into account the clinical characteristics of the patient (level of evidence B). Recommendations regarding specific agents are listed in Table 2.

Class IIA

- 1) In patients without risk factors for proarrhythmia, antiarrhythmic drugs may be initiated as outpatients (level of evidence B).
- 2) In patients with structural heart disease (including those with left ventricular [LV] dysfunction) amiodarone may be initiated as outpatients (level of evidence B).

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TABLE 1
Recommended drugs for the conversion of atrial fibrillation

Class I	Ibutilide (level of evidence A)
	Flecainide (level of evidence A)
	Procainamide (level of evidence B)
	Propafenone (level of evidence A)
Class IIA	Chronic oral amiodarone (level of evidence B)
Class III	Sotalol (level of evidence B)

3) An atrioventricular (AV) nodal blocking agent is recommended in patients treated with a class IC antiarrhythmic drug (level of evidence B).

Class IIB

1) Patients treated with sotalol or dofetilide should be reassessed if QTc exceeds 480 ms (level of evidence C).

Class III

1) Sotalol should not be used for rate control alone in patients with permanent AF (level of evidence C).

INTRODUCTION

Antiarrhythmic drug therapy to maintain sinus rhythm has not been demonstrated in randomized clinical trials to improve prognosis or prevent thromboembolic complications in patients with AF. Therefore, drug therapy to restore and maintain sinus rhythm should be limited to those patients who have a greater symptomatic burden of AF. Patients with AF may be completely unaware of their arrhythmia or may present with palpitations, poor exercise tolerance or symptoms of congestive heart failure. In general, younger patients with paroxysmal arrhythmia and patients with decreased LV compliance tend to be more symptomatic. Uncommonly, uncontrolled AF with a rapid ventricular response rate may cause LV dysfunction, which is reversible after rhythm reversion or control of the ventricular response.

MECHANISMS OF ACTION OF ANTIARRHYTHMIC DRUGS IN AF

AF is due to the coexistence of multiple reentrant atrial wavelets which are often initiated by arrhythmogenic foci located within the pulmonary veins (1-3). During AF, electrical remodelling of atrial myocytes occurs as a defense mechanism against excessive calcium overloading. This results in a shortened atrial action potential duration and refractory period, thus favouring reentry (4,5). In addition, underlying heart disease, renin-angiotensin system activation and persistent arrhythmia may lead to atrial structural changes also favouring intra-atrial reentry (6).

The primary action of class I drugs is blockade of sodium channels and, therefore, slowing of atrial conduction, especially at pivot points of reentrant circuits (7). In addition, these drugs suppress automaticity and increase atrial refractory periods at faster rates (8). As a result, these drugs increase the size of functional reentrant circuits and increase the probability that a circulating wavelet encounters refractory tissue, thus extinguishing itself (9,10).

TABLE 2
Chronic antiarrhythmic drug selection

Patients with structurally normal hearts	
First choices	Propafenone Flecainide Sotalol*
Second choice	Amiodarone
Alternative choices	Disopyramide Dofetilide†
Patients with structurally abnormal hearts	
Coronary artery disease with normal ventricular function	
First choice	Sotalol*
Second choice	Amiodarone
Additional choices	Dofetilide† Propafenone
Left ventricular dysfunction (with or without congestive heart failure)	
First choice	Amiodarone
Second choice	Dofetilide†
Hypertension with left ventricular hypertrophy	
First choices	Sotalol* Amiodarone Propafenone Flecainide

*Contraindicated in women older than 65 years of age taking diuretics;
†Dofetilide is available in Canada through Health Canada's special access program

Class III drugs such as dofetilide and sotalol prolong atrial action potential and the refractory period by blocking repolarizing potassium currents (11). These effects may prevent premature atrial complexes from initiating AF (12) and may cause conversion of AF by prolonging refractoriness sufficiently without affecting conduction velocity.

Amiodarone has multiple effects including slowing of atrial conduction (as described for class I drugs) and classic class III properties. Unlike other antiarrhythmic drugs, amiodarone may reverse the electrophysiological and biochemical remodeling associated with AF (13).

DRUG CONVERSION OF AF

Drug therapy may be used for conversion in patients with hemodynamically stable AF in whom long-term maintenance of sinus rhythm is desired. Therapy to control the ventricular rate response to AF should be initiated before or simultaneously with therapy to convert the arrhythmia.

Before attempting drug conversion, patients should be adequately anticoagulated to prevent postconversion thromboembolic complications (see Connolly and Gillis, pages 71B-73B). Because thromboembolism is associated with the return of mechanical atrial contraction after conversion, the risk of thromboembolic complications after cardioversion is similar whether conversion is achieved electrically or with drugs.

DRUG EFFICACY FOR AF CONVERSION

Recent-onset AF (less than 48 h duration) terminates spontaneously in approximately 50% of cases. Commonly used drugs for rate control (digoxin, calcium channel blockers and

TABLE 3
Frequently used drugs to convert atrial fibrillation

Drug	Dose	Efficacy	Risks	Cost (dose)*
Class IA				
Procainamide	15 mg/kg to 17 mg/kg iv	++	5% hypotension	\$6.28 (1 g)
Class IC				
Propafenone	600 mg orally	+++	Hypotension, 1:1 flutter	\$1.74 (600 mg)
Flecainide	300 mg to 400 mg orally	+++	Hypotension, 1:1 flutter	\$3.09 (300 g)
Class III				
Amiodarone combined iv and oral loading (1.0 g iv for 24 h and 400 mg bid for one week)		+	Hypotension, phlebitis, gastrointestinal	\$78.00 (1 g iv)
Ibutilide	1 mg to 2 mg iv	++	2% to 3% TdP	\$262.50 (1 mg)

*Based on actual costs in one Canadian hospital pharmacy, iv Intravenously; TdP Torsade de pointes

beta-blockers) are no better than placebo for AF conversion. The decision to await spontaneous conversion (while actively controlling rate) versus pursuing pharmacological or electrical conversion depends on the duration of AF and the symptomatic status of the patient. In general, pharmacological conversion will accelerate AF conversion.

If AF persists beyond 48 h, spontaneous termination is less common and active therapy is recommended. Drug conversion, although less effective than electrical cardioversion, avoids the need for general anaesthesia and may reduce the early recurrence of AF (30% to 40% of patients electrically cardioverted).

Table 3 summarizes the reported efficacy of antiarrhythmic drugs to convert AF. The details of individual trials may be found in the references listed or in systematic reviews of the subject (14).

Many trials include patients with atrial flutter. Because the conversion rate for atrial flutter is greater for sotalol and ibutilide, the reported efficacy rates for AF are probably overestimated. Trials also excluded patients with known sick sinus syndrome and intraventricular conduction delays. As a result, the incidence of bradycardia complicating drug conversion may be underestimated and antiarrhythmic drugs must be used with caution.

Several clinical trials have shown that the duration of AF is the main determinant of the efficacy of antiarrhythmic drugs in converting AF. Only 20% to 30% of patients with AF lasting more than 48 h will convert with currently available oral or intravenous antiarrhythmic agents.

CLASS I DRUGS

Oral quinidine has been used for many years for AF conversion (15-22). Its use has been largely abandoned because of a high incidence of gastrointestinal side effects and a risk of torsade de pointes ventricular arrhythmia (particularly after AF conversion). Procainamide continues to be used in a large number of centres and is more effective than placebo (23-25). Comparative studies have shown it to be inferior to ibutilide and flecainide (26-29).

Class IC agents such as flecainide and propafenone terminate recent onset AF in 50% to 80% of patients (15-17,30-44). Most studies have used single oral doses and have excluded patients with LV dysfunction and intraventricular conduction abnormalities. Conversion rates increase up to 24 h after administration. In general these drugs were well tolerated.

CLASS III DRUGS

Studies (20,21,45-47) of sotalol for conversion of AF suggest a conversion rate of 20% to 30%. In comparative trials (47), it has been found to be inferior to quinidine and ibutilide and no more efficacious than placebo. As a result, sotalol is not recommended for acute conversion of AF. Ibutilide is a newer intravenous class III medication that converts AF to sinus rhythm in 30% to 50% of cases (26,27,45,48). It has been demonstrated to be superior to procainamide and sotalol in comparative studies. Its main limitation is the occurrence of torsade de pointes ventricular arrhythmia in 2% to 3% of patients.

Studies (18,19,49-61) of amiodarone to convert AF have had variable results. It has moderate efficacy (30% to 40%) in patients with persistent AF when treated with prolonged oral loading regimens (three to four weeks) (49,55,56). However, intravenous amiodarone has been shown to be of limited value in some but not all acute conversion studies (51-53,57-59,61). For this reason, it should not be used routinely for conversion of AF.

DRUG PRETREATMENT BEFORE ELECTRICAL CARIOVERSION

The majority of recurrences of AF occur within one month of electrical cardioversion and frequently occur within the first hour after conversion (62).

Antiarrhythmic drugs may be useful as pretreatment before electrical cardioversion to increase the success rate of the procedure and to prevent early recurrences of AF (63). Conflicting data exist concerning the utility of calcium channel blockers to prevent early recurrences of AF after electrical cardioversion and, for this reason, it cannot be recommended at this time (64-66). Two randomly assigned studies (67,68) have shown that blockade of the renin-angiotensin system improves the proportion of amiodarone-treated patients remaining in sinus rhythm after electrical cardioversion. This approach is promising but needs further confirmatory studies.

DRUG THERAPY FOR MAINTENANCE OF SINUS RHYTHM

This section is summarized in Table 4. In the absence of a reversible cause, AF is usually recurrent. Placebo-controlled trials have shown that the one-year recurrence rate of AF in the absence of an antiarrhythmic drug is approximately 75%. Antiarrhythmic drug therapy is usually necessary to decrease the number of episodes in patients with paroxysmal AF and to prevent recurrence in patients with persistent AF.

TABLE 4
Drugs frequently used to maintain sinus rhythm

Drug	Dosage (mg/day)	Efficacy (%)*	Cost per month (dose) [†]
Class IA			
Disopyramide	400–750	50	\$54 (250 mg bid)
Class IC			
Propafenone	450–900	50	\$59 (150 mg tid)
Flecainide	100–300	50	\$73 (100 mg bid)
Class III			
Sotalol	80–320	50	\$74 (80 mg tid)
Amiodarone	100–400	70	\$53 (200 mg daily)
Dofetilide [‡]	0.5–1	60–70	–

*Efficacy is defined by the absence of atrial fibrillation one year after initiating therapy; [†]As provided by a commercial pharmacy in Montreal, Quebec; [‡]Dofetilide is available in Canada through Health Canada's special access program. bid Twice daily; tid Three times daily

The dosages, efficacy and side effects of different antiarrhythmic drugs are summarized in Tables 4 and 5 (69-83). Of the presently available oral antiarrhythmic drugs, amiodarone has been demonstrated in comparative studies to be more efficacious than other drugs (75,76). However, it also has significant noncardiac side effects limiting its widespread use as an agent of first choice. Other agents have the potential for significant proarrhythmia when given to patients with underlying heart disease (69,77,78). As a result, the choice of a chronic antiarrhythmic drug in an individual patient is usually guided by the safety profile of the drug with respect to the clinical characteristics of the patient (Table 2).

Patients without underlying heart disease can be treated initially with sotalol, propafenone or flecainide. These drugs, while less effective than amiodarone, have fewer side effects in this population. While no clear advantages are apparent among sotalol, propafenone or flecainide, individual patients may respond more favourably to one agent over another. For example, patients in whom physical activity frequently precipitates AF may respond better to a pure beta-blocker or sotalol. Occasionally, patients who experience AF during intense vagal reactions may respond to disopyramide. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (81), in which serial drug selection and cardioversion was performed as needed, sinus rhythm was maintained in 82% and 73% of patients after one and three years, respectively.

The overall goal of antiarrhythmic drug therapy is to suppress symptoms due to AF. Patients may have occasional breakthrough arrhythmia without excessive symptoms. In these patients, therapy should not be considered a failure and should be continued. If significant arrhythmia does recur, dose increases or an alternative agent should be considered. Throughout the clinical course of an individual patient, the relevance of antiarrhythmic drug therapy should be reassessed. In some patients, AF will recur with minimal symptoms due to adequate rate control. In others, the arrhythmia will recur despite multiple drug trials. Leaving the patient in permanent AF with adequate rate control and anticoagulation is an appropriate therapy at this stage. If the patient remains too symptomatic, then a non-pharmacological form of therapy should be considered.

TABLE 5
Toxicity of antiarrhythmic drugs

Drug	Side effects
Class IA	
Disopyramide	Congestive heart failure Torsade de pointes Dry mouth, blurred vision, urinary retention Bradycardia
Class IC (propafenone and flecainide)	
	Congestive heart failure Ventricular tachycardia Bradycardia Atrial proarrhythmia (1:1 flutter)
Class III	
Sotalol	Bradycardia Torsade de pointes Beta-blocker side effects
Amiodarone	Photosensitivity Bradycardia Gastrointestinal upset Thyroid dysfunction Phlebitis Hepatic toxicity Neuropathy Pulmonary toxicity Torsade de pointes (rare)
Dofetilide*	Torsade de pointes

*Available in Canada through Health Canada's special access program

ANTIARRHYTHMIC DRUG TOXICITY

This section is summarized in Table 5. All antiarrhythmic drugs have potentially serious side effects, which may limit therapy. Class IA and class III drugs may cause torsade de pointes ventricular arrhythmia in 1% to 3% of cases (this arrhythmia rarely occurs with amiodarone). Risk factors for torsade de pointes include hypokalemia, hypomagnesemia, a prolonged baseline QT interval, being female, LV dysfunction and renal failure (in the case of sotalol and dofetilide) (82,83). To minimize the risk of torsade de pointes, serum potassium, magnesium and renal function should be measured periodically. Periodic electrocardiograms should be performed and the antiarrhythmic drug should be reassessed if excessive QT prolongation occurs (QT greater than 480 ms). Patients taking a class IA or class III drug should avoid other medications which may prolong the QT interval. These include domperidone, erythromycin, clarithromycin and some antipsychotic medications. Complete lists are available at <<http://www.torsades.org>>.

All drugs may aggravate bradycardia due to coexisting sinus node dysfunction or AV block. Drug discontinuation or implantation of a permanent pacemaker may become necessary in these patients.

Atrial flutter frequently coexists in these patients or can occur because of antiarrhythmic drug transformation of AF. This occurs most frequently with class IC drugs. Because these drugs slow atrial conduction, the atrial rate is often much slower than that observed with classic atrial flutter, thus allowing the possibility of 1:1 AV conduction (82). To prevent this complication, a negative dromotropic drug (digoxin, beta-blocker, diltiazem or verapamil) is recommended as adjunctive therapy when class IC drugs are used.

Class I drugs may exacerbate congestive heart failure and, therefore, should not be administered to patients with LV dysfunction. They may also provoke ventricular arrhythmias in these patients and are associated with an increased risk of sudden death (77,78,82). Class I drugs are also proarrhythmic during experimental episodes of acute myocardial ischemia. As a result, they should be used with caution in patients with stable coronary artery disease, even in those with normal LV function.

Amiodarone may aggravate bradycardia and rarely causes torsade de pointes (when it occurs it is usually in association with severe bradycardia). In general, noncardiac toxicity (as listed in Table 5) limits its use. To minimize these effects, patients should use adequate sun protection when outdoors. Clinical history, hepatic enzymes and thyroid function should be monitored periodically. Patients should be questioned for new pulmonary symptoms and, if present, further pulmonary evaluation is indicated to exclude possible pulmonary toxicity.

INPATIENT VERSUS OUTPATIENT INITIATION OF ANTIARRHYTHMIC DRUG THERAPY

Patients with no underlying heart disease have a low risk of proarrhythmia. As a result, antiarrhythmic drug initiation can be generally started as an outpatient if sinus node dysfunction or AV conduction disturbances are not present. Special caution should be taken in patients currently in AF because underlying sinus node function may be unknown. Dofetilide has specific dosing and labelling requirements necessitating inpatient

initiation in all patients. Sotalol may be initiated as an outpatient in an individual without risk factors for torsade de pointes.

Patients with underlying heart disease have a higher risk of proarrhythmia. Drugs should be initiated inpatient with electrocardiogram monitoring if a drug other than amiodarone is used. Amiodarone has been shown to be safe even when given as an outpatient in patients with LV dysfunction. Inpatient initiation should be considered if underlying conduction abnormalities are present.

CONCOMITANT MEDICAL THERAPY IN PATIENTS WITH AF

Appropriate treatment of coexisting cardiovascular conditions is important, especially hypertension and LV dysfunction. For example, in the AFFIRM study (81), hypertension was the predominant cardiovascular condition in 50% of patients and was prevalent in 70% of patients. Several lines of evidence suggest that blockade of the angiotensin-renin system may have salutary effects in patients with AF. Angiotensin-converting enzyme (ACE) inhibition attenuates electrical (84) and structural (85) remodelling in experimental models of AF. Clinical data (86,87) suggest that treatment with an ACE inhibitor reduces the incidence of recurrent AF in patients with LV dysfunction. In addition, as mentioned earlier, pretreatment with angiotensin receptor blockers or an ACE inhibitor reduces the occurrence of AF after electrical cardioversion in amiodarone-treated patients (67,68).

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Pharmacological and nonpharmacological methods for rate control

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P Dorian, SP Connors. Pharmacological and nonpharmacological methods for rate control. *Can J Cardiol* 2005;21(Suppl B): 26B-30B.

In many patients with atrial fibrillation, the most appropriate strategy is 'rate control', designed to slow down the rapid ventricular rates often seen with atrial fibrillation. Based on the hypothesis that symptoms, especially palpitations and exercise intolerance, are due to rapid ventricular rates with activity, optimum rate control usually requires reducing ventricular rates at rest and during activity. Beta-blockers and nondihydropyridine calcium channel blockers are likely more effective than digoxin alone, and the adequacy of rate control is best assessed with heart rate measurement during activity or with ambulatory electrocardiographic monitoring. Taking a patient's symptoms into account, reasonable target ventricular rates are less than 80 beats/min at rest and less than 100 beats/min, on average, over 24 h.

Key Words: Atrial fibrillation; Atrial fibrillation therapy; Ventricular rate control

Traitement médicamenteux et non médicamenteux de la fibrillation auriculaire pour la maîtrise de la fréquence cardiaque

Chez de nombreux patients atteints de fibrillation auriculaire (FA), le traitement le plus approprié est la maîtrise de la fréquence cardiaque (FC), qui consiste à ralentir la réponse ventriculaire rapide, qui accompagne souvent la FA. D'après l'hypothèse selon laquelle les symptômes, en particulier les palpitations et l'intolérance à l'effort, sont dus à la réponse ventriculaire rapide durant les activités, la maîtrise optimale de la FC exige en général une réduction de la réponse ventriculaire au repos et à l'effort. Les bêta-bloquants et les inhibiteurs calciques non dihydropyridiniques sont probablement plus efficaces que la digoxine seule, et la meilleure façon d'évaluer le degré de maîtrise de la FA est de mesurer la FC durant une activité ou de procéder à un ECG ambulatoire. Compte tenu des symptômes du patient, il est raisonnable de viser une fréquence ventriculaire inférieure à 80 battements/min au repos et à 100 battements/min, en moyenne, sur 24 h.

RECOMMENDATIONS

Class I

- 1) Rate control should be undertaken for improvement of symptoms and control of ventricular rate (level of evidence C).
- 2) Administer nondihydropyridine calcium channel blocking agents (ie, diltiazem, verapamil) or beta-blocking agents as initial rate-slowing therapy in active and younger patients (level of evidence B).
- 3) Administer beta-blocking agents combined with digoxin to control ventricular rate in patients with heart failure (level of evidence C).
- 4) Consider pacemaker implantation and atrioventricular (AV) nodal ablation for patients with persisting symptoms due to rapid or irregular ventricular rate, in whom oral drug therapy is ineffective or not tolerated (level of evidence A).
- 5) In patients with a rapid ventricular rate associated with pre-excitation over an accessory bypass tract (Wolff-Parkinson-White syndrome), administer intravenous procainamide or ibutilide or perform direct current cardioversion if unstable (level of evidence B).

Class IIa

- 1) Assess ventricular rate at rest and during exercise and modify target rates depending on patients' symptoms (level of evidence C).

- 2) Administer digoxin as the initial therapy in elderly and inactive patients (level of evidence C) or as adjunctive therapy to calcium channel blocking or beta-blocking agents in younger and active patients (level of evidence C).

RATE CONTROL IN ATRIAL FIBRILLATION

In addition to the loss of AV synchrony, many patients with persistent or paroxysmal atrial fibrillation (AF) develop symptoms attributable to a usually rapid and irregular ventricular rate.

The present article will discuss the detailed management of 'rate control' therapy intended to slow ventricular rate response.

Even in patients for whom the 'rhythm control' strategy is selected, AF may still recur in a substantial minority (1,2). If the drug used for rhythm control does not have independent AV nodal blocking properties (drugs such as flecainide, propafenone, quinidine and disopyramide), additional AV nodal blocking drugs are often useful to control ventricular response in the case that AF recurs. Although drugs such as propafenone and flecainide modestly prolong AV nodal refractoriness, their use as monotherapies may be associated with no slowing of ventricular response, or even a markedly more rapid ventricular rate in case of atrial arrhythmia recurrence; this latter situation may arise if the atrial arrhythmia becomes 'organized' and is slowed by the antiarrhythmic drug, thus permitting 1:1 AV conduction, a type of proarrhythmia most often observed during exercise (3). Beta-blockers or calcium channel blockers should be used in the prevention of rapid ventricular rate if this proarrhythmia occurs.

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For patients treated with sotalol or amiodarone using the rhythm-control strategy, additional AV nodal blocking agents may not be necessary, but treatment should be individualized based on the ventricular response in cases of documented recurrence.

Ventricular response patterns during AF

In most patients not on antiarrhythmic drugs, ventricular rates are rapid and irregular during AF. The irregularity is probably caused by variable degrees of concealed conduction of AF wavefronts that reach the anterior or posterior inputs to the AV node and are either conducted to the ventricle or are blocked but cause relative refractoriness of the AV node for subsequent impulses. The ventricular rate is a complex result of the frequency and orientation of atrial wavefronts reaching the AV node, the intrinsic refractory properties of the AV node, and autonomic modulation (via vagal and sympathetic influences) of AV nodal behaviour. As a result, ventricular rates can be extremely rapid but not irregular ('pseudo regularization') in patients with very short AV nodal refractory periods, especially in young patients who are under conditions of adrenergic stress. On the other hand, in some patients, particularly the elderly, ventricular rates may be in the normal physiological range, or even relatively slow in the absence of any AV nodal blocking drugs. Ventricular rates can be markedly influenced by patient activity and setting, such that a patient can have marked bradycardia at rest or at night and then have marked tachycardia during daytime activities.

Clinical significance of ventricular response rates

The rapid and irregular rates during AF, rather than the loss of AV synchrony, primarily contribute to the preponderance of symptoms (4,5). Rapid rates during AF can also cause or contribute to left ventricular (LV) systolic dysfunction (often called 'tachycardiomyopathy'), cause or worsen myocardial ischemia, and possibly increase the risk of ventricular tachycardia or fibrillation in predisposed individuals.

The severity of symptoms attributable to AF and the prevailing ventricular rate are not always well correlated. In some patients, LV systolic function improves after ventricular rate control, and longstanding rapid ventricular rates may contribute to the future risk of development of heart failure; however, the degree of 'harm' associated with rapid ventricular rates during AF is not known. In patients with minimal symptoms and normal LV systolic function, even if they have rapid ventricular rates, it is speculative that the benefits of rate control outweigh the risks, or that rate control increases the quality and/or quantity of life.

Therapeutic benefit from rate control

Only a few published studies (1,2,6-8) of rate control in AF have systematically evaluated the effect of rate control on quality of life or patient-related symptoms. There are no studies that attempt to correlate the extent of rate control with the extent of symptom improvement: such a study would verify the implicit hypothesis that tighter rate control (ie, ventricular rates in a desirable range) results in better symptom improvement than less-than-stringent rate control. Most studies assessing the effectiveness of drugs to control ventricular rate during AF focus on the heart rate itself, rather than the quality of life or symptoms. In a study by Steeds et al (9), sotalol and atenolol resulted in a median 10 mm improvement of symptom severity

on a 0 mm to 100 mm visual analog scale, with no improvement in general health quality using the Nottingham Health Survey. In the Pharmacological Intervention in Atrial Fibrillation (PIAF) study (7), 80% of patients reported 'improvement', with a similar improvement in patients treated with diltiazem, titrated to achieve a resting heart rate of 85 beats/min or less, compared with amiodarone with cardioversion (the rhythm control strategy). In a randomized study (6) of AV nodal blocking drugs versus AV junction ablation, there was a similar improvement in exercise tolerance, symptoms attributable to AF and the quality of life in both the pharmacological rate control arm and the AV node ablation arm (15 of 16 patients received calcium channel blockers for rate control).

There are a large number of randomized studies (1,6,10-22) comparing beta-blockers or calcium channel blockers with digoxin and/or placebo, both with respect to rate control and exercise tolerance in persistent AF. Most studies of calcium blocking agents resulted in no change in maximum exercise tolerance, although a few showed an improvement. Most studies of beta-blockers indicate that they are highly effective alone or in combination with digoxin at controlling ventricular response, but no study showed an increased exercise tolerance, and only some studies showed decreased exercise tolerance and decreased myocardial O₂ consumption (9,16-19,23,24). In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) rate control substudy (25), significantly more patients achieved 'successful' rate control using beta-blockers than using calcium channel blockers, although the comparison was not randomized. Digoxin was the least effective drug at controlling ventricular response in this substudy. In a crossover study of beta-blockers, digoxin and calcium channel blockers for rate control, Farshi et al (14) found that the beta-blocker plus digoxin combination was the most effective at rate control compared with combination or individual drugs. However, circadian variability was most inhibited by this drug combination, and there was no difference in maximum exercise tolerance among any of the agents or combinations used.

Digoxin as a monotherapy is less effective at slowing ventricular rates than calcium channel blockers or beta-blockers (3,5,15,26-28). Digoxin, in combination with either beta-blockers or calcium channel blockers, enhances the effectiveness of the latter agents (14,16,17).

The data are sparse on the use of amiodarone as a rate-controlling agent. Due to its calcium channel blocking and antiadrenergic effects, amiodarone can slow the ventricular rate during AF. Because of its side effects and toxicity, however, amiodarone should rarely be used to control ventricular rate, and should be reserved for patients in whom other rate-controlling strategies are ineffective or unfeasible.

In summary, digoxin is only moderately effective at restoring ventricular rates to the physiological range. Both calcium channel blockers and beta-blockers are effective at reducing ventricular response, in particular when combined with digoxin. Although beta-blockers may be somewhat more effective at reducing ventricular rates than calcium channel blockers, they are more likely to be associated with a reduction in exercise tolerance. There are more data to support the benefit of calcium channel blockers in improving exercise tolerance and patient well-being than there are for beta-blockers. Suggested dose ranges for ventricular rate-slowing drugs are illustrated in Table 1.

TABLE 1
Drugs used to control ventricular rate during atrial fibrillation

Drug	Common total daily dose (mg)	Comments
Beta-blockers		
Bisoprolol	2.5–10	Higher doses can be considered in selected cases
Metoprolol	25–200	Higher doses can be considered in selected cases
Atenolol	25–100	Higher doses can be considered in selected cases
Calcium channel blockers		
Verapamil	180–480 (sustained release)	Less data supporting long-term efficacy than for diltiazem
Diltiazem	120–480 (extended release)	Different formulations are available
Digoxin	0.125–0.25	Less effective as monotherapy

Most studies of rate control have excluded patients with heart failure or severe LV dysfunction and, thus, the risk-benefit relationship of either beta-blockers or calcium channel blockers for rate control in patients with heart failure is unknown. Because beta-blockers are independently indicated in patients with a prior myocardial infarction or symptomatic heart failure, beta-blockers seem to be a logical treatment of choice in this clinical setting.

In patients with LV dysfunction likely caused by 'tachycardiomyopathy', restoration and maintenance of sinus rhythm is associated with improved ventricular function (29). Following AV junction ablation and permanent ventricular pacing, LV systolic function improves in patients with LV dysfunction (4,30). Acute rate control with intravenous digoxin or diltiazem leads to an increase in LV ejection fraction measured by a radionuclide ventriculogram (portable radionuclide detector) (31). In patients with AF, ventricular function seems to decline as the heart rate increases, suggesting that systolic function improves as the heart rate slows below a patient-specific range (32).

Target end points for rate control

There are no controlled studies systematically assessing the relative benefits of varying degrees of rate control. The American College of Cardiology/American Heart Association/European Society of Cardiology (33) recommendations for heart rate control suggest measuring heart rate response both at rest and during exercise and reducing the rate to the 'physiological range'; this range is undefined. In the largest study with protocol-specified recommendations for target rates in persistent AF, the AFFIRM study (25) recommended administering digoxin, beta-blockers, calcium channel blockers, or a combination to achieve a resting heart rate less than 80 beats/min and a heart rate during a 6 min walk of less than 110 beats/min, or an average heart rate of less than 100 beats/min on a 24 h Holter monitor. In this study of 2027 patients, the resting heart rate was reduced to the desired range 75% of the time with beta-blockers and 66% of the time with calcium channel blockers. Following exercise, rates were in the target range 85% of the time with beta-blockers and 72% of the time with calcium channel blockers. However, the patients were not administered drugs randomly, and there were systematic differences in the patient

clinical profiles in groups treated with varying rate control drugs (specific doses and types of beta-blockers and calcium channel blockers were not detailed). Five per cent of patients eventually required AV nodal ablation and permanent pacing because of the inability to control ventricular rates with drug therapy alone; and 7% received a pacemaker for bradycardia, presumably caused by or contributed to by the rate-controlling agents used.

Practical considerations in rate control management

Resting heart rate is poorly correlated with heart rate during daily activities or during a 6 min walk (8) and, thus, using resting heart rate alone to assess the adequacy of ventricular rate control is inadequate.

In assessing the adequacy of rate control, it is important to take patient symptoms and well-being into consideration. General well-being may improve, remain the same or even worsen with AV nodal blocking therapy and, as some symptoms such as palpitations or light-headedness improve, other symptoms such as fatigue and exercise intolerance may appear or worsen. Patients can develop specific drug-related adverse symptoms such as ankle swelling (with calcium channel blockers), daytime sleepiness or cold extremities (with beta-blockers). Rate controlling agents should usually be commenced at a relatively low dose, with systematic and gradual up-titration to achieve heart rates in the ranges specified in the AFFIRM study (25), provided that patient well-being continues to improve and that no adverse events develop during drug up-titration.

In most cases, it is reasonable to begin therapy with either a rate-slowing calcium channel blocker (diltiazem or verapamil) or a beta-blocker. Digoxin can subsequently be added as adjunctive therapy if necessary. In patients with a pre-existing indication for a beta-blocker, such as a history of coronary artery disease with myocardial infarction, LV dysfunction or a history of heart failure, beta-blockers are indicated and, therefore, should be used preferentially. In patients with heart failure, beta-blockers should be initiated at low doses to avoid acute exacerbation of heart failure symptoms. In patients with absolute or relative contraindications to beta-blockers, and possibly in young or active patients in whom beta-blocker adverse effects may be the most bothersome, initial therapy with a calcium channel blocker (adding adjunctive digoxin if necessary) is reasonable. In older, particularly sedentary patients, therapy with digoxin alone may be adequate and is recommended as initial therapy, with dose adjustment depending on renal function.

Patient symptoms and well-being should be carefully evaluated at every patient visit. If the resting ventricular rate is faster than the desired maximum rate, AV nodal blocking therapy may be up-titrated immediately. If the resting heart rate is in the desired range, some measure of ventricular rate during activity or exercise is still required. A titratable amount of physical activity in the office setting may be considered (eg, a 6 min walk or stair climbing). In most outpatient settings, routinely performing 6 min walks is impractical, and 24 h Holter monitoring may be considered. In some individuals, Holter monitoring reveals nocturnal bradycardia and daytime tachycardia; the average heart rate in these patients may be within the target range, even as daytime heart rates are rapid and associated with symptoms. Such individuals may require further up-titration of AV nodal blocking therapy, paying special attention to the potential risk of symptomatic nocturnal

bradycardia. Importantly, asymptomatic nocturnal bradycardia does not reflect an indication for permanent pacing, even if there are nocturnal pauses of 3 s or more. Discontinuing digoxin in patients with marked nocturnal bradycardia can be considered.

The role of AV nodal ablation and pacing in rate control for AF

A number of well-controlled studies have indicated that in selected patients, AV nodal ablation and pacing effectively controls ventricular rates and results in a symptomatic and functional improvement, as well as an improvement in the quality of life. In a meta-analysis of studies of AV nodal ablation and pacing, Wood et al (30) showed improvements in symptoms and exercise tolerance, both in patients with pre-existing normal and poor LV function. One smaller study (34) has suggested AV nodal ablation and pacing results in improved LV function and possibly symptom improvement, even in patients with 'drug-controlled' ventricular rates during AF.

However, studies (6,8,35) that randomly assigned patients to AV nodal ablation versus rate-slowing drug therapy were not able to show significantly better results with AV nodal ablation on any of the end points of exercise tolerance, symptomatic improvement or improvements in LV function. In addition, AV nodal ablation and pacing results in permanent pacemaker dependency, requires two independent procedures, each with a low risk of complication, and has been associated with a small but not negligible risk of sudden death, presumably related to the sudden slowing of heart rate following the

procedure (33). Although a large retrospective series of patients subjected to AV nodal ablation versus rate control did not demonstrate a significantly higher sudden death rate than expected for age and underlying cardiac disease following AV nodal ablation, Ozcan et al (36) reported a 2.1% sudden death rate following AV nodal ablation; some deaths were possibly related to the procedure. Importantly, patients are obligatorily paced 100% of the time following AV nodal ablation. Recent studies have (37) suggested that long-term right ventricular apical pacing may be associated with a deterioration of LV function and, thus, the possible long-term risks of continuous right ventricular apical pacing following AV nodal ablation need to be considered. Finally, not all patients improve symptomatically following AV nodal ablation, and some patients have unexpected functional deterioration, even though LV function is maintained or improved. A recent randomized trial (38) of biventricular versus right ventricular pacing in conjunction with AV node ablation for AF suggests that there may be less frequent deterioration of LV function in the group assigned to biventricular paced. Biventricular pacing can be considered with AV node ablation, especially if there is pre-existing LV dysfunction (38).

Thus, although AV nodal ablation and pacing can be beneficial in select patients with symptomatic AF, the procedure should be reserved for those who have relatively severe symptoms and who cannot be effectively treated with existing drug treatments for rate control. Patients should be fully informed of the risks and benefits of AV node ablation and pacing.

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Catheter ablation therapy for atrial fibrillation

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Catheter ablation therapy for the treatment of atrial fibrillation (AF) has evolved considerably in the past decade. Although the therapy was initially limited to ablation of the atrioventricular node to ensure adequate rate control for patients with rapid AF, the possibility of catheter-based rhythm control has now been demonstrated in several studies. Atrial extrasystoles originating from the pulmonary veins are now known to be triggers for the initiation of AF. Consequently, attempts at ablation have focused on the ablation of these triggers or on electrical isolation of these veins using radiofrequency ablation. More recently, three-dimensional electroanatomical imaging techniques have allowed for the development of left atrial ablation techniques, whereby long, linear lesions are created around the pulmonary venous ostia. Both of these techniques have shown interesting success rates in the treatment of symptomatic paroxysmal AF. The present article reviews the evolution of these techniques and lists the recommendations for the use of catheter ablation for both rate and rhythm control of AF.

Key Words: *Atrial fibrillation; Atrium; Catheter ablation; Pulmonary veins*

Traitement ablatif de la fibrillation auriculaire par cathéter

Le traitement ablatif de la fibrillation auriculaire (FA) par cathéter a considérablement évolué au cours de la dernière décennie. Bien qu'à l'origine, il se soit limité à l'ablation du nœud auriculoventriculaire pour promouvoir un contrôle adéquat du rythme chez les patients ayant une FA rapide, la possibilité de contrôler le rythme par cathéter a désormais été documentée lors de plusieurs études. Les extrasystoles auriculaires dont l'impulsion émane des veines pulmonaires déclencheraient la FA. Par conséquent, les mesures d'ablation ont porté sur la neutralisation de ces déclencheurs ou l'isolement des veines par ablation par radiofréquence. Plus récemment, les techniques d'imagerie électroanatomique tridimensionnelle ont permis la mise au point de méthodes d'ablation auriculaire gauche reposant sur la création de longues stries autour de l'orifice pulmonaire. Ces deux techniques ont donné lieu à des taux de succès intéressants pour le traitement de la FA paroxystique symptomatique. Le présent article passe en revue l'évolution des techniques et dresse la liste des recommandations d'utilisation de la technique ablatif par cathéter dans le but de contrôler la régularité et la fréquence dans la FA.

RECOMMENDATIONS FOR CATHETER ABLATION FOR RHYTHM CONTROL

Class I

- 1) In patients with atrial fibrillation (AF) and preexcitation, catheter ablation of the accessory pathway is recommended, particularly if associated with syncope, rapid ventricular rates, or if the accessory pathway has a short refractory period (level of evidence B).

Class IIa

- 1) In young patients with lone paroxysmal AF, an electrophysiological study should be considered to exclude a reentrant tachycardia as a potential etiology for AF, and if present, curative ablation should be performed (level of evidence B).
- 2) Patients with highly symptomatic paroxysmal AF refractory to medical therapy should be considered for an ablation procedure aimed at maintaining sinus rhythm (level of evidence B).

RECOMMENDATIONS FOR CATHETER ABLATION FOR RATE CONTROL

Class I

- 1) Patients with highly symptomatic permanent AF with rapid ventricular rates in whom oral rate-control drug therapy is insufficiently effective or not tolerated should be considered for atrioventricular (AV) node ablation and pacemaker implantation (level of evidence B).
- 2) Patients with highly symptomatic paroxysmal AF in whom attempts at rhythm control have been abandoned and in whom pharmacological rate control is insufficiently effective or not tolerated should be considered for AV node ablation and pacemaker implantation (level of evidence B).

INTRODUCTION

Other articles in the present supplement to *The Canadian Journal of Cardiology* (Wyse and Simpson, pages 15B-18B;

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Talajic and Roy, pages 19B-25B; Dorian and Connors, pages 26B-30B) have outlined some of the issues involved in deciding between rate-control and rhythm-control strategies in patients suffering from AF, and they have explained some of the more recent studies suggesting that maintaining a reasonably controlled ventricular response may be as beneficial as restoring sinus rhythm. However, an important cohort of patients may merit more vigorous attempts to maintain sinus rhythm. In general, patients with paroxysmal rather than persistent AF tend to be more symptomatic. They are less responsive to rate-slowng agents that frequently cause bradycardia during sinus rhythm and do not adequately relieve the symptoms while in AF. As well, younger patients with lone AF have been underrepresented in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study (1), where the mean age of subjects was 70 years, and where only 12% had no other cardiac pathology. Of importance, some of the large trials comparing rate-control and rhythm-control strategies used exclusively pharmacological methods with all of their attendant proarrhythmic potential to maintain sinus rhythm, thus making it impossible to comment on the potential benefits of rhythm control using catheter ablative therapies. Catheter-based interventions for the maintenance of sinus rhythm, despite requiring an invasive procedure, may obviate some of the long-term side effects and proarrhythmic risks of antiarrhythmic drug therapy, and these interventions are associated with improvements in quality of life when compared with standard antiarrhythmic therapy (2). Thus, in highly symptomatic patients with paroxysmal AF, exploration of nonpharmacological treatment options is warranted.

MECHANISMS OF AF

Attempts at developing curative ablative therapy have traditionally focused on depriving AF of one of its two primary substrates: the substrate for the maintenance of AF, or the substrate for AF initiation. Early studies by Moe et al (3,4) and Allesie et al (5) described the multiple wandering wavelet hypothesis of AF and explained how these wavelets require an adequate extent of contiguous, electrically active tissue through which to propagate in order to sustain AF. Persistent, rapid atrial rates lead to a process of electrical remodelling whereby atrial refractoriness decreases, thereby enhancing the substrate for AF maintenance (6,7). Canine models have suggested that congestive heart failure can lead to atrial fibrosis causing heterogeneous conduction in the atria, thus also promoting this substrate for AF maintenance (8).

The concept that certain triggers may play a role in the initiation of AF was initially evoked by Scherf (9), who proposed that rapidly firing ectopic foci could entrain the atria into dysynchronous activity. The presence of accessory pathways and reentrant supraventricular tachycardia may also serve to initiate AF, although whether this is through rapid atrial rates degenerating into AF or through abnormalities in the atrial refractory periods is debatable (10-13). Nonetheless, ablating this potential trigger can avoid recurrences not only of AV reentrant tachycardia but also of AF. The notion of triggers that specifically induce AF gained prominence when Haissaguerre et al (14) detailed the initiation of AF by atrial ectopic beats that usually originate in the pulmonary veins. These triggers arise in the sleeve of atrial tissue, which extends from the left atrium for several centimetres into the vein (15). Although the pulmonary veins appear to be the source of most of the triggers that initiate

AF, venous structures with similar atrial tissue extensions, such as the superior vena cava (16), the coronary sinus (17,18) and the ligament of Marshall (19,20), have also been reported as generating ectopic triggers for AF. Other sites of ectopic atrial tachycardia may occasionally initiate AF (21,22).

ABLATION THERAPIES FOR AF

Other articles in the present supplement (Pagé and Skanes, pages 35B-39B, Gillis et al, pages 41B-44B) have described AV node ablation and pacemaker implantation as a method for rate control in patients with refractory, symptomatic AF, particularly when associated with tachycardia-induced cardiomyopathy. Even when employing very rigorous pharmacological rate-control strategies, a number of patients will still require AV node ablation, as evidenced by the fact that 5.2% of patients in the AFFIRM trial necessitated such an intervention to achieve adequate rate control (1). This strategy has been shown to significantly improve quality of life and significantly reduce doctor visits, hospital admissions and antiarrhythmic drug trials (23). This therapy has also been shown to reduce the number of episodes of congestive heart failure in this group of patients (23). However, AV node ablation and pacemaker implantation is likely most beneficial in patients that have a more persistent form of AF, where rate control is the sole objective. Patients with paroxysmal AF can also derive symptomatic relief from this type of ablation because it will prevent excessively rapid rates and irregularity, the two major causes of symptoms, by switching to a solely ventricular pacing mode during episodes of AF. Importantly, though, some patients may remain symptomatic from these changes in rhythm and pacing mode.

Despite being an effective palliative therapy, there are some concerns about rendering patients pacemaker-dependent, especially younger patients with no other underlying cardiac disease who will, over time, require multiple pacemaker changes. Antithrombotic therapy must also be maintained in this group, as these patients will either remain in AF or have recurrences, with a significant proportion progressing to permanent AF. Nonetheless, because of its high efficacy at reducing symptoms, AV nodal ablation and pacemaker implantation play an important role in the management of highly symptomatic patients.

ABLATING THE SUBSTRATE THAT MAINTAINS AF

Initial attempts at developing truly curative ablation strategies for AF centred around the same basic premise as surgical therapies: segment the atria so as to deprive the multiple wandering wavelets of an adequate spatial extent through which to propagate, thus targeting the substrate for the maintenance of AF. In electrophysiology, this was done by extending and connecting the natural barriers to conduction, such as the crista terminalis, the vena cava, the mitral and tricuspid valves and the pulmonary veins, by creating linear lesions between these structures using radiofrequency ablation. Although multiple surgical incisions can create effective barriers to conduction, when using radiofrequency ablation, linear lesions can only be created by dragging the catheter incrementally across the endocardium during energy application. This can be challenging, especially when lesions need to be applied over a long area, and particularly when working through a transeptal sheath to make lesions in the anatomically complex left atrium. Pathological analyses have demonstrated the difficulty in achieving complete linear lesions in the canine model (24-26); while incomplete linear lesions are

ineffective at best, they may also provide a substrate for further or new atrial re-entrant arrhythmias (27). Early experiences with these ablations were disappointing, as right atrial lesions alone had success rates as low as 33%, with some patients still requiring antiarrhythmic treatment (28). The addition of left atrial lesions augmented the success rate somewhat, but also resulted in procedures that were technically more difficult and more time consuming. Jais et al (29) subsequently reported their attempts at deploying a series of right and left atrial linear lesions to treat AF, but they only achieved a 57% success rate and encountered a high rate of serious complications such as pericardial effusions, pulmonary embolus, inferior myocardial infarction, transient ischemic attack and thrombosis of the left pulmonary veins. These experiences underscore two more potential difficulties associated with trying to ablate the substrate for AF maintenance: first, that creating complete, contiguous linear lesions can be challenging, often resulting in ineffective procedures; and second, that prolonged, repeated energy applications and the lengthy procedure times required to achieve these complete lesions can lead to thrombus and embolus formation (30,31), thus explaining some of the encountered complications.

ABLATING THE SUBSTRATE THAT INITIATES AF

The elucidation of the substrate for the initiation of AF as being ectopic beats originating primarily in the pulmonary veins led to the important clinical correlate that identification and ablation of these foci could actually prevent AF. In a series of 45 patients, Haissaguerre et al (14) reported that 94% of initiating triggers originated in the pulmonary veins, and ablation resulted in a long-term success rate of 62%. These patients had initiating triggers located up to 4 cm inside the veins. However, infrequently firing ectopics can be difficult to localize in these more distal areas of the pulmonary veins where secondary- and tertiary-level branching occurs, and this rendered the task of ablation long and arduous. One report (32) showed that 32% of patients with paroxysmal AF undergoing an attempt at pulmonary vein trigger ablation had insufficient ectopy at the time of the study to allow adequate localization of the origin of the arrhythmia. Further complicating these ablations was the fact that multiple initiating triggers could originate from different branches of the same pulmonary vein or from the other pulmonary veins (33,34).

Because previous attempts at a catheter-based Maze procedure have caused severe pulmonary vein stenosis and pulmonary hypertension (35), there has always been concern about the possibility of pulmonary vein stenosis complicating these AF ablation procedures. Establishing the incidence of this particular complication is difficult because the development of symptoms is often delayed, and imaging modalities are not particularly sensitive or specific in detecting this problem. Initial case reports (36-38) have suggested that symptoms of this complication could be delayed up to three months following an ablation procedure, and that stenosis occurred most frequently when ablating more distally or in smaller caliber veins. In larger series, the reported incidence has varied from 3% to 8% (32,33). Identifying predictors of stenosis has been difficult (39), but it is generally felt that limiting the extent of ablation (both the energy used and the circumferential degree of ablation) (33) and remaining as close to the ostium as possible during applications reduces the incidence of this complication.

The challenge of ablating all potential arrhythmogenic triggers while reducing the possibility of pulmonary vein stenosis

led to the development of a more anatomically based procedure. Because the majority of atrial ectopics responsible for the initiation of AF originate in the pulmonary veins, a procedure designed to electrically isolate these veins could prevent egress of triggering ectopics into the left atrium, thus preventing the initiation of AF (34,40). The development of a circular catheter with 10 electrodes of 1 mm each has allowed better identification of these exit points between the pulmonary veins and the left atrium. Using such a catheter, Haissaguerre et al (41) defined the perimetric distribution of pulmonary vein potentials and, hence, the extension of atrial tissue within 162 pulmonary veins. Pulmonary vein isolation was achieved by ablating the site of earliest activation within the pulmonary vein, and AF was eliminated in 71% of patients. Thus, the end point for the procedure became the electrical isolation of the potentially arrhythmogenic pulmonary veins from the left atrium, limiting the potential for more distal pulmonary vein stenosis by maintaining the application of radiofrequency energy to the ostium of the veins.

THE EVOLUTION OF CURATIVE ABLATION TECHNIQUES

New developments have focused on newer tools and techniques designed to make the ablative procedure simpler and more efficacious. The use of catheters that deliver larger lesions appear to decrease procedural time and improve success rates (40). In particular, irrigated-tip catheters may decrease some of the complications associated with pulmonary vein isolation (42). Intracardiac ultrasound also appears to enhance the facility with which these procedures are performed by allowing better visualization of the left atrium and the pulmonary veins during the ablation and also by allowing titration of energy delivery and monitoring of pulmonary vein stenosis (43-45).

The advent of three-dimensional electroanatomic mapping systems has permitted the development of different ablation techniques. One such technique, demonstrated in studies by Pappone et al (46,47), involves encircling a wide berth around the pulmonary veins. In those studies, circumferential lesions in the left atrium at a distance from the pulmonary veins were made around each ostium, or in some cases around two adjacent ostia. This technique provided a success rate of 80% at 10 months. Interestingly, recurrence rates were less in patients that had a larger ablation area (47), suggesting that the elimination of pulmonary vein triggers combined with the reduction of effective atrial conducting tissue mass provided additional benefit to standard pulmonary vein isolation. More recently, a comparison of pulmonary vein isolation and this technique of encircling them by performing a left atrial ablation (48) demonstrated a six-month success rate of 67% for patients in the pulmonary vein isolation group compared with 88% for those in the left atrial ablation group. This increased success rate might be explained by the fact that this ablation technique targets multiple mechanisms of AF: isolating the foci of triggers in the pulmonary veins, containing microreentry circuits and eliminating the substrate for macroreentry.

CONCLUSIONS

Until recently, AV node ablation was the only catheter-based option for patients with AF and failed attempts at medical management. Subsequent refinements in technique are making catheter-based, rhythm-control strategies more viable by helping

to improve procedural success rates and reduce complications. Furthermore, the modification in the substrates achieved by more extensive left atrial ablation lesions may extend the indications to those with persistent AF and significant structural heart disease, where the predominant problem appears to be the substrate for the maintenance of AF. Should further studies confirm the latest efficacy and safety results of these ablation techniques, then ablation may become a potential first-line treatment for patients with lone paroxysmal AF. Thus, catheter ablation has an important role to play as either an adjunctive or an alternative to standard pharmacological therapy for both the rate-control and rhythm-control strategies for the management of AF.

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Surgical treatment of atrial fibrillation

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Surgery aims to eliminate atrial fibrillation (AF) through direct modification of the arrhythmogenic substratum. The Maze procedure, developed two decades ago, has proven to be clearly effective in restoring sinus rhythm in AF patients with or without associated organic cardiac disorders. Indications for surgery may be tailored to the clinical situation involved. In patients with continuous AF associated with structural heart disease (eg, valvular, congenital or coronary artery disease), the performance of a concomitant AF ablation procedure proven to add minimal morbidity to the operation may be highly beneficial to patient outcome. It is likely, although not entirely proven, that the restoration and maintenance of sinus rhythm after mitral valve surgery promotes survival by preventing tachycardia-induced cardiomyopathy and stroke. Novel strategies for AF surgery involve the use of alternate energy sources to create the lines of block in the atria and the simplification of the lesion pattern compared with the earlier Cox-Maze procedure. Published clinical data support the contention that left atrial ablation techniques performed concomitantly with valvular and/or coronary artery bypass surgery are likely to result in a 70% to 90% cure rate of AF in patients with preoperatively documented AF. Despite the lack of evidence for long-term outcome benefit, intraoperative pulmonary vein ablation, feasible with minimal morbidity, clearly appears to be an improvement over simply ignoring AF in patients undergoing cardiac surgery. Left atrial appendectomy appears warranted in patients with chronic persistent AF.

Key Words: *Arrhythmia surgery; Atrial fibrillation surgery; Left atrial appendage; Radiofrequency; Stroke; Valvular atrial fibrillation*

Le traitement chirurgical de la fibrillation auriculaire

La chirurgie vise à mettre fin à la fibrillation auriculaire (FA) par une modification directe du substrat arythmogène. La technique du labyrinthe, mise au point il y a une vingtaine d'années, s'est montrée vraiment efficace pour rétablir le rythme sinusal chez des patients atteints de FA, associée ou non à des troubles cardiaques organiques. Les indications de la chirurgie peuvent être adaptées à différentes situations cliniques. Dans les cas de FA permanente, associée à une cardiopathie structurale (lésion valvulaire, congénitale ou coronarienne), la réalisation d'une intervention concomitante de suppression de la FA, qui augmente de très peu le risque de morbidité associé à l'opération peut s'avérer grandement bénéfique. Par ailleurs, il est probable, mais non confirmé encore, que le rétablissement et le maintien du rythme sinusal après une opération valvulaire mitrale puissent améliorer la survie en prévenant la myocardiopathie d'origine tachycardique et les accidents vasculaires cérébraux. Des techniques chirurgicales novatrices utilisent des sources nouvelles d'énergie pour créer les lignes de segmentation des oreillettes tout en simplifiant la forme des lésions par rapport à celles produites par l'intervention originelle de Cox, en labyrinthe. Des données cliniques publiées étayent le point de vue selon lequel les techniques d'ablation tissulaire de l'oreillette gauche, pratiquées en même temps qu'une intervention chirurgicale valvulaire ou un pontage coronarien sont susceptibles de se solder par un taux de guérison de 70 % à 90 % chez les patients souffrant de FA avérée en phase préopératoire. Malgré l'absence de données sur les résultats à long terme, l'ablation peropératoire des veines pulmonaires, intervention réalisable tout en étant associée à une très faible morbidité, paraît comme une nette amélioration par rapport au simple traitement abstentionniste de la FA chez les patients subissant une opération cardiaque. Enfin, l'auriculotomie gauche semble justifiée chez les patients présentant de la FA chronique.

RECOMMENDATIONS

Class I

- 1) Patients undergoing intraoperative ablation of atrial fibrillation (AF) should be anticoagulated postoperatively unless they have a strong contraindication to oral anticoagulation therapy (level of evidence C).

Class IIa

- 1) In patients undergoing mitral valve replacement or repair with a history of symptomatic persistent or paroxysmal AF, concomitant intraoperative AF ablation should be considered to increase the likelihood of the restoration of sinus rhythm (level of evidence B).

Class IIb

- 1) Patients with symptomatic persistent or paroxysmal AF undergoing other cardiac surgery (eg, coronary artery bypass grafting, aortic valve replacement or both) may

be considered for intraoperative AF ablation (level of evidence C).

- 2) Patients with refractory, symptomatic AF not associated with organic heart disease and without comorbidities may be considered for surgical ablation when other nonpharmacological procedures have failed (level of evidence C).
- 3) Patients who have undergone intraoperative AF ablation should be re-evaluated for anticoagulation therapy after three months of follow-up according to the general recommendations made after valvular surgery (level of evidence C).

INTRODUCTION

Earlier attempts at surgical therapy of AF targeted the reduction of rapid ventricular rate by interrupting the nodohisian pathway and inserting a permanent pacemaker (1). Soon after these first attempts at ventricular rate control, Scheinman et al (2)

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introduced the concept of catheter-based ablation techniques. However, these procedures led to permanent pacemaker dependency. To overcome this problem, surgical procedures aimed at preserving the patient's own sinus nodal function were introduced (3-5). In spite of the relative success in suppressing most of the symptoms associated with uncontrolled ventricular response, these procedures hardly offered any advantage over radiofrequency catheter ablation of the nodohisian pathway (6).

Further developments in arrhythmia surgery were aimed at the elimination of AF through direct modification of the arrhythmogenic substrate. Varying degrees of surgical modification may be tailored to the clinical situation involved (7). In the case of occasional paroxysmal 'lone' AF, where symptoms may be the main treatment objective, the invasiveness of surgical therapy has a major impact on decision making. However, in patients with structural heart disease (eg, valvular or congenital) or associated coronary artery disease, the performance of a concomitant AF ablation procedure, proven to add minimal morbidity to the operation, may be highly beneficial to patient outcome.

INDICATIONS FOR SURGICAL THERAPY

The physiological objectives of AF surgery are to prevent symptoms associated with rapid and irregular heart beat, to avoid blood stasis in the atrium and the attendant risk of thromboembolic events, and to preserve atrial function, which ensures optimal cardiac performance. However, the clinical value of surgical AF ablation procedures needs to be assessed with respect to the rate of freedom from AF recurrence, the rate of freedom from thromboembolic events, and the improvement of long-term survival.

The need for AF surgery during mitral valve operations

There is no large-scale randomized clinical trial that demonstrates the long-term benefits of a concomitant Maze procedure or any of its later modifications. However, inferences can be made based on a historical comparison of the results of valvular operations. The maintenance of sinus rhythm after successful cardioversion promotes both atrioventricular synchrony and active diastolic ventricular filling (8). The restoration and maintenance of sinus rhythm after mitral valve surgery may improve survival by preventing tachycardia-induced cardiomyopathy and stroke. AF occurs in 30% to 50% of patients undergoing mitral valve surgery (9-13). These studies have also demonstrated that preoperative AF is a strong determinant of postoperative AF (9-13). According to Jessurun et al (14), preoperative sinus rhythm, preoperative paroxysmal AF and preoperative chronic continuous AF would confer a relative risk of AF recurrence of 1.18 (95% CI 0.54±79), 2.35 (95% CI 1.8±54) and 19.2 (95% CI 0.8±12), respectively. In the same study, AF continued in 94% of the cases with preoperative chronic AF, whereas sinus rhythm persisted in 86% of patients undergoing mitral valve surgery with preoperative sinus rhythm (14). Similarly, paroxysmal AF persisted after surgery in 95% of the patients with preoperative AF, despite antiarrhythmic drugs. At the end of follow-up, more patients with preoperative chronic AF had died than those with preoperative sinus rhythm or paroxysmal AF, and AF persisting after surgery tended to determine survival ($P=0.05$). Other studies (13,15) also showed that patients with AF had a worse survival rate after mitral valve repair than patients in sinus rhythm.

Results of the Maze-III procedure

Interpretation of published results from the classic Maze-III procedure is confounded by the inconsistency of patient selection regarding the severity of symptoms, the type and duration of AF, and whether the operation was performed for 'lone' or 'valvular' AF. Reports (16-20) of the Cox-Maze operation have demonstrated a long-term elimination of AF in 84% to 98% of cases. Only a few studies have demonstrated a long-term benefit of the Maze procedure in reducing late morbidity and improving functional outcomes. Bando et al (21) showed that the addition of a Maze procedure to mitral valve operations did not increase morbidity in the immediate postoperative period. Their results indicated that a combined Maze procedure restored sinus rhythm in 84% of patients at three years after surgery, whereas only 6% of patients with mitral valve replacement alone avoided recurrent AF. Although survival benefit from the Maze procedure is not yet fully demonstrated, a number of reports (16-26), mainly with case-matched comparisons, have shown that the procedure is highly effective in restoring sinus rhythm compared with valvular surgery alone. Of further interest, 97% of the patients in the series by Bando et al (21) were free from late stroke at five years after surgery, compared with only 79% of patients who underwent mitral valve replacement alone. That study also showed that, according to multivariate analysis, the omission of a Maze procedure was the most significant risk factor for the development of late stroke. However, their selection criteria for actually performing a Maze procedure may have introduced a significant bias, suggesting that more diseased atria are more important for patient outcome than the arrhythmia itself.

Some surgeons suggest avoiding the Maze procedure in addition to mitral valve replacement with mechanical valves, arguing that these patients receive permanent systemic anticoagulation therapy anyway. However, in the study by Bando et al (21), most of the late strokes among patients receiving warfarin occurred in patients with mechanical valves. These findings confirmed that the restoration of sinus rhythm after mitral valve surgery by a Maze procedure is the most effective means of preventing late strokes, even for patients with mechanical valves. This propensity to reduce stroke rate may be related to the resection of the left atrial appendage and to the preserved atrial transport function. Several groups have reported their results with Doppler echocardiography after AF surgery. Most of them claimed a 75% to 90% incidence of biatrial contraction (27-32). However, atrial function is likely to remain abnormal in such patients who already have damaged atria (28). The resection or obliteration of the left atrial appendage may have contributed to the low incidence of late stroke. Although controversial, left atrial appendectomy is considered to have a high potential for stroke rate reduction in several studies (33-36). However, at least two reports (36,37) suggest that incomplete obliteration of the left atrial appendage may, in fact, promote stroke.

In summary, the Maze procedure has proven effective in restoring sinus rhythm in AF patients with or without associated organic cardiac disorders. Although attempts to restore postoperative sinus rhythm at the time of mitral valve surgery may appear worthwhile, the definitive proof of a long-term survival benefit has yet to be determined in a randomized study.

CHANGING CONCEPTS IN AF SURGERY

For arrhythmias associated with stable macroreentrant circuits (eg, Wolff-Parkinson-White syndrome), the ablation process

TABLE 1
Energy sources for atrial fibrillation surgical ablation

Radiofrequency	Nonirrigated monopolar coil
	Irrigated monopolar coil
	Irrigated tip
	Nonirrigated bipolar jaws
	Irrigated, malleable bipolar jaws
Microwave	Rigid linear probe
	Flexible catheter
Cryoablation	Malleable linear coil
	Rigid focal probes
Laser	Rigid linear probe*
High-frequency ultrasounds	Flexible catheter*

*Not yet commercially available in Canada

TABLE 2
Summary of atrial fibrillation (AF) surgical approaches

Procedure	Advantages	Disadvantages
Cox-Maze-III (Cut-and-sew)	High success rate (freedom from AF); low TEE rate	Increased operative difficulty/time; reduced atrial function
Full Maze-III design using ablation energy	Easier to learn; proven efficacy (85% early, 75% late freedom from AF)	Risk of left atrial flutter; unknown effect on late survival
Left atrial RF ablation including LAA resection	Easy to perform with valvular surgery (75% to 88% freedom from AF after five years)	Does not address right atrial flutter; unknown effect on late survival
Pulmonary veins 'en bloc' isolation	Easier to perform; amenable to minimally invasive approaches	Does not address right atrial flutter; unknown effect on late TEE rate and late survival

LAA Left atrial appendage; RF Radiofrequency; TEE Thromboembolism

follows the classic paradigm of arrhythmia surgery that is based on the identification of the arrhythmia mechanism, the anatomical localization of the arrhythmogenic substrate and the design of effective surgical technique ablating the determined target (38,39). The same paradigm linked to the use of radiofrequency energy led to the development of percutaneous procedures that have proven to be highly effective for arrhythmias due to discrete anatomical substrates (40). AF, however, remains the most complex and least understood among the supraventricular arrhythmias, despite the significant research advances that have taken place in the past few years (41). Nevertheless, nearly two decades ago, a group at Washington University (St Louis, Missouri, USA) (42-44) came up with the idea that multiple lesions created in both atria aimed at suppressing all possible AF mechanisms might lead to an effective procedure. The two major principles of the operation were the fragmentation of the atria into smaller myocardial segments not able to withstand microreentrant circuits, and the creation of connecting lines of block to the mitral and tricuspid valve annuli to prevent macroreentry in the left or right atria. Although these concepts aimed for the suppression of the maintenance mechanism of AF, they inadvertently affected the triggering mechanisms through the isolation of the pulmonary

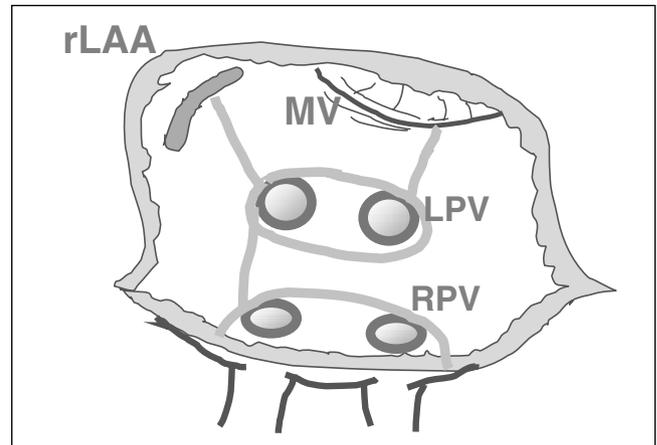


Figure 1) Left atrial lesion pattern currently used for atrial fibrillation ablation. Inside view of the left atrium from an atriotomy in the Waterston groove (standard for mitral valve [MV] surgery). Pulmonary veins are encircled in pairs. Connecting lesions are made between pulmonary veins, the mitral valve annulus and the left atrial appendage, which is resected or tightly closed. LPV Left pulmonary veins; rLAA Resected left atrial appendage; RPV Right pulmonary veins

veins. New information on the electrophysiological triggers of AF came well after the development phase of the Cox-Maze procedure. A major step in the understanding of AF came more recently when Haissaguerre et al (45) found that ectopic activity initiating AF originates in the pulmonary vein ostia. This work had a remarkable impact on the clinical management of AF (40), and not only paved the way to catheter-based interventions, but also contributed to the design of new operative approaches. Although it appears quite clear that ectopic foci within or near the pulmonary vein orifices are the major arrhythmogenic event in patients with paroxysmal AF, intra-operative mapping studies in patients with mitral valve disease are rather scarce (46-51). Moreover, in most series, the success rate achieved by Cox et al (16) could hardly be duplicated, as the rate of freedom from AF recurrence varied between 70% and 90% (17-19,21-25). The Cox-Maze procedure was also performed at the expense of long pump runs, prolonged cardioplegic arrest, increased risk of bleeding, increased risk of postoperative fluid retention and poor atrial function (24). The new knowledge regarding the role of pulmonary vein-left atrial junction, combined with the low adoption rate of the Maze procedure in the surgical community, led several groups to evaluate novel strategies based on the following changes: the use of alternate energy sources replacing cutting and sewing to create the lines of block (Table 1); and the simplification of the lesion pattern consisting of the omission of some of the Maze-III incisions (Table 2 and Figure 1).

The first attempts at replacing the Maze incisions were based on radiofrequency energy (52-60). Sie et al (53) and Güden et al (54) used an irrigated tip monopolar radiofrequency catheter, with which lesions can be drawn on the endocardium with a pen-like action. Actuarial freedom from AF was 80% and 70% at three and five years, respectively. Raman et al (32) used a dry monopolar coil to create right and left atrial lesions, and they reported 100% freedom from AF at 12 months. Clinical data suggest that left atrial ablation alone can afford the same results as biatrial ablation (54,56-58,60).

Although variable, reported results indicate success rates ranging between 70% and 90% (52-60). Mohr et al (58) achieved an 85% cure rate with a continuous lesion connecting all four pulmonary veins to the mitral valve annulus. Smaller series using left atrial ablation patterns with microwave energy or cryosurgery have also reported acceptable results (61,62). The difficulty in drawing any firm conclusion from these data comes from the fact that these series are not comparable in terms of incidence of type of AF, duration of AF before the operation, the definition of success, the left atrial diameter and the lesion pattern itself. Many series indicate that large quiescent atria and an AF duration of more than 15 years would hamper the expected benefit of the procedure (18-24). Figure 1 shows the most commonly used left atrial lesion pattern. This pattern, created by means of either irrigated tip or coiled monopolar radiofrequency devices, only takes approximately 14 min to complete (55). Despite this apparent simplicity, damage to adjacent structures (eg, esophageal perforation) may occur, particularly with the use of dry monopolar coil radiofrequency devices (63). Finally, the feasibility of left atrial ablation on the closed heart would be of particular interest in patients with aortic valve diseases or coronary bypass procedures. This will be made possible by the refinement of newer devices (eg, bipolar radiofrequency clamps) (61,64).

Although these comments seem to favour the use of intraoperative AF ablation devices in patients with documented AF preoperatively (see recommendations), we believe that in patients undergoing mitral valve surgery without documented

AF before surgery, there is no evidence to date supporting prophylactic intraoperative ablation. Elderly patients (over 80 years of age) or patients with a high risk of perioperative morbidity/mortality with few or no AF symptoms should not undergo intraoperative ablation therapy for AF. Younger patients with documented asymptomatic AF undergoing mitral valve surgery should be considered for the AF ablation procedure only in centres with considerable experience in AF surgery, given the fact that the proposed procedure should not add any risk to the primary operation.

APPROACHES TO 'LONE' AF

Approaches to the patient with 'lone' AF should be entirely different from that of the patient with concomitant cardiac pathologies. In the former case, epicardial ablation with microwave technology with open chest, thoracoscopic or robotic techniques is currently under development (61,65). To date, the role of these procedures as a stand-alone alternative or combined with catheter-based techniques is not known.

In summary, published clinical data suggest that left atrial ablation performed concomitantly with valvular and/or coronary artery bypass surgery is likely to afford a 70% to 90% cure rate in patients with preoperatively documented AF. Despite the lack of evidence of its long-term outcome benefit, intraoperative pulmonary vein ablation, feasible with minimal morbidity, appears to be a promising procedure to reduce postoperative AF in patients undergoing cardiac surgery. Left atrial appendectomy appears warranted in patients with chronic persistent AF.

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Pacing for the prevention of atrial fibrillation

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Multiple randomized clinical trials have demonstrated that atrial or dual-chamber pacing prevents paroxysmal and permanent atrial fibrillation (AF) in patients with symptomatic bradycardia as the primary indication for cardiac pacing. The benefit of atrial pacing for the prevention of AF is observed predominantly in patients with sinus node dysfunction. Emerging evidence also suggests that the risk of AF is directly linked to the proportion of time that ventricular pacing occurs. Consequently, pacemakers should be programmed to minimize the amount of ventricular pacing in patients with intrinsic atrioventricular conduction. Temporary atrial pacing following heart surgery may be of benefit for the prevention of perioperative AF. Atrial pacing has not been shown to prevent AF in patients without symptomatic bradycardia. In addition, selective pacing algorithms designed to prevent AF have minimal or no incremental benefits for the prevention of AF. At present, the role of selective atrial lead site(s) for the prevention of AF remains uncertain.

Key Words: Atrial fibrillation; Atrial pacing; Dual-chamber pacing

La prévention de la fibrillation auriculaire par la stimulation cardiaque

Selon de nombreux essais cliniques avec hasardisation, la stimulation auriculaire et la stimulation bicavitaire préviennent la fibrillation auriculaire (FA) paroxystique ou permanente chez les patients présentant de la bradycardie symptomatique comme principale indication de stimulation cardiaque. L'avantage de la stimulation auriculaire pour la prévention de la FA s'observe surtout chez les patients atteints d'un dysfonctionnement du nœud sinusal. D'après des données récentes, le risque de FA serait directement lié au temps où il y a stimulation ventriculaire. Aussi les stimulateurs cardiaques devraient-ils être programmés de manière à réduire le plus possible la stimulation ventriculaire chez les patients ayant une conduction auriculo-ventriculaire intrinsèque. La stimulation auriculaire temporaire après une intervention chirurgicale cardiaque peut s'avérer utile pour prévenir l'apparition de FA en phase périopératoire. Par contre, on n'a pas réussi à montrer que la stimulation auriculaire prévenait la FA chez les patients ne présentant pas de bradycardie symptomatique. De plus, les algorithmes sélectifs de stimulation, conçus pour prévenir la FA offrent un avantage minime, voire aucun avantage supplémentaire, quant à la prévention de la FA. Jusqu'à maintenant, le rôle des sièges sélectifs d'implantation des électrodes auriculaires pour la prévention de la FA reste incertain.

RECOMMENDATIONS

Class IIa

- 1) Atrial pacing (with or without a ventricular lead) should be considered in patients with symptomatic bradycardia to decrease the probability of developing atrial fibrillation (AF) and progressing to permanent AF (level of evidence A).
- 2) The proportion of the time the ventricles are paced should be minimized in patients with intrinsic atrioventricular (AV) conduction to reduce the incidence of AF (level of evidence B).
- 3) Temporary atrial pacing should be considered following heart surgery to reduce the incidence of perioperative AF (level of evidence B).

Class III

- 1) Atrial pacing for the prevention of AF in the absence of symptomatic bradycardia is not recommended (level of evidence B).
AF is very common in patients with a pacemaker, particularly in those patients with a sinus node dysfunction as the primary indication for cardiac pacing (1-3). Emerging evidence

suggests that atrial pacing can prevent AF in select patient populations (3).

MECHANISMS FOR THE PREVENTION OF AF

The potential mechanisms by which atrial pacing might prevent AF include:

- 1) Maintenance of AV synchrony prevents retrograde ventriculoatrial conduction and prevents the development of mitral and/or tricuspid valvular regurgitation that leads to stretch-induced changes in atrial repolarization, a potential electrophysiological substrate for AF (4-6).
- 2) Elimination of bradycardia-induced dispersion of atrial repolarization, a potential electrophysiological substrate for AF (2,7).
- 3) Overdrive suppression of atrial premature beats, a trigger for AF (8,9).
- 4) Continuous atrial pacing at selected sites may change atrial activation patterns and prevent the development of intra-atrial re-entry if an atrial premature beat occurs (9,10).
- 5) Pacing in the ventricle may induce ventricular dysfunction and secondarily increase the risk of developing AF (11).

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TABLE 1
Randomized trials of physiological pacing and the impact on atrial fibrillation (AF)

	Study (reference)			
	Danish (13)	CTOPP (14,17)	CTOPP extended (16)	MOST (15)
n	225	2568	2568	2050
Age (years)	71±17	73±10	73±10	74 (67–80)
Indication	SND	SND/AVB	SND/AVB	SND
Follow-up (years)	5.5	3.1	6.4	3.0
Mode	AAI/VVI	Phys/VVIR	Phys/VVIR	DDDR/VVIR
AF risk (%/year)	4.1 vs 6.6	5.3 vs 6.3	4.5 vs 5.7	7.9 vs 10.0
RR reduction (%)	46	18	20	21
P	0.012	0.05	0.009	0.008

AAI Single-chamber atrial pacing; AVB Atrioventricular block; CTOPP Canadian Trial of Physiologic Pacing; DDDR Dual-chamber, rate-modulating pacing; MOST Mode Selection Trial; Phys Physiologic atrial-based pacing; SND Sinus node dysfunction; vs Versus; VVI Ventricular pacing; VVIR Ventricular rate-adaptive pacing

ATRIAL PACING FOR THE PREVENTION OF AF IN PATIENTS WITH A PACEMAKER

Many retrospective studies (12) and three prospective randomly assigned clinical trials (13-17) have reported that atrial or dual-chamber pacing reduces the probability of developing paroxysmal and permanent AF in patients with symptomatic bradycardia as the primary indication for cardiac pacing. The results of the randomized clinical trials are summarized in Table 1. The Danish (13), Canadian Trial of Physiologic Pacing (CTOPP) (14,16,17) and Mode Selection Trial (MOST) investigators all reported a significant reduction in AF over time (RR reductions of 18% to 46%). The MOST investigators also reported a 56% RR reduction in the development of permanent AF over three years in patients randomly assigned to physiological pacing compared with ventricular pacing ($P < 0.001$). The United Kingdom Pacing and Cardiovascular Events (UKPACE) investigators (18) randomly assigned 2021 patients, who were 70 years of age or older with a high-grade AV block, to dual-chamber or ventricular pacing. In contrast to the Danish, CTOPP and MOST studies, the UKPACE investigators did not observe a reduction in AF in patients assigned to dual-chamber pacing; however, it is probable that the study enrolled fewer patients with sinus node disease, in whom atrial pacing appears to have greater benefit.

The MOST investigators reported a substudy analysis of the impact of ventricular pacing on adverse outcomes, including AF in 1339 patients (11). Patients who were more frequently paced in the ventricle were more likely to develop AF. The risk of developing AF increased by 0.7% and 1% for each 1% increase in ventricular pacing in the ventricular rate-adaptive pacemaker and dual-chamber, rate-modulating pacing (DDDR) groups, respectively. Nielsen et al (19) randomly assigned 177 patients who were candidates for atrial pacing to single-chamber atrial pacing (AAI) or DDDR with a short (150 ms) or long (300 ms) AV interval (19). This study was stopped prematurely because the initiation of a multicentre trial comparing AAI to DDDR pacing in Denmark. The authors reported that the risk of developing AF was greater in those patients randomly assigned to DDDR with a short AV delay (23.3%) or a long AV delay (17.5%) compared with those patients randomly assigned to AAI (7.4%). Consistent with

the proarrhythmic potential of ventricular pacing even in an AV synchronous mode, we recently reported that AF burden increased significantly early following AV junction ablation (9.7 ± 2.2 h/day) compared with preablation (2.6 ± 1.2 h/day) in 21 patients maintained on stable antiarrhythmic drug therapy during follow-up (20). These patients comprised a subset of patients randomly assigned to a trial of atrial pacing versus no pacing preablation. These results suggest that atrial pacing per se may not be antiarrhythmic but that ventricular pacing may be proarrhythmic by virtue of the deleterious hemodynamic effects that may occur as a consequence of retrograde ventriculoatrial conduction and/or valvular regurgitation but also secondary to ventricular dyssynchrony arising from right ventricular pacing.

Overall, the results of these clinical trials suggest that the benefit of atrial pacing for the prevention of AF occurs predominantly in the patient population with sinus node dysfunction. Based on the CTOPP trial results, nine patients with a pacemaker need to be treated to prevent one AF case over 10 years. This includes patients with both sinus and AV conduction disease. Based on the MOST results, the number needed to treat to prevent permanent AF in patients with sinus node dysfunction over three years is nine patients. The incremental cost of physiological pacing compared with ventricular pacing is less than one dollar per day. Given that AF is frequently unrecognized in pacemaker patients, that anticoagulation is underused for the prevention of stroke in this population and that antiarrhythmic drug therapy for the prevention of AF may be harmful, atrial pacing seems to be a cost-effective therapy for the prevention of a condition associated with substantial morbidity.

Furthermore, the emerging data also suggest that every effort should be undertaken to minimize the amount of ventricular pacing in this subgroup. This can be achieved by more widespread use of rate-modulating AAI, programming long AV delays, programming AV search hysteresis algorithms or considering backup ventricular pacing at low rates (40 beats/min to 50 beats/min) for patients with infrequent bradycardia.

ATRIAL PACING FOR THE PREVENTION OF AF IN NONBRADYCARDIA AF PATIENTS

At present, there is no evidence to suggest that atrial pacing prevents AF in patients with frequent AF in the absence of documented significant sinus bradycardia. The Atrial Pacing Peri-Ablation for Paroxysmal Atrial Fibrillation (PA³) study (21) randomly assigned 97 patients with frequent paroxysmal AF being considered for AV junction ablation to atrial pacing versus no pacing. The time to first recurrence of AF and the AF burden measured over three months using the pacemaker counters were similar in the atrial pacing group compared with the nonpacing group. In the second phase of this trial (22), 76 patients were randomly assigned to DDDR versus atrial-sensed ventricular synchronous pacing following AV junction ablation to test the hypothesis that atrial pacing compared with AV synchrony would prevent AF (22). The time to first recurrence of sustained AF was similar between groups. Moreover, AF burden increased substantially over time in both groups and, after one year, 42% had lapsed into permanent AF. A subgroup analysis in the PA³ population revealed that patients maintained on constant antiarrhythmic drug therapy throughout the study developed significant increases in AF burden and were more likely to develop permanent AF early postablation compared with patients in whom AV junction ablation was deferred (20).

SELECTIVE PACING ALGORITHMS DESIGNED TO PREVENT AF

A number of selective pacing algorithms have been developed to prevent AF (3). These algorithms have been designed to prevent pauses following atrial premature beats, to overdrive suppress premature beats or to promote a consistent atrial activation sequence. The Atrial Dynamic Overdrive Pacing Trial (ADOPT) investigators (23) randomly assigned 399 patients with sinus node dysfunction and paroxysmal AF to DDDR or DDDR plus dynamic atrial overdrive pacing. Patients were followed for one, three and six months following pacemaker insertion. The investigators reported a very modest but statistically significant reduction in symptomatic AF during follow-up. However, the absolute risk reduction for AF diminished over time (1.25% at one month compared with 0.36% at six months). Both groups experienced a significant reduction in symptomatic AF over time. The AF Therapy Investigators (24) reported that several atrial pacing algorithms in the Vitatron Selection device (Viatron, Netherlands) significantly reduced AF burden over time (24). Other studies have not confirmed these benefits. The Atrial Septal Pacing Clinical Efficacy Trial (ASPECT) Investigators (25) randomly assigned 298 patients with symptomatic bradycardia and AF to septal or right atrial appendage (RAA) pacing sites. Following a one-month stabilization period, patients were randomly assigned to AF prevention algorithms ON or OFF and followed for three months. Patients were then crossed over to the alternate pacing strategy for an additional three months. The combined AF prevention algorithms did not significantly reduce AF burden. The Pacing in Prevention of AF (PIPAF) Study investigators (26) randomly assigned 192 patients with bradycardia and AF to a trial of three AF prevention algorithms in a six-month crossover design. The primary outcome measure (total mode switch duration) was similar when the AF prevention algorithms were programmed ON (11.9±27.7 days) compared with when they were programmed OFF (11.6±26.5 days; not statistically significant). The Atrial Therapy Efficacy and Safety Trial (ATTEST) Investigators (27) randomly assigned 370 patients in a parallel study design to a comparison of atrial antitachycardia pacing (ATP) plus three AF pace prevention algorithms with DDDR pacing. Over three months of follow-up, more than 15,000 episodes of atrial tachycardia were treated with atrial ATP therapy. Over 40% of the episodes were classified as being effectively terminated by the pacemaker; however, no significant

reduction in AF burden was observed in the group randomly assigned to the AF prevention treatment arm.

Overall, these studies suggest that current AF pace prevention algorithms in implantable devices have minimal or no incremental benefit for the prevention of AF. Without question, atrial ATP therapy is of benefit in terminating atrial tachycardia or atrial flutter in select patients (28,29). Whether other subgroups that are likely to benefit can be identified requires further study.

SITE-SPECIFIC ATRIAL PACING FOR PREVENTION OF AF

A number of experimental and clinical studies (30-32) have reported that septal pacing, dual-site right atrial pacing or biatrial pacing shorten total atrial activation time and reduce overall dispersion of atrial refractoriness. In cardiac surgery populations, multiple small randomly assigned trials have reported that right atrial, dual-site right atrial, left atrial and biatrial pacing prevent perioperative AF (33). Biatrial pacing may be more effective than right atrial pacing alone.

A number of clinical trials have evaluated the effect of various atrial pacing sites for the prevention of AF in the pacemaker population. Pacing at Bachmann's bundle compared with pacing at the RAA has been reported to prevent the development of permanent AF (47% versus 75%, respectively; $P<0.05$) (34). A significant reduction in AF burden has been reported in patients randomly assigned to septal pacing near the triangle of Koch (47±84 min/day) compared with patients randomly assigned to RAA pacing (140±217 min/day; $P<0.05$) (35). However, this result was not confirmed by a larger randomly assigned trial (25) of RAA pacing versus septal pacing. Dual-site right atrial pacing (RAA and coronary sinus or lead location) offers a modest benefit for the prevention of AF compared with RAA pacing (36). Biatrial pacing has been reported (37) to prevent paroxysmal and permanent AF in patients with markedly delayed intra-atrial conduction. At present, the role of selective atrial lead site(s) for the prevention of AF in the pacemaker population remains uncertain. Given the complexity and added expense of additional leads, a single-site location would be preferable.

ACKNOWLEDGEMENTS: Dr Gillis is a Medical Scientist of the Alberta Heritage Foundation for Medical Research.

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Atrial fibrillation following cardiac surgery

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Atrial tachyarrhythmias, usually atrial fibrillation or atrial flutter, are the most common complications of cardiac surgery. Atrial tachyarrhythmias are associated with patient discomfort/anxiety, hemodynamic deterioration, cognitive impairment, thromboembolic events (including stroke), exposure to the risks of antiarrhythmic treatments, longer hospital stays and increased costs. Many approaches to the prevention of postoperative atrial tachyarrhythmias have been studied. Of these, studies using perioperative beta-blocking agents or amiodarone provide level A evidence of efficacy and, in properly selected patients, have shown a high degree of safety. Less convincing, level B evidence exists for the use of postoperative temporary atrial pacing and for perioperative intravenous magnesium treatment. The treatment of postoperative atrial tachyarrhythmias is similar to those occurring in other settings and includes excluding other potential causes of atrial tachyarrhythmias, antithrombotic or anticoagulation therapy, control of the ventricular response rate and consideration of restoring/maintaining sinus rhythm. The selection of therapies to achieve these goals should consider the sympathetic nervous system discharge state of the postoperative environment and the natural history of postoperative atrial fibrillation, which includes spontaneous resolution of the arrhythmogenic tendency after approximately six weeks. The Canadian Cardiovascular Society Consensus Conference recommendations for the prevention of atrial tachyarrhythmias after cardiac surgery and for the treatment of atrial tachyarrhythmias that occur after cardiac surgery are presented along with evidence that supports these recommendations.

Key Words: *Atrial fibrillation; Cardiac surgery; Consensus guidelines; Postoperative*

La fibrillation auriculaire après une intervention chirurgicale cardiaque

Les tachyarythmies auriculaires (TA), habituellement la fibrillation auriculaire ou le flutter auriculaire, sont les complications les plus fréquentes de la chirurgie cardiaque. Ces troubles du rythme sont associés à divers inconvénients : malaises et anxiété, détérioration hémodynamique, déficience cognitive, accidents thrombo-emboliques (y compris l'accident vasculaire cérébral), exposition aux risques des traitements antiarythmiques, prolongement du séjour à l'hôpital et augmentation des coûts. De nombreuses interventions visant à prévenir les TA postopératoires ont fait l'objet d'étude. Parmi celles-ci, l'administration de bêta-bloquants ou d'amiodarone en phase périopératoire a été associée à des données d'efficacité de niveau A et, chez les patients bien sélectionnés, à un degré élevé d'innocuité. La stimulation auriculaire temporaire postopératoire et l'administration intraveineuse de magnésium en phase périopératoire donnent des résultats moins probants (niveau B). Le traitement des TA postopératoires est le même que celui qui est appliqué dans d'autres contextes et il consiste en l'exclusion d'autres causes possibles de TA, en l'administration d'un traitement anticoagulant ou antithrombotique, en la maîtrise de la fréquence ventriculaire et dans le rétablissement et le maintien possibles du rythme sinusal. Le choix des traitements pour atteindre les objectifs visés devrait tenir compte de l'état de décharge du système nerveux sympathique après une opération et de l'évolution naturelle de la fibrillation auriculaire postopératoire, notamment de sa tendance à disparaître spontanément au bout de six semaines environ. Sont présentées dans l'article les recommandations consensuelles de la Société canadienne de cardiologie concernant la prévention et le traitement des TA après une intervention chirurgicale cardiaque, ainsi que les données à l'appui de ces recommandations.

RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF ATRIAL FIBRILLATION FOLLOWING CARDIAC SURGERY

Class I

- 1) Patients who have been receiving a beta-blocker before cardiac surgery should have that therapy continued through the operative period in the absence of the development of a new contraindication (level of evidence A).
- 2) Temporary ventricular epicardial pacing electrode wires should be placed at the time of cardiac surgery to allow for backup pacing as necessary (level of evidence C).
- 3) Postoperative atrial fibrillation (AF) with a rapid ventricular response rate should be treated with a beta-blocker, a nondihydropyridine calcium antagonist or

amiodarone to establish ventricular rate control. In the absence of a specific contraindication, the order of choice is as listed (level of evidence B).

Class IIa

- 1) Patients who have not been receiving a beta-blocker before cardiac surgery should be considered for prophylactic therapy to prevent postoperative AF with a beta-blocker or amiodarone (level of evidence A) or with atrial pacing or magnesium (level of evidence B).
- 2) Postoperative AF may be appropriately treated with either a ventricular response rate-control strategy or a rhythm-control strategy (level of evidence A).
- 3) Consideration should be given to anticoagulation therapy if postoperative AF persists for more than 48 h (level of evidence C).

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- 4) When anticoagulation therapy, rate-control therapy, and/or rhythm control therapy has been prescribed for postoperative AF, formal reconsideration of the ongoing need for such therapy should be undertaken six to eight weeks later (level of evidence B).

POSTOPERATIVE ATRIAL TACHYARRHYTHMIAS

Incidence of postoperative atrial tachyarrhythmias

Given that AF and atrial flutter are facilitated by atrial trauma, atrial stretch, atrial ischemia, epicardial inflammation, hypoxia, acidosis, electrolyte disturbances and the refractoriness changes that accompany sympathetic nervous system discharge, and given that all of these factors are often present immediately after cardiac surgical procedures, it is not surprising that AF and atrial flutter are frequent complications of these procedures. Indeed, atrial tachyarrhythmias are the most common postoperative complication of cardiac surgery that requires intervention or prolongs intensive care unit and total hospital stay (1-10). The incidence of AF and atrial flutter after cardiac surgery ranges from approximately 30% for patients undergoing isolated coronary artery bypass graft (CABG) surgery to approximately 40% for patients undergoing valve replacement or repair, and this incidence increases to approximately 50% for patients undergoing both procedures (11). Furthermore, there is evidence that the incidence of postoperative AF and atrial flutter is increasing because older individuals with a higher prevalence of atrial tachyarrhythmia risk factors are more commonly having these surgeries (2,8).

The peak incidence of these atrial tachyarrhythmias is between postoperative days 2 and 4. Of the patients who develop an atrial tachyarrhythmia, 70% do so before the end of postoperative day 4, and 94% do so before the end of posthospital day 6 (8).

Risk factors for postoperative atrial tachyarrhythmias

Independent patient characteristics that predict the occurrence of atrial tachyarrhythmias after cardiac surgery include older age, being male, history of hypertension, requirement for an intraoperative balloon pump, requirement for prolonged ventilation (greater than 24 h), and withdrawal of beta-blocker therapy (2-8,12,13). As in the general population (14), age has the greatest predictive value. Operative variables reported to be atrial tachyarrhythmia risk factors include the procedure performed (isolated CABG, valve repair/replacement or both), the number of bypass grafts, the duration of the surgery and the aortic cross-clamp time (2,15-17).

Consequences of postoperative atrial tachyarrhythmias

Postcardiac surgery atrial tachyarrhythmias may be transient and cause little morbidity. However, for some patients these tachyarrhythmias have important consequences including patient discomfort/anxiety, hemodynamic deterioration, cognitive impairment, thromboembolic events including stroke, exposure to the risks of arrhythmia treatments, longer hospital stay and increased health care costs (2,4,8,9,18-23). Linear regression models indicate that postoperative atrial tachyarrhythmias are independently associated with an increase in health care costs and the duration of hospital stay (8,24).

Prophylaxis against postoperative atrial tachyarrhythmias

Many therapies have been evaluated for the prevention of postoperative AF and atrial flutter after cardiac surgery

(17,25-74). In the section that follows, published meta-analysis data are provided and referenced when current. When published meta-analysis data are either unavailable or are not current, individual study data were meta-analyzed using a random-effects model and are provided without a reference.

Seven randomized trials (17,25-30) have evaluated digoxin therapy in 709 patients. One trial showed a significant advantage for digoxin (26), one showed a significant disadvantage (28), and the other five showed no difference between treatment and control group outcomes (17,25,27,29,30). The OR for the postoperative incidence of atrial tachyarrhythmia in our weighted meta-analysis of prophylactic digoxin therapy studies is 0.91 (95% CI 0.59 to 1.40, $P =$ not significant [NS]).

Three randomized trials (31-33) have evaluated verapamil in 432 patients. No trial showed a significant advantage or disadvantage to having therapy. The OR in our weighted meta-analysis of prophylactic verapamil therapy studies is 0.94 (95% CI 0.56 to 1.58, $P=$ NS).

Twenty-seven randomized trials (34) evaluated beta-blocker prophylaxis in 3840 patients. Sixteen of the 27 trials showed a significant advantage for beta-blocker therapy. No beta-blocker trial showed a significant disadvantage to having therapy. The OR in this meta-analysis (34) of prophylactic beta-blocker therapy studies was 0.39 (95% CI 0.28 to 0.52, $P<0.0001$). Sotalol is a beta-blocker that also has important class III antiarrhythmic drug effects. Eight randomized trials (34) evaluated sotalol prophylaxis in 1294 patients. One of these trials produced a neutral result and the other seven trials reported a statistically significant benefit from sotalol therapy. The OR in that meta-analysis (34) of prophylactic sotalol drug therapy studies was 0.35 (95% CI 0.26 to 0.49, $P<0.0001$). Four trials (34) compared sotalol prophylaxis with that of other beta-blockers in 900 patients. One of these trials produced a neutral result and the other three trials reported a statistically significant benefit from sotalol therapy. Compared with other beta-blocker drugs, the OR in that meta-analysis (34) of prophylactic sotalol drug therapy studies was 0.50 (95% CI 0.34 to 0.74, $P<0.0001$). However, one trial comparing sotalol with metoprolol in doses considered to provide equivalent beta-blockade reported a higher prevalence of postoperative bradyarrhythmias with sotalol prophylaxis (35).

Fourteen randomized trials (36-49) evaluated amiodarone prophylaxis in 2823 patients. Eight (37,38,40,43,45,47-49) of the 14 trials showed a significant advantage for amiodarone therapy. No amiodarone trial showed a significant disadvantage to having therapy. The OR in our meta-analysis of prophylactic amiodarone therapy studies is 0.59 (95% CI 0.50 to 0.69, $P<0.001$). In a recent study involving 600 patients (49), the prophylactic effect of amiodarone was consistent in subgroup analyses of young and older patients, patients undergoing isolated CABG, undergoing valve repair/replacement with or without concomitant CABG, and patients also receiving or not receiving beta-blocker therapy.

Thirteen randomized trials (30,42,50-60) evaluated intravenous magnesium prophylaxis in 2009 patients. Two of the 13 trials showed a significant advantage for magnesium therapy (53,54). No magnesium trial showed a significant disadvantage to having therapy. The OR in our meta-analysis of prophylactic magnesium therapy studies is 0.83 (95% CI 0.65 to 1.06, $P=$ NS).

Two randomized trials (61,62) evaluated procainamide prophylaxis in 146 patients. Neither showed a significant

TABLE 1
Prophylactic therapies for the prevention of postoperative atrial tachyarrhythmias

Therapy	Dose*	OR†	Cautions	Adverse effects
Preoperative beta-blocker	Any usual therapeutic dose (ie, metoprolol 50 mg po q12h or q8h for at least 2 preoperative days, day of surgery, and at least 6 postoperative days)	0.39 (0.28 to 0.52)	Reactive airways disease, decompensated CHF	Sinus bradycardia, AV block, hypotension, bronchospasm
Preoperative amiodarone	10 mg/kg/day (rounded to nearest 100 mg) divided into two daily po dosages for 6 preoperative days, day of surgery, and 6 postoperative days‡	0.61 (0.50 to 0.74)	30% to 50% reduction in the doses of other drugs with antiarrhythmic or sinus/AV nodal effects and warfarin will be required	Sinus bradycardia, AV block hypotension, torsade de pointes VT (rare), pulmonary toxicity (rare)
Postoperative amiodarone	900 mg to 1200 mg IV over 24 h beginning within 6 h of surgery, then 400 mg po three times daily each of the next 4 days§	0.53 (0.39 to 0.71)	30% to 50% reduction in the doses of other drugs with antiarrhythmic or sinus/AV nodal effects and warfarin will be required	Sinus bradycardia, AV block hypotension, torsade de pointes VT (rare), pulmonary toxicity (rare)
Magnesium sulfate	1.5 g IV over 4 h first preoperative day, immediately postoperatively and next 4 postoperative days¶. Other trials have omitted the preoperative dosage	0.83 (0.65 to 1.06)	Renal failure	Hypotension (rare), sedation (very rare), respiratory depression (very rare)
Atrial pacing	Right, left or biatrial pacing for 3 to 4 days postoperatively**. Rate set to overdrive sinus rate either manually or using sensing algorithms	0.67 (0.54 to 0.84)	May increase atrial tachyarrhythmias if pacing continues in setting of sensing malfunction	Diaphragmatic stimulation, increased myocardial oxygen requirements, possible increased infection rate

*Doses used in the randomized studies vary widely and the optimal doses for this indication have not been established. The doses provided are those used in the largest positive trial of that therapy and are referenced to that study; †The ORs provided are from meta-analyses of the studies of each prophylactic approach (not for the single study referenced for dose). For further information on doses, see references 49‡, 40§, 57¶ and 72**. Comparisons of the efficacies of various prophylactic approaches require randomized trials, which, for the most part, have not been performed. Accordingly, comparisons among the ORs provided in the Table should be avoided. AV Atrioventricular; CHF Congestive heart failure; IV Intravenous; po By mouth; q Every; VT Ventricular tachycardia

advantage for procainamide therapy. The OR in our meta-analysis of these underpowered prophylactic procainamide therapy studies is 0.47 (95% CI 0.22 to 0.99, $P=0.05$). The well-documented hazards of class I antiarrhythmic drug therapies in patients with structural heart disease have precluded acceptance of this form of postoperative atrial tachyarrhythmia prophylaxis.

Finally, 12 randomized trials (40,63-73) evaluated atrial pacing prophylaxis in 1708 patients. Three of the 12 trials showed a significant advantage for atrial pacing therapy (64,72,73). No atrial pacing trial showed a significant disadvantage to having therapy. The OR in our meta-analysis of prophylactic atrial pacing therapy studies is 0.67 (95% CI 0.54 to 0.84, $P<0.0001$).

In summary, published clinical trial evidence supports the contention that beta-blockers, amiodarone, atrial pacing and (perhaps) magnesium therapy prevent postoperative AF and atrial flutter after cardiac surgery (Table 1). To determine if such prophylactic therapy was associated with a reduction in any of the presumed adverse consequences of postoperative atrial tachyarrhythmias, a meta-analysis (74) of 13 of the trials summarized above that also reported on length of hospital stay was performed. That analysis suggested that prophylactic therapy is associated with a significant reduction of 1.0 ± 0.2 days ($P<0.001$) in the length of hospital stay, and with a nearly significant reduction of US\$1287±673 ($P=0.056$) in hospital costs. Although there was a directional trend in the reduction of the incidence of postoperative cerebrovascular accidents with an OR of 0.50 (95% CI 0.22 to 1.17), this trend was not statistically significant. Of note, two completed trials (49,75) were powered to specifically detect a reduction in the length of hospital stay in patients receiving prophylactic therapy for prevention of atrial tachyarrhythmias. A large beta-blocker

trial (75) did not identify a reduction in hospital stay. A large amiodarone trial (49) demonstrated a trend toward a reduction in total hospital stay duration. Furthermore, a previous meta-analysis limited to amiodarone trials (34) found a significant reduction in the length of hospital stay in amiodarone-treated patients.

Treatment of postoperative atrial tachyarrhythmias

The treatment options for AF and atrial flutter that occur after cardiac surgery are similar to those of AF and atrial flutter that occur in other settings. The therapeutic goals that are considered include prevention of thromboembolic events, slowing the ventricular response rate, conversion to sinus rhythm and maintenance of sinus rhythm. Nevertheless, the postoperative setting does have features that may favour some strategies over others. First, the natural history of postoperative AF and flutter after cardiac surgery is dominated by self-terminating, but frequently recurrent, tachyarrhythmia episodes and resolution of the tachyarrhythmia propensity in six to eight weeks, regardless of the treatment approach used (76-78). Second, the adrenergic discharge in the postoperative state lessens the effectiveness of therapies that do not include beta-blockade.

Several studies have demonstrated associations between AF after cardiac surgery and cerebrovascular events (2,3,8,20,21) and cognitive impairment (19). Accordingly, in the absence of a specific contraindication, anticoagulation therapy is recommended for patients with prolonged (greater than 48 h) AF. Once initiated, anticoagulation therapy is usually continued for at least six weeks.

In the postoperative setting, therapy for ventricular rate control for atrial tachyarrhythmias is usually required. Because the postsurgical state includes adrenergic discharge, beta-blocker

therapy is often very effective. When beta-blocker therapy is ineffective, poorly tolerated or contraindicated, the other therapeutic options for ventricular response rate control include a nondihydropyridine calcium antagonist (eg, diltiazem or verapamil) or amiodarone. In the postoperative state, therapy with digoxin is usually insufficient for adequate control of the ventricular response rate. Specific information regarding the doses, efficacies and adverse effects of these rate-control therapies are provided in Dorian and Connors, pages 26B-30B.

The general considerations for the advisability of conversion of a sustained atrial tachyarrhythmia in the postoperative setting are similar to those in other settings. However, because early recurrence of the atrial tachyarrhythmia is the rule rather than the exception, pharmacological cardioversion or direct current cardioversion after the initiation of pharmacological therapy to prevent atrial tachyarrhythmia recurrences are preferred over isolated direct current cardioversion provided that time is not of the essence. Intravenous ibutilide has been studied as a rapidly acting approach for pharmacological cardioversion of atrial tachyarrhythmias after cardiac surgery (79). In that study, ibutilide infusion was associated with conversion to sinus rhythm in 48% of patients. Success rates were higher in patients with atrial flutter than in patients with AF. The major adverse effect of ibutilide administration was the precipitation of torsade de pointes ventricular tachycardia in approximately 2% to 5% of those who receive it in this setting (79). Specific information regarding the doses, efficacies and adverse effects of rhythm-control therapies are provided in Talajic and Roy, pages 19B-25B.

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Atrial arrhythmias and special circumstances

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L Harris, RM Gow, JA Kirsh, GJ Klein, SC Siu. Atrial arrhythmias and special circumstances. *Can J Cardiol* 2005;21(Suppl B):51B-60B.

The present paper discusses the general principles of management of atrial fibrillation and atrial flutter under special circumstances. Management recommendations, which encompass initial assessment, initial arrhythmia management and chronic pharmacological therapy, are outlined for patients with hypertrophic cardiomyopathy, Wolff-Parkinson-White syndrome and congenital heart disease. Recommendations are also made for pregnant patients and pediatric patients without congenital heart disease. Discrepancies between the authors' recommendations and those from the American College of Cardiology/American Heart Association/European Society of Cardiology are discussed.

Key Words: Atrial arrhythmias; Atrial arrhythmias in a pediatric population; Congenital heart disease; Hypertrophic cardiomyopathy; Intra-atrial reentrant tachycardia; Pregnancy; Wolff-Parkinson-White syndrome

RECOMMENDATIONS FOR MANAGEMENT OF ATRIAL FIBRILLATION IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Class I

- 1) Anticoagulate patients with paroxysmal, persistent or permanent atrial fibrillation (AF) with warfarin (international normalized ratio 2.0 to 3.0) (level of evidence B).

Class IIa

- 1) Strategies to maintain sinus rhythm are generally preferred over rate control (level of evidence C).
- 2) Amiodarone is generally the preferred antiarrhythmic agent for maintenance of sinus rhythm (level of evidence C).

DISCUSSION

AF is the most common arrhythmia in hypertrophic cardiomyopathy (HCM), occurring in 20% to 25% of patients, and is generally associated with increased risk of complications including sudden and nonsudden death, heart failure and stroke (1-9). The results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial notwithstanding (10), restoration and maintenance of sinus rhythm has been considered an important priority because of the increased morbidity and mortality associated with AF in

Arythmie auriculaire et situations particulières

Le présent article porte sur les grands principes du traitement de la fibrillation auriculaire et du flutter auriculaire dans des situations particulières. On y traitera plus précisément de la prise en charge recommandée de ce type d'arythmie, comprenant l'évaluation initiale, le traitement de départ et le traitement médicamenteux prolongé, dans les cas de myocardiopathie hypertrophique, de syndrome de Wolff-Parkinson-White et de cardiopathie congénitale. À cela s'ajoutent des recommandations sur les femmes enceintes et les enfants non porteurs d'une cardiopathie congénitale. Enfin, il sera question des différences entre les recommandations des auteurs et celles de l'*American College of Cardiology*, de l'*American Heart Association* et de la Société européenne de cardiologie.

HCM (1,11). Although rigorous comparative studies are not available, amiodarone has been considered the most effective and safest drug for the maintenance of sinus rhythm (12-15). Other antiarrhythmics have been used, but disopyramide has been recommended (16) in the absence of large comparative trials, possibly due to its reported favourable hemodynamic effects in patients with obstruction (17). Rate-control, when desired, is achieved with the usual agents, namely, beta-blockers and calcium channel blockers such as verapamil. Digoxin has theoretical disadvantages in obstruction and is less effective in most contexts. Nonpharmacological therapies including operative and catheter ablation have not been specifically evaluated in HCM, but their role in management of AF in this context is likely to increase.

Finally, the high incidence of stroke in HCM (4,11,18) has led to a prevalent recommendation for anticoagulation with warfarin (1,16) even in the absence of a large specific trial in HCM. There are as yet insufficient data to recommend use of oral antithrombin agents in this context.

Discrepancies with American College of Cardiology/American Heart Association/European Society of Cardiology guidelines

These recommendations are comparable with those of the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) (16). We do not, however, recommend disopyramide specifically over other

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agents due to insufficient data supporting its preferential use. We also recommend a preferential rhythm control strategy supported in the body of the text of the ACC/AHA/ESC guidelines but not listed as a recommendation.

RECOMMENDATIONS FOR MANAGEMENT OF AF IN THE WOLFF-PARKINSON-WHITE SYNDROME

Class I

- 1) Catheter ablation of the accessory pathway is recommended in symptomatic patients with AF (level of evidence B).
- 2) Operative ablation of the accessory pathway is indicated in patients with problematic or life-threatening AF where catheter ablation is not feasible (level of evidence B).
- 3) Antiarrhythmic therapy with amiodarone, sotalol, disopyramide, flecainide, propafenone, quinidine or procainamide is recommended when corrective ablation is not feasible (level of evidence C).
- 4) Immediate electrical cardioversion is recommended where AF occurs with a rapid ventricular response and hypotension (level of evidence B).
- 5) Intravenous procainamide or ibutilide is recommended in AF with predominantly preexcited complexes when the patient is hemodynamically stable (level of evidence C).
- 6) Verapamil, diltiazem or beta-blockers are indicated for rate control when AF occurs without preexcitation (level of evidence C).

Class III

Intravenous beta-blocking agents are not generally useful and digitalis, diltiazem or verapamil is contraindicated in patients with a rapid ventricular response related to preexcitation (level of evidence B).

DISCUSSION

The unique feature of AF in the Wolff-Parkinson-White (WPW) syndrome is the presence of one or more accessory pathways in addition to the normal atrioventricular (AV) conduction system that may allow conduction to the ventricles. Accessory pathways may have extremely short effective refractory periods, allowing very rapid ventricular rates in the event of AF (19). This may result in ventricular fibrillation and sudden death (20). AF in a patient with WPW may result from any cause unrelated to the preexcitation, and ablation of the accessory pathway in such instances may not prevent subsequent AF (21). However, AF in WPW is most frequently related to supraventricular tachycardia which then degenerates into AF (20). A second unique feature in the WPW syndrome is the nature of the accessory pathway. Unlike the AV node, accessory pathways are composed of working muscle fibres. Consequently, drugs that usually prolong AV node refractoriness such as digitalis, verapamil and beta-blockers do not prolong refractoriness in accessory pathways. AV node-blocking drugs are contraindicated in patients with AF and predominantly preexcited QRS complexes because they do not slow the ventricular rate and may be

detrimental. Intravenous verapamil in particular may precipitate hemodynamic collapse due to its negative inotropic effect and by accelerating the ventricular rate probably due to a reflex sympathetic effect (22). Intravenous sodium- and potassium-blocking drugs such as procainamide and ibutilide prolong the refractory period of the accessory pathway and slow the ventricular response in preexcited AF (22,23). They may also result in conversion to sinus rhythm. Intravenous amiodarone has not been extensively evaluated for acute treatment of arrhythmias related to WPW. It has been shown to terminate AV reentrant tachycardia and prolong the effective refractory period of the accessory pathway (23,24). At best, it would not be expected to be very useful for acute treatment because of the slow onset of its antiarrhythmic effect. Ventricular fibrillation has been reported during administration of intravenous amiodarone during preexcited AF (25).

Catheter ablation of the accessory pathway is currently the treatment of choice for symptomatic WPW syndrome. Where catheter ablation is not feasible, surgical ablation of the accessory pathway is advised in patients with life-threatening AF.

The management of the asymptomatic individual with WPW is only peripherally related to the current guidelines and will not be discussed in detail. Although an argument can be made for recommending catheter ablation in such an individual (26,27), the risk of catheter-related complications with ablation is at least comparable with the risk of sudden death as an initial presentation (28). Catheter ablation can nonetheless be offered to the patient who, after a balanced discussion, prefers a small procedural risk to a comparable but more long-term risk related to WPW.

Discrepancies with ACC/AHA/ESC guidelines

These guidelines do not differ substantively from other guidelines. Some discrepancies are as follows:

- 1) Operative therapy is suggested where ablation is technically not feasible.
- 2) Medical therapy is recommended where neither catheter nor operative accessory pathway ablation is feasible.
- 3) AV nodal blocking drugs are recommended in patients with AF and non-preexcited QRS while ACC/AHA/ESC guidelines do not include this in final recommendations.
- 4) While AV node-blocking drugs such as verapamil are contraindicated in preexcited AF with a rapid ventricular response, the rationale cited in the text of the ACC/AHA/ESC guidelines for this suggests that the mechanism is related to prolonging AV node refractoriness resulting in preferential accessory pathway conduction (16). It is our view that the AV node is not relevant when there is rapid preexcited AF (due to repetitive retrograde concealment into the AV node related to rapid preexcited response) and that the major factors related to deterioration include the delay resulting from an ineffective intervention combined with the negative inotropic effect of verapamil in particular.

RECOMMENDATIONS FOR THE MANAGEMENT OF AF IN PREGNANCY

Class I

- 1) Control the rate of ventricular response with digoxin, a beta-blocker or a calcium channel antagonist (level of evidence C).
- 2) Perform electrical cardioversion in patients who become unstable due to AF (level of evidence C).
- 3) Administer antithrombotic therapy (anticoagulant or acetylsalicylic acid [ASA]) throughout pregnancy in all patients with persistent or paroxysmal AF (level of evidence C).
- 4) In patients at risk of thromboembolism, administer heparin during the first trimester and after 36 weeks' gestation. Unfractionated heparin may be administered by intravenous infusion or by twice-a-day subcutaneous injection (dose adjusted to maintain an activated partial thromboplastin time two to three times the control value). Alternately, low molecular weight heparin can be used (dose adjustment guided by anti-Xa levels) (level of evidence C).
- 5) Administer warfarin or heparin during the second trimester to patients with AF and at high thromboembolic risk (level of evidence C).

Class IIa

- 1) For symptomatic patients or those with poorly tolerated AF, pharmacological or electrical cardioversion may be considered (level of evidence C).

DISCUSSION

AF during pregnancy is usually associated with the presence of maternal structural heart disease or hyperthyroidism (29-32). A rapid ventricular response to AF can have deleterious effects on both mother and fetus.

In a pregnant woman who develops AF, diagnosis and treatment of the underlying condition causing AF is the first priority (33). The ventricular rate should be controlled with digoxin, a beta-blocker or a calcium channel antagonist (33-35). All currently available antiarrhythmic drugs have the potential to cross the placenta and to be excreted in breast milk. Sotalol, quinidine, mexilitine, flecanide and amiodarone have been used successfully during pregnancy in a small number of cases (35-39). Amiodarone may impair neonatal thyroid function and should be reserved for situations in which alternative antiarrhythmic agents are either contraindicated or ineffective (40,41). In the event of hemodynamic instability, electrical cardioversion can be performed without fetal damage (42).

The optimal antithrombotic regimen for pregnant women with AF has not been defined. Because the risk of thromboembolism resulting from AF is high in the presence of structural heart disease, anticoagulation should be administered in pregnant women with structural heart disease and AF.

Warfarin should be avoided especially in the first trimester (risk of embryopathy) and last month (risk of intracranial hemorrhage during vaginal delivery) (43). The risk of embryopathy may be dose-dependent; in one study (44), no embryopathy was reported when the daily warfarin dose was 5 mg or less. Heparin, which does not cross the placenta, is the anticoagulant of choice

at some centres as an extension of its use in pregnant women with prosthetic heart valves or venous thromboembolism. However, the relative efficacy of unfractionated heparin, low molecular weight heparin, or warfarin in the prevention of thromboembolism in pregnant women with AF has not been defined.

AF in the absence of structural heart disease (lone AF) is uncommon during pregnancy. Because serum levels of several coagulation factors are increased during pregnancy (45), pregnant women with lone AF may not be at as low a risk of thromboembolism as nonpregnant individuals. Decisions for the treatment of lone AF during pregnancy (no treatment versus ASA) will need to be tailored for the individual patient.

RECOMMENDATIONS FOR MANAGEMENT OF ATRIAL ARRHYTHMIAS IN PATIENTS WITH CONGENITAL HEART DISEASE

Atrial tachycardias (ATs) are being recognized increasingly as an important cause of morbidity in patients with repaired, palliated or untreated congenital heart disease. The arrhythmia is most frequently a macroreentrant AT. Although often labelled as atrial flutter, it is now preferably called intra-atrial reentrant tachycardia (IART). However, multiple mechanisms for atrial arrhythmias exist in these patients and AF is also well described. Many of the medical issues that are important in adults with AF are relevant to the patient with congenital heart disease and AT – the potential for 1:1 AV conduction, a predisposition to thrombus formation and the potential for further compromise of heart function. Therefore, the more generic term (AT) will be used for the purpose of the following recommendations to encompass these different arrhythmias.

Recommendations for cardioversion of AT

Class I

- 1) Immediately perform electrical cardioversion in patients with AT who are hemodynamically unstable (level of evidence C).

Class IIa

- 1) Electrical cardioversion for the early restoration of sinus rhythm is advisable in patients with newly diagnosed AT after appropriate anticoagulation. For patients with pacemakers, cardioversion may also be accomplished by overdrive pace termination of AT (level of evidence C).
- 2) All patients with congenital heart disease and AT should be managed as patients with AF and structural heart disease with respect to anticoagulation (level of evidence C).
- 3) In addition, all patients with complex heart lesions require a transesophageal echocardiogram before elective cardioversion if no prior anticoagulation or if anticoagulation is subtherapeutic, independent of arrhythmia duration. (A complex heart lesion in this setting is defined as one with excessive atrial enlargement [in particular, right atrial enlargement] and scarring, sluggish blood flow and predisposition to atrial thrombus formation even in sinus rhythm, often accompanied by systemic ventricular dysfunction and/or right to left shunting – as such, it most commonly applies to the patient post-Fontan operation but can

also be encountered in other clinical situations such as Ebstein's anomaly) (level of evidence C).

- 4) Strategies to maintain sinus rhythm are generally preferred over rate control (level of evidence C).

Class IIb

- 1) Pharmacological cardioversion of AT may be considered in patients who are hemodynamically stable and who have a controlled ventricular rate (level of evidence C).

Recommendations for pharmacological therapy to maintain sinus rhythm

Class I

- 1) Patients placed on antiarrhythmic drugs require periodic ambulatory monitoring to identify proarrhythmia, in particular, bradycardia (level of evidence C).

Class IIa

- 1) Class III drugs (amiodarone and sotalol) are generally the preferred antiarrhythmic agents for the maintenance of sinus rhythm (level of evidence C).

Class IIb

- 1) If a class Ic drug is to be used for preventing recurrence of AT, the concomitant administration of drugs to modify AV node conduction is advised. Consideration should be given to commencing antiarrhythmic drug therapy under electrocardiographic monitoring in hospital (level of evidence C).

Recommendations for heart rate control

Class I

- 1) Patients with persistent or permanent AT should have heart rate control assessed at rest and with exercise (level of evidence C).
- 2) Beta-blockers or calcium channel blockers are to be administered to slow the ventricular response rate in patients with persistent or permanent AT with rapid ventricular response not requiring immediate electrical cardioversion (level of evidence C).

Class IIa

- 1) Adjunctive therapy with digoxin may be used to control the ventricular rate. Use of digoxin alone is not recommended (level of evidence C).

Recommendations for long-term antithrombotic management in patients with congenital heart disease and AT

Class I

- 1) Anticoagulation with adjusted-dose warfarin is advised in patients with complex high-risk lesions who have had an episode of AT (level of evidence C).

Class IIa

- 1) Anticoagulation with adjusted-dose warfarin should be considered in all other patients with congenital heart disease and recurrent episodes of AT (level of evidence C).

Class IIb

- 1) The usefulness of anticoagulation or ASA in patients with congenital heart disease who have minimal residual lesions and who have experienced a single episode of AT is uncertain. The decision to initiate anticoagulation with adjusted-dose warfarin should then be based on conventional risk factors (see Connolly and Gillis, pages 71B-73B) (level of evidence C).

Recommendations for the nonpharmacological management of patients with congenital heart disease and AT

Class I

- 1) Cardiac pacing should be considered in patients with sinus node or AV node conduction disorders when pharmacological management causes symptomatic or hemodynamically relevant bradycardia (level of evidence C).
- 2) Ablation therapy directed at the arrhythmia substrate is beneficial and should be considered in selected patients with recurrent episodes of AT in whom there is a reasonable expectation of success (level of evidence C).

Class IIa

- 1) Ablation therapy directed at the arrhythmia substrate can be useful in patients with recurrent AT following the Fontan operation (level of evidence C).

Recommendations for surgery in patients with congenital heart disease and recurrent AT

Class I

- 1) All patients presenting with AT require full clinical assessment and investigation to evaluate anatomically correctable abnormalities (level of evidence C).
- 2) Concomitant atrial arrhythmia surgery is recommended in patients with symptomatic, recurrent AT who will be undergoing an operative procedure to correct anatomical abnormalities (level of evidence C).

Class IIa

- 1) Arrhythmia mapping and surgery as primary indications for surgery are reasonable and may be considered in patients with arrhythmias refractory to medical and ablation therapy without a coexisting anatomical/hemodynamic indication for surgery (level of evidence C).

DISCUSSION

Description of mechanism of IART

The mechanism for the atrial arrhythmias in congenital heart disease has been well studied and new insights have arisen with the advent of current sophisticated mapping techniques. In general, IART is considered to be a macroreentrant tachycardia that is dependent on both functional and fixed barriers such as scar tissue, suture lines and anatomical structures such as the crista terminalis (46-48). Typical atrial flutter may coexist with IART (49). Similarly, AF is also well described and has been shown to occur in nearly one-third of patients being referred for electrical cardioversion (50). While IART is encountered in both children and adults with congenital heart

disease, AF is uncommon in children. Risk factors for the development of AF appear to be residual left-sided disease and long-term palliation.

Description of electrocardiography findings of IART

IART is an atrial arrhythmia that is independent of the AV conducting system. The marked variability of the reentrant circuits makes the electrocardiographic appearance quite variable. In general, there is discernable atrial activity with slower rates than are seen with typical atrial flutter. The cycle lengths are usually more than 260 ms and less than 450 ms. There is an increased likelihood of 1:1 AV conduction with the longer atrial cycle lengths (51).

Prevalence

Significant atrial arrhythmias occur with different prevalence depending on the underlying anatomical and surgical substrate. Examples of high-risk situations are previous Mustard/Senning operation, previous Fontan operation, atrial septal defect (ASD) repair and Ebstein's anomaly. Long-term follow-up data show that IART develops in 30% of patients following the Mustard/Senning operation (52), in 50% following the Fontan operation (53,54) and in 23% following ASD repair (54). Despite previous emphasis on ventricular arrhythmias, patients with repair of tetralogy of Fallot also appear to be at increased risk of symptomatic atrial arrhythmias (55).

Clinical impact of atrial arrhythmias

There is a significant clinical consequence of atrial arrhythmias in patients with congenital heart disease and IART; reduction in exercise capacity has been well documented and, in part, appears to be due to more rapid AV conduction during exercise (56). Similarly, overall functional status deteriorates and is demonstrated by a reduction in Ability Index (57). Important residual hemodynamic abnormalities are found in over 80% of patients in some studies (57). Recurrent IART is also associated with an increased risk of sudden death (58).

Thrombus formation

Investigation by transesophageal echocardiogram has shown thrombus formation in up to 33% of patients who are asymptomatic after the Fontan operation (59,60). There appears to be abnormalities of procoagulant and anticoagulant factors, as well as increased factor VIII levels (58). Some of these have been shown to precede surgery (61). These findings have implications for the management of patients who may require electrical or pharmacological cardioversion. A much higher index of suspicion needs to exist to suggest that a clot may form during an atrial arrhythmia, and appropriate steps need to be taken. Thrombi have been identified by transesophageal echocardiogram in up to 42% of patients with congenital heart disease and nonfibrillation atrial arrhythmias (62). Recent guidelines advise the same anticoagulation management for patients with atrial flutter and AF (63).

Medical management

There have been few, if any, controlled trial data looking at the efficacy of different antiarrhythmic agents in converting IART to sinus rhythm, or looking at efficacy of control of ventricular

rate in chronic IART. Sotalol has been shown in one series to convert atrial flutter to sinus rhythm in 85% of children, with the majority occurring within 24 h (64). Long-term management with sotalol showed that only 63% were free from recurrence at two years (65). Amiodarone is considered to be the most effective single agent in some studies (66) but its use is limited by the well-known side effects. Adults with congenital heart disease appear to be particularly susceptible to amiodarone-induced thyroid abnormalities, with 36% of patients demonstrating dysfunction in one report (67). Because of the younger age of many of the congenital patients with IART, and the slower atrial rate, 1:1 AV conduction may be seen in as many as 50% of episodes (68). Recommendations for control of the ventricular rate including using beta-blockers, calcium channel blockers and digoxin are extrapolated from adult studies in AF. Ibutilide and dofetilide have proven to be effective and relatively safe for the conversion of atrial flutter in adults, with conversion rates as high as 63% (69). However, no comprehensive data are available describing their use in patients with IART and congenital heart disease.

Pacemaker therapy

Pacemakers are predominantly inserted for sinus node or AV node conduction disease, which is common in many postoperative patients. Pacemakers may be required in patients who are prescribed antiarrhythmic medication to treat IART. An improvement in arrhythmia frequency has been observed after pacing alone in patients in whom the IART appeared to be bradycardia-dependent (70). Initial results with antitachycardia pacemakers were encouraging before their withdrawal from the market (71). The current generation of antitachycardia pacemakers appears promising as an adjunctive therapy. Overall efficacy is 54%, and there appears to be higher success in Mustard/Senning operation patients (68). One limitation is that episodes with 1:1 AV conduction are not treated for safety reasons, and misclassification of arrhythmia is common. Standard permanent pacemakers may be used to successfully overdrive IART (72) and success with atrial defibrillators has been described (73).

Catheter-based ablation therapy

Catheter techniques have evolved quite rapidly from a diagnostic to therapeutic tool. They have also been responsible for a rapid increase in our understanding of the substrates involved in the maintenance of macroreentrant circuits within the atria of patients with repaired congenital heart disease. Essentially, structural (eg, the orifices of the great veins, crista terminalis, AV valve rings) and surgically induced obstacles (eg, suture lines, scars) provide the pathways for circuits which are often dependent on narrow pathways between adjacent obstacles (74). These narrow pathways, or isthmuses, are ideal sites for ablation of critical parts of the arrhythmia circuit.

The exact location of these critical pathways varies with the underlying anatomical substrate and the precise nature of the surgery performed. Enough knowledge has been gained that some prediction is possible and more focused attempts at ablation considered. For example, the tricuspid valve region is the critical region in the majority of patients with previous Mustard/Senning operations and in those with repaired congenital heart disease (eg, tetralogy of Fallot) (75). Patients

with previous Fontan operation tend to have IART, which is dependent on the lateral right atrial wall (75).

Initial attempts at ablation using standard fluoroscopic bipolar electrogram techniques showed a reasonable acute success with a high recurrence rate. The evolution of sophisticated computerized mapping techniques has resulted in improved acute and long-term success (76,77). Acute, in laboratory success is as high as 80% to 90% (77). Recurrence rate depends to some extent on the underlying anatomy. Rates vary from 12% in patients with previous Mustard/Senning operations (78) to 62% for patients with previous Fontan operations and multiple circuits (79).

Overall, catheter ablation techniques are a reasonable option in patients with recurrent IART in whom a relatively high success rate, with low risk, can be anticipated. Examples are patients with previous ASDs, repaired congenital disease with IART or typical atrial flutter (eg, repair of tetralogy of Fallot), and patients with previous Mustard/Senning operations. The decision is less clear in patients with previous Fontan operation who may have multiple circuits and who have a much higher chance of early recurrence.

Cardiac surgery and congenital heart disease

Surgery for hemodynamic indications: in the patient with congenital heart disease, the onset of atrial arrhythmias often heralds a change in the hemodynamic status of the patient – for example, worsening pulmonary and/or tricuspid regurgitation in the patient with previous tetralogy of Fallot repair. The AT should therefore not be managed in isolation and it is recommended that all patients presenting with AT undergo full clinical assessment and investigation to identify anatomically correctable abnormalities.

Surgery for management of IART: The surgical approach to the management of recurrent IART is receiving more attention. Although arrhythmia surgery alone is considered occasionally, most reports describe the arrhythmia surgery taking place with concomitant surgery to improve abnormal hemodynamics or repair structural abnormalities (80-83). The actual approach may differ with variations of the right atrial Maze operation being most common.

Diagnostic electrophysiology and hemodynamic studies are usually performed preoperatively, although this is not universal. The atrial lesions may be created by cryoablation (81), radiofrequency ablation (84) or surgical incisions (83). Right-sided surgery is usually done alone for IART, although the left side may be included if there is left atrial dilation. Pulmonary vein isolation or left atrial Maze operation may be performed if there is clinical AF. The overall mortality rate may be as low as 0% (81,83), and as high as 13% for complex Fontan revision at the time of arrhythmia surgery (82).

Recurrence rates also vary between 0% and 25%. Although direct comparative data are not available, in general, the arrhythmia recurrence rate appears to be less than that after catheter-based ablation procedures. It has been suggested that older patients having surgery to correct hemodynamic abnormalities should have 'prophylactic' right atrial Maze operation (81). There are no data to support this position. It is recommended that arrhythmia surgery in this patient population be performed at an appropriately experienced centre.

AF AND ATRIAL FLUTTER IN THE PEDIATRIC PATIENT WITHOUT CONGENITAL HEART DISEASE

The strength of recommendations is compromised by the absence of level I and level II studies, making all recommendations level of evidence C.

Recommendations: Acute management

Class I

- 1) Perform electrical cardioversion if there is severe hemodynamic compromise.
- 2) Unless otherwise contraindicated, anticoagulate with heparin for urgent cardioversion in patients in whom the duration of arrhythmia is greater than 48 h or is uncertain.
- 3) Administer beta-blockers, calcium channel blockers and, less frequently, digoxin to achieve acute rate control. Intravenous calcium channel blockers should be avoided in infants who are more susceptible to their negative inotropic effects.
- 4) Consider transesophageal atrial pacing, which has been shown to be particularly effective in terminating neonatal atrial flutter.
- 5) In patients not on anticoagulation or subtherapeutically anticoagulated, perform transesophageal echocardiography before cardioversion if arrhythmia has been present for greater than 48 h or is of uncertain duration.
- 6) In stable patients with duration of AF greater than 48 h or of uncertain duration in whom a decision has been made to attempt cardioversion, optimize rate control and anticoagulate to an international normalized ratio of 2.0 to 3.0 for three weeks before cardioversion.

Class IIa

- 1) Transesophageal echocardiography is recommended in individuals in whom it is considered that the transthoracic echocardiogram has not provided sufficient imaging quality to rule out thrombus.

Recommendations: Chronic management

Class IIa

- 1) Consider drugs with class IC and class III actions as preferred agents for prevention of recurrence of atrial arrhythmias. AV node blockade should be considered as adjunctive therapy when using class IC drugs.
- 2) Consider radiofrequency ablation of recurrent atrial flutter.
- 3) Antithrombotic therapy with ASA, if not contraindicated, may be considered in young patients with recurrent episodes who are considered low risk of stroke.

Investigation

Class I

- 1) Echocardiography to rule out cardiomyopathy and/or structural heart disease is recommended in patients with newly presenting atrial flutter and AF.

- 2) Holter monitoring and exercise testing should be performed in young patients with chronic atrial arrhythmia because of the increased occurrence of 1:1 conduction.

DISCUSSION

This review focuses on AF and atrial flutter in children, and in young adults without congenital heart disease. Atrial arrhythmias in children with congenital heart disease have been discussed in conjunction with the adult patient. Most of the management issues have been addressed in detail elsewhere in this consensus report. AF is rarely seen in the pediatric patient without congenital heart disease, and the largest series, published nearly 30 years ago, was able to identify only 35 cases over a 22-year period (85). Other pediatric studies have combined AF and atrial flutter, making it difficult to ascertain the frequency of fibrillation in many conditions.

PREDISPOSING FACTORS

Structurally normal heart

Children with structurally normal hearts may have atrial flutter or AF. This is particularly true for fetal and neonatal atrial flutter which is infrequently associated with congenital heart disease (86). In older children, however, an underlying cardiac abnormality is the norm. Lone AF was seen in only one patient in Radford and Izukawa's study (85), and a collaborative study showed that only 8% of 380 children with atrial flutter had a normal heart (60). Familial AF has been described (87), with fetal presentation being documented in one case (88).

WPW

Children with WPW syndrome may develop AF, although this is much more common in adults. Clinical AF was found during follow-up in only three of 105 children with WPW syndrome (89), and has only rarely been described in young children (90,91). The inducibility of AF during an electrophysiology study in children depends on the clinical circumstances. AF was induced in 12 of 14 patients who presented with syncope and preexcitation (92), and in more than 90% of those who presented with a life-threatening event or clinical AF (93). AF is induced infrequently in children younger than six years of age, and most frequently in children older than 12 years of age (94). There were two other important observations from the paper by Bromberg et al (93). First, a slow ventricular response during induced AF was not observed. Second, there was a large discrepancy between the shortest preexcited RR intervals during induced AF and the shortest preexcited intervals during rapid atrial pacing. This last observation suggests that using pacing techniques alone (such as esophageal pacing) may not accurately risk-stratify children with an antegradely conducting accessory pathway. It is still advisable, however, to attempt to define the conduction properties of an accessory pathway as completely as possible.

Cardiomyopathy

AF occurs in children with various cardiomyopathies. Isolated case reports have included cases of restrictive cardiomyopathy (95); however, HCM and dilated cardiomyopathy are the most important in this patient population. McKenna et al (96) found an 8% incidence of nonsustained AT in 53 children with HCM. One other child had pre-excitation and recurrent

AV reentry tachycardia and one developed AF during follow-up. Invasive electrophysiological studies have helped to define the mechanisms of supraventricular arrhythmia in HCM. In 55% of patients with clinical AF the arrhythmia could be induced, whereas it was induced in only 7% of those without the clinical arrhythmia.

There has been concern that AF heralds a poor prognosis and that symptomatic deterioration occurs with the onset of rapid atrial rates. Indeed, Stafford et al (97) reported a youth who developed ventricular fibrillation as a consequence of rapid ventricular conduction during AF. Overall, the current evidence supports the observations of increased complications, including sudden death, in patients with HCM who develop AF. Therefore, the preferred management is for rhythm rather than rate control as per these and other guidelines (1). Careful assessment of hemodynamics is important after establishing sinus rhythm.

Although a variety of supraventricular arrhythmias have been described in dilated cardiomyopathy, AF is particularly frequent and occurs in 10% to 20% of patients. Atrial arrhythmias were diagnosed in 22% of the pediatric patients described by Friedman et al (98). AF and atrial flutter were found in 70% of these (16% of all patients), but were not predictive of a poor prognosis. Ventricular arrhythmias were found in 24% of all patients, with ventricular tachycardia being documented in 46% of these. Other studies (99) have shown that the presence of arrhythmias (atrial and ventricular combined) is a risk factor and that AF was common. However, atrial arrhythmias have not been shown to be an independent indicator of a poor outcome in children. Although it is theoretically important to maintain sinus rhythm in any child with dilated cardiomyopathy for as long as possible, there is no data to support this strategy as being superior to rate control if AF develops. In adults, the AFFIRM trial (10) found that a rhythm control strategy was associated with a higher risk of death in patients with congestive heart failure.

Patients with some neuromuscular disorders may manifest cardiac disease (100). AF has been described in patients with cardiac involvement in Emery-Dreifuss muscular dystrophy (101), fascioscapulohumeral muscular dystrophy (102) and muscular dystrophy (103). Atrial flutter and AF were associated with a worse outcome in pediatric patients following heart transplant (104).

Miscellaneous factors

AF occurs in up to 40% of adults with rheumatic mitral valve disease, and although progressive mitral valve disease may occur in childhood, the incidence of AF is less than 5% (105). Hyperthyroidism has only rarely been implicated in causing AF in children (106). In one study (107), none of 92 hyperthyroid patients younger than 40 years of age developed AF. Methylprednisolone pulse therapy has caused AF in children (108). Other causes that have been implicated are electric injury (109) and alcohol ingestion (110). Although pericarditis has been suggested as an independent cause of AF (111), this is disputed (112).

MANAGEMENT

The general principles of management of AF and atrial flutter for children do not differ from those for adult patients. Common ground will only be touched on, while any special issues relating to children will be dealt with in more detail. As

stated previously the strength of recommendations in this patient group is compromised by lack of level I and level II studies. Thus, the recommendations can only be classified as level of evidence C.

Initial assessment

The immediate evaluation includes a clinical assessment of the hemodynamic impact of the arrhythmia, electrocardiographic documentation and basic blood work as suggested for adult patients. Esophageal or epicardial wire studies, with or without adenosine, can be used to sort out difficult diagnoses. This technique is particularly useful in neonates who often have rapid (300 beats/min) reentrant supraventricular tachycardias that may be difficult to differentiate from atrial flutter by routine electrocardiography (113). A stable patient with atrial flutter and AF who is being admitted for assessment should be monitored with a 24 h Holter tape to assess periods of rapid conduction that may not be apparent. Recommendations for echocardiography are as for adult patients. Young children with excellent transthoracic imaging may not require transesophageal echocardiography.

Initial arrhythmia management

Immediate cardioversion may be required in a hemodynamically compromised patient with rapidly conducting atrial flutter or AF. Consideration should be given to initiating anticoagulation before cardioversion. In more stable patients, control of AV conduction can be achieved with intravenous calcium channel blockers, or beta-blockers (114). Intravenous calcium channel blockers should be avoided in infants younger than one year of age because they are more sensitive to their negative inotropic and vasodilator effects. Intravenous digoxin may be used in young patients. Esophageal pacing may also be used to terminate atrial flutter, and is particularly effective in neonates (113). If transesophageal pacing is not effective and rapid conduction

continues, cardioversion is the treatment of choice. Older children can be managed with initial rate control and elective cardioversion. Children with AF who require anticoagulation need AV rate control, and the principles do not differ from those for adult patients.

Chronic pharmacological therapy

The question of using pharmacological therapy to maintain sinus rhythm following successful reversion of AF in children/adolescents has not been studied. It seems appropriate to follow the adult management guidelines. AF due to reversible causes (such as alcohol ingestion) does not require ongoing therapy. Neonatal atrial flutter tends not to recur, and ongoing therapy is usually not indicated. The choice of rate or rhythm control depends to some extent on patient preference, and whether there is a significant compromise of quality of life during recurrence of AF. Appropriate attention to rate control in the younger population who is more likely to have rapid ventricular rates during exercise is required. Analysis of the adult data indicates a preference for atenolol, metoprolol, diltiazem or verapamil (115). Digoxin should only be used as a secondary medication (116). The choice of pharmacological therapy to maintain sinus rhythm is unclear because no controlled studies have been performed in children. Based on adult studies the type III drugs (sotalol or amiodarone) could be considered the preferred initial prophylactic drug therapy (114). Type IC agents (flecainide and propafenone) may be used. The role of radiofrequency ablation in this group of patients (excluding those with WPW) has not been defined. Chronic anticoagulation with warfarin may be required in some young patients but ASA can be considered if they do not have risk factors for thromboembolism. Unfortunately, these factors have not been as clearly delineated in the young patient as in the adult. Anticoagulation in patients with congenital heart disease is discussed in the relevant section.

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Management of atrial fibrillation in the emergency department and following acute myocardial infarction

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Atrial fibrillation (AF) is the most common arrhythmia managed by emergency physicians and there is increasing evidence that selected patients with acute AF can be safely managed in the emergency department without the need for hospital admission. The principles of management are identification and treatment of precipitating or underlying causes, hemodynamic stabilization/rate control, reduction of thromboembolism risk and the conversion/maintenance of sinus rhythm.

A strategy of rate or rhythm control should be chosen based on the patient's clinical status, the duration of AF, the experience of the treating physician and the status of anticoagulation.

Before either electric or pharmacological cardioversion, anticoagulation should be considered. Most patients should be given heparin or low molecular weight heparin while preparing for cardioversion. All patients should be considered for long-term anticoagulation based on their thromboembolic risk and bleeding risk from antithrombotic therapy. Following restoration of sinus rhythm, a decision regarding the use of antiarrhythmic drugs should be made based on the estimated frequency of recurrence and degree of symptoms.

In the setting of acute myocardial infarction, beta-blockers should be administered whenever possible. If beta-blockers are contraindicated, the rate can be slowed with digoxin or amiodarone. Cardioversion should be performed if the patient is hemodynamically unstable. Class IC antiarrhythmic drugs should not be administered in this setting.

Key Words: *Anticoagulation; Atrial fibrillation; Electrical cardioversion; Emergency department; Myocardial infarction*

RECOMMENDATIONS FOR THE MANAGEMENT OF ATRIAL FIBRILLATION IN THE EMERGENCY DEPARTMENT

Class I

- 1) In stable patients with a duration of atrial fibrillation (AF) greater than 48 h or of uncertain duration in whom a decision has been made to attempt cardioversion, optimize rate control and anticoagulate to an international normalized ratio (INR) of 2.0 to 3.0 for three weeks before cardioversion (level of evidence C).
- 2) In patients with a duration of AF greater than 48 h or of uncertain duration who are highly symptomatic after efforts to achieve adequate rate control, transesophageal echocardiography (TEE) to exclude atrial thrombus can be considered before cardioversion (level of evidence B).

Le traitement de la fibrillation auriculaire au service d'urgence et après un infarctus aigu du myocarde

La fibrillation auriculaire (FA) est le trouble du rythme le plus fréquent, traité par les urgentologues, et, selon des données de plus en plus nombreuses, il est possible de traiter en toute sécurité des épisodes aigus de FA au service d'urgence, sans recourir à l'hospitalisation, chez certains patients. Le traitement repose sur quatre grands principes : la recherche et le traitement des causes déclenchantes ou des causes sous-jacentes, la stabilisation hémodynamique et la maîtrise de la fréquence cardiaque, la diminution du risque de thrombo-embolie, ainsi que le rétablissement et le maintien du rythme sinusal.

Il faudrait choisir une stratégie de traitement entre la maîtrise de la fréquence cardiaque et la maîtrise du rythme cardiaque selon l'état clinique du patient, la durée de la FA, l'expérience du médecin traitant et le degré d'anticoagulation.

Il faudrait envisager un traitement anticoagulant avant de procéder à la cardioversion électrique ou médicamenteuse. On devrait administrer à la plupart des patients soit de l'héparine ordinaire, soit de l'héparine de faible masse moléculaire pendant la préparation à la cardioversion. L'anticoagulation devrait être envisagée à long terme chez tous les patients, compte tenu du risque de thrombo-embolie et du risque de saignement associé au traitement antithrombotique. Une fois que le rythme sinusal a été rétabli, il faudrait prendre une décision quant à l'emploi d'antiarythmiques, selon la fréquence prévue des récidives et l'intensité des symptômes.

Dans les cas d'infarctus aigu du myocarde, il faudrait administrer des bêta-bloquants chaque fois que c'est possible. Si les bêta-bloquants sont contre-indiqués, on peut ralentir la fréquence cardiaque par la digoxine ou l'amiodarone. La cardioversion est souhaitable chez les patients se trouvant dans un état instable sur le plan hémodynamique. Enfin, les antiarythmiques de classe IC ne devraient pas être prescrits dans le présent contexte.

- 3) Select a strategy of rate control or rhythm control based on symptoms and clinical variables (see text; level of evidence B).
- 4) When a decision is made to cardiovert patients with an AF duration of less than 48 h, synchronized electrical cardioversion or pharmacological cardioversion may be used. See Talajic and Roy, pages 19B-25B (level of evidence C).
- 5) When electrical cardioversion is chosen, use biphasic waveform when available to increase success and reduce cardioversion energy (level of evidence B).
- 6) After acute conversion of an episode of AF or atrial flutter, long-term antithrombotic therapy should be prescribed based on thromboembolic risk and bleeding risk from antithrombotic therapy. See Connolly and Gillis, pages 71B-73B (level of evidence A).

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- 7) In patients with AF and pre-excitation, perform urgent cardioversion if the patient is hemodynamically unstable. If stable, consider using class I (eg, procainamide) or class III (eg, ibutilide) antiarrhythmic agents (level of evidence C).
- 8) Hospital admission can be limited to highly symptomatic patients, those with structural heart disease, those who have had an embolic event or those at high risk for thromboembolism, and those with failure of rate control in the emergency department (ED) (level of evidence C).

Class IIa

- 1) Anticoagulation therapy with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) should be considered for most patients presenting to the ED with AF. Exceptions include those already on warfarin with an INR greater than 2.0, or those in whom the short-term risk of bleeding on anticoagulation therapy is thought to exceed the risk of thromboembolism (level of evidence C).
- 2) After conversion to sinus rhythm has been achieved, decide whether antiarrhythmic drug therapy is indicated based on the estimated probability of recurrence and the symptoms during AF (level of evidence C).

Class III

- 1) Do not administer digoxin, calcium channel blocking agents or beta-blocking agents alone to patients with pre-excitation during AF (level of evidence B).
- 2) Do not administer adenosine to attempt rate control or cardioversion during AF (level of evidence B).

RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS WITH AF AND ACUTE MYOCARDIAL INFARCTION

Class I

- 1) Use electrical cardioversion for patients requiring urgent restoration of sinus rhythm for hemodynamic reasons (level of evidence C).
- 2) Administer beta-blockers to slow a rapid ventricular response in patients without contraindication to beta-blockers. Diltiazem may be used as an alternative. These agents may be given orally or intravenously, depending on the urgency (level of evidence C).
- 3) Administer intravenous digitalis or amiodarone to slow a rapid ventricular response in patients with impaired left ventricular (LV) function (level of evidence C).
- 4) Administer heparin for patients with AF and acute myocardial infarction (MI), unless contraindicated (level of evidence C).

Class III

- 1) Do not administer class IC antiarrhythmic drugs in patients with AF in the setting of acute MI (level of evidence C).

INTRODUCTION

AF accounts for approximately one-third of hospital admissions for cardiac arrhythmias, and is the most common arrhythmia managed by emergency physicians (1). The incidence of AF is steadily increasing, likely owing mainly to the increasing age of the population (2). There is increasing evidence that selected patients with acute AF can be safely managed in the ED without the need for hospital admission (3,4).

There exists a wide range of management practices regarding patients with AF, which highlights the need for evidence-based consensus guidelines for the management of these patients (5).

CLASSIFICATION OF AF

There is no universal consensus on the classification of AF, but a clinically useful and widely used classification exists in the American College of Cardiology/American Heart Association/European Society of Cardiology practice guidelines for the management of AF (6). In this classification, paroxysmal AF is self-terminating, and persistent AF requires treatment for termination. In permanent AF, sinus rhythm cannot be maintained after cardioversion of AF or a decision has been made to leave the patient in AF.

The term 'lone AF' refers to AF in the absence of demonstrable underlying cardiovascular disease (eg, coronary artery disease, valvular disease, heart failure and cardiomyopathy) or a history of hypertension. Physicians frequently overlook hypertension as a cause of AF, and patients should not be labelled as having 'lone AF' in the presence of a history of hypertension. 'Lone AF' occurs in 3% to 35% of AF cases, depending on the population studied (7).

AF occurring in the setting of Wolff-Parkinson-White (WPW) syndrome deserves special mention because rapid atrioventricular conduction through the accessory pathway may precipitate ventricular fibrillation (VF). In these patients, drugs that block atrioventricular conduction (digoxin, beta-blockers and nondihydropyridine calcium channel blockers) are relatively contraindicated because they do not slow conduction through the accessory pathway and, therefore, may precipitate VF.

MANAGEMENT PRINCIPLES IN PATIENTS WHO PRESENT TO THE ED WITH AF

The principles of management are identification and treatment of precipitating or underlying causes, hemodynamic stabilization/rate control, reduction of thromboembolism risk, and conversion/maintenance of sinus rhythm.

In all patients presenting to the ED with acute AF, consideration should be given to the establishment of an intravenous line, continuous electrocardiographic monitoring and supplemental oxygen if needed. Most patients should have their hemoglobin, electrolytes and creatinine checked, with additional tests as indicated by special circumstances.

Identification and treatment of precipitating or underlying causes

AF may be related to acute temporary causes such as alcohol use ('holiday heart syndrome'), surgery, electrocution, MI, myocarditis, pericarditis, pulmonary embolism or other pulmonary diseases, and hyperthyroidism and other metabolic disorders (1). Successful treatment of these underlying conditions may result in the resolution of the AF.

Other supraventricular tachycardias or WPW syndrome may be associated with AF, and treatment of these dysrhythmias

may reduce the frequency of AF recurrence. AF is a common postoperative complication of both cardiac and noncardiac surgery.

The initial evaluation of AF should include characterization of the arrhythmia as paroxysmal or persistent if possible, determining the cause and defining associated cardiac and extracardiac factors.

Hemodynamic stabilization/rate control

The heart rate is generally considered controlled when it is between 60 beats/min and 80 beats/min at rest (6), but rates of up to 100 beats/min are usually well tolerated. Overly aggressive rate control can risk causing symptomatic bradycardia. Adenosine is only briefly effective for rate control in AF, owing to its very short duration of action of only a few seconds. It does not cardiovert the patient and is associated with a significant risk of causing serious ventricular arrhythmias in WPW syndrome patients with AF.

Drugs used for rate control include beta-blockers (eg, metoprolol, esmolol), calcium channel blockers (eg, diltiazem, verapamil), digoxin and amiodarone. The selection of a beta-blocker or calcium channel blocker should be based on the patient's clinical condition and the physician's experience. Beta-blockers are preferable for acute MI, ischemic heart disease and 'holiday heart syndrome', but contraindicated for asthma. Beta-blockers and calcium channel blockers are both relatively contraindicated for WPW syndrome and decompensated heart failure. Beta-blockers may be very effective for rate control in compensated heart failure, although clinical trials verifying this have not been performed.

Digoxin is often inappropriately used as a first-line agent for rate control despite the fact that it has some important limitations (8). These limitations include the fact that it has little or no effect in terminating AF, and that it may promote AF by shortening the atrial refractory period (9). Peak systemic levels are not achieved for up to 6 h, and there is a delay of the effect on heart rate reduction of at least 1 h in most patients (10-14). Because the effect of digoxin is predominantly mediated by enhanced vagal tone, it is less effective for rate control in patients with high sympathetic tone. However, digoxin may be a useful adjunctive agent when used in conjunction with beta-blockers or nondihydropyridine calcium channel blockers, allowing lower doses of these drugs to be used (eg, in patients with LV systolic dysfunction).

Reduction of thromboembolism risk

Most patients presenting to the ED with AF should be considered for anticoagulation therapy with either UFH or LMWH. Exceptions include those patients already on warfarin with a therapeutic INR greater than 2.0, or those in whom the short-term bleeding risk from anticoagulation is believed to exceed the risk of thromboembolism. Anticoagulation therapy should be used regardless of the method (chemical or electrical) used to restore sinus rhythm (6).

An AF duration of 48 h is considered the point beyond which the thromboembolic risk of acute conversion is considered significant. These patients require a minimum of three weeks of anticoagulation therapy with warfarin to an INR of greater than 2.0 before attempted cardioversion; for three weeks before anticoagulation therapy, antiarrhythmic drugs (eg, amiodarone, sotalol and propafenone) should be avoided. An alternative strategy is the use of TEE to guide

cardioversion (15-20). The absence of atrial thrombus at the time of TEE does not remove the need for subsequent anticoagulation.

Following cardioversion, most patients should be considered for warfarin anticoagulation therapy (to a goal INR of 2.0 to 3.0) for a minimum of one month, and possibly indefinitely. The decision regarding the duration of anticoagulation should take into account patient preference, the risk of AF recurrence, the risk of thromboembolism and the risk of bleeding from anticoagulation therapy.

Following acute cardioversion, the decision to anticoagulate with UFH or LMWH before attainment of a therapeutic INR with warfarin is controversial. Warfarin, when used alone, may theoretically increase the risk of thromboembolism in the first few days following initiation because it antagonizes protein C. In most patients, however, the risks and inconvenience of UFH or LMWH therapy for an average of two to seven days (the general time needed to attain a therapeutic INR) outweigh their benefits, except in patients with a very high risk of thromboembolism.

Conversion/maintenance of sinus rhythm

In hemodynamically unstable patients (eg, acute coronary syndromes, hypotension or pulmonary edema), consideration should be given to acute electrical cardioversion; however, AF seldom causes significant hemodynamic compromise in the absence of significant underlying cardiac disease, and electrical cardioversion in these patients will usually only be of modest benefit unless the ventricular rate is particularly fast (greater than 140 beats/min) (6). Additionally, cardioversion may be unsuccessful (or only briefly successful) unless the underlying cardiovascular problem is successfully treated. Patients with severe underlying cardiovascular disease often have permanent AF, with rapid rates during acute decompensation.

Although the results of two recent large clinical trials (21,22) suggest that many patients with persistent AF are best treated with a strategy of rate control rather than rhythm control, the optimal initial strategy for patients presenting to the ED with acute-onset or recent-onset AF is controversial and has not been subjected to rigorous clinical trials.

Spontaneous conversion of AF to sinus rhythm within 24 h is common, occurring in up to two-thirds of patients (23-25). The decision regarding the timing and method (chemical or electrical) of cardioversion depends on a number of factors, including patient and physician preference, expertise and available facilities.

Chemical cardioversion is simpler but less efficacious than electrical cardioversion, being successful in approximately 50% to 80% of patients presenting to the ED with recent-onset AF. Electrical cardioversion is effective in approximately 80% to 90% of similar patients (26-28), but requires intravenous sedation. Patients in whom chemical cardioversion is unsuccessful can be considered for electrical cardioversion.

Options for oral chemical cardioversion include propafenone, flecainide and amiodarone. Oral amiodarone is less effective for early cardioversion, but may result in cardioversion at a later time. Sotalol has not been shown to be more effective than placebo in effecting cardioversion, but has been shown to maintain sinus rhythm (2). Intravenous options include procainamide, ibutilide and amiodarone.

All patients undergoing electrical or chemical cardioversion require continuous electrocardiographic monitoring

and temporary pacing capability. Standard drugs used for cardiac resuscitation need to be readily available.

The decision to initiate maintenance antiarrhythmic therapy following conversion to sinus rhythm should involve consideration of the likelihood of recurrence of AF and the risks of antiarrhythmic drug therapy. Outpatient (rather than inpatient) initiation of antiarrhythmic drug therapy is controversial but may be considered for patients who are asymptomatic, have a normal QT interval and have no significant underlying structural or ischemic cardiovascular diseases (3,4,29-31). Amiodarone, however, appears to be safer than other antiarrhythmic agents and may be considered for outpatient initiation in patients with structural heart disease, including LV dysfunction (see Talajic and Roy, pages 19B-25B, Drugs for Termination and Maintenance of Sinus Rhythm). Hemodynamically stable patients with WPW syndrome and AF of a duration less than 48 h are best managed with class I (eg, procainamide) or class III (eg, ibutilide) agents.

ELECTRICAL CARIOVERSION

The efficacy of cardioversion depends on the nature of the underlying heart disease and the current density delivered to the atria. Large paddles result in lower impedance than smaller ones, but when the paddles are too large, the current density through the cardiac tissue is insufficient to cause cardioversion, whereas smaller paddles may produce too much current density and cause injury. A paddle or gel-electrode diameter of 8 cm to 12 cm is generally recommended (6). If paddles are used, then firm-chest-wall pressure will maximize the delivered current and minimize the potential for a cutaneous electrical burn.

Synchronization of the electrical discharge with the intrinsic cardiac rhythm is necessary to ensure that the vulnerable phase of the cardiac cycle (80 ms before to 30 ms after the apex of the T wave) is avoided, thus reducing the risk of precipitating ventricular tachycardia or VF. Because all currently available external cardioverter/defibrillators revert to the unsynchronized mode after each shock, they need to be changed back to synchronized mode before delivery of the next shock.

The optimum electrode positioning is controversial, but the evidence suggests that the anterior-posterior position is more effective for cardioversion, despite the fact that the impedance is greater with this approach because of the greater distance between the electrodes (6,32-34).

When the resting heart rate is relatively slow (less than 60 beats/min), atropine can be given before cardioversion to reduce the risk of postprocedural bradycardia; however, there are no published data to support this practice.

In patients scheduled for elective outpatient electrical cardioversion, frequent INR monitoring to ensure that the INR is consistently in the therapeutic range (2.0 to 3.0) will reduce the risk of thromboembolism.

Biphasic cardioverters/defibrillators have been shown to be more efficacious than monophasic devices (35-37). Because biphasic devices require delivery of a much lower energy for cardioversion, the potential for cutaneous and cardiac injury is reduced with these devices. As a general rule, biphasic devices require delivery of approximately one-half the energy of monophasic devices to effect cardioversion.

There is a general tendency for physicians to underdose the delivered energy when attempting to cardiovert patients. This can result in higher cumulative doses (if multiple attempts are

required), longer sedation times and more 'unsuccessful' cardioversions. The literature suggests that the most appropriate initial dose is 100 joules biphasic (or 200 joules monophasic). Higher initial doses should be considered if a higher dose was required on a previous successful attempt. Lower initial doses should be considered for frail, low body weight, elderly and postoperative patients.

CRITERIA FOR HOSPITAL ADMISSION

Hospital admission can be limited to highly symptomatic patients, those with structural heart disease, those who have had an embolic event or are at high risk for thromboembolism, and those with failure of rate control in the ED (3,4,30,31).

Inpatient electrocardiographic monitoring may also be required for high-risk patients (eg, advanced age and renal failure) who, following cardioversion, are started on oral antiarrhythmic therapy with high proarrhythmia potential (eg, sotalol).

Patients with noncardiac causes of AF (eg, pneumonia) may require admission for investigation and treatment of the underlying condition.

PATIENTS WITH AF AND ACUTE MI

The incidence of AF with acute MI in the modern era has been reported to be between 10.4% and 22% (38-40). Older age, higher Killip class, ventricular dysfunction and extent of ischemic burden are generally acknowledged as the major risk factors for AF (39,41-46). AF is associated with increased mortality (39) and a higher stroke rate (40).

Measures directed at reducing infarct size, ischemia and preserving LV function according to current standards would be expected to reduce the incidence of AF, as was demonstrated by angiotensin-converting enzyme inhibition (38). With a paucity of controlled trials evaluating therapy for AF in the setting of acute MI, current therapy is largely guided by consensus and therapeutic strategies recommended for AF in the general context (41).

There is no proven benefit of a rhythm-control strategy over a rate-control strategy; such decisions must be individualized. Rate control with beta-blockers is preferable when feasible because of the general benefits of beta-blockers in ischemic syndromes, but calcium channel blockers and digitalis are also acceptable. Intravenous and oral amiodarone are useful for rate control, especially when other rate control agents are relatively or absolutely contraindicated, such as with bronchospasm or heart failure. Intravenous and oral amiodarone are also useful for rhythm control (46,47).

Electrical cardioversion is the treatment of choice when acute restoration of sinus rhythm is desirable for hemodynamic improvement. Ibutilide has shown efficacy in acute restoration of sinus rhythm with atrial flutter and, to a lesser extent, with AF (48-50). Its use in acute MI has not been specifically and extensively evaluated but it is safe and effective in AF of relatively recent onset in critical care settings and after cardiac surgery. Serious adverse effects have been reported in patients with congestive heart failure (51). In the future, it is possible that ibutilide will have a greater role in the conversion of AF in the setting of acute MI.

The use of class I antiarrhythmics and sotalol were associated with lower unadjusted one year mortality in patients with AF in the global use of strategies to open occluded coronary arteries (GUSTO)-III trial (46). Class IC drugs are

not generally recommended in ischemic syndromes (52). Sotalol and amiodarone are efficacious for rhythm control, with amiodarone associated with a low proarrhythmia risk and no significant negative inotropic effect. Dofetilide (53,54) is not currently approved in Canada, but has shown safety and efficacy in rhythm control in patients with ventricular dysfunction after MI. Heparin is generally used in AF with acute MI, and long-term anticoagulation with persistent or permanent AF is dictated by the presence of established risk factors (55).

The recommendations are generally based on consensus and do not differ appreciably from those recommended by the American College of Cardiology/American Heart Association/European Society of Cardiology (41). The recommendations in the present article are directed at management issues in AF that are unique to a context of acute MI, with general recommendations otherwise applicable.

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Similarities and differences between atrial flutter and atrial fibrillation

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CS Simpson, LB Mitchell, GJ Klein. Similarities and differences between atrial flutter and atrial fibrillation. *Can J Cardiol* 2005;21(Suppl B):67B-70B.

Atrial flutter and atrial fibrillation have a complex relationship that has mechanistic, diagnostic, therapeutic and prognostic components. While thromboembolic risk management and pharmacological strategies share many similarities, there are important differences. Radiofrequency ablation should be considered to be an early, first-line alternative to pharmacological strategies for many patients with atrial flutter.

Key Words: Atrial fibrillation; Atrial flutter; Guidelines; Pharmacological strategy; Radiofrequency ablation

The electrocardiographic pattern of atrial flutter (AFL) (which consists of regular atrial activity at a rate of 240 beats/min to 340 beats/min usually with no intervening isoelectric periods) reflects the dominant macroreentrant electrophysiological mechanism of AFL, and distinguishes AFL from atrial fibrillation (AF). Nevertheless, there is a strong clinical relationship between AFL and AF. A single patient may have, at different times, paroxysms of both AFL and AF (1,2). Antiarrhythmic drugs are known to facilitate the transformation of disorganized AF into more organized AF (3-5), and patients who have undergone successful ablation procedures to cure AFL may go on to develop AF (6-10).

The precise nature of the relationship between these two rhythm disturbances is not fully understood. At the time of spontaneous conversion from AF to AFL, the AF cycle length changes just before AFL develops (11). AF may induce electrophysiological remodelling of atrial tissue, facilitating the development and persistence of the reentrant circuit of typical AFL (12-14). AFL, in turn, may give rise to AF if the cycle length is sufficiently short enough to provoke fibrillatory conduction (15). This may be particularly true of atypical AFL (16-19). Ectopic beats from the pulmonary veins have been postulated to be the obligatory triggers for activation of the AFL reentrant circuit (20) and have also been implicated in the transition from AFL to AF (21). In some patients, AFL and AF may even occur simultaneously (22).

Classical AFL (also known as typical or counterclockwise AFL) is due to a macroreentrant right atrial circuit in which the wavefront proceeds up the interatrial septum, down the right atrial free wall and through the cavotricuspid isthmus. This results in the classic electrocardiographic pattern of negative sawtooth flutter waves in leads II, III and aVF, along with positive flutter waves in lead V1. Reverse typical AFL (also known as clockwise AFL) uses the same circuit but in the reverse direction. This produces positive flutter waves in leads II, III and aVF, along with negative flutter waves in lead V1. Atypical AFLs are

Les ressemblances et les différences entre le flutter auriculaire et la fibrillation auriculaire

Le flutter auriculaire et la fibrillation auriculaire ont un rapport complexe, qui comporte à la fois des éléments mécanistes, diagnostiques, thérapeutiques et pronostiques. Même si le traitement du risque de thrombo-embolie et la pharmacothérapie ont plusieurs ressemblances, il existe également des différences importantes. L'ablation par courant de radiofréquence devrait être considérée comme une première bonne solution de rechange au traitement médicamenteux chez de nombreux patients atteints de flutter auriculaire.

those that have less characteristic macroreentrant wavefronts and other regular electrocardiographic atrial activation patterns. In the present report, the term 'AFL' is used in a generic way that includes all of these electrophysiological mechanisms.

RECOMMENDATIONS

Pharmacological management

Class I

- 1) When pharmacological management for patients with AFL is selected, either the rate-control strategy or the rhythm-control strategy is appropriate (level of evidence C).
- 2) The pharmacological agents used for rate control and rhythm control for patients with AFL are the same as those used for patients with AF (level of evidence C).
- 3) When a class IC or IA agent is chosen to treat a patient with AFL, an atrioventricular (AV) node blocking agent should generally be used concurrently (level of evidence C).

As with AF, the pharmacological treatment of AFL can be directed to achieve ventricular rate control (the rate-control strategy) or to attempt to restore and maintain sinus rhythm (the rhythm-control strategy). Because rate control can be more difficult to achieve in patients with AFL versus patients with AF, the rhythm-control strategy is often the primary approach to therapy. Nevertheless, the objective benefits of this strategy over effective rate control are unproven.

For macroreentrant AFL, including typical and reverse typical AFL, antiarrhythmic drug therapy that prolongs the refractory period within the reentrant circuit would be expected to inhibit the advancing wavefront (23-26) and, thereby, prevent the initiation and maintenance of AFL. The class III drugs (amiodarone, dofetilide, ibutilide and sotalol) are widely used both for the conversion to and maintenance of normal sinus

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rhythm. For the acute termination of AFL, ibutilide appears to be the most effective (27,28). Antiarrhythmic drugs in class IA (disopyramide, procainamide and quinidine) and those in class IC (flecainide and propafenone) may also be useful for either the conversion to or maintenance of sinus rhythm.

The shortcoming of each of these antiarrhythmic drug therapies is antiarrhythmic drug-related proarrhythmia. Class III drugs can produce torsade de pointes in 1% to 4% of patients (29). Class I drugs (particularly class IC) can slow the AFL rate dramatically to the point where the unencumbered AV node can conduct the slower AFL to the ventricles in a 1:1 ratio, leading to a substantial increase in the ventricular response rate (30). Accordingly, patients should be treated with an AV node-blocking agent concurrently whenever class I drugs are selected, except when AV node conduction is known to be poor.

When a rate-control strategy is chosen for the treatment of patients with AFL, drugs that prolong the refractory period of the AV node are effective (beta-blockers, nondihydropyridine calcium channel blockers and digitalis), just as they are in patients with AF. Nevertheless, rate control in patients with AFL may be more difficult to achieve than in patients with AF.

RECOMMENDATIONS: THROMBOEMBOLIC RISK MANAGEMENT

Class I

- 1) As with AF, AFL patients at high risk for systemic emboli should receive chronic oral anticoagulation therapy (level of evidence B).
- 2) Patients should have therapeutic international normalized ratio (INR) measurements on warfarin for at least three weeks before and at least three weeks following the restoration of sinus rhythm (whether by pharmacological therapy, electrical cardioversion or catheter ablation). Alternatively, cardioversion may be accomplished without prior long-term anticoagulation therapy if the atria have been cleared by low-risk findings on a transesophageal echocardiogram. Following a transesophageal echocardiogram-guided strategy, patients should be subsequently anticoagulated for at least four weeks (level of evidence C).

There are no randomized controlled trials that have examined the efficacy of any antithrombotic strategy in patients with AFL. However, several lines of evidence suggest that patients with AFL face an increased risk of thromboembolic events, which can be stratified on the basis of traditional risk factors (age 65 years or older, clinical evidence of left ventricular systolic dysfunction, history of hypertension, history of diabetes mellitus or history of a previous thromboembolic event).

In several series, the risk of thromboembolism has been found to be elevated in patients with AFL (30-34), particularly after conversion to normal sinus rhythm. One study (35) has suggested that at least some of this excess risk may be attributed to those patients with AFL who also have paroxysms of AF. This elevated thromboembolic risk may also be expressed at the time of catheter ablation for cure of AFL (36,37). Patients with AFL and impaired left atrial appendage function have also been reported to be at higher risk for thromboembolic events (38,39). Independent of left atrial appendage function, left atrial thrombus and spontaneous contrast ('smoke') appear to occur with higher frequency in AFL patients (40,41). Finally, one patient series (42) reported that all AFL patients who had

suffered a postcardioversion thromboembolic event were either not taking warfarin or were suboptimally anticoagulated. In contrast, none of the patients in this series who were well anticoagulated suffered a thromboembolic complication. These reports and clinical experiences demonstrating that many (perhaps most) patients with AFL also have periods of AF lead to a recommendation that the antithrombotic considerations for patients with AFL should be similar to those of patients with AF. When warfarin therapy is chosen, the target INR is 2.0 to 3.0.

RECOMMENDATIONS: CATHETER ABLATION

Class I

- 1) Curative catheter ablation for symptomatic AFL may be offered as a first-line therapy and presented as a reasonable alternative to pharmacological therapy (level of evidence B).
- 2) AV node ablation with permanent pacing should be reserved for patients with symptomatic AFL despite optimal medical therapy when curative ablation is not feasible (level of evidence C).

Catheter ablation of the cavotricuspid isthmus has emerged as a safe and effective strategy for the management of patients with isthmus-dependent AFL (43-48). Technologies that allow for larger atrial myocardial lesions appear to generate the best results (49). A large, prospective, randomized trial (50) has established the superiority of isthmus ablation to antiarrhythmic drug therapy in terms of success rate, quality of life and lower recurrence of AFL in follow-up. A single-centre study (51) examining catheter ablation in older patients found it to be safe and efficacious even in the elderly. Given the potential for electrical remodelling in AFL, similar to that seen in patients with AF (52), a compelling argument can be made for early intervention with catheter ablation for the treatment of patients with problematic isthmus-dependent AFL.

Notwithstanding the advantages of catheter ablation for the treatment of selected patients with AFL, early and late occurrences of AF following successful isthmus ablation are common (46,53,54). A previous history of AF, the presence of significant mitral regurgitation, and left ventricular systolic dysfunction all predict the occurrence of AF following successful ablation of AFL. Therefore, AFL ablation may not be appropriate for these patients with a high risk of subsequent AF in the absence of demonstrated failure of antiarrhythmic drug therapy. Emerging 'hybrid' strategies, however, are currently exploring combinations of pacing, antiarrhythmic drugs, isthmus ablation and pulmonary vein isolation; these strategies appear promising for patients who have both AFL and AF (55).

On occasion, usually after the failure of both pharmacological therapy and isthmus ablation, patients with problematic AFL may be treated with catheter ablation of the AV node to create an iatrogenic complete AV block, with the ventricular rate then governed by a permanent pacemaker.

RECOMMENDATIONS: ELECTRICAL CARDIOVERSION OF AFL

Class I

- 1) Electrical cardioversion of AFL should be carried out for the same indications as AF. The technique is the same as that for cardioversion of AF (level of evidence B).

Electrical cardioversion of persistent AFL is a safe, effective and economical procedure (56-58). Patients presenting with acute onset AFL who are unstable should be promptly cardioverted with synchronized direct current energy, as with a patient with AF. More stable patients may undergo elective or semi-elective cardioversion in the same way as a patient with AF, with similar attention to precardioversion anticoagulation (at least three weeks with therapeutic INRs). Postcardioversion anticoagulation also appears to be important (as it is for the patient with AF) as discussed in the above thromboembolic risk management section of the present article.

The only difference between the cardioversion of AFL and AF is the recommended starting energy. Many authorities (59-61) have recommended a starting energy of 50 joules (J). However, these recommendations were based on anecdotal experience and consensus. Since these recommendations were made, one trial (53) has reported that an initial energy of 100 J is superior to an initial energy of 50 J, with 100 J reducing the number of shocks required per case and having a first shock success rate of 85% (compared with 70% for a first shock of 50 J). Another study (62) in patients with long-standing AFL that

had been present for more than 30 days reported that an initial 100 J shock was successful 68% of the time.

Atypical AFL

Patients with substantially disordered atrial electrophysiology, including those with congenital heart disease and previous cardiac surgery, may develop atypical AFL. Interatrial reentrant circuits can form around atrial septal defects, atriotomy scars, the crista terminalis, AV valves, venae cavae and pulmonary veins. New mapping technologies permit the delineation of these circuits, making catheter ablation feasible for these complex arrhythmias (18,62-68).

CONCLUSIONS

AFL and AF have a complex relationship that has mechanistic, diagnostic, therapeutic and prognostic components. Pharmacological management and thromboembolic risk management considerations are similar for the two rhythm abnormalities. Radiofrequency ablation should be considered as an early alternative for many patients with problematic AFL.

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Therapies for the prevention of stroke and other vascular events in atrial fibrillation and atrial flutter

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SJ Connolly, AM Gillis. Therapies for the prevention of stroke and other vascular events in atrial fibrillation and atrial flutter. *Can J Cardiol* 2005;21(Suppl B):71B-73B.

Stroke is the major clinical cause of atrial fibrillation (AF). Treatments to reduce the risk of stroke and other vascular events are an important part of AF management. Oral anticoagulation is effective against stroke and has an acceptable risk of adverse events (primarily bleeding). Acetylsalicylic acid is less effective than oral anticoagulants but better tolerated. Anticoagulants are recommended for AF patients with risk factors for stroke.

Key Words: *Acetylsalicylic acid; Anticoagulation; Atrial fibrillation; Prevention; Stroke*

Traitements préventifs de l'AVC et autres complications vasculaires associés à la fibrillation et au flutter auriculaire

L'AVC est la principale cause clinique de la fibrillation auriculaire (FA). Les traitements visant à réduire le risque d'AVC et autres complications vasculaires sont une partie importante de la prise en charge de la FA. L'anticoagulation orale est efficace contre l'AVC et comporte un risque acceptable de réactions indésirables (principalement les saignements). L'acide acétylsalicylique est moins efficace que les anticoagulants oraux, mais elle est mieux tolérée. Les anticoagulants sont recommandés chez les patients qui font de la FA et qui sont exposés à des facteurs de risque d'AVC.

RECOMMENDATIONS

Class I

- 1) All patients with atrial fibrillation (AF) or atrial flutter (AFL) should be stratified for risk of stroke and vascular events, and for risk of bleeding with anticoagulation therapy (level of evidence A).
- 2) Patients with AF or AFL at high risk of stroke should receive oral anticoagulation unless there is an excessive risk of hemorrhage (level of evidence A).
- 3) Patients with AF or AFL at intermediate risk should receive either oral anticoagulation or acetylsalicylic acid (ASA) (75 mg/day to 325 mg/day), and low-risk patients may receive ASA unless there is excessive risk of bleeding (level of evidence B).
- 4) Patients undergoing direct current cardioversion for AF or AFL should receive therapeutic oral anticoagulation for at least three to four weeks before, and at least three to four weeks after, the procedure. Low-risk patients may undergo cardioversion without oral anticoagulation if performed within 48 h of arrhythmia onset. Transesophageal echocardiography (TEE)-guided cardioversion (following protocol from the Assessment of Cardioversion Using Transesophageal Echocardiography

[ACUTE] trial) is an acceptable alternative to oral anticoagulation (level of evidence C).

- 5) When reversal of oral anticoagulation is required (ie, for surgery), therapy should be discontinued five to six days beforehand. Consideration should be given to the use of heparin or low-molecular-weight heparin during this period in higher risk patients (level of evidence C).

STROKE, VASCULAR EVENTS AND RISK STRATIFICATION

The risk of stroke and vascular events in AF is well documented. AF increases the overall risk of stroke to a rate of 4.5% per year (1). This risk, however, varies by an order of magnitude according to the clinical factors associated with AF. In healthy, young AF patients with no other clinical conditions, the risk of stroke and other vascular events is less than 1% per year (2). On the other hand, in elderly patients with multiple risk factors (such as prior stroke or hypertension), the risk of vascular events may exceed 10% per year (3). Therefore, risk stratification should guide therapy. In 1996, the Canadian Cardiovascular Society (CCS) issued guidelines recommending risk stratification according to the proposal from the AF investigators (4). Subsequently, in 1998, the American College of Chest Physicians issued guidelines that updated this

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TABLE 1
Risk factor stratification

High-risk factors	Moderate-risk factors
History of stroke/TIA	Age between 65 and 75 years
Hypertension	Diabetes
Reduced LV function	Coronary artery disease without
Age over 75 years	LV dysfunction
Mitral stenosis	
Prosthetic heart valve	

LV Left ventricular; TIA Transient ischemic attack

approach, incorporating new information regarding the value of echocardiography. The risk stratification outlined by the American College of Chest Physicians in 1998 is widely accepted, comprehensive and recommended (5). Patients are divided into low, medium and high categories of risk based on clinical parameters. Tables 1 and 2 present this risk stratification system.

Intermittent AF is associated with a risk of stroke that is similar to that of permanent AF. In an analysis of patients involved in the Stroke Prevention in Atrial Fibrillation (SPAF) trials (6), the annual risk of stroke was found to be 3.2% in patients with intermittent AF and 3.3% in those with permanent AF. Patients with a single episode of AF can, in general, be considered to be similar to patients with recurrent AF. The minimum duration of AF that requires antithrombotic therapy is unknown. It has recently been recognized that AF recurrence is often not symptomatic, even in patients with a history of highly symptomatic episodes. Physicians should not rely on symptoms to assess the value of using antithrombotic therapy in AF. Although data regarding AFI are sparse, there is considerable overlap between AFI and AF within patients. It appears prudent to manage patients with AFI in a manner similar to that recommended for AF.

THERAPEUTIC RECOMMENDATIONS

The 1996 CCS guidelines (4) recommended oral anticoagulation for patients with AF who were stratified to the high-risk group. These recommendations were based on the results of placebo-controlled trials of anticoagulation in AF. Several trials published in the intervening period have served to solidify these recommendations. A reanalysis of all currently available evidence, including a meta-analysis of placebo-controlled trials and comparative trials (7), showed that oral anticoagulation is a highly effective therapy, resulting in a greater than 60% reduction in stroke. ASA reduces the risk of stroke by approximately 20%. ASA therapy has been evaluated at a variety of doses, from 50 mg/day to 1200 mg/day in patients with AF, without any clear indication that any particular dose is superior (7). The Antithrombotic Trialists' Collaboration supports the use of doses from 75 mg/day to 325 mg/day in a wide variety of patient groups (8). Therefore, this dose range of ASA is preferred when ASA is to be used in AF. Compared with ASA, oral anticoagulation is more effective (50% reduction in stroke, 30% reduction in vascular events), but confers a higher risk of bleeding. In the most recent meta-analysis of oral anticoagulation versus ASA trials (9), oral anticoagulation reduced the risk of stroke by 45% (hazard ratio [HR]=0.55, 95% CI 0.43 to 0.71) and reduced the risk of overall cardiovascular events by 29% (HR=0.71, 95% CI 0.59 to 0.85).

TABLE 2
Antithrombotic therapy by risk group

Risk factors	Recommended therapy
Any high-risk factors or more than one moderate-risk factor	Warfarin (target international normalized ratio of 2.5 [range 2.0 to 3.0])
One moderate-risk factor	Acetylsalicylic acid 75 mg/day to 325 mg/day, or warfarin (target international normalized ratio of 2.5 [range 2.0 to 3.0])
No high-risk factors and no moderate-risk factors	Acetylsalicylic acid 75 mg/day to 325 mg/day

Compared with ASA, oral anticoagulation increased the risk of major bleeding by 71% (HR=1.71, 95% CI 1.21 to 2.41). In 1996, the target international normalized ratio (INR) recommended for anticoagulant prophylaxis was between 2.0 to 3.0. Hylek et al (10) have confirmed that this recommendation is appropriate and have emphasized the increased risk of stroke associated with INR values below 2.0.

Several randomized trials (11,12) of oral anticoagulation in AF have used an extensive screening process to eliminate patients at increased risk of hemorrhage. These studies estimated that these criteria would exclude 15% to 30% of patients with AF. The known risk factors for hemorrhage include prior stroke, advanced age and underlying malignancy. As has been noted in a number of guidelines, including the 1996 CCS consensus conference guidelines, the physician must balance the benefits of stroke prevention against the risks of hemorrhage for each patient in which antithrombotic therapy is to be used. ASA therapy may be appropriate for patients in whom the risk-to-benefit ratio of hemorrhage versus stroke prevention is high with oral anticoagulation.

Although the benefit of warfarin in preventing thromboembolic events in patients with AF has been unquestionably demonstrated, many patients do not receive the drug because of the rigours involved in monitoring the INR and maintaining a therapeutic level. These challenges could lead to underutilization and either bleeding or thromboembolism if the INR is too high or too low, respectively. These drawbacks to warfarin have led to the investigation of new agents that act on different phases of the coagulation process, such as direct thrombin inhibition (13,14). Other studies have focused on combinations of antiplatelet agents. The ability to administer drugs without significant drug or food interaction and with consistent dosing would improve patient acceptance of antithrombotic therapy and provide consistent therapeutic efficacy.

CONVERSION TO SINUS RHYTHM

Patients undergoing electrical cardioversion of AF or AFI face a risk of thromboembolism that has been estimated to be between 1% and 5% in case series. The 1996 CCS guidelines recommended that patients undergoing electrical cardioversion be treated with therapeutic anticoagulation for at least three to four weeks before and at least three to four weeks after the procedure. Cardioversion within 48 h of the onset of AF could be performed without anticoagulation. Although not based on the results of clinical trials, this recommendation is widely accepted in the international cardiology community. It is reasonable to continue this approach, although caution is now advised for cardioversion of the high-risk AF patient without oral anticoagulation or TEE, even within 48 h of onset. In 2001, the practice

of using TEE to assess the risk of thromboembolism associated with cardioversion was evaluated in the ACUTE study (15), a major clinical trial in which patients with AF lasting more than two days or those with AF with previous AF were randomized to a TEE-guided approach or the conventional approach. Patients randomly assigned to the TEE-guided strategy received anticoagulation with heparin just before TEE, and subsequent cardioversion was refused if no thrombus was identified in the left atria or its appendage. Oral anticoagulation therapy was started and continued for four weeks after cardioversion. Cardioversion was postponed if left atrial thrombus was identified by TEE. Similar outcomes were observed in the two groups for stroke, bleeding and maintenance of sinus rhythm at eight weeks postcardioversion. The TEE-guided approach to

cardioversion provided results that were comparable to the standard approach. In general, there is no reason to prefer TEE, although it is useful when prompt cardioversion is desired.

TEMPORARY DISCONTINUATION OF ORAL ANTICOAGULATION

It is occasionally necessary to discontinue oral anticoagulation for invasive procedures and elective surgery. In general, INR levels return to normal within five to six days; therefore, discontinuation for this period is recommended, as is an evaluation of the INR on the morning of surgery. In high-risk patients, the risk of stroke during this period would justify the use of heparin or low-molecular-weight heparin until 6 h to 12 h before surgery.

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