Non-invasive Evaluation of the Effect of Metoprolol on the Atrioventricular Node during Permanent Atrial Fibrillation

Valentina DA Corino[1], Frida Sandberg[2,3], Luca T Mainardi[1], Sara R Ulimoen[4], Steve Enger[4], Arnljot Tveit[4], Pyotr G Platonov[3,5], Leif Sornmo[2,3]

[1] Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy
[2] Department of Biomedical Engineering, Lund University, Lund, Sweden
[3] Center for Integrative Electrocardiology at Lund University, Lund University, Lund, Sweden
[4] Department of Medical Research Bærum Hospital, Vestre Viken Hospital Trust, Drammen, Norway
[5] Arrhythmia Clinic, Skåne University Hospital, Lund, Sweden

Abstract

The aim of this study was to evaluate changes in AV nodal properties during administration of metoprolol, using a novel ECG-based method for parameter estimation. The AV nodal parameters account for the probability of an impulse not passing through the fast pathway, the absolute refractory periods of the slow and fast pathways (aRPs and aRPf), representing the functional refractory period, and related prolongation in the respective refractory periods. Twenty patients (age 71 $\pm$ 8 years, 14 men) with permanent AF from the RATe control in Atrial Fibrillation (RATAF) database were included in this study. Recordings during baseline and metoprolol administration were analyzed. Furthermore, simulated RR series were generated mimicking metoprolol administration. During metoprolol administration, aRP was significantly prolonged in both pathways (aRPs: 342 $\pm$ 39 vs. 408 $\pm$ 81 ms, p<0.001; aRPf: 432 $\pm$ 74 vs. 527 $\pm$ 83 ms, p<0.001). Similar results were found for the simulated RR series: both aRPs and aRPf were significantly prolonged with metoprolol. The AV nodal parameters reflect expected changes after metoprolol administration, i.e., a prolongation in functional refractory period. The simulations suggest that aRP may serve as an estimate of the functional refractory period.

1. Introduction

During atrial fibrillation (AF), conventional electrophysiological techniques for evaluation of refractory period of the atrioventricular (AV) node cannot be used. This is due to the impossibility of applying an atrial pacing protocol in patients with AF, and thus the refractory period of the AV node cannot be assessed. However, the effect of a drug on AV nodal electrophysiology during AF without the 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.

We have recently developed a method for noninvasive assessment of AV nodal characteristics [1, 2] 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 to, e.g., 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 β1-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 in patients 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 [3–5]. Simulated data were generated in which the AV node refractory period and the AV conduction interval were altered to mimic metoprolol administration; this data was analyzed in order to verify that our method can capture these alterations.

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 three weeks or more 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 obtained. A detailed protocol of the study is described elsewhere [6]. In the present study, we analyzed two 15-min segments in 20 patients: baseline and metoprolol administration starting at 2pm (when the drug effect was found to be maximal). Metoprolol is well-described in the literature. 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 [3–5].

2.2. Simulated data

Simulated RR series were generated by using the computer model of ventricular rhythm during AF and ventricular pacing proposed by Lian et al. [7]. This model accounts for concealed conduction, 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. The study in [4] 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 four different patients (one parameter setting for each patient); 100 simulations were made for each patient. When passing from baseline to metoprolol, the AV conduction interval and AV node effective refractory period were prolonged according to [4], while the remaining parameters were kept the same

2.3. Definition of the AV node model

In the present model, the AV node is treated as a lumped structure which accounts for concealed conduction, relative refractoriness, and dual AV nodal pathways. Atrial impulses are assumed to arrive to the AV node according to a Poisson process with mean arrival rate λ. Each arriving impulse results in ventricular activation unless blocked by a refractory AV node. The probability of an atrial impulse passing through the AV node depends on the time elapsed since the previous ventricular activation t. The refractory period is defined by both a deterministic part aRP and a stochastic part, the latter rRP, modeling prolongation due to concealed conduction and/or relative refractoriness and assumed to be uniformly distributed over the interval

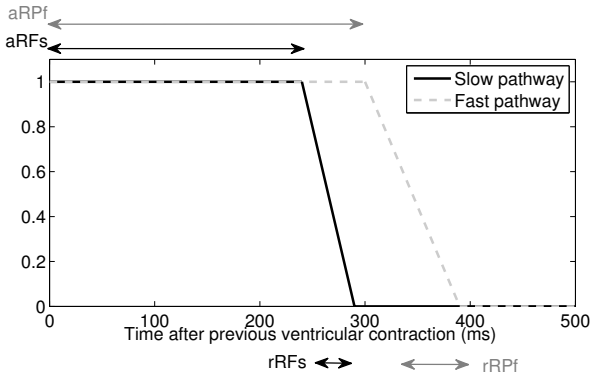

Figure 1. Probability of an atrial impulse to be blocked for the slow (black solid line) and the fast (grey dashed line) pathway. aRPs = absolute refractory period of the slow pathway, aRPf = absolute refractory period of the fast pathway, rRPs = relative refractory period of the slow pathway, rRPf =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

[0, rRP]. Hence, all atrial impulses arriving to the AV node before the end of the refractory period aRP are blocked. Then follows an interval [aRP, aRP+rRP] with linearly increasing likelihood of penetration into the AV node (see Figure 1). Finally, no impulses can be blocked if they arrive after the end of the maximally prolonged refractory period aRP+rRP. The refractory period of the slow pathway is defined by the parameters aRPs and rRPs, whereas the fast pathway refractory period is defined by aRPf and rRPf. The probability of an atrial impulse to pass through the slow pathway with the shorter refractory period is equal to α, and accordingly for the other pathway is probability $(1-\alpha)$.

Hence, non-blocked atrial impulses occur according to an inhomogeneous Poisson process with intensity function $\lambda\beta_i(t)$, where $\beta_i(t)$ characterizes the time-dependent refractoriness and is either equal to $\beta_1(t)$ or $\beta_2(t)$, depending on the pathway used by the atrial impulse. With the assumption that AV conduction time is incorporated into $\beta_i(t)$, ventricular activations immediately occur following a non-blocked atrial impulse. Consequently, ventricular activations also occur according to an inhomogeneous Poisson process with intensity function $\lambda\beta_i(t)$.

It can be shown that the joint PDF is given by [1]

$$p_x(x_1,\ldots,x_M) = \prod_{m=1}^{M} (\alpha p_{x,1}(x_m) + (1-\alpha)p_{x,2}(x_m)), \tag{1}$$

where M is the total number of intervals, and

$p_{x,i}(x_m), i = 1, 2$, is given by

$$p_{x,i}(x) = \begin{cases} 0, \quad x < aRP_i \\ \frac{\lambda(x - aRP_i)}{rRP_i} \exp\left\{\frac{-\lambda(x - aRP_i)^2}{2rRP_i}\right\}, \\ \quad aRP_i \le x < aRP_i + rRP_i \\ \lambda \exp\left\{\frac{-\lambda rRP_i}{2} - \lambda(x - aRP_i - rRP_i)\right\}, \\ \quad x \ge aRP_i + rRP_i. \end{cases} \tag{2}$$

2.4. Model parameter estimation

Since the property of statistical independence is not fully valid for observed RR intervals, preprocessing of the original RR interval series is needed to reduce the interdependence of successive RR intervals. For this purpose a linear transformation which removes correlation of successive RR intervals is applied to the observed RR series.

All model parameters, except λ, are estimated from the RR intervals using ML estimation.

The atrial impulses are assumed to arrive to the AV node according to a Poisson process with rate λ. An estimate of λ is obtained by [2] $\lambda = AFR/(1 - \delta AFR)$ where AFR is the atrial fibrillatory rate estimated from the ECG (independently of the AV node parameters), and δ is minimum time interval between successive impulses arriving to the AV node.

The model parameters $\alpha, \tau_1^{min}, \tau_2^{min}, \tau_{p,1}$, and $\tau_{p,2}$ are estimated by jointly maximizing the log-likelihood function with respect to $\boldsymbol{\theta} = \begin{bmatrix}\alpha & \tau_1^{min} & \tau_2^{min} & \tau_{p,1} & \tau_{p,2}\end{bmatrix}^T$.

Since no closed-form solution could be found for $\hat{\boldsymbol{\theta}}$, combined with the fact that the gradient is discontinuous, the multi-swarm particle swarm optimization (MPSO) is here used to optimize the log-likelihood function. Briefly, a multi-initialization with N concurrent swarms is employed in MPSO [8]. Each swarm is moved within a search area to find the optimal solution. After a certain number of optimization epochs, particles are exchanged between swarms to avoid local maxima.

3. Results

3.1. Real data

Figure 2 illustrates the effect of metoprolol on the model parameter estimates in two patients. A significant prolongation in refractory periods of both the slow and fast pathway after metoprolol can be observed. Prolongation of the refractory periods causes the fitted RR models (probability density functions) to be right-shifted, see the bottom panel of Figure 2. The fast pathway is the most used in the patient on the left column: α = 0.13 at baseline and α = 0.38 after metoprolol (as shown by the filled part of the marker).

Table 1. Metoprolol effect in the study population.

Parameter	Baseline	Metoprolol	p-value
HR (bpm)	110 ± 24	86 ± 16	$p < 0.001$
AFR (fpm)	380 ± 41	355 ± 66	0.03
aRPs (ms)	342 ± 39	408 ± 81	$p < 0.001$
aRPf (ms)	432 ± 74	527 ± 83	$p < 0.001$
rRPs (ms)	176 ± 155	254 ± 244	ns
rRPf (ms)	254 ± 256	344 ± 282	p = 0.05

Table 2. Metoprolol effect on absolute refractory period (ms) in simulated data. *p<0.05

Slow Pathway		
Setting	**Baseline**	**Metoprolol**
1	429 ± 25	427 ± 23
2	372 ± 25	389 ± 30*
3	381 ± 24	426 ± 19*
4	384 ± 17	407 ± 27*

Fast Pathway		
Setting	**Baseline**	**Metoprolol**
1	482 ± 44	474 ± 42
2	426 ± 39	436 ± 37*
3	429 ± 39	478 ± 44*
4	430 ± 38	463 ± 43*

In the other patient, the most used pathway changes from the slow to the fast one after metoprolol.

The effect of metoprolol on HR, AFR, and refractory periods is shown in Table 1. AFR and HR were significantly decreased by metoprolol. aRPs and aRPf were significantly prolonged ($p < 0.001$). Also, rRP tended to be longer after metoprolol in both pathways, but was significantly prolonged only in the fast pathway.

3.2. Simulated data

Table 2 shows average values of aRPf and aRPs for simulated data mimicking four patients. A significant prolongation of refractory periods in both pathways can be observed in three out of four settings.

4. Discussion

In this study, we aimed at assessing noninvasively the changes induced by metoprolol on the AV node characteristics in patients with AF. We applied our recently proposed method [1,2] on data recorded during administration of the beta-blocker metoprolol. The presented results are

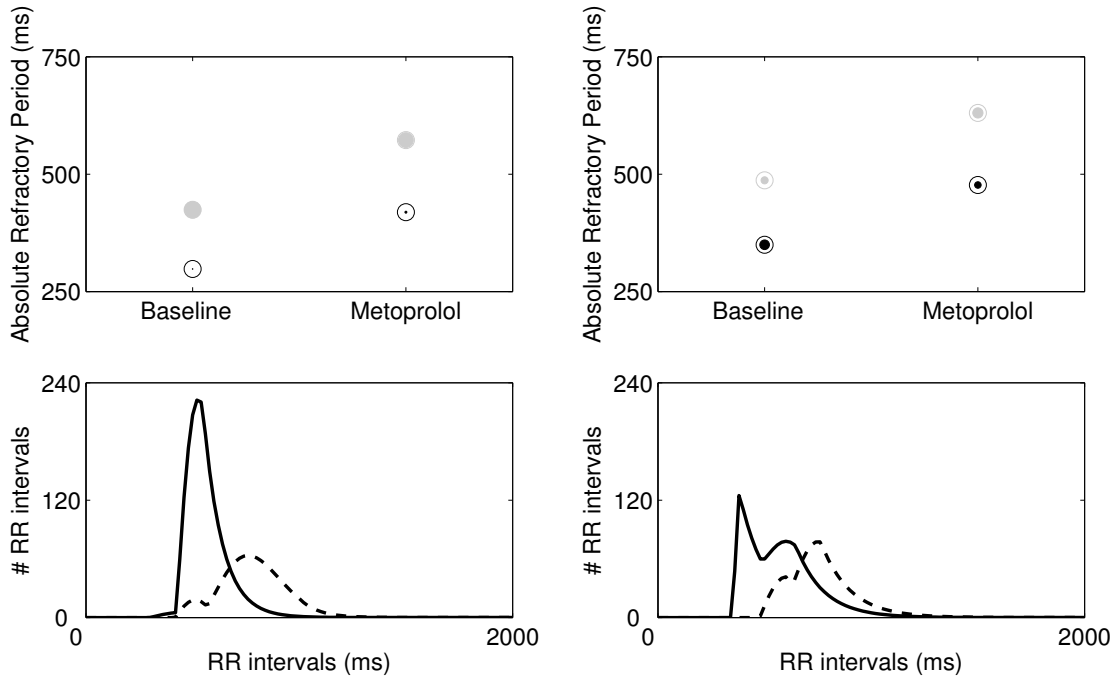

Figure 2. Example of two patients assuming metoprolol (each column represents a patient). Top panel: refractory periods of the slow (black) and fast (gray) pathways at baseline and after metoprolol administration: the filled part of the marker is proportional to the probability of atrial impulses to choose that pathway. Bottom panel: The RR fitted model during baseline (solid line) and after metoprolol administration (dashed line).

in agreement with previous invasive studies, that found a prolongation in the AV node refractory period as well as in the atrio-His conduction interval [3–5]. Analysis of simulated data showed that the method is able to capture the main change induced by metoprolol, i.e., prolonged absolute refractory period, which includes AV conduction interval and AV node effective refractory period.

Acknowledgements

PP was supported by research grants from The Swedish Heart-Lung Foundation; LS and FS were supported by Swedish Research Council grant 621-2012-3509.

References

[1] Corino V, Sandberg F, Mainardi L, Sörnmo L. An atrioventricular node model for analysis of the ventricular response during atrial fibrillation. IEEE Trans Biomed Eng 2011; 58:3386–3395.

[2] Corino V, Sandberg F, Lombardi F, Mainardi L, Sörnmo L. Atrioventricular nodal function during atrial fibrillation: Model building and robust estimation. Biomed Signal Proc Control 2013 in press;.

[3] Marchlinski F, Buxton A, Waxman H, Josephson M. Electrophysiologic effects of intravenous metoprolol. Am Heart J 1984;107:1125–1131.

[4] Camm A, Ward D, Whitmarsh V. The acute electrophysiological effects of intravenous metoprolol. Clin Cardiol 1982; 5:327–331.

[5] Rizzon P, Biase MD, Chiddo A, Mastrangelo D, Sorgente L. Electrophysiological properties of intravenous metoprolol in man. British Heart Journal 1978;40:650–655.

[6] Ulimoen S, Enger S, Carlson J, Platonov P, Pripp A, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation. Am J Cardiol 2013;111:225–230.

[7] Lian J, Müssig D, Lang V. Computer modeling of ventricular rhythm during atrial fibrillation and ventricular pacing. IEEE Trans Biomed Eng 2006;53:1512–1520.

[8] Niu B, Zhu Y.and He X, Wu H. MCPSO: A multi-swarm cooperative particle swarm optimizer. Appl Math Comput 2007;2:1050–1062.

Address for correspondence:

Valentina D.A. Corino
Dipartimento di Elettronica, Informazione e Bioingegneria
Politecnico di Milano
via Golgi 34, 20133 Milano, Italy
valentina.corino@polimi.it