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Non-invasive Evaluation of the Effect of Metoprolol on the AV node during Permanent Atrial Fibrillation

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Condensed abstract

The aim of this study is to monitor changes in AV nodal properties during administration of metoprolol from ECG data.

The AV nodal parameters reflect expected changes in the AV node functional refractory periods.

These results are supported by simulated data.

What's new?

- Changes in AV nodal electrophysiology in patients with AF are assessed noninvasively from ECG during metoprolol administration. The changes observed in the AV nodal parameters agree with the expected changes, thus this method may be used to assess drug effects on the AV node in patients with AF.
- Simulated RR series were generated that mimic metoprolol administration through prolonged AV conduction interval and AV node effective refractory period. The results confirmed that the AV nodal parameters provide useful information of the functional refractory period.

Abstract max 250 words

Aims During atrial fibrillation (AF), conventional electrophysiological techniques for assessment of refractory period or conduction velocity of the atrioventricular (AV) node cannot be used. We aimed at evaluating changes in AV nodal properties during administration of metoprolol from ECG data, and to support our findings with simulated data based on results from an electrophysiological study.

Methods Sixty patients (age 71 ± 9 years, 42 men) with permanent AF were included in the RATE control in Atrial Fibrillation (RATAF) study. Two 15-minute segments, during baseline and metoprolol administration, starting at 2pm were analyzed in this study. Atrial fibrillatory rate (AFR), heart rate (HR), and AV nodal parameters were assessed. The AV nodal parameters account for the probability of an impulse not taking the fast pathway, the absolute refractory periods of the slow and fast pathways (aRPs and aRPf), representing the functional refractory period, and their respective prolongation in refractory period. In addition, simulated RR series were generated that mimic metoprolol administration through prolonged AV conduction interval and AV node effective refractory period.

Results During metoprolol administration, AFR and HR were significantly decreased and aRP was significantly prolonged in both pathways (aRPs: 337 ± 60 vs. 398 ± 79 ms, $p < 0.01$; aRPf: 430 ± 91 vs. 517 ± 100 ms, $p < 0.01$). Similar results were found for the simulated RR series, both aRPs and aRPf being prolonged with metoprolol (aRPs: 413 ± 33 vs. 437 ± 43 ms, $p = 0.01$; aRPf: 465 ± 40 vs. 502 ± 69 ms, $p = 0.02$).

Conclusion The AV nodal parameters reflect expected changes after metoprolol administration, i.e., a prolongation in functional refractory period. The simulations confirmed that aRPs and aRPf may serve as an estimate of the functional refractory period.

1 Introduction

Rate control of atrial fibrillation (AF) is a commonly used treatment option [1], especially since clinical studies have shown similar outcomes for rate and rhythm control strategies [2, 3]. Rate control drugs may act on atrial and/or atrioventricular (AV) node properties to reduce and thus to control ventricular rate. However, the electrophysiological effects of drugs on the AV node are still not completely understood during AF. During drug development, the cardiac electrophysiological effects are usually assessed invasively during sinus rhythm. In particular, the electrophysiological effects on the AV node, its refractory period and the conduction velocity through the node itself, are evaluated for different purposes, e.g., compare drugs response [4], to assess dose-dependent effect [5, 6], and to compare administration method (i.e., oral versus i.v. [7]). However, an atrial pacing protocol cannot be applied in patients with AF, and thus these aspects cannot be assessed. The effect of a drug on AV nodal electrophysiology during AF without a need for cardiac catheterization would dramatically increase method availability and widen the target patient population, e.g., during the early clinical phases of drug development or when optimizing the therapy.

To date the atrial fibrillatory rate (AFR) and the heart rate (HR) have been used to noninvasively assess drug effects in patients with AF. The AFR has been used to monitor drug effects [8-10] and to assess the outcome of pharmacologic and catheter-based AF intervention [11, 12]. HR itself [13] or its variability and irregularity have been used to assess the effect of drugs [14, 15], and the effect of autonomic stimulation [16]. However, the relationship between AFR and HR is not well understood. Even if the AV node plays a fundamental role in linking AFR and HR, most studies have been confined to investigating the correlation between atrial and ventricular rate, independently of the AV node [17, 18]. Only a few noninvasive studies estimated the refractory period of the AV node from the RR series [19-22].

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We have recently developed a method for noninvasive assessment of AV nodal characteristics [23, 24] in patients with AF. The method estimates the refractory periods of the two AV nodal pathways, the probability of an impulse not passing through the fast pathway, and the prolongation of the refractory periods due e.g. to concealed conduction. All parameters are estimated from noninvasive information contained in the surface ECG, i.e., the f-waves and the RR intervals.

The aim of the present study is to monitor changes in AV nodal properties during administration of metoprolol, a β 1-selective blocking drug used for rate control. It is hypothesized that the parameters reflect the changes in AV nodal properties observed in earlier electrophysiological studies performed during sinus rhythm. Previous studies on patients in sinus rhythm showed that metoprolol prolongs both the effective and the functional refractory period of the AV node as well as the atrio-His conduction interval [25-27]. Simulated data were generated in which the AV node refractory period and the atrio-His conduction interval were altered to mimic metoprolol administration; this data was analyzed in order to verify that our method can capture these changes. An important goal of our method is to get information on the effect of drugs on AV nodal electrophysiology in patients with AF so that a targeted therapy can be given.

2 Methods

2.1 Patients

The present study is based on patient data collected in the RATE control in Atrial Fibrillation (RATAF) study. The RATAF study was a prospective, randomized, investigator-blind, crossover study designed to compare four drug regimens (metoprolol, diltiazem, verapamil, and carvedilol) used to reduce the ventricular heart rate in patients with permanent AF. Each drug was given for more than three weeks to ensure an adequate period of washout of the previous treatment and steady-state plasma concentrations. Before starting the first treatment and at the last day of each

of the 4 treatment periods, 24-h Holter recordings were made. A detailed protocol of the study is described elsewhere [13].

The regional ethics committee and the Norwegian medicines agency approved the study, registered at www.clinicaltrials.gov (clinical trial no. NCT00313157) and conducted in accordance with the Helsinki Declaration. Each patient provided written informed consent before any study-related procedures were performed. The clinical characteristics of the patients are shown in Table 1.

In this study, we analyzed two 15-min segments: baseline and metoprolol administration starting at 2pm (when the drug effect was found to be maximal). Metoprolol is well-described in literature [25-29]. It is used clinically to control the ventricular response, and is known to prolong AV nodal refractory periods as well as the atrio-His conduction interval [25-27].

2.2 Simulated data

Simulated RR series were generated by using the computer model of ventricular rhythm during atrial fibrillation and ventricular pacing proposed by Lian et al. [30] and used in [31, 32]. Realistic ventricular rhythms during AF can be reproduced and used to explain, e.g., the effect of pacing. This model was selected for the present study because it offers detailed characterization of the electrophysiological dynamics of the AV node. In particular, it accounts for the atrio-His conduction interval and the AV effective refractory period separately, both dependent on the interval between the end of the last AV refractory period and the current AV activation time. Concealed conduction is also taken into account [33].

The study in [26] is used to set the parameter values of the computer model, since that study investigates the cardiac electrophysiological effects of metoprolol in patients undergoing intracardiac stimulation studies for paroxysmal palpitations. During the electrophysiological procedure, the atrio-His conduction interval and the AV node effective refractory period was

measured at baseline and after metoprolol injection. We used these measurements to simulate the characteristics of eight different patients (one parameter setting for each patient); 100 simulations were made for each patient. When passing from baseline to metoprolol, only the AV conduction interval and the AV node effective refractory period were changed according to Table 2 [26], i.e., both the AV conduction interval and the AV node effective refractory period were prolonged.

2.3 AV Node Parameters

We have recently proposed a method to noninvasively estimate five parameters characterizing the AV node in patients with AF, namely the refractory periods of the two AV nodal pathways, the probability of an impulse not passing through the fast pathway, and the prolongation of the refractory periods [23, 24].

In the method, the AV node is treated as a lumped structure that accounts for both temporal and spatial summation of the electrical activity of the cells. Atrial impulses arrive to the AV node completely random, and therefore the arrival times are characterized by the basic Poisson process whose mean arrival rate is assumed to be proportional to AFR. The AFR is determined from the f-waves of the ECG, extracted with spatiotemporal QRST cancellation [34] and subjected to spectral analysis using a noise-resistant method [35].

Each impulse arriving to the AV node is assumed to produce a ventricular activation unless blocked by a refractory AV node. The slow and the fast AV nodal pathways are characterized by their absolute refractory period (aRPs and aRPf, respectively with $aRPs < aRPf$) and relative refractory period (rRP s and rRPf, respectively), see Figure 1. The definition of aRP includes both the effective refractory period of the AV node and the AV conduction interval, and therefore aRP may serve as an estimate of the functional refractory period. The relative refractory period accounts not only for relative refractoriness but also for concealed conduction. The probability of

an impulse not to pass through the fast pathway, i.e., to pass through the slow one, is denoted with α . The parameter α is the global probability of impulses to pass through the slow pathway, and it does not give information on which pathway the single impulse passes through. Apart from AFR, all parameters (i.e., aRPs, aRPf, rRPs, rRPf, and α ; “s” and “f” denote slow and fast, respectively) are determined using the maximum likelihood estimation. A detailed description of the method and the technique for estimating the parameters is found in [23, 24]. It should be emphasized that, in contrast to the model which underlies the present method, the above-mentioned computer model is unsuitable for use in parameter estimation.

3 Results

3.1 Real data

Figure 2 illustrates the effect of metoprolol on the RR series in four patients. The top panels show the values of the refractory periods of the slow and fast pathways at baseline and after metoprolol. The bottom panels show the fitted RR models (probability density functions) at baseline and after metoprolol. In all patients, a significant prolongation in refractory periods can be observed. Prolongation of the refractory periods causes the fitted RR models to be right-shifted, see the bottom panel of Figure 2. It can be observed that the fast pathway is the most used in patients 1 and 3, as the filled part of the marker, representing the aRPf, is larger than aRPs and therefore the fast pathway is more often used. On the contrary, in patient 2 the slow pathway is the most used and finally in patient 4 the most used pathway changes from the slow to the fast one after metoprolol.

Table 3 shows the effect of metoprolol on HR, AFR, and refractory periods. As expected, AFR and HR were significantly decreased by metoprolol. The aRP was significantly prolonged for both

pathways, whereas rRP was not significantly different between baseline and metoprolol. In addition, the probability α (mean value \pm standard deviation of 0.35 ± 0.20 at baseline, 0.33 ± 0.18 during metoprolol) showed that the fast pathway was the most frequently used in all patients. A prolongation of 19 ± 21 % and 24 ± 30 % was found for aRPs and aRPf respectively.

3.2 Simulated data

Table 4 shows the average values of absolute and relative refractory periods for the simulated data. The mean and standard deviation for each setting are shown as well as the average values. A significant prolongation of refractory periods can be observed in almost all settings and in the total average.

The mean percentage of prolongation of aRPs and aRPf for the simulated data is 6 ± 6 % and 8 ± 9 %, respectively. These results agree with the prolongation of the functional refractory period reported on in [26], see Table 2, which were equal to 10 ± 7 %.

4 Discussion and Conclusions

In this study, we have applied our recently proposed method for noninvasive assessment of AV nodal characteristics [23, 24] on data recorded during administration of the beta-blocker metoprolol. The aim is to assess in what way metoprolol modifies the AV node characteristics in patients with AF.

All previous studies assessing AV nodal characteristics after metoprolol administration were invasive and included patients during sinus rhythm. On the contrary, our study is noninvasive and involves AF patients. The presented results are in agreement with those of previous studies. Even if different doses of metoprolol were tested in those studies, they all found a prolongation in the AV node refractory period as well as in the atrio-His conduction interval [25-28]. These studies measured the atrio-His conduction interval and the AV node effective and functional

refractory periods, while aRP can serve as an estimate of the functional refractory period, being the combination of the effective refractory period and the AV conduction interval. In previous studies, the average prolongation of the functional refractory period was found to range from 10 to 90 ms in [27] and from 5 to 80 ms in [26]. These results agrees with our results where the average prolongation of the slow and fast pathway was 60 and 90 ms, respectively.

A first attempt to assess AV nodal properties during drug administration was reported in [36]. They assessed the effect of metoprolol and amiodarone on atrial and ventricular activity during AF, in post-surgical patients, using unipolar epicardial recordings. Results from three patients treated with metoprolol showed changes in the atria and the AV node, specifically an increase in AV node refractory period and the minimum conduction time. It should be noted that their study was invasive and that an ad-hoc procedure was used to estimate the AV nodal parameters.

In a study by Raine et al. [29] no significant difference in AFR was found before and after metoprolol infusion in AF patients. On the contrary, we found a significant decrease in AFR, suggesting that metoprolol acts on the atrial level as well as on AV nodal properties to decrease HR. This difference may be explained by different patients characteristics and/or by the different doses of the two protocol.

We assessed the effect of metoprolol not only on real data but also on simulated since such data can help to verify that the method captures the overall change due to prolonged AV conduction interval and AV node effective refractory periods as metoprolol induces. Results from simulated data, with changes in the AV node effective refractory period and the AV conduction interval, showed a prolongation in the estimated aRP, that is thus confirmed to be a combination of the two AV node properties. The prolongation of aRP for real and simulated data, calculated as a percentage, are in agreement, even if the parameter values from real data were more dispersed than those of the simulated data. This result is due to the lower variability of the simulated RR

series and the larger number of real data recordings.

In conclusion, evaluation of AV nodal electrophysiology during AF is made possible when using an AV node model. The results show that the parameters reflect expected changes in AV nodal properties, i.e., a slower conduction through the AV node for metoprolol. The model is suitable for assessing the drug effect on AV electrophysiology during AF, especially for antiarrhythmic compounds aimed at rate control during AF tested in clinical trials during the first clinical phases of drug development.

Limitation: the computer model for producing simulated data is based on the same basic assumption as our method, namely that the atrial impulses arrive to the AV node as a Poisson process. However, the computer model involves far more parameters (15 instead of 6) which account for much more electrophysiological detail.

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Conflict of interest: none declared.

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Table 1: Demographic characteristics and cardiovascular history in the study population

Variable	Value
Gender (male/female)	42 / 18
Age (years)	71 ± 9
AF duration (months)	11 (2-121)
BMI	27 ± 4
Diabetes	3
Hypertension	25

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Table 2: AV node parameters from Camm's study [26].

Patient	A-H (ms)		AV nodal ERP (ms)		AV nodal FRP (ms)	
	Baseline	Metoprolol	Baseline	Metoprolol	Baseline	Metoprolol
1	50	75	310	290	385	390
2	90	110	320	315	350	360
3	70	115	250	270	370	450
4	90	110	260	310	310	315
5	85	100	260	290	350	380
6	70	85	300	330	390	450
7	70	95	360	405	390	440
8	50	120	310	370	330	370

A-H: atrio-His conduction interval; ERP: effective refractory period; FRP: functional refractory period

Table 3: Metoprolol effect in the study population . * p<0.05

Parameter	Baseline	Metoprolol
<i>Atrial and ventricular rate during AF</i>		
AFR (fpm)	386 ± 47	367 ± 63 *
HR (bpm)	110 ± 22	88 ± 15 **
<i>AV node parameters</i>		
aRPs (ms)	337 ± 60	398 ± 79 **
aRPf (ms)	430 ± 91	517 ± 100 **
rRPs (ms)	237 ± 200	280 ± 230
rRPf (ms)	208 ± 203	356 ± 260 **

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Table 4: Metoprolol effect on simulated data.

Setting	aRPs		aRPf	
	Baseline	Metoprolol	Baseline	Metoprolol
1	424 ± 22	409 ± 25 *	470 ± 43	454 ± 44 *
2	429 ± 25	427 ± 23	482 ± 44	474 ± 42
3	372 ± 25	389 ± 30 *	426 ± 39	436 ± 37 *
4	381 ± 24	426 ± 19 *	429 ± 39	478 ± 44 *
5	384 ± 17	407 ± 27 *	430 ± 38	463 ± 43 *
6	415 ± 20	438 ± 24 *	469 ± 46	498 ± 53 *
7	473 ± 25	518 ± 24 *	549 ± 66	638 ± 78 *
8	426 ± 20	485 ± 24 *	568 ± 42	572 ± 64 *
Mean ± SD	413 ± 33	437 ± 43	465 ± 40	502 ± 69
p-value paired t-test	0.014		0.025	

* p<0.05 comparing each setting

Figures caption

Figure 1: Probability of an atrial impulse to be blocked for the slow (black solid line) and the fast (grey dashed line) pathway. aRPs = absolute refractory period of the slow pathway, aRPf = absolute refractory period of the fast pathway, rRPs = relative refractory period of the slow pathway, rRPf = relative refractory period of the fast pathway.

Figure 2: Example of four patients assuming metoprolol. Top panel: refractory periods of the slow (black) and fast (gray) pathways at baseline and after metoprolol administration: the filled part of the marker is proportional to the probability of atrial impulses to choose that pathway. Bottom panel: The RR fitted model from the different protocol phases.

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Figure 1

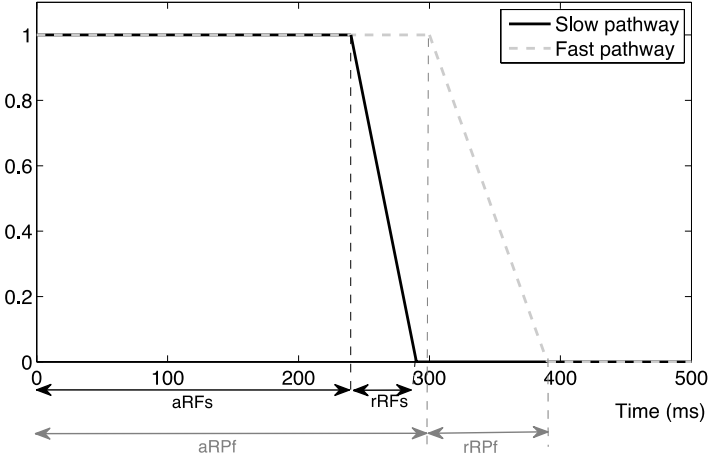


Figure 2

