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Rate Control in Atrial Fibrillation

Choice of Treatment and Assessment of Efficacy

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Abstract

The clinical relevance and high social costs of atrial fibrillation have boosted interest in rate control as a cost-effective alternative to long-term maintenance of sinus rhythm (i.e. rhythm control). Prospective studies show that rate control (coupled with thromboembolic prophylaxis) is a valuable treatment option for all forms of atrial fibrillation. The rationale for rate control is that high ventricular rates, frequently found in atrial fibrillation, lead to haemodynamic impairment, consisting of a variable combination of loss of atrial kick, irregularity in ventricular response and inappropriately rapid ventricular rate, depending on the type of underlying heart disease. Long-term persistence of tachycardia at a high ventricular rate can lead to various degrees of ventricular dysfunction and even to tachycardiomyopathy-related heart failure. Identification of this reversible and often concealed form of left ventricular dysfunction can permit effective management by rate (or rhythm) control.

Although acute rate control (to reduce ventricular rate within hours) is still often based on digoxin administration, for patients without left ventricular dysfunction, calcium channel antagonists or β-adrenoceptor antagonists (β-blockers) are generally more appropriate and effective. In chronic atrial fibrillation, long-term rate control (to reduce morbidity/mortality and improve quality of life) must be adapted to patients' individual characteristics to grant control during daily activities, including exercise. According to current guidelines, the clinical target of rate control should be a ventricular rate below 80–90 bpm at rest. However, in many patients, assessment of the appropriateness of different drugs should include exercise testing and 24h-Holter monitoring, for which specific guidelines are needed.

In practice, rate control is considered a valid alternative to rhythm control. Recent prospective trials (e.g. the Pharmacological Intervention in Atrial Fibrillation [PIAF] and the Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM] trials) have shown that in selected patients, rate control provides similar benefits, more economically, in terms of quality of life and long-term mortality.

The choice of a rate control medication (digoxin, β-blockers, calcium channel antagonists or possibly amiodarone) or a non-pharmacological approach (mainly atrioventricular node ablation coupled with pacing) must currently be based on clinical assessment, which includes assessing the presence of underlying heart disease and haemodynamic impairment. Definite guidelines are required for each different subset of patients. Rate control is particularly tricky in patients with heart failure, for whom non-pharmacological options can also be considered. The preferred pharmacological options are β-blockers for stabilised heart failure and digoxin for unstabilised forms.

Atrial fibrillation is the most common form of cardiac arrhythmia and its prevalence is expected to continue to rise.[1] The costs resulting from atrial fibrillation management are impressive; in the US, atrial fibrillation causes far more hospital admissions than any other arrhythmia, accounting for almost a million patient days spent in hospital per year.[2] The high social costs and the clinical relevance of atrial fibrillation have helped fuel interest in rate control, as an alternative strategy to restoration and maintenance of sinus rhythm (i.e. rhythm control). Since no definite algorithm currently exists to select the most appropriate form of treatment in individual cases, therapy is still primarily guided by clinical presentation (table I).

The most widely used classification of atrial fibrillation is that proposed by Gallagher and Camm,[4] which distinguishes acute and chronic forms, the latter being subdivided into paroxysmal, persistent and permanent varieties on clinical grounds (table I). Rate control (of the ventricular response to atrial fibrillation) is a treatment option for all these forms.

In the present review, the premises for both acute and long-term rate control are outlined, together with a list of potential endpoints. Regarding acute rate control, the roles of calcium channel antagonists

Table I. Treatment options for different types of atrial fibrillation (reproduced from Waktare and Camm,[3] with permission from Elsevier Science)

Arrhythmia	Arrhythmia characteristics	Short-term treatment goal	Long-term treatment goal	Potential treatments
Paroxysmal atrial fibrillation	Terminates spontaneously	Rate control	Prophylaxis of atrial fibrillation recurrences	AA drugs for prophylaxis, preventive pacing, ablation, atrial defibrillator
Persistent atrial fibrillation	Will not terminate spontaneously but can be converted to sinus rhythm	Cardioversion to sinus rhythm, rate control	Prophylaxis of atrial fibrillation recurrences, rate control	AA drugs for conversion, external CV, internal CV, atrial defibrillator, AA drugs for rate control, AA drugs for prophylaxis, preventive pacing, pacing to stop atrial fibrillation
Permanent atrial fibrillation	Will not terminate spontaneously, cannot be converted to sinus rhythm	Rate control	Rate control	AA drugs for rate control, AV node modification, AV node ablation + pacing, ablation

AA = antiarrhythmic; **AV** = atrioventricular; **CV** = cardioversion.

and β-adrenoceptor antagonists (β-blockers) as alternatives for digoxin are highlighted. Turning to long-term control, appropriate ways of monitoring ventricular rate are initially examined, followed by the influence of atrial fibrillation on left ventricular function and quality of life. A discussion follows of data from recent randomised, controlled trials comparing the use of long-term rate control with a strategy based on rhythm control in terms of both clinical endpoints and social costs. This leads to a review of the repertoire of pharmacological and non-pharmacological interventions that can currently – or might eventually – be used for different clinical presentations. To conclude, the ways in which rate control treatment can currently be tailored to the needs of individual patients is summarised, with suggestions of areas where further evidence-based guidelines are required.

1. Premises for Rate Control

High ventricular rates are frequently found in atrial fibrillation. That is, the ventricular rates have been reported to be between 95–170 bpm (mean 120 bpm) in recent onset (acute) atrial fibrillation,[5] 123 or 134 bpm in the paroxysmal form,[6,7] and between 82–170 bpm (mean 108 bpm) in chronic atrial fibrillation.[8]

High ventricular rates have important haemodynamic consequences. In an animal model,[9] the effects of atrial fibrillation with rapid heart rate on cardiac output have been related to the absence of active atrial transport (determining a 15% decrease) and irregularity in ventricular rhythm (accounting for a further 15% drop). Moreover, the long-term persistence of tachycardia at a high ventricular rate can lead to various degrees of ventricular dysfunction and even congestive heart failure.

The haemodynamic impairment induced by atrial fibrillation is usually a variable combination of loss of atrial kick, irregularity in ventricular response, and inappropriately rapid ventricular rate.[10] Depending on the type of underlying heart disease, different degrees of haemodynamic impairment may occur. The loss of atrial kick can remarkably decrease cardiac output, especially in patients with impaired diastolic function (i.e. with hypertensive heart disease or hypertrophic cardiomyopathy). The treatment of atrial fibrillation by rate control may therefore contemplate a variety of goals. These include improvement in quality of life by attenuating symptoms or arrhythmia-related complications, together with reduction of morbidity and (if possible) mortality. Precise endpoints have to be defined for each of these goals. A series of potential endpoints for acute and long-term rate control are:

Table II. Drugs for acute control of ventricular rate in atrial fibrillation

Drug	Time for rate control	Effect on ventricular rate	Loading dose (IV)	Maintenance dose (IV)	Limitations	Type of patients	Oral maintenance dose for long-term rate control (mg)
Digoxin	Hours	↓	0.25mg every 2 hours up to 1.5mg	0.125–0.25 mg/day	Hyper-adrenergic state	Elderly/CHF	0.125–0.375
Diltiazem	Minutes	↓↓	0.25–0.35 mg/kg over 2 min	5–15 mg/hour		Potentially all patients, also CHF (with caution)	120–360
Verapamil	Minutes	↓↓	0.075–0.15 mg/kg over 2 min	N/A	Negative inotropic effect		120–360
Esmolol	Minutes	↓↓	0.5 mg/kg over 1 min	0.05–0.2 mg/kg/min	Negative inotropic effect		N/A
Metoprolol	Minutes	↓↓	5mg every 5 min up to 15mg	N/A	Negative inotropic effect		50–200
Propanolol	Minutes	↓↓	0.15 mg/kg	N/A	Negative inotropic effect		80–240

CHF = congestive heart failure; **IV** = intravenous; **N/A** = not available; ↓ denotes a reduction – the number of arrows is indicative of the extent of the reduction.

- ventricular rate at rest;
- ventricular rate on 24h-Holter monitoring (average heart rate);
- ventricular rate during paroxysmal atrial fibrillation;
- pattern of ventricular rate changes during exercise;
- exercise duration and exercise tolerance;
- prevention/regression of rate-related symptoms;
- prevention/regression of atrial fibrillation-related left ventricular dysfunction or tachycardiomyopathy;
- prevention/regression of cardiac structural remodelling;
- prevention of atrial fibrillation-related morbidity;
- prevention of atrial fibrillation-related mortality.

2. Acute Rate Control

Medium/long-term rate control may aim to overcome a variety of adverse effects, whereas acute rate control focuses on rapidly stabilising patients' conditions by reducing ventricular rates within minutes or hours of treatment. Table II lists the agents (with their intravenous doses) that are used to achieve rapid rate control in patients with the various forms of atrial fibrillation.

Traditionally, acute rate control has been based (both in cardiology internal medicine departments) on the administration of digoxin.[5] However, studies have now shown that the effects of digoxin are not particularly rapid. For example, Roberts et al.[11] reported that achievement of rate control by digoxin takes an average of 9.5h in patients with atrial fibrillation/flutter. Moreover, almost half of these patients subsequently lost their rate control before being discharged. In addition, digoxin does not seem to be suitable for the treatment of paroxysmal atrial fibrillation; in a controlled study, digoxin failed to reduce the mean ventricular rate more than placebo.[7]

Despite its known limitations, digoxin is still widely used for rate control.[12] A survey of 2490 patients admitted to Canadian hospitals in 1994, revealed that digoxin was used in as many as 67–84% of patients with chronic and paroxysmal atrial fibrillation.[13] A cost-benefit analysis performed by Roberts et al.[11] indicated that digoxin-treated patients with atrial fibrillation have long hospital stays with high treatment and management costs. These findings all highlight the limitations of

using digoxin alone for acute rate control. However, digoxin should still be considered a drug of choice in patients with left ventricular dysfunction.[12]

The alternative drugs that are now available for acute rate control vary as to the rapidity and extent of their effects, and their potential limitations (table II). Relative contraindications exist for verapamil and β-blockers in patients with left ventricular dysfunction, where the negative inotropic effects of these drugs may be detrimental. Cautious use of diltiazem in the setting of congestive heart failure has been validated by a multicentre, randomised, double-blind, placebo-controlled study.[14] Many of the drugs used for acute rate control require intravenous administration with pump infusion, and are, therefore, best used either under telemetrically monitored conditions or in an intensive care unit (table II). Following the initial achievement of rate control, treatment may continue with oral administration of the same agents. Amiodarone has also been adopted for acute rate control in critically ill patients, despite its relatively low efficacy in the first hour after administration.[15,16] In particular, Clemo et al.[17] reported that ventricular rate began to slow within 30–60 minutes of intravenous administration of amiodarone, prior to improvements in systemic blood pressure in the absence of haemodynamic adverse effects. However, amiodarone cannot be recommended for atrial fibrillation lasting more than 24–48 hours, unless the patient has been receiving anticoagulants (with international normalised ratio in the therapeutic range for 3–4 weeks) or atrial thrombosis has been excluded by transoesophageal echocardiography. These precautions are made necessary by the known phenomenon of atrial stunning[18] and the consequent risk of embolism secondary to drug-induced atrial fibrillation conversion.

3. Long-Term Rate Control

Long-term rate control differs from acute therapy not only in its time setting but also in its goals. Whereas acute rate control aims to stabilise patients in order to gain the time needed to choose the best treatment for them, long-term control attempts to overcome a series of cardiac changes that tend to develop during chronic atrial fibrillation. Long-term therapy has to be carefully adapted to patients' individual characteristics in order to grant rate control during all their daily activities, including exercise. Moreover, it has to confer a satisfactory quality of life.

3.1 At Rest and During Exercise

Achievement of rate control at rest does not necessarily imply that the heart rate will remain under control during exercise. It has been known since 1924 that digoxin is unable to limit the excessive increase in ventricular rate during exercise in patients with atrial fibrillation.[5] Today, a series of alternatives to digoxin are available. Table III summarises the results of a recent survey of 45 randomised, controlled trials published between 1982 and 1997 regarding 15 drugs used for rate control in atrial fibrillation.[19] Several of the reported trials examined the effects of different agents on the heart rate reached during exercise and on exercise toler-

Table III. Analysis of pharmacological rate control studies according to the meta-analysis reported by Segal et al.[19]

Drug	No. of trials	Total no. of patients	Effect on HR at rest	Effect on HR during exercise	Effect on exercise tolerance
Digoxin	8	389	↓in 7/8 trials	Not ↓in 4/4 trials	↑ in 2/4 trials
Verapamil	5	88	↓ in 5/5 trials	↓ in 5/5 trials	↑in 3/4 trials
Diltiazem	5	219	↓ in 2/2 trials	↓ in 2/2 trials	↑ in 2/2 trials
β-Blockers	12	197	↓ in 7/12 trials	↓ in 9/9 trials	↓in 3/9 trials

HR = heart rate; ↓ denotes a reduction; ↑ denotes an increase.

ance. For example, in an open-label, randomised, crossover study, Farshi et al.[20] compared five different rate control regimens including digoxin, diltiazem, atenolol, digoxin plus diltiazem and digoxin plus atenolol. The results of this study showed that mean ventricular rate was significantly lower with digoxin plus atenolol than with digoxin plus diltiazem and that peak systolic blood pressure was lowest in the atenolol-treated group. A systematic review performed by Segal et al.[19] supported the concept that calcium channel antagonists (verapamil, diltiazem) do improve exercise tolerance.

For β-blockers and digoxin, contrasting results have been reported. In a study based on the cardiopulmonary exercise test involving patients with permanent atrial fibrillation, Lundstrom and Ryden[21] found that calcium channel antagonists were able to improve exercise capacity, peak oxygen uptake/consumption (VO_2) and workload at the anaerobic threshold. Nevertheless, this objective improvement in exercise tolerance was not associated with significant differences in maximal perceived exertion, as measured by patients' objective assessment (Borg scale). Taken together, these observations strongly underline the importance of exercise testing in the assessment of the appropriateness of rate control medications in individual patients.

The pattern of response of heart rate during exercise may vary considerably from patient to patient even during rate control treatment. Corbelli et al.[22] investigated the pattern of chronotropic response during exercise in a series of patients with permanent atrial fibrillation receiving treatment for rate control. Different patterns of chronotropic response were recorded in patients with permanent atrial fibrillation compared with control patients. Remarkably, all 19 patients with persistent atrial fibrillation presented an abnormal response during exercise (either inappropriate bradycardia, inappropriate tachycardia, or early tachycardia followed by inappropriate tachycardia).

3.2 24h-Holter Monitoring

Diurnal variations in sinus rhythm occur due to the influence of the autonomic nervous system. Patients with atrial fibrillation show similar percentage changes with respect to overall (24h) average rate compared with controls.[23] Therefore, diurnal variations in ventricular rate during atrial fibrillation seem to mirror those occurring during sinus rhythm. However, in the absence of any treatment, mean ventricular rates are significantly higher with atrial fibrillation than with sinus rhythm, even on 24h-Holter monitoring.

Many studies have assessed the effects of different rate control therapies during atrial fibrillation by 24h-Holter monitoring. In 1985, Theisen et al.[24] examined the effects of single-dose and long-term treatment with diltiazem (90mg three times daily) in 10 patients with stable atrial fibrillation. In half of the patients, the longest and shortest RR intervals lengthened proportionately, whereas in the remaining five patients there was a disproportionate increase in the longest interval. This could be explained by an increase in atrial fibrillation rate in both groups, accompanied only in the second one by a prolongation in the atrioventricular node refractory period (both modifications would widen the RR interval by increasing the concealed conduction phenomenon).

Two years later, in 1987, Channer et al.[25] used Holter monitoring to compare three alternative drug regimens, namely, standard-dose digoxin, double-dose digoxin and standard-dose digoxin plus verapamil, which were in use at the time for rate control. They found that doubling the maintenance dosage of digoxin reduced both maximum and minimum heart rate but did not decrease overall heart rate variability (because of the more profound nocturnal bradycardia). Furthermore, daytime pauses were significantly prolonged (the serum digoxin toxicity threshold was reached in 36% of patients but without development of symptoms). The addi-

tion of verapamil had a similar effect on maximum heart rate but a less marked effect on minimum rate, leading to an overall reduction in variability.

More recently, Hnatova et al.[26] reported that digoxin decreases the extremes of ventricular cycle length variability during fast episodes of paroxysmal atrial fibrillation without affecting the mean variability of ventricular periods. In 1999, Farshi et al.[20] compared the effects of digoxin, diltiazem, atenolol, digoxin plus diltiazem, and digoxin plus atenolol in patients with atrial fibrillation. The two combination regimens granted the greatest decrease in mean ventricular rate. Atenolol alone was more effective than either digoxin or diltiazem alone. Patients treated with digoxin maintained similar circadian variability in ventricular rate to those treated with diltiazem. By comparison, atenolol lowered the rate predominantly during the daytime without abolishing the circadian pattern. The most effective regimen for attenuating increases in the ventricular rate over the 24h period was digoxin plus atenolol, probably because of a synergistic effect in reducing adrenergic activity while augmenting vagal activity.

Long-term treatment with amiodarone was evaluated by 24h-Holter monitoring in the congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT).[27] A significant long-term reduction of average and maximum ventricular rates was found during amiodarone treatment, compared with placebo. However, in view of its relevant adverse effects,[28] extreme caution is needed if amiodarone is used for rate control only.[29,30] The presence or absence of congestive heart failure, in patients with atrial fibrillation, has different effects on circadian variations of average ventricular rate. Hayano et al.[31] found that patients with severe congestive heart failure have a reduced range of ventricular rate variations on 24h-Holter monitoring.

Overall, both the spontaneous variability that occurs in ventricular rate during atrial fibrillation and the varying effects of drug treatments used in rate control, highlight the usefulness of 24h-Holter monitoring for more accurate assessment of individual patients. Indeed, 24h-Holter monitoring provides the only way of exploring diurnal and nocturnal ventricular rate variations in individual patients receiving particular rate control treatments. Moreover, it can reveal therapy-related alterations (long pauses or ventricular arrhythmias) that usually go undetected at routine ECG. Detection at Holter monitoring of phases of low ventricular rate with pauses ≥3.0 seconds during treatment with drugs acting on the atrioventricular node leads to implantation of a VVI or VVI-R pacemaker to correct excessive bradycardia (although detailed clinical indications have yet to be defined).[10]

3.3 What is the Optimal Ventricular Rate During Atrial Fibrillation?

As shown in figure 1, a series of many factors can influence the mean ventricular rate during atrial fibrillation. The definition of the optimal ventricular rate during atrial fibrillation (i.e. the ventricular rate at which the haemodynamic performance is the best in any single patient) is rather tricky. Indeed, assessment of the best target for rate control remains to be defined in different subsets of patients. Table IV summarises current recommendations for rate control based on mean ventricular rate at rest, during exercise and at 24h-Holter monitoring. The target of rate control is often defined as ventricular rates of ≤80–90 bpm at rest and ≤110–115 bpm during moderate exercise.

The problem of the optimal ventricular rate during exercise appears to be a crucial point in rate control. In various species of mammals, a linear relationship has been demonstrated between resting heart rate and life expectancy.[36] Thus animals with the highest resting heart rates such as mice and hamsters, have the shortest life expectancy, whereas at the other extreme elephants and whales have the longest expectancy. However, humans constitute an

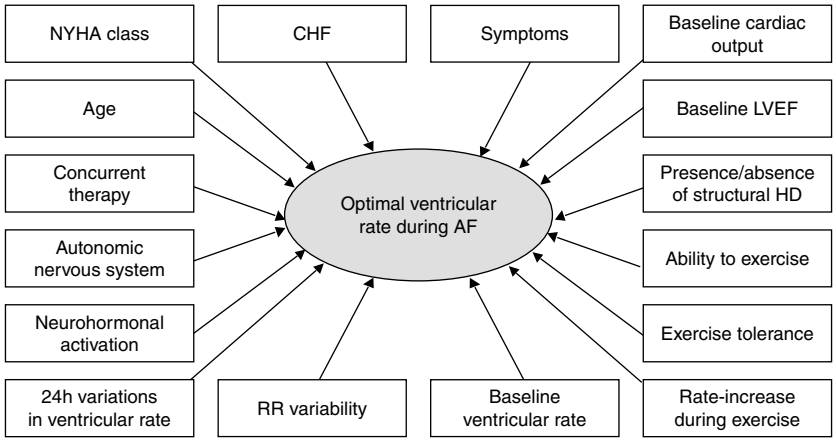

Fig. 1. Factors conditioning the optimal ventricular rate during atrial fibrillation (AF). **CHF** = chronic heart failure; **HD** = heart disease; **LVEF** = left ventricular ejection fraction; **NYHA** = New York Heart Association.

exception to this general tendency. We do not know how much this general effect is relevant to the individual patient with regards to the mean ventricular rate during atrial fibrillation, or whether a reduction in mean ventricular rate with respect to baseline would translate into an improvement in survival. However, previous trials dealing with the long-term survival of patients with congestive heart failure have shown that the effect on mortality (i.e. worsening or improvement in survival) was strictly related to changes in heart rate obtained by active treatment.[37]

As shown in table IV, the current guidelines for rate control involve the assessment of ventricular rate at rest, during exercise or during daily activities. Indeed, no clear definition currently exists of how to monitor the appropriateness of rate control medications. Extensive use of exercise testing and Holter monitoring to improve rate control interventions would imply increased costs for the management of patients with chronic persistent atrial fibrillation. An interesting suggestion for the assessment of ventricular rate in patients with chronic persistent atrial fibrillation has been formulated by Wasmer et al.[38] In their study, a group of 39 patients with chronic persistent atrial fibrillation, with or without medications for rate control, underwent assessment of ventricular rate control after 5 minutes of rest, after walking 50 yards (approximately 46m) and after 1 minute of stair-stepping, as well as after 24h-Holter monitoring. The results indicated that it is possible to calculate the average ventricular rate, the minimum daily ventricular rate and the average maximum ventricular rate, as assessed by Holter moni-

Table IV. Recommended ventricular heart rate targets of rate control

Study (year)	VHR at rest (bpm)	VHR during exercise		VHR at 24h-Holter
		moderate (bpm)	maximal	(bpm)
Crijns et al. (1998)[32]	<90	<110	N/A	N/A
Falk (1997)[5]	<90	N/A	N/A	N/A
AFFIRM (1997)[33]	≤80	≤110	N/A	≤100
Levy et al. (1998)[34]	60–80	90–115	N/A	N/A
Naccarelli (2000)[35]	≤80	N/A	<80% max HR	≤90

AFFIRM = Atrial fibrillation follow-up investigation of rhythm management; **HR** = heart rate; **N/A** = not available; **VHR** = ventricular heart rate.

toring, by means of simple formulas containing measurements of resting heart rate, walking heart rate and heart rate after 1 minute at stairs. If these findings are confirmed in a larger patient population, this approach may provide a simple and inexpensive way of assessing the adequacy of rate control in ambulatory patients.

3.4 Indices of Left Ventricular Function

3.4.1 Tachycardiomyopathy and Rate-Related Haemodynamic Impairment

A series of haemodynamic and structural effects have been described as a consequence of high ventricular rate lasting for weeks and months, which may develop with either regular tachycardia or atrial fibrillation. These can be summarised as follows:[9]

- reduction of ejection fraction;
- diastolic dysfunction;
- elevation of filling pressure;
- increase of end-systolic pressure;
- increase of end-diastolic volume;
- reduction of cardiac output;
- elevation of pulmonary artery pressure;
- elevation of systemic vascular resistance;
- reduction of contractile reserve;
- increase in plasma levels of atrial natriuretic peptide, epinephrine (adrenaline), norepinephrine (noradrenaline) and aldosterone;
- loss of myocytes with reactive cellular hypertrophy;
- accumulation of glycogen into the myocardial cells;
- interstitial fibrosis;
- change in myocytes spatial organisation.

The immediate haemodynamic effects at the onset of atrial fibrillation are related to high ventricular rate and loss of atrial kick. However, following persistence of ventricular rate higher than 120 bpm, other haemodynamic effects secondary to chronic tachycardia can develop.[9] In experimental models of chronic tachycardia, a definite time course has been described for the development of the haemodynamic impairment.[9] As shown in figure 2, if rate or rhythm control is accomplished, regression of haemodynamic impairment occurs with different time courses for cardiac output, left ventricular ejection fraction, ventricular filling pressure, and end-diastolic and end-systolic volume.

A series of clinical observations has led to the concept of tachycardiomyopathy. This refers to a form of tachycardia-induced left ventricular dysfunction due to high ventricular rates (>120 bpm), which is reversible with rate or rhythm control.[39-42] By definition, tachycardiomyopathy is an impairment of left ventricular function secondary to chronic tachycardia, partially or completely reversible with normalisation of the ventricular rate.[43] In a patient with atrial fibrillation with intermediate or fast ventricular rates and evidence of left ventricular dysfunction, the clinical challenge is to define to what the extent of the ventricular dysfunction is dependent on tachycardiomyopathy and how much it is due to an underlying primary disease. This intriguing question is rather like the 'chicken and the egg' dilemma.[43] The problem is of great clinical relevance since some patients who had been referred to a heart failure clinic for transplantation did not

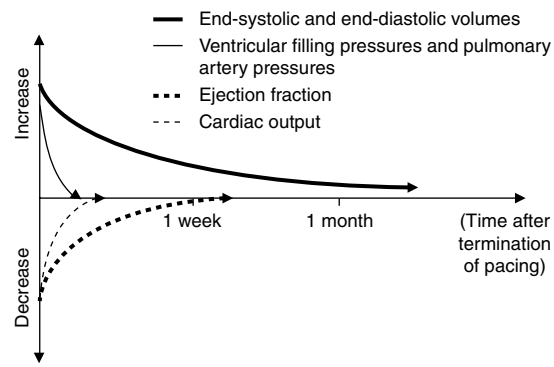

Fig. 2. Time course of the normalisation of haemodynamic parameters in experimental tachycardiomyopathy after termination of rapid atrial pacing (reproduced from Schumacher and Luderitz,[9] with permission from Elsevier Science).

require a transplant because they were actually affected by tachycardiomyopathy, which was reversed after adequate rate control.[40] Van den Berg et al.[44] hypothesised that some patients with chronic atrial fibrillation and left ventricular dysfunction who do not present with overt tachycardiomyopathy, may have a concealed form of this condition. This so-called concealed tachycardiomyopathy could be due to a non-physiological rate response or a loss of rate control during exercise and daily activity, or even to irregularities in ventricular rate.

Among the various types of response to exercise exhibited by patients with chronic atrial fibrillation, inappropriate tachycardia is fairly frequent[22] and could form the basis for the development of some form of ventricular dysfunction. Moreover, irregular heart rate, itself, could induce haemodynamic impairment, as demonstrated in acute studies.[45,46] In a chronic setting, negative effects of irregular heart rate have recently been reported in patients with atrial fibrillation and 'normal' ventricular response, who were undergoing radio-frequency ablation of the atrioventricular node. Evaluating the effects of a regular ventricular rate obtained by radio-frequency ablation of the atrioventricular node compared with baseline, Ueng et al.[47] recorded a rapid and marked haemodynamic improvement with a reduction in filling pressure and a 10% increase in cardiac output. Twelve months after ablation, patients showed an improvement in symptoms and overall activity, coupled with a reduction in New York Heart Association (NYHA) class, hospitalisation frequency and episodes of congestive heart failure.[47] Furthermore, patients who were undergoing atrioventricular node ablation had long-term improvements in exercise tolerance and left ventricular ejection fraction compared with patients undergoing medical rate control, who showed no change in any of the main haemodynamic or echocardiographic parameters.[47]

The published data on the effects of atrioventricular node ablation on left ventricular systolic performance are summarised in table V. The effect on left ventricular ejection fraction was characterised by a general improvement, while the percentage of patients showing some evidence of tachycardiomyopathy ranged from 18–63%. However, no epidemiological conclusion is possible, due to differences in the criteria for assessing the degree of left ventricular dysfunction, in the methods used for follow up, and in the definitions used for tachycardiomyopathy.

The Ablate and Pace Trial[52] offers valuable information regarding the prevalence of tachycardia-related cardiomyopathy in patients with atrial fibrillation who are affected by left ventricular dysfunction. Sixty-three patients with atrial fibrillation (chronic in 33% of patients) underwent atrioventricular node ablation plus pacemaker implant. At baseline, mean left ventricular ejection fraction was 32 ± 8% with a mean ventricular rate of 90 ± 26 bpm. At

Table V. Data from literature on tachycardiomyopathy or systolic dysfunction associated with atrial fibrillation treated with ablation of the atrioventricular node

Study (year)	n	LVEF cut-off for systolic dysfunction (%)	Mean LVEF (± SD)		Patients with tachycardiomyopathy (%)
			baseline	follow up	
Rodriguez et al. (1993)[41]	12	≤50	43 ± 8	54 ± 7	25
Edner et al. (1995)[42]	14	<50	32 ± 11	45 ± 11	21
Geelen et al. (1997)[48]	7	≤50	N/A	N/A	42
Brown et al. (1997)[49]	12	<50	29 ± 9	N/A	25
Dupuis et al. (1997)[50]	8	<50	31 ± 11	48 ± 12	63
Twidale et al. (1998)[51]	22	<45	32 ± 9	42 ± 15	18
Redfield et al. (2000)[52]	63	≤45	31 ± 9	41 ± 17	25

LVEF = left ventricular ejection fraction; **n** = number of patients; **N/A** = not available.

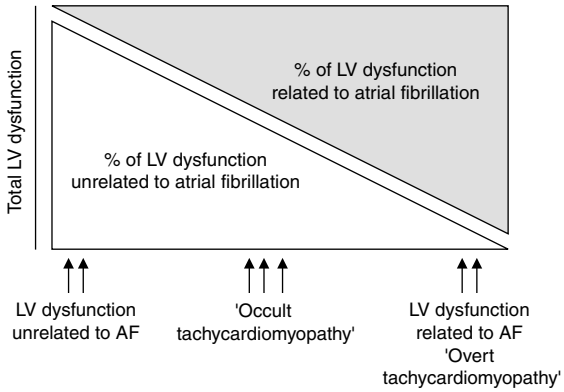

Fig. 3. Possible and variable relationships between atrial fibrillation (AF) and left ventricular (LV) dysfunction in patients presenting with chronic persistent atrial fibrillation associated with LV dysfunction. As schematically shown in the figure, the overall spectrum of interplay between atrial fibrillation and LV dysfunction is complex: except in extreme conditions when LV dysfunction is clearly related or clearly unrelated to atrial fibrillation, LV dysfunction may be partly related to atrial fibrillation and partly due to other causes.

12 months, the left ventricular ejection fraction either increased by ≥15% or reached >45% in 25% of patients. This subset seems to have obtained regression of a form of ventricular dysfunction due to tachycardiomyopathy.

Chronic tachycardia should be considered an important warning sign of tachycardiomyopathy. Indeed, if tachycardia is consistently present for more than 10–15% of the day, it will lead to ventricular dysfunction.[53] Even only relatively high ventricular rates can cause this kind of dysfunction. In an echocardiographic study in implanted patients, Chew et al.[54] showed that overnight atrial pacing at 80 bpm was associated with worse diastolic and systolic functions the following morning with respect to pacing at 50 bpm.

Improvements in haemodynamic and ventricular dysfunction obtained by sinus rhythm restoration or by rate control can be complete, partial or absent. The key point is whether the response is predictable. Few studies based on the evaluation of long-term changes in left ventricular function have compared the option of electrical cardioversion (when suitable) with rate control. However, Paelinck et al.[55] reported that low-dose dobutamine stress echocardiography may be able to predict the recovery of left ventricular dysfunction due to atrial fibrillation. Sixty patients presenting with atrial fibrillation for at least 3 months underwent dobutamine stress echocardiography. Those who showed an improvement in left ventricular ejection fraction during the test also showed corresponding benefits during follow up, whereas those with no improvement did not. However, further data are required to confirm the ability of dobutamine stress echocardiography to predict the recovery of left ventricular dysfunction due to tachycardiomyopathy.

In clinical practice, a diagnosis of tachycardiomyopathy should be considered in all patients with atrial fibrillation coupled with a ventricular systolic dysfunction that does not clearly pre-date the onset of atrial fibrillation.[52] The relationship between atrial fibrillation and ventricular dysfunction is probably more complex than simply cause and effect (figure 3). While it is likely that in some patients left ventricular dysfunction occurs as a direct result of atrial fibrillation (i.e. true and overt tachycardiomyopathy), at the other end of the spectrum there may be patients in whom no relationship exists at all. However, as shown in figure 3, there may also be intermediate patients in whom a primary form of left ventricular dysfunction coexists with a secondary component provoked by a concealed or occult tachycardiomyopathy.

3.4.2 Rate Control in Patients with Heart Failure

Another major factor in the decision whether and how to use rate control as a treatment strategy for atrial fibrillation is the presence of heart failure. Indeed, as many as 10–50% patients with chronic heart failure have associated atrial fibrillation.[56] In almost all respects, the management of atrial fibrillation in the presence of mild-to-moderate heart failure remains a difficult task. Van Den Berg et al.[57] evaluated the outcome of 24 patients presenting with NYHA class II-III heart failure who were submitted to electrical cardioversion. The procedure was completely unsuccessful in 25% of patients and after 6 weeks overall sinus rhythm was maintained in only 37.5% of patients. No change in peak VO_2 was observed in patients who regained sinus rhythm with respect to those who stayed in atrial fibrillation.

Digoxin has always been the traditional agent used for rate control in patients with both atrial fibrillation and chronic heart failure;[12] and still maintains its role as a first-line agent, especially in the presence of unstabilised heart failure. However, the limitations of digoxin in achieving optimal control of ventricular rate during exercise and daily activity have prompted a search for alternative pharmacological or non-pharmacological options for patients with heart failure.

β-Blockers, especially carvedilol, appear to be an attractive alternative, in view of their favourable effects both on heart failure and rate control.[58,59] A series of trials has validated the use of β-blockers in the treatment of heart failure, independently of the presence/absence of atrial fibrillation. Over 10 000 patients with heart failure were enrolled in more than 20 published placebo-controlled trials assessing the use of both selective β_1-receptor blockers (metoprolol and bisoprolol) and carvedilol (which blocks α_1-, β_1- and β_2-receptors). The results of these trials clearly indicated that β-blockers should be prescribed, with appropriate drug titration, to all patients with heart failure and left ventricular systolic dysfunction without contraindications (class I indications, level of evidence: A).[60]

In regard to the prognostic effects of β-blockers, the Cardiac Insufficiency Bisoprolol Study II (CIBIS II)[61] showed that the benefit of bisoprolol on mortality, cardiovascular mortality and hospitalisation for heart failure differed between patients in sinus rhythm and patients with atrial fibrillation (significance was not reached in the subgroup of patients with atrial fibrillation). In a population of 28 patients with heart failure (NYHA class II) due to idiopathic dilated cardiomyopathy who were receiving chronic digoxin treatment for persistent atrial fibrillation, Agarwal and Venugopalan[58] initiated carvedilol therapy in 14 patients, in addition to digoxin. During the 3-month study period, the patients in the carvedilol group showed significant reductions in resting and maximal heart rates during exercise, along with improved treadmill exercise time. These results probably reflect the superiority of carvedilol over digoxin in rate control during exercise and daily activities.

In a prospective analysis of data from the US Carvedilol Heart Failure Trials Program, Joglar et al.[59] found that only 12.4% of the entire randomised population also had atrial fibrillation and that almost all these patients were on digoxin therapy. The data indicated that carvedilol provided significant improvements in ejection fraction and in global assessment, while non-significant reductions were recorded in resting pulse, in hospitalisations/deaths and in total number of deaths.[62] The small sample size may have limited the power of this evaluation.

Further data are required to assess the impact on prognosis of β-blockers when heart failure is associated with atrial fibrillation. However, in view of their positive effects on heart rate, β-blockers, especially carvedilol, should currently be considered a treatment of choice for rate control in atrial fibrillation patients with stabilised heart failure.

The effects of atrioventricular node ablation plus pacemaker implant and pharmacological rate control have been compared in 54 patients with chronic atrial fibrillation and heart failure over a 10-month period.[63] No long-term change in fractional shortening or left ventricular ejection fraction was found in either treatment group. An entry requirement was a resting heart rate >90 bpm on enrolment; at 10 months, a significant reduction in palpitation-score was observed only in the group who underwent ablation.

In patients who have chronic persistent atrial fibrillation as well as chronic heart failure (NYHA Class III) and who require pacemaker implantation due to atrioventricular node ablation or slow ventricular rate, the traditional choice is a VVIR device with a catheter stimulating from the right ventricular apex. Recently, biventricular devices have been proposed as a new type of pacing aimed at attenuating heart failure by correction of left ventricular dyssynergy due to intraventricular conduction delay (occurring, for example, during non-physiological ventricular activation from the right ventricular apex).[64-66] The choice of pacing modality is particularly relevant when the device is to be used for rate control in combination with atrioventricular node ablation, in view of its potential haemodynamic and clinical implications. Controversial data have been reported on the effects of biventricular pacing in patients with atrial fibrillation associated with chronic heart failure and a wide QRS complex who were implanted because of slow ventricular rate or atrioventricular node ablation. Two studies, which included a small number of patients,[67,68] showed that biventricular pacing seems to provide major clinical advantages with respect to right ventricular pacing. However, in a recent randomised, controlled study[69] biventricular pacing did not lead to significant advantages according to intention-to-treat analyses. Further studies are needed to assess the cost-benefit ratio of biventricular pacing when used in combination with atrioventricular node ablation for rate control in patients with heart failure.

3.5 Atrial Fibrillation and Quality of Life

Quality of life is a particularly important treatment endpoint in chronic conditions, such as atrial fibrillation, where patients expect to participate as partners in therapeutic decisions. To allow comparisons among different groups of patients, quality of life needs to be measured by standardised tools. One of the most widely used validated instruments is the Medical Outcomes Study Short-Form 36 Health Survey (SF-36). A series of studies[70,71] performed with the SF-36 questionnaire have shown that patients with different forms of atrial fibrillation have an impaired quality of life compared with age-matched controls. Remarkably, quality of life is significantly affected even by the silent form of atrial fibrillation.[72] At present interventions for atrial fibrillation management have to be evaluated also in terms of quality of life and this has been done in most recent prospective trials (i.e. the Pharmacological Intervention in Atrial Fibrillation [PIAF][73] and the Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM][74]).

3.6 Management of Atrial Fibrillation: Rate versus Rhythm Control

Management of atrial fibrillation may be based either on rate control (to control the ventricular rate response) or rhythm control (to maintain sinus rhythm). It should be noted that rhythm control is more expensive and requires a higher number of hospitalisations.[73] The potential advantages and disadvantages of these two alternative strategies are summarised in table VI. The overall improvement in symptoms obtained with both rhythm and rate control raises the question as to which is the better strategy. A series of randomised clinical trials have been undertaken to compare the benefits and risks of the two approaches.

Table VI. Benefits, risks and outcomes for rhythm control (cardioversion) and rate control treatments for atrial fibrillation management (reproduced from Coletta et al.,[75] with permission from Elsevier Science)

Rhythm control (cardioversion)	Rate control
Possible benefits	
Improved overall cardiac efficiency	Avoidance of antiarrhythmic drugs
Reduced thromboembolic risks	Benefits of continued anticoagulant therapy
Reduced risks for concurrent anticoagulant therapy	
Potential risks	
Proarrhythmic risks of antiarrhythmic drugs	Risk of continued anticoagulation
Risk due to adverse effects of antiarrhythmic drugs	Risk of tachycardiomyopathy if ventricular rate control is inadequate
Risk of reduced perceived need for anticoagulants if sinus rhythm is restored	
Acute relapse of atrial fibrillation precipitating worsening heart failure	
Actual outcome	
Reduced use of anticoagulants	Trend towards reduced mortality
High rate of atrial fibrillation recurrence	Lower costs
Need for more cardioversion procedures	More symptoms due to arrhythmia
Possible increase in stroke risk	
Increase in hospitalisations for heart failure	

In the PIAF study,[73] 52 patients were randomly allocated to rate control with diltiazem or to rhythm control with amiodarone. The patients receiving amiodarone not only showed better maintenance of sinus rhythm, but also exhibited greater improvement in symptoms and superior exercise tolerance. However, this did not translate into improved quality of life with respect to the diltiazem group. Patients treated with amiodarone also had higher rates of hospital admission and of drug discontinuation due to adverse effects.

A further comparison of the long-term effects of rate and rhythm control is provided by the Strategies of Treatment of Atrial Fibrillation (STAF) pilot trial.[76] This study randomly assigned 200 patients with atrial fibrillation either to rate control or to a strategy based on cardioversion and maintenance of sinus rhythm with class IA antiarrhythmic drugs or amiodarone. The results at a mean follow up of 20 months broadly confirm the findings of the PIAF trial, with few long-term differences emerging in terms of morbidity or symptoms. In the rhythm control group, the failure rate at 12 months was rather high (about 60%). However, significantly fewer strokes were recorded with rhythm control than with rate control. Interestingly, quality of life improved in both treatment groups, independently of achievement of sinus rhythm. This result may be partially explained by the greater amount of patient guidance made available during the treatment period.[77]

The Mayo Clinic group[78] have reported data on long-term mortality after atrioventricular node ablation plus pacemaker implant performed for rate control in patients with atrial fibrillation (chronic in 50%). No difference was found in the long-term overall survival between patients who underwent ablation and medically treated patients, even within the heart failure and coronary artery disease subsets.

To help define the optimal approach in terms of morbidity and mortality, the AFFIRM study[74] enrolled 4060 patients (mean age 69.7 years) on the basis of the following inclusion criteria: age ≥65 years (or <65 years with a risk factor for stroke); atrial fibrillation with ≥6 hours total duration in the past 6 months; and atrial fibrillation documented by

an electrocardiogram in the past 12 weeks or duration of continuous atrial fibrillation <6 months. Over a 5-year follow-up period, the prevalence of sinus rhythm declined in both the rate and rhythm control arms (by nearly 40% and over 60%, respectively). There was no difference between the two groups with regard to the primary endpoint of total mortality at a mean follow up of 3.5 years, although a non-significant trend towards higher mortality was found in the rhythm control arm. Further non-significant trends, in favour of rate control, were observed in the occurrence of disabling ischaemic stroke, hospitalisation and new arrhythmias. Some of these findings may be explained by the higher rate of warfarin discontinuation that occurred in the rhythm control group. The study supports the concept that in the type of population enrolled, rate control is an acceptable primary strategy. A similar conclusion was reached by the Rate Control Versus Electrical Cardioversion for Persisitent Atrial Fibrillation (RACE) study,[79] which enrolled 522 patients with persistent atrial fibrillation or flutter who had undergone one or two electrical cardioversions in the previous 2 years.

3.7 Treatment Options for Rate Control

The most appropriate treatment options for specific subsets of patients (in terms of improvement of symptoms and cardiac performance, reduction in morbidity and mortality, and cost-benefits) remain to be defined. This issue is of great importance since rate control can be achieved by a broad range of interventions (figure 4), ranging from the administration of digoxin, or more recently developed drugs, to interventional procedures such as atrioventricular node ablation or modification. Experimental proposals have also been made, including the use of adenosine agonists,[80] parasympathetic stimulation[81,82] or even gene therapy[83] (based on experimental evidence of focal modification of the electrical conduction of the atrioventricular node by viral gene transfer).

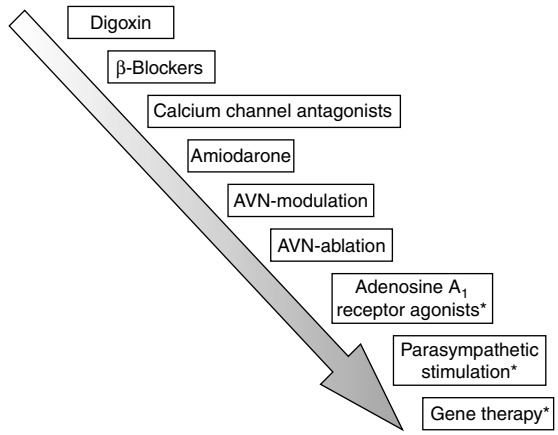

Fig. 4. Temporal evolution of treatments for rate control: well-established, new and investigational approaches. **AVN** = atrioventricular node. * Investigational treatment.

A series of suggestions for rate control in current clinical practice, primarily based on the type of underlying heart disease and on left ventricular performance, are shown in table VII (approved and currently used treatments only are included). At present, the choice among the various options has to be based on clinical assessment and evaluation of underlying heart disease and haemodynamic impairment.

In patients who do not show evidence of heart failure or ventricular dysfunction, the preferred medications are calcium channel antagonists or β-blockers. In this subset of patients, digoxin alone is not recommendable as a single drug therapy because of its limited efficacy during exercise. However, digoxin may be combined with calcium channel antagonists or β-blockers to improve efficacy by a synergetic effect when appropriate rate control by a single drug is not achieved.

For patients with ischaemic heart disease, β-blockers are the treatment of choice. In patients with chronic obstructive pulmonary disease, where β-blockers are specifically contraindicated, rate control is primarily based on calcium channel antagon-

Table VII. Treatment options for rate control based on various cardiovascular conditions (reproduced from Blitzer et al.,[84] with permission from Blackwell Publishing)

Treatment option	No HD	Hypertension	Ischemic HD	CHF	COPD
First-line	Calcium channel antagonists	Calcium channel antagonists/β-Blockers	β-Blockers	Digoxin	Calcium channel antagonists
Second-line	β-Blockers	β-Blockers/Calcium channel antagonists	Calcium channel antagonists/Digoxin	β-Blockers	
Less effective/ desirable	Digoxin	Digoxin	Ablation & Pace	Amiodarone, Ablation & Pace	Digoxin

Ablation & Pace = atrioventricular node ablation and pace maker implant; **CHF** = congestive heart failure; **COPD** = chronic obstructive pulmonary disease; **HD** = heart disease.

ists. In patients with chronic heart failure, digoxin maintains its role as a first-line agent. At the same time, β-blockers, especially carvedilol, are an attractive alternative, in view of their favourable effects on both heart failure and rate control.[58,59] It should be noted that digoxin is to be preferred in patients with unstabilised heart failure, in whom the use of β-blockers and calcium channel antagonists is specifically contraindicated.

There are certain clinical settings where rate control is particularly difficult or using medications requires special caution. For instance, atrial fibrillation in the setting of brady-tachycardia syndrome usually requires pacemaker implantation. In athletes with paroxysmal atrial fibrillation, bradycardia may limit the use of rate control drugs. When atrial fibrillation is the result of thyrotoxicosis, appropriate rate control may be a difficult target until thyroid function has been normalised.

Another possible drug for rate control is clonidine, which was originally conceived as an antihypertensive agent. At doses that modestly lower diastolic blood pressure, clonidine exerts electrophysiological effects on the sinus node.[85] Therefore, the drug has been evaluated both for acute rate control in haemodynamically-stable recent-onset atrial fibrillation[86,87] and (in combination with digoxin) for chronic atrial fibrillation.[88] The results of these studies lead us to think that clonidine could represent a useful option only for selected patients not suitable for β-blockers or calcium channel antagonists. However, further studies are needed to evaluate its effects during 24h-Holter monitoring and exercise tests. Moreover, the characteristics of those atrial fibrillation patients who stand to benefit from clonidine remain to be identified.

A non-pharmacological alternative for rate control is atrioventricular node ablation coupled with pacemaker implantation. Currently, this so-called ablate and pace strategy is indicated when drugs (even in combination) fail to achieve appropriate rate control.[10] In clinical practice, only a small fraction of patients seem to require atrioventricular node ablation. In the AFFIRM trial,[74,89] rate control was based either on pharmacological treatment (digoxin and/or β-blockers, calcium channel antagonists) or on atrioventricular node ablation coupled with pacemaker implantation; however, the latter therapeutic option was applied in only 5% of patients randomised to the rate control strategy. The concerns surrounding atrioventricular node ablation are mainly related to its irreversible effects on atrioventricular conduction, leading to pacemaker dependency. This strategy is also likely to preclude subsequent use of innovative non-pharmacological treatments aimed at curing atrial fibrillation that are currently under investigation.[10] Thus, age is probably an important factor in the decision whether to implement atrioventricular node ablation and it might be advisable to limit this treatment option to elderly patients. A possible alternative to atrioventricular node ablation could be atrioventricular node modification, where catheter ablation is used to modify atrioventricular node conduction by elimi-

nating the posterior input to the atrioventricular node only, without induction of a complete block. This technique can reduce the ventricular rate during atrial fibrillation, but it has limitations and is rarely used at present.[10]

4. Conclusion

In light of recent evidence, ventricular rate control has now become an acceptable mode of long-term management of various forms of atrial fibrillation, providing a cost-effective alternative to rhythm control. Rate control is capable of improving symptoms, quality of life and left ventricular function. It may also reduce the need for hospitalisation. Definitive guidelines on when to use rate over rhythm control are required. The global effects of these two alternative options on mortality in specific subgroups of patients are currently under evaluation.

Although two randomised trials[74,79] indicate that, in patients similar to those enrolled, rate control is an acceptable primary strategy, at present, the choice between rate and rhythm control has to be based on clinical judgement and remains patient-specific. In patients with left ventricular diastolic dysfunction, who need to conserve atrioventricular synchrony, pharmacological attempts should be made to maintain sinus rhythm. However, the limited efficacy of current pharmacological options for maintaining sinus rhythm in the long term (<40–60% efficacy at 1 year) suggests that many patients who are typical candidates for rhythm control will eventually be destined to rate control.

With the exception of patients with heart failure, digoxin alone should no longer be considered a first-line treatment for either acute or long-term rate control. In general, long-term control should be primarily based on the use of β-blockers and/or calcium channel antagonists, with or without the addition of digoxin. In some selected patients, clonidine or amiodarone may also be indicated, although further data are required to obtain a more appropriate assessment of the benefit-risk profile of these two agents.

Choice of the most appropriate agent should be based on clinical evaluation, considering the presence of underlying heart disease (as indicated in table VII), concurrent diseases and tolerance to the drug regimen. In the presence of chronic heart failure, appropriate titration of β-blockers, especially carvedilol, with/without digoxin is to be recommended. Exercise testing and Holter monitoring may provide useful information for individual tailoring of rate control. The target of rate control is often defined as ventricular rates of ≤80–90 bpm at rest and ≤110–115 bpm during moderate exercise (see table IV).

One non-pharmacological treatment for rate control is atrioventricular node ablation. Since atrioventricular node ablation inevitably leads to pacemaker dependency, this option must be limited to patients with excessive ventricular rate not amenable to pharmacological treatment who also have ventricular dysfunction and/or are elderly. In patients with tachycardiomyopathy, atrioventricular node ablation is associated with reductions in symptoms and improvements in quality of life and cardiac function. The greatest limitations of atrioventricular node ablation are its irreversibility, pacemaker dependency and the loss of atrioventricular synchrony. Moreover, atrioventricular node ablation precludes subsequent use of possible future treatments (such as pulmonary vein disconnection and/or ablation of the atrial substrate) aimed at curing atrial fibrillation with long-term maintenance of sinus rhythm, which have yet to be completely validated or are currently restricted to a few selected patients.

Another possible non-pharmacological treatment for rate control is atrioventricular node modulation. This approach aims to decrease ventricular rate by radiofrequency applications without the need for pacemaker implant. At present, however, this rather

tricky procedure is rarely used in view of its limited efficacy and the risk of atrioventricular block.

Atrioventricular node ablation coupled with pacemaker implantation (the so-called ablate and pace strategy) is a non-pharmacological rate control option that can be used in patients with or without heart failure. Further studies are required to assess whether biventricular pacing in patients with heart failure who are candidates for atrioventricular node ablation may offer clinical advantages with respect to conventional VVIR pacing from the right ventricular apex.

Recently, prospective studies have been planned to compare rhythm control with rate control coupled with anticoagulation. However, specific guidelines need to be defined on how to implement rate control strategies in clinical practice, indicating when it is appropriate and cost-effective to use drugs or, alternatively, atrioventricular node ablation in various subsets of patients, considering age, underlying heart disease and clinical presentation. Moreover, the ideal target of rate control needs to be better defined. It is clear that the appropriateness of rate control has to be based on the achievement of a target heart rate (≤80–90 bpm at rest), but it is not clear whether 24h-Holter monitoring and exercise tests are required in all patients, or whether quality of life and cardiac performance should be secondary, or even primary, endpoints.

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