Drug Effect Evaluation during Permanent Atrial Fibrillation using an AV-node Model

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Abstract

The purpose of the present study is to evaluate the effect of rate control drugs on the AV node characteristics during atrial fibrillation (AF) using a model-based approach. A statistical model of the AV nodal function is employed, defined by parameters which characterize the arrival rate of atrial impulses, the refractoriness of the fast and the slow AV-nodal pathway and the probability of atrial impulse to pass through either of the two pathways. The RATAF (RATe control in Atrial Fibrillation) study database consists of recordings from 60 patients with permanent AF at baseline and on treatment with metoprolol, verapamil, diltiazem and carvedilol, respectively. The resulting model parameter estimates indicate that the refractory period of the slow pathway as well as that of the fast pathway increased significantly during treatment with all four drugs. The results suggest that the proposed AV-node model can be used for non-invasive evaluation of the effect of rate control drugs.

1. Introduction

During atrial fibrillation (AF), the atrioventricular (AV) node is continuously bombarded with atrial impulses. The ventricular activity during AF is irregular and manifested by shorter RR intervals than during normal sinus rhythm, and is largely determined by AV nodal blocking of the impulses. Electrophysiologic factors such as intrinsic refractoriness of the AV node and concealed conduction influence the ventricular response [1]. The existence of two dominant pathways through the AV node, each with different electrophysiological properties, has been documented previously [2]. Even though these properties play a prominent role in ventricular rate control, they are not routinely evaluated in clinical practice.

Recently we presented a statistical model of the AV nodal function during AF intended for noninvasive analysis of the ventricular response during AF [3, 4]. The model is defined by the arrival rate of atrial impulses to the AV node, the probability of conduction through the fast and the slow AV nodal pathway, respectively and the refractoriness of the two AV nodal pathways. The model parameters can be obtained by means of maximum likelihood estimation from the surface ECG only. Results from previous studies using head-up tilt test data suggest that the model can be used to non-invasively estimate AV-node characteristics [4].

The purpose of the present study is to use the model based approach to analyze the effect of four different rate control drugs, namely metoprolol, verapamil, diltiazem and carvedilol, on the AV-node electrophysiologic characteristics. The proposed model is briefly described in Sec. 2 while Sec. 2.1 deals with details of the model parameter estimation, particularly those related to the handling of artifacts and noise in the ECG recordings. The database is summarized in Sec. 3 and results are presented in Sec. 4.

2. Methods

In the present model [3, 4], 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 $\lambda$. Each arriving impulse immediately 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 $\tau$ and a stochastic part, the latter modeling prolongation due to concealed conduction and/or relative refactoriness and assumed to be uniformly distributed over the interval $[0, \tau_p]$. Hence, all atrial impulses arriving to the AV node before the end of the refractory period $\tau$ are blocked. Then follows an interval $[\tau, \tau + \tau_p]$ with linearly increasing likelihood of penetration into the AV node. Finally, no impulses can be blocked if they arrive after the end of the maximally prolonged refractory period $\tau + \tau_p$.

The refractory period length are assumed to be different depending on the penetrating pathway: the slow AV-nodal pathway refractory period is defined by the parameters $\tau_1$ and $\tau_{p,1}$, whereas the fast AV-nodal pathway refractory period is defined by $\tau_2$ and $\tau_{p,2}$. The probability of an atrial impulse being conducted through the slow AV-nodal pathway is equal to $\alpha$, and accordingly the probability of conduction through the slow pathway is $(1 - \alpha)$. The slow AV-nodal pathway refractory period is shorter than that of the fast AV-nodal pathway, $\tau_1 \leq \tau_2$.

For this model, the time intervals $x_i$ between consecutive ventricular activations, i.e., corresponding to the RR intervals, will be independent. It can be shown that the joint probability density function (PDF) is given by [3]

$$p_x(x_1, x_2, \ldots, x_M) = \prod_{m=1}^{M} (\alpha p_{x,1}(x_m) + (1 - \alpha)p_{x,2}(x_m)),$$

where $M$ is the total number of intervals, and $p_{x,i}(x_m), i = 1, 2$, is given by

$$p_{x,i}(x) = \begin{cases} 
\lambda(x - \tau_i) \exp\left\{ -\lambda(x - \tau_i) \right\} & \text{if } 0 \leq x < \tau_i \\
\lambda \exp\left\{ -\lambda \tau_{p,i} \right\} - \lambda(x - \tau_i - \tau_{p,i}) & \text{if } x \geq \tau_i + \tau_{p,i}.
\end{cases}$$

(2)

To account for the interdependence between successive RR intervals, the deterministic part of the refractory period is assumed to depend on the preceding RR interval, so that a longer RR interval is followed by a longer refractory period, and vice versa.

### 2.1. Model parameter estimation

The model parameters are estimated from consecutive 30 min segments of the 24-h ambulatory ECG recordings. Signal quality control is crucial, as signal segments with excessive noise will produce invalid parameter estimates and therefore have to be detected and excluded prior to analysis. The arrival rate of atrial impulses $\lambda$ is estimated from the atrial activity of the ECG, obtained using spatiotemporal QRST-cancellation [5]. First, a minute-by-minute AF frequency trend is estimated for the whole 24-h recording using an HMM-based approach [6]. Then, $\lambda$ is taken as the average AF frequency within the segment of interest, after correction to account for atrial refactoriness [4]. Although the HMM frequency tracking approach is designed to be robust to noise, invalid frequency estimate can be produced when the signal contains excessive noise of several minutes duration. Consequently, the AF frequency trends may lack values. If more than 70% of the AF-frequency trend values in a 30-minute segment are missing, the average AF frequency is considered to be unreliable and the ECG segment is excluded from analysis.

All other model parameters, namely $\alpha$, $\tau_1$, $\tau_2$, $\tau_{p,1}$, and $\tau_{p,2}$, are estimated from the RR series by maximizing joint PDF in eq. (1) with respect to $\theta = [\alpha \tau_1 \tau_2 \tau_{p,1} \tau_{p,2}]^T$. Prior to the maximum likelihood (ML) estimation, RR intervals adjacent to beats with abnormal morphology, such as ectopic beats and artifacts, are removed from the RR series; a beat is considered to have abnormal morphology if less than 1% of the beats in the 24-h recording have a similar morphology. If more than 20% of the RR intervals in a 30 minute segment are removed, the distribution of the RR intervals in the series is considered to be unreliable and the segment is excluded from analysis. Since the property of statistical independence is not fully valid for observed RR intervals, approximate decorrelation is performed prior to ML-estimation to reduce the interdependence between subsequent RR intervals [7]. The corresponding parameters of a single pathway model, $[\alpha \tau_1 \tau_{p,1}]^T$ are also estimated. The Bayes information criterion is used to determine the most appropriate model [4]. Since no closed-form solution could be found for $\hat{\theta}$, combined with the fact that the gradient is discontinuous, the multi-swarm particle swarm optimization (MPSO) is in the present study proposed for optimizing the log-likelihood function [7].

Given the definition of $p_{x,i}(x)$ in (2), the estimate of $\tau_1$ is closely related to the shortest RR interval in the 30 min segment. Thus, to reduce the influence of occasional incorrect RR intervals that was not successfully removed in the previous step, an iterative procedure for the ML-estimation is employed [7]. First, 1% of the shortest intervals are removed from the decorrelated RR series $x$, and ML estimation is performed on the truncated series $x_0$. Since $x_0$ is assumed to be free from incorrect RR intervals, the initial estimate $\hat{\theta} = [\alpha(0) \tau_1(0) \tau_2(0) \tau_{p,1}(0) \tau_{p,2}(0)]^T$ can serve as a reference. The removed RR intervals are then reversed to the truncated series one by one in order of size, so that $\tilde{x}_i = [x_{i-1} x(i)]$ where $x(i)$ is the longest interval removed from $\tilde{x}_{i-1}$; ML estimation is performed for each $\tilde{x}_i$. The estimates corresponding to the maximum
value of the log likelihood function are chosen as the correct ones.

3. Database

The RATAF (RATe control in Atrial Fibrillation) database consists of 24-h ECG recordings from 60 patients (mean age $71 \pm 9$ years, 18 women) during baseline and treatment with carvedilol, diltiazem, verapamil and metoprolol, respectively. The database is described in detail in [8]. Out of the original 299 recordings, 16 (5.4%) recordings (6 baseline, 2 carvedilol, 2 diltiazem, 5 verapamil and 1 metoprolol) was excluded from analysis due to insufficient signal quality caused by e.g. dropped sensors or excessive noise. Hence 283 recordings from 60 patients were included in this study.

4. Results

The majority of the 30-min segments in each recording were accurately represented by the model, i.e. the fit between the estimated model PDF and an empirical PDF was $>80\%$ [3]. Out of 10590 analyzed segments, 10099 (95.5%) were accurately represented using the model. If the model fit was not considered to be accurate, the estimated model parameters were disregarded and excluded from statistic analysis.

Figure 3 displays histograms of the decorrelated RR series and the corresponding estimated model PDF from 30-min segment of ECG from one patient recorded at the same time of the day during baseline and during treatment with carvedilol, diltiazem, verapamil, and metoprolol, respectively. For this patient, both the fast pathway refractory period and the slow pathway refractory period were longer during treatment with each of the four drugs compared to the baseline recording.

The segments recorded between 1 PM and 4 PM were selected for comparison, as the effect of the drugs was assumed to be maximal during this time interval. For each recording, the estimated model parameters of all 30-min segments in the selected time interval were averaged, and a paired-sample Wilcoxon signed rank test was employed for statistical analysis.

The resulting model parameter estimates indicate that the refractory period of the slow pathway $\tau_1$ increased significantly during treatment with carvedilol, diltiazem, verapamil, and metoprolol compared to baseline, see Fig. 1. The estimated refractory period $\tau_1$ was significantly longer during treatment with diltiazem and verapamil compared to carvedilol, and significantly longer during treatment with verapamil compared to metoprolol.

The model refractory period of the fast pathway $\tau_2$ increased significantly during treatment with carvedilol, diltiazem, verapamil, and metoprolol compared to baseline, see Fig. 2. The estimated refractory period $\tau_2$ was significantly longer during treatment with diltiazem compared to carvedilol. The results are summarized in Table 1.

5. Conclusions

A statistical model of AV nodal function during AF, with parameters that characterize dual AV nodal pathways, concealed conduction, and relative refractoriness, is used to analyze the recordings from 60 patients at baseline and during treatment with metoprolol, carvedilol, verapamil
and diltiazem, respectively. The resulting model parameter estimates indicate that the refractory period of the fast AV-nodal pathway as well as that of the slow AV-nodal pathway increased significantly with all four drugs. The results suggest that the proposed AV-node model can be used to correctly and non-invasively evaluate the effect of rate control drugs.

### References


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