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Is mean heart rate a reliable predictor in the pharmacotherapy of patients with atrial fibrillation?

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Abstract

Background: *Atrial fibrillation (AF) is the most common form of cardiac arrhythmia. A number of studies have demonstrated that heart rate control is the first line therapy for patients with AF. However, the correct ventricular rate and the parameters to be assessed are still open to question. The aim of the study was to evaluate whether mean heart rate (mHR) in 24-hour ECG Holter monitoring (HM) is useful parameter for the assessment of ventricular rhythm control in patients with AF. Additionally, we investigated whether other parameters such as episodes of tachy AF, irregularity of rhythm and the patient's awareness of "palpitations" play an important role in controlling ventricular rate in AF.*

Methods: *Patients with chronic brady-tachy AF who had undergone VVI pacemaker implantation between 2 and 9 days earlier (a mean of 5.6 days previously) with optimal pharmacotherapy and mHR below 90 bpm were enrolled in this study. The studied parameters included mHR and the coefficient of irregularity (CI), based on HM and the percentage of fast ventricular rates (tachy AF episodes defined as a heart rate of > 120 bpm) derived from the pacemaker memory data. Symptoms such as "palpitations" were marked with a "+" over a period of 24 hours.*

Results: *Forty two patients (18 male, 24 female) with a mean age of 70.2 ± 8 years were included in the study. Their mHR in HM ranged from 48 bpm to 79 bpm, with a mean of 64.8 ± ± 7.5 bpm. Despite of a correct mHR, in 21 patients (50%) tachy AF episodes were observed. accounting for 1% to 8% beats, with a mean of 2.7 ± 2.02%. CI in HM varied from 0.9 to 0.33 with a mean of 0.23 ± 0.06. Significant irregularity, a CI above 0.2, together with a correct mHR was found in 73% patients. In the majority of patients with a low CI of < 0.2 (10 out of 11) there were no tachy AF episodes. A significant CI (> 0.2) was found in 10 out of 18 patients (56%) with a correct mHR and without tachy AF episodes. Palpitations were noted in 16 out of 21 patients with the correct mHR who had tachy AF episodes and 9 out of 10, also with the correct mHR, in whom no such episodes were recorded. All these patients had a significant ventricular rate irregularity with a CI of > 0.2.*

Conclusions: *The parameter of mHR derived from HM is not sufficient for controlling ventricular rate in the majority of patients with brady-tachy AF. It seems that evaluating tachy*

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AF episodes, rhythm irregularity and symptoms experienced by the patient are also necessary for establishing for correct control of the heart rate in patients with AF. The CI could be superior to other parameters for the assessment of patients with AF who have correct mean heart rate. (Folia Cardiol. 2006; 13: 473–479)

Key words: atrial fibrillation, heart rate irregularity, ventricular rate control

Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia [1]. A number of studies have demonstrated that heart rate control is the first line therapy for patients with AF [2]. Analysis of randomised trials have revealed no benefit either in modality, morbidity or stroke prevention in rhythm over rate control in AF patients [3–7]. According to ACC/AHA/ESC guidlines, one-day mean heart rate (mHR) in 24-hour ECG Holter monitoring (24 HM) is currently considered as an established parameter for ventricular rate control in AF patients [8]. It would seem that mHR is the optimal endpoint for the treatment of patients with AF [9]. Another established criterion for ventricular rate control is to maintain a rate of 60–80 bpm at rest and 90–115 bpm during exercise [10, 11]. Correct ventricular rate control is of such importance because a long-lasting fast or irregular rate can lead to tachycardia-induced cardiomyopathy [12, 13]. Unfortunately, tachy AF episodes and significant irregularity may sometimes occur in patients with a correct mHR. The correct ventricular rate and the parameters that should be assessed to optimize rate control is still debatable.

The aim of the study was to evaluate whether mHR in 24 HM is the correct parameter for the assessment of ventricular rate control in patients with AF. Additionally, we investigated whether other parameters, such as episodes of tachy AF, rhythm irregularity and patient awareness of "palpitations", play an important role in controlling ventricular rate in AF.

Methods

A total of 48 patients were enrolled in the study, each of whom had been implanted with a single-chamber ventricular pacemaker (Biotronik, Actros SR) in the Department of Cardiology of the Medical University of Łódź. The indications for pacemaker implantation were documented episodes of heart-rate pauses of over 3 s in HM with complete or incomplete Morgagni–Adams–Stokes syndrome. The correct ventricular rate defined by 24 HM in patients with optimal pharmacological treatment was a mHR below 90 bpm in readings taken between 2 and 9 days (at a mean of 5.6 days) following implantation.

The diagnostic memory data collection function of the Biotronik pacemakers was begun simultaneously with the start of traditional HM. Ventricular sense events (Vs) and ventricular paced events (Vp) were evaluated by means of an event counter. The pacemaker was reprogrammed to the VVI mode of 40 bpm for the intrinsic ventricular rate in AF recording.

The criteria for the enrolment of patients for the final analysis were as follows:

— mHR according to ACC/AHA/NASPE Guidelines below 90 bpm [10];
— a percentage of paced events during 24 HM below 5%.

24-hour Holter recordings

Ambulatory ECG Holter recordings were taken by means of analogue Oxford MR 45-4 recorders with a pacemaker option and typical CS2, CM5 and IS leads; the recordings were analysed using the Oxford Medilog Excel 2 system according to ACC/AHA Guidelines [14]. Both automatic and manual analyses were performed. After the recordings had been edited and visually verified, the following parameters were assessed: the percentage of native rhythm beats (Vs), percentage of paced beats (Vp), mean heart rate (mHR) and maximum heart rate. Manual verification of ECG data also included analysis of fusion and pseudofusion beats. Fusion beats were determined when spikes did not change the T-wave morphology in QRS complexes. The event counter classified fusion beats as ventricular paced events (Vp) and the mean heart rate was evaluated by means of 24 HM. The coefficient of irregularity (CI), defined as standard deviation/mHR, was assessed in every patient. According to Greenhut's et al. [15] study, irregularity of the ventricular rate in AF was established as significant when there was a CI > 0.2.

Pacemaker memory data

As mentioned, the diagnostic memory data collection of the Biotronik pacemakers was begun simultaneously with the start of traditional HM. From the different Actros S diagnostic memory functions the following data were taken into analysis:

— from the event counter: the percentage of ventricular paced events (Vp);
— from the activity report: the mean of the ventricular rate (mHR);
— from the heart-rate histogram: percentages of ventricular rates (Vs and Vp) within certain heart-rate ranges. All results were retrieved from the memory data during telemetry using the Biotronik PMS 1000 programmer. 24 HM and pacemaker memory data were terminated at the same time. Episodes of tachy AF were defined when ventricular rate was > 120/min. Percentage of beats with rate > 120/min among all recorded beats during 24 hour recording was considered as a measure of tachy AF intensity.

Patients' clinical symptoms (heart palpitation)

Every symptom of a fast or irregular ventricular rate, such as heart palpitations, during 24 HM was noted by patients with in a patient's diary.

Statistical analysis

All data were calculated as mean values with standard deviation.

Results

The final analysis included 42 patients (18 male and 24 female), with a mean age of 70.2 ± 8 years. Six patients with a mHR > 80 bpm were excluded from the study. Clinical data and medication for 42 patients with AF and a VVI pacemaker are shown in Table 1.

The majority of the patients, 32 (76%), were classified as within NYHA classes I or II of heart failure. Six patients were in NYHA class III, while in 4 patients heart failure symptoms were not reported. The left ventricle ejection fraction in ECHO examination ranged from 22% to 81%, with a mean of 60.9%. Coronary artery disease was present in 10 patients and 8 of these had myocardial infarction.

Table 1. Clinical data and cardiovascular medications in 42 patients with atrial fibrillation and implanted pacemaker.

Hypertension	17
Valvular heart disease	2
Non-ischaemic cardiomyopathy	2
Coronary artery disease	10
Cardiac glycosides	25
Beta-blockers	37
Calcium channel blockers	10

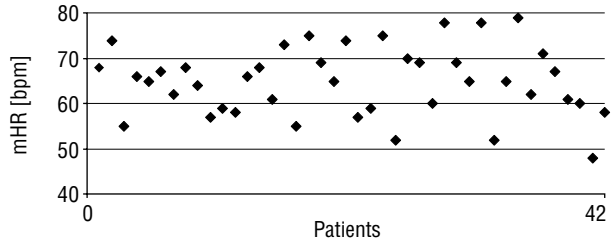

Figure 1. The mean heart rate (mHR) in 42 patients recorded in 24-hour ECG Holter monitoring (24 HM). ◆ Value of mHR in studied patients during 24 HM.

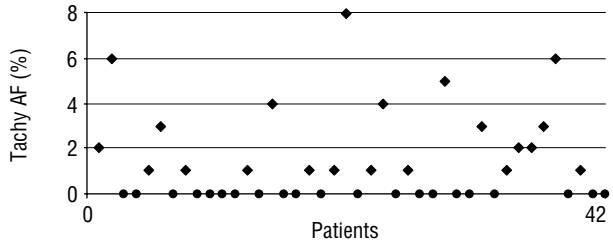

Figure 2. Percentage of tachy AF episodes in 42 patients with correct mean heart rate in daily pacemaker memory data. ◆ Patients with tachy AF; ● Patients without tachy AF.

Mean 24 hour heart rate

The mHR during 24 HM ranged from 48 bpm to 79 bpm, with a mean of 64.8 ± 7.5 bpm. The mHR in 42 patients is shown in Figure 1.

Tachy AF episodes

In 21 patients (50%) with mHR within approved ranges, data retrieved from the pacemaker memory recorded tachy AF episodes (tachy AF) ranging from 1% to 8% of beats, with a mean of 2.7 ± 2.0%. The maximal heart rate was 202 bpm. Remaining 21 patients did not have tachy AF episodes. The percentage of tachy AF episodes in all 42 patients during 24 HM is shown in Figure 2.

Coefficient of irregularity

In the patients studied CI was between 0.9 and 0.33, with a mean of 0.23 ± 0.06. CI values in 42 patients with AF are shown in Figure 3. Significant irregularity, defined as CI > 0.2, was observed in

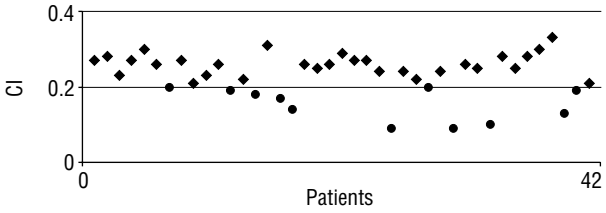

Figure 3. Coefficient of irregularity (CI) in 42 patients with atrial fibrillation (AF) during 24-hour ECG Holter monitoring. ◆ Patients with AF and significant ventricular rate irregularity (CI > 0.2). • Patients with AF and without significant ventricular rate irregularity (CI ≤ 0.2).

73% patients with acceptable mHR. In 63% of these patients, tachy AF episodes were recorded in 24-hour pacemaker memory data. In contrast, in 10 out of 11 patients with a low CI (< 0.2), no tachy AF episodes were noted. It is also of interest that of 11 patients with CI < 0.2 tachy episodes were only recorded in one.

The results in Figure 4 show that a correct mHR and absence of tachy AF episodes are not sufficient to claim that ventricular rate in patients with AF is acceptable. Significant ventricular rate irregularity (CI > 0.2) was found in 10 out of 18 patients (56%) with a correct mHR and without tachy AF episodes.

Analysis of patient symptoms (heart palpitation)

In 36 patients (85%), heart palpitations were reported during 24 HM. Symptomatic palpitations were found in 16 of 21 patients with tachy AF episodes. Other patients, although they had tachy AF episodes recorded, they did not report any symptoms. It is important to underline, that 9 out of 10 patients without tachy AF episodes and with a correct mHR reported palpitations and that in all of these CI was significantly high (CI > 0.2).

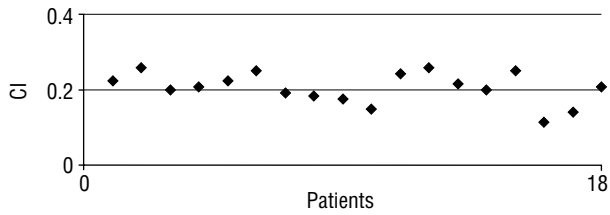

Figure 4. Coefficient of irregularity (CI) in 18 patients with correct mean heart rate (mHR) and without tachy AF episodes during 24-hour ECG Holter monitoring. ◆ Patients with correct mHR and without tachy AF.

Discussion

The control of ventricular rate is an essential aspect of the management of permanent AF. Patients with AF have been the subjects of intense investigation over the past two decades (PAF, RACE, AFFIRM, HOT CAFE). Two management strategies have emerged over the years: rhythm control, using anti-arrhythmic drugs and electrical cardioversion to maintain sinus rhythm, and rate control, designed to reduce symptoms by controlling an unusually rapid and irregular ventricular response to AF. Reports have recently been published of randomised trials which have found that these two strategies are equivalent when measured by a variety of endpoints [3–7].

If achieving rate control is made the goal, it is essential to define this term adequately. Unfortunately, evidence-based data to guide the clinician are in short supply, and many published definitions of rate control are somewhat arbitrary. Among many parameters used to control ventricular rate, mHR obtained from 24 HM is an accepted approach [9]. It is important to mention that according to ACC/AHA/ESC guidelines the ventricular rate in AF patients should be evaluated at rest and with exercise test. The patients in our study were elderly, with a mean age of over 70, and it was decided not to perform the exercise test. Additionally, according to Kowey et al. [2], monitoring of the mHR in 24 HM seems to be the gold standard in the complete assessment of patients with AF, allowing the heart rate trend to be assessed over 24 hours during daily activity. Appropriate rhythm control is important since a fast ventricular rate > 120/min might lead to tachycardiomyopathy [16]. Tachycardia-induced cardiomyopathy is defined as a condition characterised by ventricular myocardial dysfunction resulting solely from an increased ventricular rate [17]. Gossage et al. [18] first described tachycardia-induced cardiomyopathy in 1913 in patients with atrial fibrillation. In the following years many studies were published which showed that a prolonged uncontrolled fast ventricular rate can lead to tachycardiomyopathy [19–22]. The ventricular rate is therefore a major determinant of the onset and progression of tachycardia-induced cardiomyopathy and may result in an altered geometry and function of the ventricle, an increase in left ventricular area, mitral regurgitation, elevated left ventricular end-diastolic pressure and decreased left ventricular wall thickness and ejection fraction [23]. These abnormalities in left ventricular function result from disturbances in the structure and biochemical

processes of the myocytes [9]. Proper control of ventricular rate in patients with tachycardiomyopathy leads to faster improvement in left ventricular function than regression of pathology of myocytes. However, reversal may not occur or may not be complete in all cases [24, 25].

All these data suggest the importance of ventricular rate control for preventing tachycardiomyopathy. The mean heart rate is determined by the number of fast and slow ventricular rates. Where the proportions of fast and slow rhythms are similar, mHR may be read as correct, and this may result in a false assessment of heart rate control.

In the majority of the patients in our study, the tachy AF episodes were symptomatic, 76% of patients claiming "heart palpitation". Such a significant percentage of patients with tachy AF and symptoms implies that clinical assessment of AF patients on the basis of mHR only must be approached with caution.

The number of tachy AF episodes was calculated from the heart-rate histogram retrieved from pacemaker memory data. Previous studies have demonstrated that there is a very high correlation between pacemaker and 24 HM data [26]. The analysis of tachy AF episodes could be done using Holter monitoring, however, such approach is very time-consuming. The automatic function in pacemakers facilitates this process.

Ventricular rate irregularity is an independent factor which can lead to tachycardia-induced cardiomyopathy [27–29]. Sometimes it is impossible to determine whether it is a fast or an irregular rate that causes tachycardiomyopathy [30, 31]. Our strategy for the management of ventricular rate should be aimed at these two factors.

The first experimental study by Naito showed that in dogs after complete atrioventricular nodal ablation cardiac output significantly increased when irregular pacing (150/min) was maintained [30]. Daoud et al. [31] reported data on 11 patients who underwent atrioventricular ablation and who were paced 80/min and 120/min on average with diferent modes of regularity. During irregular rhythm, cardiac output decreased by 12%. The studies in patients that followed confirmed these results [32–38]. There are few theories trying to elucidate causes of the detremental effects of irregulatr heart rate on hemodynamic parameters even in AF patients with acceptable range of heart rate. First, stroke volume of left ventricle in a cycle after a long pause is not able to fully compensate decreased stroke volume after short RR interval [35]. Secondly, level of atrial natriuretic factor is higher during irregular rhythm because pressure in the atria is changeable with tendency to increase with longer duration of atrial fibrillation [36]. Thirdly, sudden changes in cycle length compromise contractility of the myocardium [37]. Therefore, the assessment of irregularity of heart rate in patients with atrial fibrillation is of major importance.

The coefficient of irregularity, a quotient of standard deviation and mHR (SD/HR), is an established ventricular irregularity parameter [15]. It could be calculated from HM and it has been used in some clinical studies of patients with AF [15, 38].

In our study significant irregularity with a CI of > 0.2 was found with a correct mHR in 76% of patients. It may be concluded that in more than half the patients with heart-rate control based only on mHR there is a risk of tachycardiomyopathy developing. Additionally, in 56% of patients with a correct mHR and without tachy AF episodes a CI of > 0.2 was noted. It may be that CI is more important as a parameter for controlling ventricular rate in AF than the mHR of tachy AF episodes. Control of mHR alone may be insufficient to prevent tachycardiomyopathy in the treatment of patients with permanent AF. On the other hand tachy AF episodes were only found in 1 out of 11 patients with a low CI. This may additionally indicate the clinical value of CI for controlling ventricular rate.

Symptoms such as heart palpitation can have a negative influence on the quality of life in AF patients. Arrhythmia worsens quality of life in 2/3 of AF patients [39, 40]. According to Jung's and Luderitz's published data, the most frequently reported symptom is "heart palpitation" [40]. This is nearly always correlated with tachy AF episodes. In our study heart palpitations were reported by patients with tachy AF episodes as well as those with significant irregularity. In the majority of patients (90%) with these symptoms a high CI of > 0.2 was found. This suggests that CI is a very important factor, which can influence and lead to deterioration in the quality of life of AF patients. It is important to underline that the pharmacological treatment of patients with AF is able to reduce tachy AF episodes but not ventricular irregularity [41].

Only 10 of 42 patients with mean heart rate < 90/min (an accepted criterion for rate control) did not have tachy AF episodes or significant heart rate irregularity. This is clear evidence that mHR alone is unable to ensure correct ventricular rate control.

This is one of the first published studies to show that mHR is not sufficient for the management of patients with AF. It would appear to be essential to examine other parameters and CI may be one of the most important in controlling ventricular rate and preventing tachycardiomyopathy.

Limitations of the study

Only patients with brady-tachy AF and an implanted pacemaker were included in the study. It is open to question whether the same results would be obtained in AF patients without indications for pacemaker implantation. However the mean percentage of ventricular pacing (< 5%) during the VVI 40 bpm mode, should not influence our results.

Conclusions

1. Mean heart rate derived from Holter monitoring is insufficient as a parameter for controlling ventricular rate in the majority of patients with brady-tachy atrial fibrillation.
2. It seems that tachy atrial fibrillation episodes, rhythm irregularity and patient symptoms, and not only mean heart rate, are necessary for the correct control of heart rate in patients with atrial fibrillation.
3 The coefficient of irregularity in patients with a correct mean heart rate may be superior to other parameters for the assessment of rhythm control in patients with atrial fibrillation.

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