

Pharmacological and nonpharmacological methods for rate control

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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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