Statistical Modeling of Atrioventricular Nodal Function during Atrial Fibrillation
An Update

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Abstract: This paper introduces a number of advancements of our recently proposed model of atrioventricular (AV) node function during atrial fibrillation (AF). The model is defined by parameters characterizing the arrival rate of atrial impulses, the probability of an impulse choosing either one of the two AV nodal pathways, the refractory periods of these pathways, and their prolongation. In the updated model, the characterization of AV nodal pathways is made more detailed and the number of pathways is determined by the Bayesian information criterion. The performance is evaluated on ECG data acquired from twenty-five AF patients during rest and head-up tilt test. The results show that the refined AV node model provides significantly better fit than did the original model. During tilt, the AF frequency increased (6.25 ± 0.58 Hz vs. 6.32 ± 0.61 Hz, $p < 0.05$, rest vs. tilt) and the prolongation of the refractory periods decreased for both pathways (slow pathway: 0.23 ± 0.20 s vs. 0.11 ± 0.10 s, $p < 0.001$, rest vs. tilt; fast pathway: 0.24 ± 0.31 s vs. 0.16 ± 0.19 s, $p < 0.05$, rest vs. tilt). These results show that AV node characteristics can be assessed noninvasively for the purpose of quantifying changes induced by autonomic stimulation.

1 INTRODUCTION

The atrioventricular (AV) node is subjected to the impact of atrial impulses during atrial fibrillation (AF) which leads to summation and/or cancellation of wavefronts in the AV node and, accordingly, a high level of disorganization of the penetrating impulses. As a result, the ventricular rhythm becomes much more irregular than during normal sinus rhythm. Different properties such as intrinsic refractoriness of the AV node and concealed conduction determine the characteristics of the ventricular response (Fuster et al., 2006), but they are not routinely evaluated in clinical practice mainly because of the lack of noninvasive methodology.

Statistical model-based analysis of essential AV nodal characteristics constitutes a powerful method to assess AV node properties during AF. A statistical model suitable for parameter estimation was at an early stage described in (Cohen et al., 1983): the AV node was treated as a lumped structure whose behavior represented the temporal and spatial summation of the cellular electrical activity. The atrial impulses were assumed to arrive randomly to the AV node according to a Poisson process. When the AV node was not refractory, its transmembrane potential was assumed to increase with the contribution of each arriving atrial impulse as well as to increase spontaneously. When the transmembrane potential reached a certain threshold, a new action potential initiated a ventricular beat. Despite the fact that the model was statistical in nature, the model parameters were determined from the RR series using an ad hoc procedure. A serious limitation of that procedure was that the resulting parameter estimates could assume nonphysiological values. An extension of this model was proposed (Lian et al., 2006), however, the proposed model was suitable for simulation purposes only. Other AV node models have been proposed, mainly based on the analysis of atrial electrograms recorded during electrophysiological studies (Jørgensen et al., 2002; Mangin et al., 2005); None of those models

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were accompanied by a statistical estimation procedure.

In a recent paper, we proposed a statistical model of the AV nodal function during AF which lends itself to ECG-based parameter estimation (Corino et al., 2011). The model is defined by a small set of parameters which characterizes the arrival rate of atrial impulses, the probability of an impulse choosing either one of the dual AV nodal pathways, the refractory periods of the pathways, and the prolongation of refractory periods. The parameters were estimated from the RR series using maximum likelihood (ML) estimation, except for the shorter refractory period which was estimated from the Poincaré plot of successive RR intervals, and the mean arrival rate of atrial impulses which was estimated by the AF frequency derived from the f-waves of the ECG (Sandberg et al., 2008).

Subsequent application of our AV node model suggests that certain model properties should be extended and the estimation performance improved with respect to robustness. Therefore, this paper introduces a more detailed characterization of the dual pathways. In particular, the effect of tilting on the refractory periods of the AV node was assessed by means of the model parameters.

2 METHODS

2.1 Existing 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 is suprathreshold, i.e., the 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 length of the refractory period is defined by a deterministic part τ and a stochastic part τ_p. The latter part models prolongation due to concealed conduction and/or relative refractoriness, and is assumed to be uniformly distributed in the interval $[0;\tau_p]$. Hence, all atrial impulses arriving to the AV node before the end of the refractory period τ 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 mathematical characterization of refractoriness of the i:th pathway ($i=1,2$) is thus defined by the positive-valued function $\beta_i(t)$,

$$\beta_i(t)=\begin{cases}0, & 0<t<\tau_i\\ \frac{t-\tau_i}{\tau_p}, & \tau_i\le t<\tau_i+\tau_p\\ 1, & t\ge\tau_i+\tau_p,\end{cases} \quad (1)$$

where t denotes the time elapsed since the preceding ventricular activation.

The probability of an atrial impulse to take the pathway with the shorter refractory period τ_1 is equal to α, and accordingly the other pathway is taken with probability $(1-\alpha)$. For this model, the time intervals x_i between consecutive ventricular activations, i.e., corresponding to the RR intervals, are independent. It can be shown that the joint PDF is given by (Corino et al., 2011)

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

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

$$p_{x,i}(x)=\begin{cases}0, & x<\tau_i\\ \frac{\lambda y_i}{\tau_p}\exp\left\{\frac{-\lambda y_i^2}{2\tau_p}\right\}, & \tau_i\le x<\tau_i+\tau_p\\ \lambda\exp\left\{\frac{-\lambda\tau_p}{2}-\lambda(y_i-\tau_p)\right\}, & x\ge\tau_i+\tau_p.\end{cases} \quad (3)$$

where $y_i=x-\tau_i$.

2.2 Model Parameter Estimation

2.2.1 Estimation of τ_1^{min}

Since the property of statistical independence is not fully valid for observed RR intervals, a simple functional dependence of the refractory periods related to the previous RR interval is explored. The interdependence of consecutive RR intervals can be reduced by preprocessing the original RR interval series, denoted x'_m, with the linear transformation,

$$x_m=x'_m-\hat{s}_\tau x'_{m-1}. \quad (4)$$

where $\hat{s}_\tau$, together with an estimate of the minimal refractory period $\tau_1^{\min}$, is found from the line that defines the lower envelope of the Poincaré plot using the Hough transform, see (Corino et al., 2012) for details on how to determine this line. The interval series x_m that results from (4) constitutes the data used for ML estimation.

An estimate of the refractory period $\tau_{m,1}$ of the slow pathway and the m:th activation may be obtained from the linear relationship

$$\tau_{m,1} = \tau_1^{\min} + s_\tau x'_{m-1}. \quad (5)$$

Assuming that s_τ applies to both $\tau_{m,1}$ and $\tau_{m,2}$, the problem of estimating $\tau_{m,2}$ is identical to the problem of estimating a fixed duration $\Delta\tau$ since

$$\tau_{m,2} = \Delta\tau + \tau_{m,1}. \quad (6)$$

2.2.2 Maximum Likelihood Estimation of Dual Pathway Parameters

The model parameters related to the dual AV nodal pathways and the refractory period prolongation are estimated by maximizing the log-likelihood function $\Lambda(\theta)$ with respect to θ, i.e.,

$$\begin{aligned}\hat{\theta} &= \arg\max_{\theta} \Lambda(\theta) \quad (7)\\ &= \arg\max_{\theta} \log p_x(x_1, x_2, \ldots, x_M | \theta; \hat{\lambda}, \hat{\tau}_1^{\min}),\end{aligned}$$

where $\theta = [\alpha \ \ \Delta\tau \ \ \tau_{p,i}]^T$. Since no closed-form solution could be found for $\hat{\theta}$, combined with the fact that the gradient is discontinuous, simulated annealing was employed for maximization. The optimization algorithm was initiated with 10 different, randomly chosen values for each estimation. The optimal $\hat{\theta}$ was then chosen as that value for which $\Lambda(\hat{\theta})$ is maximum, almost invariably being the dominant value.

2.3 AV Node Model Update

2.3.1 Dual Pathways

To date, no evidence has been presented which suggests that refractory period prolongation is identical for the dual AV nodal pathways. Rather, it has been found that the input regions of the atrial impulses play an important role in determining the properties of AV nodal conduction and refractoriness (Mazgalev et al., 1984). Inspired by the work in (Climent et al., 2011), our original model is here extended to account for pathway-dependent prolongation of the refractory period. Hence, prolongation is described by the two parameters $\tau_{p,1}$ and $\tau_{p,2}$, implying that the PDF $p(x_i)$ in (3) is modified so that $\tau_{p,i}$ replaces τ_p.

2.3.2 Estimation of λ

In the original AV node model, the atrial impulses were assumed to arrive to the AV node according to a Poisson process at a rate λ. An estimate of λ was obtained by first estimating the dominant AF frequency λ_{AF} from the ECG, independently of the AV node parameters, and then assuming that

$$\lambda = \lambda_{\mathrm{AF}}. \quad (8)$$

The details of the procedure for estimating λ_{AF} are described in (Corino et al., 2011). A disadvantage with such an approach is that it does not account for the fact that there is a minimum time interval δ between successive impulses arriving to the AV node. Such an interval was included in the simulation model in (Lian et al., 2006), where it was assumed that the atria depolarize again after $\delta = 50$ ms.

Evidently, the Poisson model does not impose a minimum time interval δ between successive impulses arriving to the AV node, but they can arrive immediately upon each other. Therefore, the use of (8) produces an underestimated value of λ. For Poisson-distributed impulses not arriving closer to each other than a minimum interval δ, the arrival rate λ_{AF} should be modified according to (Larsen and Kostinski, 2009)

$$\lambda = \frac{\lambda_{\mathrm{AF}}}{1 - \delta\lambda_{\mathrm{AF}}}, \quad (9)$$

2.3.3 Selection of Single or Dual Pathways

The selection of single or dual pathway model is determined by the Bayesian information criterion (BIC), defined by

$$\mathcal{C}_{\mathrm{BIC}}(k) = -2\Lambda(\hat{\theta}_k) + n_k \log(M), \quad k = 1, 2, \quad (10)$$

where the parameter estimate is either equal to $\hat{\theta}_1 = \tau_{p,1}$ for a single pathway or $\hat{\theta}_2 = [\alpha \ \ \Delta\tau \ \ \tau_{p,1} \ \ \tau_{p,2}]^T$ for dual pathways. The number of parameters n_k is thus equal to 1 or 4. The number of pathways is given by that index k which produces the lowest value of $\mathcal{C}_{\mathrm{BIC}}(k)$. The original use of simulated annealing for maximization of the log-likelihood function is here replaced with a genetic algorithm because it was found to offer much faster maximization.

3 DATA

We analyzed 25 consecutive patients with persistent AF (67 ± 7 years, 16 females) who underwent electrical cardioversion, according to the international guidelines, at the Cardiology department of San Paolo Hospital, Milan, Italy. Recordings were acquired at rest and during a passive orthostatic stimulus (75° tilting). One patient was excluded from analysis due to poor ECG quality preventing the estimation of AF frequency. Hence, the results presented below are based on 24 patients.

The ECG was recorded at rest for 10 min and, when applicable, followed by tilting, using three orthogonal leads and a sampling rate of 1 kHz. All recordings were performed in the morning in a quiet environment following 15 min of adaptation. The study was approved by the Ethics Committee, and all patients gave their written informed consent to participate.

4 RESULTS

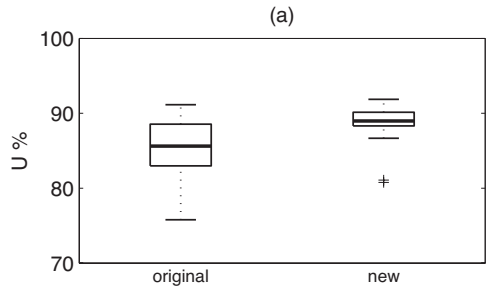
To assess if the present model could provide a better fit of the data, an index taking the underlying PDF into account is preferable. However, since the underlying PDF is unknown for ECG-derived RR intervals, an empirical PDF, denoted $\tilde{p}_x(x)$, was determined by wavelet-based density estimation (Corino et al., 2011; Ogden, 1997). The capability to model different RR series was evaluated in terms of a percentage measure of fit $\mathcal{U}$, defined by

$$\mathcal{U} = 100 \cdot \left(1 - \int_0^2 \left| p_x(x|\hat{\theta}_k; \hat{\lambda}, \hat{\tau}_1^{\min}) - \tilde{p}_x(x) \right| dx \right), \quad (11)$$

where the upper integration limit reflects the fact that very few RR intervals are longer than 2 s during AF. The reason for using wavelet-based density estimation rather than comparing $p_x(x|\hat{\theta}_k; \hat{\lambda}, \hat{\tau}_1^{\min})$ to the RR interval histogram is the poor statistical properties of the histogram (Ogden, 1997).

Figure 1 indicates that the model fit, as described by $\mathcal{U}$, was significantly better with the present model, both for rest and tilt data. Figure 2 shows an example of histogram of the transformed RR intervals and the estimated model PDF from the same patient using the original and the present model. The latter model fits the histogram much better than does the original one, $\mathcal{U}$ increasing from 84% to 89%. It can be noted that the histograms of transformed RR intervals are not exactly the same because the transformation depends on $\hat{\tau}_1$ which is different in the two models. In the following, the presented results are obtained using the present model.

To assess whether the model parameters can capture changes occurring due to increased sympathetic tone, such as during a tilt test, parameters during rest were compared to those during tilt. Table 1 compares the model parameter estimates obtained at rest and during tilt, with significant changes due to sympathetic activation in $\hat{\tau}_{p,1}$ and $\hat{\tau}_{p,2}$. The AF frequency was found to increase significantly during tilt. The probability of an atrial impulse of choosing either pathway is almost equal during rest and tilt ($\alpha = 0.5$),



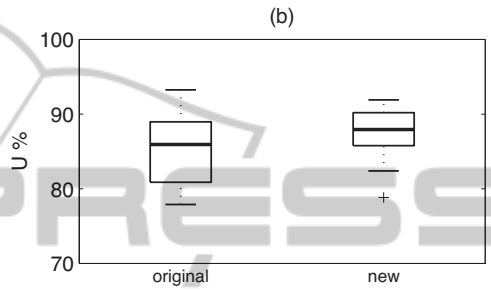


Figure 1: Boxplots of $\mathcal{U}$ for data during rest and tilt, comparing the original and the updated AV node model. * p<0.05, ** p<0.01.

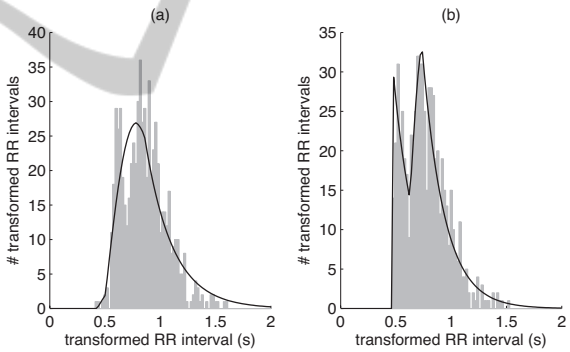


Figure 2: Histogram of transformed RR intervals and the estimated model PDF from the same patient during rest using (a) the original and (b) the new AV node model.

although α spans the range from 0.05 to 1, thus making the involvement of the pathway with slower refractory period ($\alpha < 0.5$) in about half of all recordings. The refractory periods of both pathways remain almost unchanged during tilt, whereas their prolongation, due to concealed conduction, relative refractoriness etc., are significantly shortened during tilt.

Both the mean and standard deviation of RR intervals are significantly shortened during tilt due to sympathetic activation. The mean RR interval length was 743 ± 146 ms vs. 680 ± 125 ms (rest vs. tilt, $p < 0.0001$), and the related standard deviation was 156 ± 51 vs. 137 ± 29 ms (rest vs. tilt, $p < 0.0001$).

Table 1: Comparison of rest and tilt parameters. *p<0.05, **p<0.001.

	Rest	Tilt
$\hat{\alpha}$	0.52 ± 0.24	0.51 ± 0.30
$\hat{\tau}_1^{\min}$ (s)	0.37 ± 0.09	0.38 ± 0.10
$\hat{\tau}_2^{\min}$ (s)	0.46 ± 0.12	0.47 ± 0.09
$\hat{\tau}_{p,1}$ (s)	0.23 ± 0.20	0.11 ± 0.10 **
$\hat{\tau}_{p,2}$ (s)	0.24 ± 0.31	0.16 ± 0.19 *
$\hat{\lambda}$ (Hz)	6.25 ± 0.58	6.32 ± 0.61 *

5 CONCLUSIONS

We have proposed an updated AV node model in which i) the characterization of the AV nodal pathways is made more detailed using two different parameters representing the prolongation of related refractory periods, ii) the number of pathways is determined by the BIC, and iii) the arrival rate is corrected to take into account there is a minimum time interval between successive impulses arriving to the AV node. The updated model leads to better estimation of the PDF when two peaks with different width are to be modeled, and also the most parsimonious model is selected (choosing between single or dual pathway model). Considering physiological aspects, our results indicate that tilting is associated with significant changes in AV conduction that are well-described by the model and reflected by shortening of both $\tau_{p,1}$ and $\tau_{p,2}$ during adrenergic activation. Thus, the present AV node model is adequate for studying and describing the functional characteristics of AV conduction in AF patients.

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