



Effects of antiarrhythmic drug therapy on atrioventricular nodal function during atrial fibrillation in humans[☆]

Laurence Mangin^a, Alain Vinet^b, Pierre Pagé^{b,c}, Leon Glass^{d,*}

^a *Département de Physiologie-Explorations Fonctionnelles, CHU Bichat, Université Paris VII, Paris, France*

^b *Centre de Recherche, Section Cardiovasculaire, Hôpital du Sacré-Coeur, Université de Montréal, Montréal, Canada*

^c *Department of Surgery, Division of Cardiac Surgery, Hôpital du Sacré-Coeur, Université de Montréal, Montréal, Canada*

^d *Department of Physiology, Centre for Nonlinear Dynamics in Physiology and Medicine, McGill University, McIntyre Medical Sciences Building, 3655 Promenade Sir William Osler, Montreal, QC H3G 1Y6, Canada*

Submitted 14 January 2005, and accepted after revision 18 March 2005
Available online 28 July 2005

KEYWORDS

atrioventricular node;
atrial fibrillation;
modelling;
concealed conduction;
antiarrhythmic drugs

Abstract Aims To assess the effects of metoprolol and amiodarone on atrial and ventricular activity during atrial fibrillation (AF) in post-surgical patients, and to develop and use a mathematical model of the atrioventricular (AV) node during AF that incorporates parameters describing the properties of the AV node to evaluate the physiological basis of the drug effects.

Methods and results Ten post-surgical patients were evaluated where three received no medical therapy, three received metoprolol, three received amiodarone, and one received both metoprolol and amiodarone. The medications led to increases of 37–310 ms in the mean VV interval in treated patients, but much smaller changes in the mean AA intervals in the right and left atria. The mathematical model incorporating a random influence of the concealed conduction parameter was capable of reproducing the histograms of the VV intervals based on the input from the right atrium by systematically searching parameter space.

Conclusions Changes in the ventricular rate are mainly due to the alteration in the AV nodal properties rather than changes in the atrial rhythm. The medications can

[☆] This work was supported by the Simone and Cino Del Duca Foundation, Paris, France, the CIHR, MITACS and the Research Resource for Complex Physiologic Signals (NIH).

* Corresponding author. Tel.: +1 514 398 4338; fax: +1 514 398 7452.
E-mail address: glass@cnd.mcgill.ca (L. Glass).

display differential effects on the physiological properties of the AV node, and therefore the mathematical model may help to identify novel pharmacological targets.
© 2005 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

One of the major medical problems facing cardiologists is the treatment of paroxysmal and chronic atrial fibrillation (AF) [1–7]. Despite major advances in therapies involving ablation of regions of the heart implicated in the initiation and maintenance of AF [8], in the majority of patients, medical therapies remain the treatment of choice. There is a long-standing debate on the relative efficacy of maintaining sinus rhythm vs the control of the ventricular rate. Although from a physiological perspective it is appealing to maintain sinus rhythm, recent clinical studies have demonstrated similar clinical outcomes for strategies involving either maintenance of sinus rhythm or control of the ventricular rhythm [4]. Since it is often easier to control the ventricular rate than maintain sinus rhythm, rate control of AF is an extremely important treatment option. Yet, our physiological understanding of the effects of pharmacological agents on the AV node is still limited [6,9–11]. The current paper deals with mathematical aspects of modelling of the atrioventricular (AV) node which are relevant to the determinants of ventricular response during AF. The long range goal of this approach is to develop sufficient information about the role of pharmacological agents on AV nodal physiology during AF, so that choice of therapy could be optimized based on physiological properties of the AV node.

Mathematical modelling based on physiological studies of the AV node has had a rich history [12–19] (for review of early papers see [20]), but only relatively few papers deal with modelling of the AV node during AF [21–27]. During rapid atrial pacing in normal individuals, or during normal sinus rates in individuals with compromised AV function, the ventricular response may display variety of regular Wenckebach coupling patterns between the atrial and ventricular rates. Theoretical models have been able to predict both qualitative and quantitative aspects of AV nodal conduction, as a function of stimulation frequency [14,15,20] and there is some limited knowledge of the effects of pharmacological agents on mathematical models of the AV node [9,10]. In view of the success of these mathematical models in predicting the AV node response during regular atrial and ventricular

activity, it seems reasonable to assume that the same models will be successful in predicting the ventricular response during AF. However, Jorgensen et al. found that the earlier models could not reproduce statistical features of the ventricular response based on atrial activity unless an additional term representing concealed conduction was added to the model [22]. Concealed conduction refers to a physiological effect by which a blocked beat leads to increased refractoriness of the AV node, so that the conduction time through the node is elevated relative to what it would have been if the blocked beat had not occurred [11,16,21,28–34]. During AF, the atrial activity is typically rapid so that a large fraction of the atrial activations is blocked in the AV node, and consequently the effects of concealed conduction are significant.

In the current paper we study the ventricular response during AF in 10 post-surgical patients both prior to and following the administration of medications (metoprolol and amiodarone) that are used clinically to control the ventricular response. The data collected from atrial and ventricular activity provide a unique insight into the response of the atrial and ventricular activity to drugs during AF. By developing a mathematical model for the AV node during AF, we analyze how drug therapy differentially affects the parameters describing AV nodal function.

Methods

Clinical data

Unipolar epicardial recordings were carried out in 10 patients experiencing paroxysmal AF after open-heart bypass surgery at the Hôpital du Sacré-Cœur, Montréal. The baseline clinical characteristics of the patients are shown in Table 1. After surgery, all patients had three temporary unipolar epicardial wire electrodes (Model 6492, Medtronic Inc, Minneapolis, MN, USA) attached to the muscular part of the atrium: two on the right atrium (one in the mid right atrial free wall in the sinus node region and the other in the lower third of the right atrial free wall) and one on the left

Table 1 Baseline patients characteristics

Patient	Age (yr)/ gender	LVEF (%)	Preoperative medication	Medical history	Perioperative data CAB (number of vessels grafted)/VR
1	78/M	50	Calcium antagonist	Hypertension, myocardial infarction, diabetes, stroke	3/0
2	70/M	50	0	0	1/1
3	64/F	40	0	Myocardial infarction	2/0
4	78/F	40	β -Blocker ACEI	Myocardial infarction	1/1
5	60/M	45	0	0	3/0
6	55/M	40	0	0	2/0
7	65/M	60	0	0	2/0
8	77/M	65	0	Hypertension	1/1
9	65/M	45	0	Hypertension	1/1
10	71/M	25	Nitrates ACEI	Hypertension, myocardial infarction	3/0

LVEF: left ventricular ejection fraction, ACEI: angiotensin converting enzyme inhibitor, CAB: coronary artery bypass, VR: valve replacement. Preoperative medication was stopped one day before surgery.

atrium near the left inferior pulmonary vein. Patients were monitored continuously for four days post-operatively with a Holter device (Spacelab Burdick, Model 6632, Dallas, TX, USA). Data were downloaded each day to a CD-ROM. Recordings began 24 h after heart surgery. The selected 10 patients had several episodes of AF that ended before 48 h. Every patient gave informed written consent for the test protocol, which was approved by the Ethics Committee of the Hôpital du Sacré-Cœur, Montréal.

Data analysis

Epicardial signals were acquired at 500 Hz. Left and right atrial electrograms were analyzed in segments of 3 min intervals during AF. Custom written software in MATLAB 6.5 (Mathworks, USA) was developed to detect the activation times from the electrograms. Automatic detection of the ventricular activation times was performed using the fact that the ventricular activity is synchronous on the three electrodes. Briefly, the waveforms of the channels were baseline-corrected with a polynomial fit, then summed, squared and passed through a threshold to detect the ventricular activations, which were then verified visually. Electrogram signals coming from the inferior free wall of the right atrium and near the inferior pulmonary vein of the left atrium were chosen for subsequent analysis. After applying a derivative filter, the atrial activation times were determined manually. The timing procedure was repeated three times with a change in rate of detection less than 5%. Based on these data, for each 3 min period during AF, we determined the mean intera-

trial activation times, $\langle AA_r \rangle$ and $\langle AA_l \rangle$, in the right and left atria, respectively, and the mean inter-ventricular activation times $\langle VV \rangle$. Histograms showing the distribution of the atrial and ventricular interbeat intervals were also computed.

Finite difference equation model of AV nodal function during AF

AV nodal recovery curve

Previous studies on AV nodal conduction have shown that AV nodal conduction time is a function of the preceding recovery (VA) interval, a longer recovery interval leading to a shorter conduction time. This relationship, called the AV nodal recovery curve, can be approximated by an exponential function [14,17,28].

$$AV = AV_{\min} + \alpha \exp\left(-\frac{VA}{\tau}\right)$$

where AV_{\min} is the minimum conduction time corresponding to propagation in a fully recovered tissue, α and τ are positive constants and VA is any recovery interval that exceeds the effective refractory period (θ) of the AV node.

With this model, the successive conduction times associated with a sequence of conducted beats can be predicted by a simple iterative relationship:

$$AV_{i+1} = AV_{\min} + \alpha \exp\left(-\frac{VA_i}{\tau}\right) \quad (1)$$

where AV_{i+1} is the conduction time of the $(i+1)$ st conducted beat and VA_i is the preceding recovery time. Assume that beat i was initiated at a time T_i in the atrium and conducts through

the AV node reaching the ventricle at a time $T_i + AV_1$. It is followed by a sequence of atrial activations occurring at successive times $(T_i + AA_1, T_i + AA_1 + AA_2, \dots, T_i + \sum_{j=1,k} AA_j)$, where AA_j is the time interval between the j th and $(j-1)$ th atrial activations following T_i . The recovery time associated to the k th activation is

$$RT(k) = \sum_{j=1,k} AA_j - AV_i$$

The first beat for which $RT(k \geq 1)$ becomes greater than the refractory period is a conducted beat, with conduction time:

$$AV_{i+1} = AV_{\min} + \alpha \exp\left(-\frac{\left(\sum_{j=1,k} AA_j - AV_i\right)}{\tau}\right) \quad (2)$$

The conducted beat is thus preceded by $(k-1)$ blocked activations. The procedure is iterated to determine the successive activation times.

Model of AV nodal function incorporating concealed conduction

Concealed conduction is manifest in the ventricular response when an impulse that penetrates the AV node, but fails to traverse it completely, affects the propagation of subsequent impulses [13,16,34]. During AF, atrial activations that arrive at the AV node during the refractory period (θ) are blocked (concealed). In an earlier paper, we assumed that each blocked beat led to an increment in the refractory period by a fixed amount Δ [15] (Fig. 1). As we show below, this assumption does not give adequate agreement with the data in the cases we analyze here, and so we had to modify this assumption. Since atrial activations may show varying degrees of penetration of the AV node due to the variability in their timing and conduction pathway, we assume that the blocked beats lead to an increment of the refractory period that is normally distributed. We assume that the increment in the refractory period due to a blocked beat i , is:

$$\Delta_i = \Omega_i \Delta_{\text{std}} + \Delta_{\text{mean}} \quad (3)$$

where Ω_i is a normally distributed random number with mean zero and standard deviation 1. Following a conducted beat, the refractory period is reset to θ and subsequent blocked beats again lead to a prolongation of the refractory period.

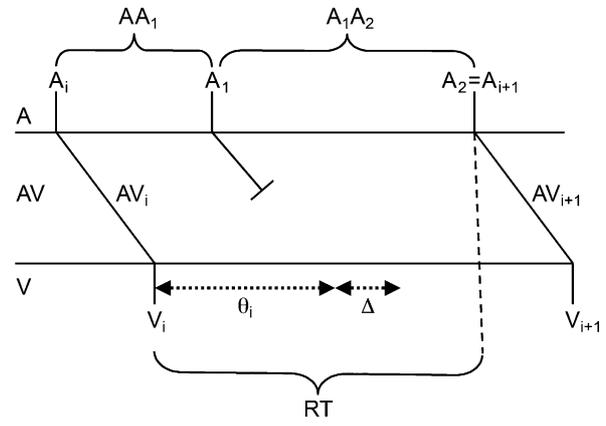


Figure 1 Schematic representation of the model. An atrial impulse arriving at the AV node at T_i is conducted to the ventricles with an AV nodal conduction time of AV_i leading to a ventricular beat at time V_i . The refractory time following this beat is initially θ_i . An atrial impulse, A_1 , arriving at the AV node at a time interval AA_1 following the first beat is blocked leading to a prolongation of the refractory period to $\theta_i + \Delta$, where $\Delta = \Omega \Delta_{\text{std}} + \Delta_{\text{mean}}$ and Ω is a normally distributed random number. The next atrial event A_2 comes in after the expiration of the new refractory period, and it is thus conducted through the AV node to the ventricles with a conduction time AV_{i+1} , which is a function of the recovery time $RT = AA_1 + A_1 A_2 - AV_i$.

Model assessment and sensitivity analysis

Starting with the experimental atrial input time series AA_{exp} and an initial ventricular activation, a sequence of computed ventricular activations VV_{model} is generated iteratively for each set of parameter values. We assessed the similarity of the distributions of VV_{model} and VV_{exp} by applying the Kolmogorov-Smirnov test which nonparametrically tests against the null hypothesis that the distributions of the VV_{model} and VV_{exp} are the same. The result of the Kolmogorov-Smirnov test P is the significance level for the null hypothesis. A small probability value P means that the cumulative distribution function of VV_{model} has a low probability of being the same as VV_{exp} , such that the null hypothesis is rejected. A high P value means that null hypothesis cannot be rejected.

The mathematical model has six parameters and it is difficult to determine the values of all six parameters. This is because the six dimensional parameter space is large, several of the parameters have a similar effect on the global dynamics and for the values of some parameters there is a weak dependence on other parameters. Consequently, except where noted otherwise, we have fixed the values of three parameters at approximately the

midpoint of their physiological values determined in previous studies [9,14,18], $\alpha = 200$ ms, $\tau = 100$ ms, $\Delta_{std} = 50$ ms, and varied the remaining parameters over their physiological ranges $0 \leq \theta \leq 300$ ms, $0 \leq \Delta_{mean} \leq 150$ ms, $0 \leq AV_{min} \leq 300$ ms. Increases in each of these parameters would be associated with depressed conduction through the AV node. However, the model allows for quantifying the mechanism of depressed conduction – e.g. increased θ will give different effects from increasing Δ_{mean} or the minimum conduction time AV_{min} .

To quantify the relative importance of the refractoriness θ and concealed conduction Δ_{mean} , a sensitivity analysis of the model using a 3-dimensional representation was performed by fixing AV_{min} , α , τ , Δ_{std} while the refractory period and concealed conduction parameters were varied. The P value for each parameter combination was determined. This 3-D [P , θ , Δ_{mean}] representation allowed us to explore the parameter space of the model. The AV nodal recovery curve with the estimated AV_{min} and α , τ parameters was also computed in order to describe the properties of the AV node during AF. The inputs to the AV node are usually assumed to come primarily from the pathways in the right atrium. Consequently, the electrode closest to the AV node in the right atrium was used as the input.

Effects of antiarrhythmic drug therapy

Epicardial recordings from 10 patients before and 1 h after antiarrhythmic drug therapy were studied. Patients 1–3 did not receive any antiarrhythmic drug. Patients 4–6 received a 24-h infusion of amiodarone (20 mg/kg). Patients 7–9 received an intravenous injection (IV) of the β_1 adrenoreceptor blocking agent metoprolol (0.2 mg/kg) and patient 10 received a combination of IV metoprolol (0.2 mg/kg) + oral amiodarone (300 mg).

Statistical analysis

MATLAB 6.5 (Mathworks, USA) software was used for the statistical analyses and for the simulations.

Results

Clinical data

Fig. 2 shows the electrograms of patient 10 from the right (c1) and left (c2) atria during sinus rhythm (panel A), during AF before administration

of metoprolol + amiodarone (panel B), and after administration of medication (panel C). The times of the atrial activation are indicated by dots above the complexes, and the times of the ventricular activation are indicated by a V. The left fibrillatory activity is extremely regular before (B-c2) and after (C-c2) the drug. Furthermore, the right-to-left atrial period ratio is above one (236 ms/177 ms) and increases after the drug (266 ms/172 ms, panel C).

Fig. 3 shows $\langle AA_r \rangle$ and $\langle AA_l \rangle$ (top panel) and $\langle VV \rangle$ (lower panel) during AF before and after the administration of medication. In patients 1–3, who did not receive medication, the only significant changes observed were in patient 2 in whom there was a decrease in $\langle AA_r \rangle$ from 160 to 154 ms, and an increase in $\langle VV \rangle$ from 441 to 467 ms. Following medication, in patients 4, 7, 9, 10, $\langle AA_r \rangle$ increased by more than 20 ms whereas the changes in $\langle AA_l \rangle$ were always less than 20 ms, the two largest changes being 19 and 18 ms in patients 7 and 9, respectively. Furthermore in all patients receiving medication, $\langle VV \rangle$ markedly increased (Fig. 3, bottom panel). Since we find negligible changes in the atrial activity but a marked increase in the mean $\langle VV \rangle$ in patients 5, 6, and 8, the changes in ventricular activity in these patients must be associated with changes in the properties of the AV node rather than changes in the atrial activity. In patients 4, 7, 9 and 10 after medication, there are changes in both the atrial and ventricular activity. In these patients the changes in the ventricular rate arise as a consequence of the changes induced by the medication in the atria and/or in the AV node.

The physiology of atrial and nodal activities is reflected in the ratios $\langle AA_r \rangle / \langle AA_l \rangle$, $\langle VV \rangle / \langle AA_r \rangle$, and $\langle VV \rangle / \langle AA_l \rangle$. In Fig. 4 we display these ratios for all patients, both before and after pharmacological therapy. For the patients in whom the ratio $\langle AA_r \rangle / \langle AA_l \rangle$ is approximately 1.0 and in whom the standard deviations of the mean atrial activation rates are comparatively small (Table 2), it is likely that there is a well-organized reentrant (or perhaps focal) activity in either the left or right atrium that serves to entrain the activity in the atria. For the patients in whom $\langle AA_r \rangle / \langle AA_l \rangle$ is greater than 1.0, it is likely that there is either a focal or reentrant regular activity in the left atrium that breaks up during propagation in the right atrium, similar to what has been observed recently in sheep [35–37].

Following administration of medication, the ratios $\langle VV \rangle / \langle AA_r \rangle$ and $\langle VV \rangle / \langle AA_l \rangle$ tended to increase, (Fig. 4B,C) indicating that the number of atrial activations that are blocked in the AV node

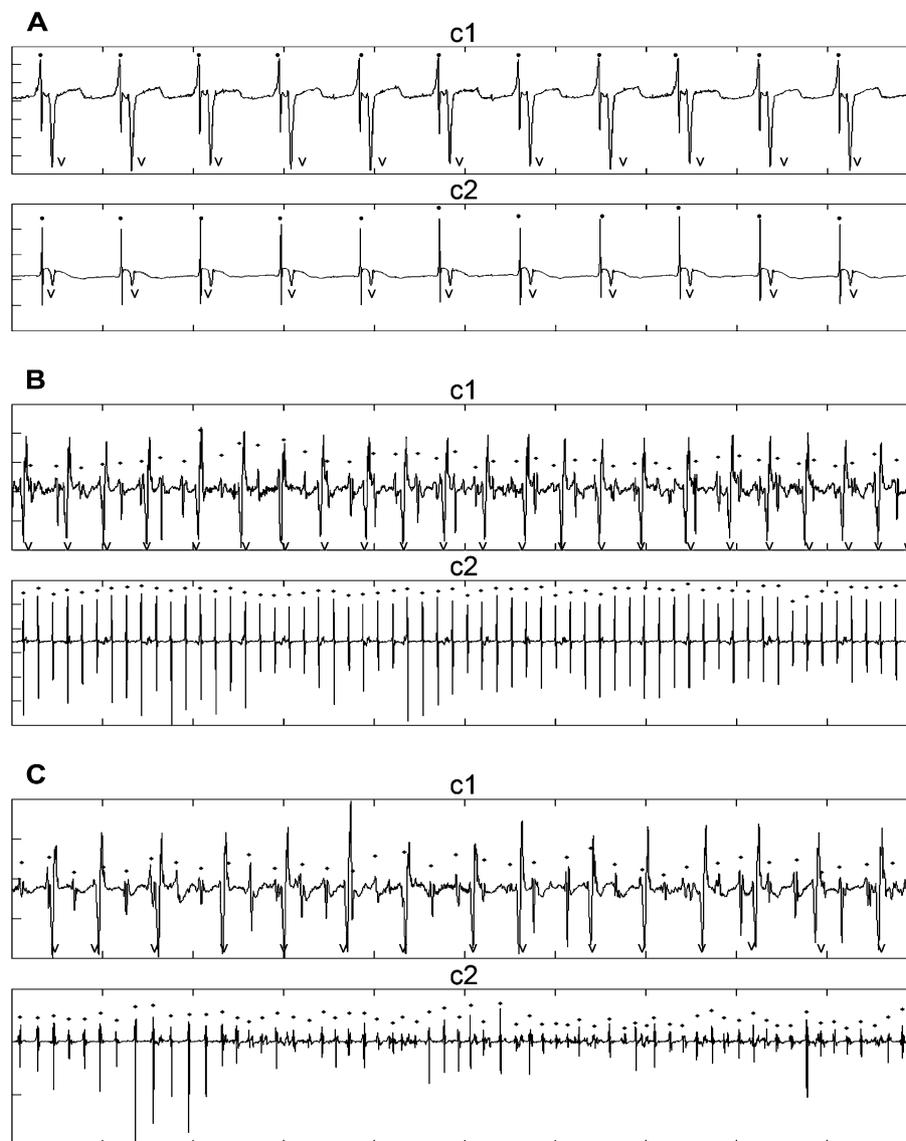


Figure 2 Epicardial atrial signals during sinus rhythm panel (A) and AF before panel (B) and after amiodarone + metoprolol in patient 10 panel (C). Traces labeled c1 are recorded from the right atrial inferior free wall, and traces labeled c2 are recorded from the left atrium near the left inferior pulmonary vein. Ten second data segments are shown. The left fibrillatory activity is regular before (B-c2) and after (C-c2) the drug.

increased following medication. It is therefore important to develop better ways to analyze the effects of blocked beats on AV nodal properties.

Mathematical quantification of AV nodal properties, refractoriness and concealed conduction during AF

The data described above document the effects of drugs on atrial and ventricular activities during AF. One of our goals is to use these data to obtain insight into the quantitative functional properties of the AV node. In contrast to electrophysiological

studies, in which properties of the AV node can be directly assessed using programmed stimulation, we use the fluctuating properties of the atrial and ventricular activities to determine the most appropriate parameters for the AV node functional properties in the context of our theoretical model.

In order to clarify our procedures, and to demonstrate the limitations of previous models that have been used to model the AV node, we first present the results of simulations using three different models of the AV node. These models are: (i) Eq. (2) without concealed conduction as proposed by Shrier et al. [14]; (ii) Eq. (2) plus concealed conduction where $\Delta_{std} = 0$, so that each

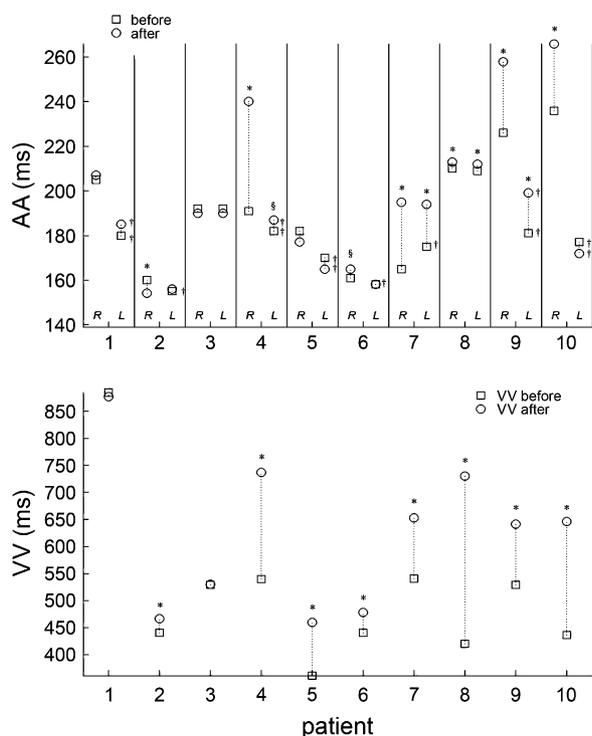


Figure 3 Top panel shows $\langle AA_r \rangle$ and $\langle AA_l \rangle$ during AF before and after the administration of medication in all the patients. * $P < 0.001$, § $P < 0.05$ after vs before medication; † $P < 0.001$ LA vs RA. Bottom panel shows the VV interval $\langle VV \rangle$ in all patients before and after medication. See text for comments.

concealed beat leads to an equal increment in the refractory time, as proposed by Jorgensen et al. [22]; (iii) Eq. (2) plus concealed conduction where Δ_{std} is a positive number, so that each concealed beat leads to a variable increment in the refractory time. The model proposed by Shrier et al. gives good predictions of the ventricular response during atrial stimulation for a variety of fixed rates [14]. However, this model does not give good agreement with the observed ventricular activity in patients with AF. This is illustrated by applying the model to patient 5 after medication. The best agreement that we obtained is shown in Fig. 5B. The shape of the histogram of the VV intervals computed from the simulated time series does not agree with the observed VV distribution (Fig. 5A). Now consider the addition of concealed conduction using the model of Jorgensen et al. [22]. The best agreement is found with $\theta = 110$ ms, $\Delta_{mean} = 120$ ms, $AV_{min} = 70$ ms, $\alpha = 240$ ms, $\tau = 195$ ms. The probability value P is higher but the histogram is multi-modal (Fig. 5C). However, when we allow the concealed beats to have varying effects by assuming Δ_{std} is finite, we find excellent agreement between the observed and simulated histograms (Fig. 5D, $P = 0.95$). In the analysis

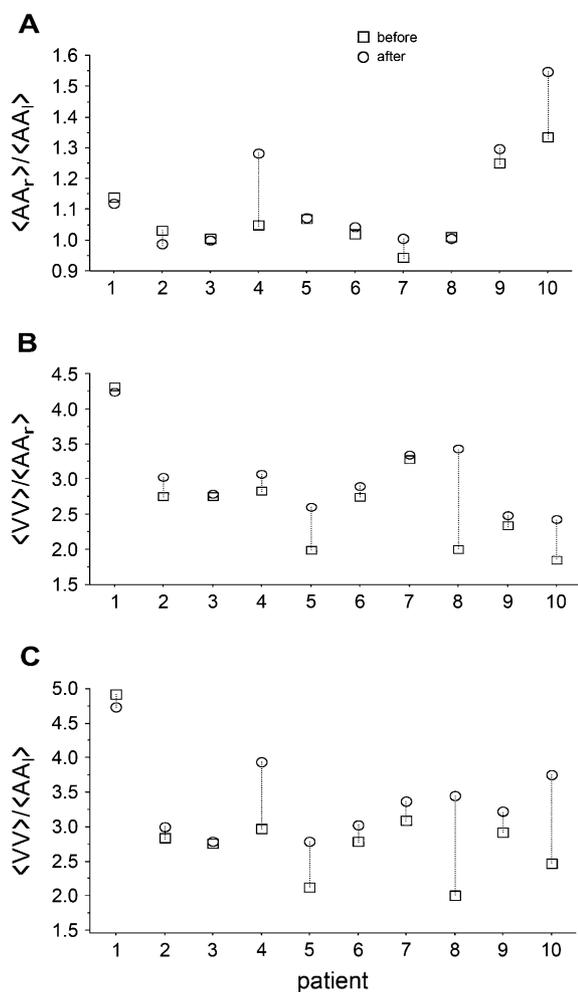


Figure 4 Ratio of $\langle AA_r \rangle / \langle AA_l \rangle$ (panel A), $\langle VV \rangle / \langle AA_r \rangle$ (panel B) and $\langle VV \rangle / \langle AA_l \rangle$ (panel C) before and after medication in all patients. See text for comments.

reported below, in order to avoid problems associated with overfitting the data, we fix the values of Δ_{std} , α , τ and allow the other parameters to vary. We obtain good agreement between the data and simulated results (Table 2). Patients treated with amiodarone had increased refractoriness, i.e. θ , and concealed conduction, Δ_{mean} . Patients treated with β -blockers had an increase in θ and the minimum conduction time AV_{min} .

Sensitivity analysis of the model

Fig. 6 explores the performance of the model for patient 5 upon variation of the refractory period θ and Δ_{mean} . A good agreement between the simulated and observed ventricular RR interval is found over a particular range of θ and Δ_{mean} . The best agreement between the computed and observed distribution of RR intervals is observed for a ridge on which θ is remarkably constant (Fig. 6 top).

Table 2 Mean right/left (RA/LA) atrial, and observed/simulated ventricular (VV) activation time with parameters estimation in patients 1–10

Patient		RA	LA	VV	Simulated VV	Parameters evaluation
1	Before	205 ± 28 (1009)	180 ± 27 (1009)†	885 ± 91 (199)	823 ± 105 (220)	$P = 0.6, \theta = 270, \Delta_{\text{mean}} = 45, AV_{\text{min}} = 330$
	After	207 ± 40 (864)	185 ± 29 (953)†	877 ± 154 (209)	888 ± 101 (203)	$P = 0.85, \theta = 340, \Delta_{\text{mean}} = 25, AV_{\text{min}} = 350$
2	Before	160 ± 33 (1074)	155 ± 35 (1101)†	441 ± 83 (387)	444 ± 88 (386)	$P = 0.7, \theta = 140, \Delta_{\text{mean}} = 50, AV_{\text{min}} = 135$
	After	154 ± 32 (1127)*	156 ± 31 (1108)	467 ± 81 (385)*	468 ± 86 (370)	$P = 0.9, \theta = 200, \Delta_{\text{mean}} = 30, AV_{\text{min}} = 120$
3	Before	192 ± 31 (950)	192 ± 26 (949)	529 ± 104 (344)	521 ± 97 (346)	$P = 0.6, \theta = 110, \Delta_{\text{mean}} = 65, AV_{\text{min}} = 210$
	After	190 ± 33 (939)	190 ± 32 (907)	530 ± 75 (393)	535 ± 98 (338)	$P = 0.6, \theta = 115, \Delta_{\text{mean}} = 50, AV_{\text{min}} = 225$
4	Before A	191 ± 36 (880)	182 ± 34 (922)†	540 ± 101 (330)	545 ± 112 (309)	$P = 0.95, \theta = 195, \Delta_{\text{mean}} = 65, AV_{\text{min}} = 140$
	After A	240 ± 30 (812)*	187 ± 25 (972)†§	737 ± 100 (254)*	741 ± 104 (263)	$P = 0.6, \theta = 200, \Delta_{\text{mean}} = 75, AV_{\text{min}} = 380$
5	Before A	182 ± 32 (1003)	170 ± 27 (1007)†	362 ± 51 (496)	363 ± 53 (504)	$P = 0.9, \theta = 110, \Delta_{\text{mean}} = 30, AV_{\text{min}} = 105$
	After A	177 ± 36 (970)	165 ± 35 (1043)†	460 ± 109 (394)*	466 ± 115 (369)	$P = 0.8, \theta = 200, \Delta_{\text{mean}} = 65, AV_{\text{min}} = 80$
6	Before A	161 ± 31 (1113)	158 ± 33 (1140)	441 ± 83 (371)	446 ± 92 (403)	$P = 0.8, \theta = 115, \Delta_{\text{mean}} = 55, AV_{\text{min}} = 150$
	After A	165 ± 39 (1296)§	158 ± 38 (1308)†	478 ± 82 (372)*	499 ± 86 (432)	$P = 0.85, \theta = 190, \Delta_{\text{mean}} = 60, AV_{\text{min}} = 130$
7	Before M	165 ± 23 (1070)	175 ± 36 (1056)†	541 ± 85 (332)	548 ± 86 (334)	$P = 0.6, \theta = 220, \Delta_{\text{mean}} = 20, AV_{\text{min}} = 190$
	After M	195 ± 35 (900)*	194 ± 33 (907)*	653 ± 113 (269)*	656 ± 116 (268)	$P = 0.95, \theta = 230, \Delta_{\text{mean}} = 60, AV_{\text{min}} = 210$
8	Before M	210 ± 18 (856)	209 ± 9 (851)	420 ± 22 (390)	419 ± 33 (429)	$P = 0.95, \theta = 105, \Delta_{\text{mean}} = 55, AV_{\text{min}} = 125$
	After M	213 ± 17 (847)*	212 ± 12 (848)*	730 ± 74 (138)*	727 ± 90 (249)	$P = 0.6, \theta = 245, \Delta_{\text{mean}} = 15, AV_{\text{min}} = 325$
9	Before M	226 ± 52 (804)	181 ± 46 (1002)†	529 ± 126 (339)	528 ± 117 (344)	$P = 0.75, \theta = 200, \Delta_{\text{mean}} = 100, AV_{\text{min}} = 100$
	After M	258 ± 65 (704)*	199 ± 61 (919)†*	641 ± 144 (279)*	651 ± 156 (278)	$P = 0.6, \theta = 220, \Delta_{\text{mean}} = 125, AV_{\text{min}} = 145$
10	Before M + A	236 ± 44 (778)	177 ± 29 (1027)†	437 ± 70 (279)	437 ± 65 (320)	$P = 0.75, \theta = 80, \Delta_{\text{mean}} = 50, AV_{\text{min}} = 175$
	After M + A	266 ± 42 (688)*	172 ± 29 (1082)†	646 ± 113 (279)*	646 ± 110 (283)	$P = 0.75, \theta = 165, \Delta_{\text{mean}} = 80, AV_{\text{min}} = 260$

All values are in ms. Data are given mean ± SD, N: number of events of the time series, VV: ventricular time series; M: metoprolol, A: amiodarone, M + A: metoprolol + amiodarone; * $P < 0.001$, § $p < 0.05$ after vs before medication, † $P < 0.001$ RA vs LA, parametric t -test. P: probability value. Three parameters are fixed: $\Delta_{\text{std}} = 50$ ms, $\alpha = 200$ ms and $\tau = 100$ ms.

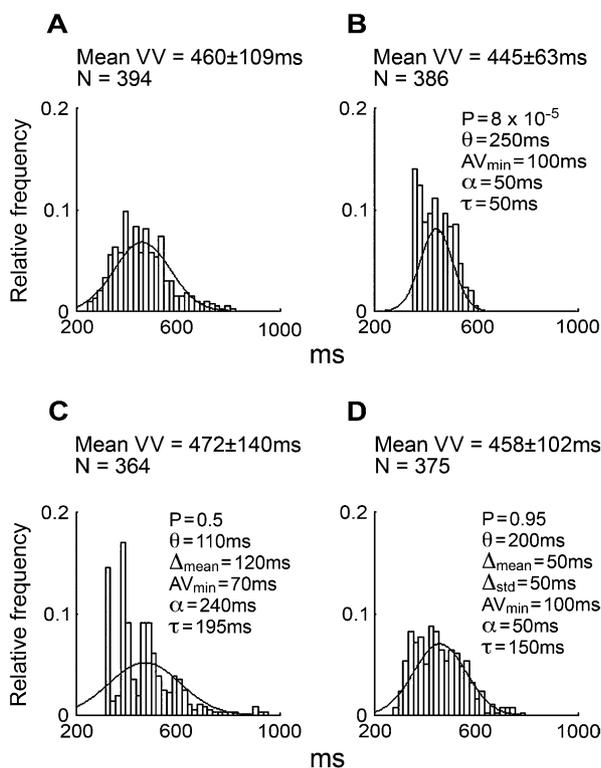


Figure 5 Observed histograms of VV intervals in patient 5 after medication. (B) Best fit using the AV nodal recovery curve without concealed conduction in the model of Shrier et al. [14]. (C) Best fit with the inclusion of the concealed conduction Δ_{mean} in the theoretical model of Jorgensen et al. [22]. (D) Best fit using the current model.

Therefore, the concealed conduction parameter plays a major role in determining the best agreement between the observed and simulated ventricular time series. After amiodarone (Fig. 6 bottom), there is a strong shift of the parameters towards larger values of θ and Δ_{mean} . There is now a ridge of values along which θ and Δ_{mean} simultaneously vary with many different combinations giving good agreement of the model with the clinical data.

Discussion

The current work provides a unique opportunity to analyze the determinants of the ventricular response during AF using a clinical and mathematical modelling approach. Left, right atrial, and ventricular activities were simultaneously recorded before and after administration of amiodarone and/or metoprolol in conscious post-operative patients. The drugs lead to a prolongation of the inter-activation time in the right atrium from 3 to

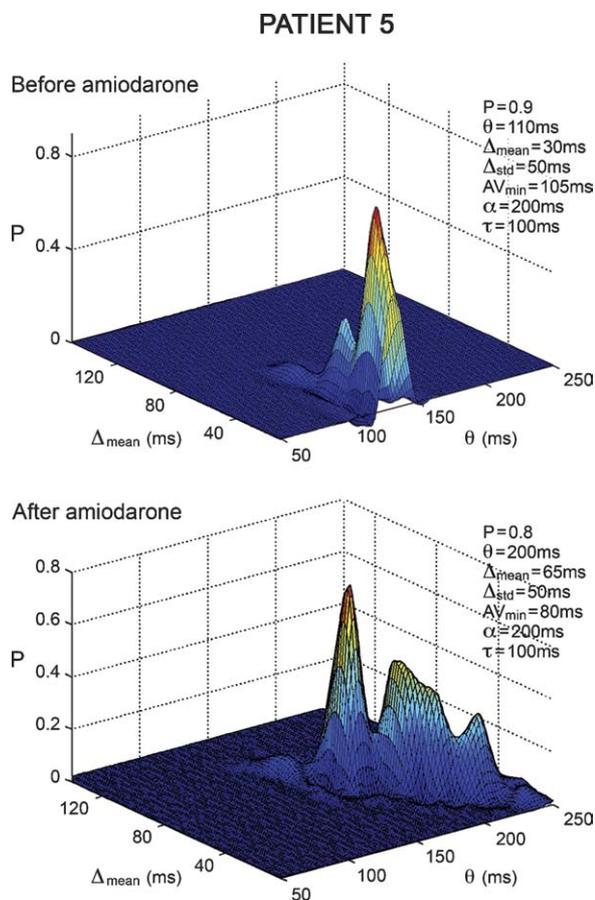


Figure 6 Sensitivity analysis of the model illustrated by a three-dimensional representation which explores the parameter space of the model (refractory period and concealed conduction parameters) of patient 5 during AF, before the medication (top) and after 1 h of amiodarone (bottom). Δ_{std} , AV_{min} , α and τ are fixed while θ and Δ_{mean} are varied. The best agreement between the computed and observed distribution of RR intervals is observed for a ridge on which θ is constant (top). The concealed conduction parameter Δ_{mean} plays a major role in determining the ventricular response. After amiodarone, the parameter space of the model is shifted towards more refractoriness.

49 ms in 5/7 treated patients, have less effects on the left atrium, but prolong much more the ventricular period. To define the effects of medication on the AV node during AF, we developed a mathematical model that includes concealed conduction. Using this model, it is possible to evaluate the role of the drugs in modifying the properties of the AV node during AF.

Pathophysiological mechanisms and effects of antiarrhythmic drugs during AF

The underlying mechanisms involved in the genesis and maintenance of AF are multiple. In patients

experiencing paroxysmal AF, the mechanism may be a focal source localized usually in one of the pulmonary veins [38]. In chronic AF, the prevailing theory is that multiple random wavelets of activation coexist to create a disorganized cardiac rhythm [39]. Recent experimental data indicate that AF may be organized by one, or a small number of high frequency reentrant sources in the LA, with fibrillatory conduction toward the RA [36,37]. Optical mapping studies in the isolated sheep heart demonstrated that during AF there were steep activation frequency gradients between the LA and the RA [37]. Mansour et al. also showed a left-to-right gradient of atrial frequencies during AF in sheep [37]. In the 10 post-operative patients experiencing paroxysmal AF, the ratio $\langle AA_r \rangle / \langle AA_l \rangle$ is greater than 1.0, for all cases except one before and one after drug (Fig. 4A).

Little information is available on the precise mechanisms of the acute effects of the drug on atrial tissue. The different actions of amiodarone at the atrial level in patients 4–6 and 10 may be related to significant intrinsic differences in the action potential duration between the LA and RA myocytes. Regional action potential variability is associated with distinctive patterns of repolarization and ionic current density [40]. Action potential duration and refractory period are shorter in the LA than in the RA free wall due to differences in the I_{Kr} current [40]. One possible explanation is that amiodarone lengthens the refractory period differently depending on the atrial area. The target ionic current responsible for such interatrial differences remains to be determined.

AV nodal function during AF

The rate-dependent conduction of the AV node depends on the complex anatomical structure of the node involving multiple cell types and both fast and slow pathways [41,42]. Nevertheless, the recovery of excitability of the I_{CaL} calcium current is among the major determinants of the dynamics. β -Adrenergic stimulation of the AV nodal tissue increases both I_{CaL} and I_K currents. These act together to produce a shorter effective refractory period as well as faster AV conduction speed, thus promoting a higher ventricular activation rate during AF. These physiological actions provide a foundation for the use of blockers such metoprolol, or antiarrhythmic drugs with class IV and class III actions as amiodarone to help control the ventricular rate during AF.

Previous studies developed a theoretical model of the AV node based on independent tests of AV nodal function during atrial pacing [10,14,15,19]. The current work combined with earlier studies demonstrates that the mathematical models developed in these studies cannot be used to compute the ventricular response during spontaneous AF [23]. We developed a model during AF that allows us to set parameters based on comparisons between the experimental and simulated histograms. Although ideally we would have liked to predict the time of occurrence of every ventricular contraction, this was not possible, likely because of the stochastic nature of the penetration of atrial activity into the AV node during AF. However, by attempting to simulate the statistical features of the histogram of VV intervals during AF, we were able to demonstrate that many plausible models of AV nodal function, are not adequate to model the AV node during AF.

The irregular ventricular rhythm that accompanies AF has been explained in terms of concealed conduction within the AV node [11,16,21,28–34]. The exact mechanism of concealed conduction remains controversial, but is thought to involve both conduction in the AV nodal slow pathway and electrotonic inhibition. It is important to understand the role of concealed conduction in determining the ventricular response rhythm during AF [29–31]. In the current model, each blocked beat leads to an increase in the refractory period of the AV node by an amount Δ that follows a Gaussian distribution. Since the atrial activity is quite regular in several of the subjects, other models in which each blocked beat has an identical effect did not lead to broad unimodal histograms similar to what was observed in most of the patients, but rather led to multi-modal histograms reflecting the variable conduction ratios between atrial and ventricular activity, see Fig. 5. The accuracy of the parameter estimation is evaluated by the sensitivity analysis exploring the parameter space of the model. Such an analysis confirms that the concealed conduction parameter Δ_{mean} plays a major role in determining the agreement between the simulated and observed VV time series, for example see Fig. 6.

Our data raises the important question of the relative roles of the medications on the atrial activity, the refractory time, and the concealed conduction. An earlier study in a porcine model of AF [11] assessed the role of metoprolol on concealed conduction. In this experiment AF was induced by delivering premature stimuli with the presence of metacholine. Metoprolol led to a significant increase in the mean interatrial activation

times in the right atrium and also led to a reduced ventricular activation rate. Since the lower atrial activation rate would be expected to lead to reduced concealed conduction, [32] van den Berg et al. concluded that concealed conduction was not a significant contributor to the pharmacological effects of metoprolol but that it acted by increasing the refractory time of the AV node [11]. However, since the parameters describing concealed conduction can also be affected by the medication, it is possible that a smaller number of blocked atrial activations would lead to an increased slowing of ventricular response. Although no direct measure of concealed conduction is possible during AF, the mathematical model suggests that changes in concealed conduction might be affected by the medication differently from changes in other physiological properties of the AV node, and, thus, might constitute distinct targets for medication.

Limitations

The main limitation of the current study is that the mathematical model of the AV node is approximate, and it is not easy to estimate the magnitude of the errors of the derived parameters. In this context, the decreased conduction through the AV node can be associated with an increase in the refractory period, an increase in the minimum conduction time, or an increase in the parameter that accounts for the concealed conduction (Fig. 5 bottom). To some extent, similar quantitative changes in the dynamics can result from an increase in any of those parameters. Thus, without a method to measure directly the magnitude of concealed conduction, definitive statements of the magnitude of the effects on the functional properties of the AV node cannot be made. Furthermore, each simulation is stochastic since Δ_{std} is a parameter that controls a random distribution. As an example, we performed for patient 5 before treatment, 10 trials of simulations to evaluate the mean and standard deviation of the three main parameters. We found that the range for those parameters as well as for the probability value is narrow: $P = 0.79 \pm 0.06$, $\theta = 110 \pm 5$ ms, $\Delta_{\text{mean}} = 28 \pm 8$ ms, $AV_{\text{min}} = 110 \pm 5$ ms.

Neither fatigue, nor facilitation has been incorporated in the model [18,43]. Whereas such contributions can account for the AV nodal response during a variety of pacing protocols, their contribution during AF are not known. To date, fatigue and facilitation have been invoked to describe observed dynamics during rapid activation

in which each atrial stimulus is conducted to the ventricles or when a small fraction of atrial activations are blocked in the AV node [15]. Further limitations arise from the difficulty of assessing atrial electrical activity during AF. Because of technical limitations necessitated by the surgical protocol, the positioning of the leads was not in the direct vicinity of the AV node. However, since in many of the patients, the activities in the right and left atria were quite regular with very similar frequencies, in many instances our measured atrial rate likely does reflect the rate impinging on the AV node. Finally, AV nodal electrophysiological properties during post-operative AF may be different than the properties during chronic AF. Catecholamine release is enhanced and autonomic regulation is altered after heart surgery [7,44]. Therefore, the current results may not be extrapolated to other types of AF.

Despite these limitations, the current study demonstrates that medications might have differential effects on various parameters describing AV nodal physiology during AF and that mathematical modelling should be able to help decipher these complex phenomena. We hope that the current study helps to stimulate further research into these clinically important phenomena.

Acknowledgments

We thank Eric Libby, Pierre Rocque and Yalin Yin for their excellent technical assistance and Dr. S. Nattel for helpful conversations.

References

- [1] Kannel WB, Abbott RD, Savage DD, et al. Epidemiology features of chronic atrial fibrillation: the Framingham study. *N Engl J Med* 1982;306:1018–22.
- [2] Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. *Stroke* 2001;32:803–8.
- [3] Fenelon G, Wijns W, Andries E, et al. Tachycardiomyopathy: mechanisms and clinical implications. *Pacing Clin Electrophysiol* 1996;19:95–106.
- [4] Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825–33.
- [5] Pagé PL, Yin Y, Corbeil-Létourneau S, et al. Premature atrial contractions after cardiac surgery: insight into mechanism of post-operative atrial fibrillation. *Pacing Clin Electrophysiol* 2003;26:1093 [abstract].
- [6] Kochiadakis GE, Kanoupakis EM, Kalebubas MD, et al. Sotalol vs metoprolol for ventricular rate control in patients with chronic atrial fibrillation who have undergone digitalization: a single-blinded crossover study. *Europace* 2001;3:73–9.
- [7] Hogue Jr CW, Hyder ML. Atrial fibrillation after cardiac operation: risks, mechanisms, and treatment. *Ann Thorac Surg* 2000;69:300–6.

- [8] Macle L, Jaïs P, Scavee C, et al. Electrophysiologically guided pulmonary vein isolation during sustained atrial fibrillation. *J Cardiovasc Electrophysiol* 2003;14:255–60.
- [9] Nattel S, Talajic M, Quantz M, et al. Frequency-dependent effects of amiodarone on atrioventricular nodal function and slow-channel action potentials: evidence for calcium channel-blocking activity. *Circulation* 1987;76:442–9.
- [10] Nayebpour M, Talajic M, Nattel S. Effects of β -adrenergic receptor stimulation and blockade on rate-dependent atrioventricular nodal properties. *Circ Res* 1992;70:902–11.
- [11] Van den Berg MP, De Langen C, Crijns HJ, et al. Effect of metoprolol on atrial fibrillatory rate, atrioventricular nodal concealed conduction, and ventricular response during atrial fibrillation in pigs. *J Cardiovasc Pharmacol* 1994;23:846–51.
- [12] Simson MB, Spear J, Moore EN. The relationships between atrioventricular nodal refractoriness and the functional refractory period in the dog heart. *Circ Res* 1979;44:121–8.
- [13] Moe GK, Abildskov JA. Observations on the ventricular dysrhythmia associated with atrial fibrillation in the dog heart. *Circ Res* 1964;14:447–60.
- [14] Shrier A, Dubarsky H, Rosengarten M, et al. Prediction of complex atrioventricular conduction rhythms in humans with use of the atrioventricular nodal recovery curve. *Circulation* 1987;76:1196–205.
- [15] Talajic M, Papadatos D, Villemaire C, et al. A unified model of atrioventricular nodal conduction predicts dynamic changes in Wenckebach periodicity. *Circ Res* 1991;68:1280–93.
- [16] Heethaar RM, De Vos Burchart RM, Van der Gon JD, et al. A mathematical model of AV conduction in the rat heart. Quantification of concealed conduction. *Cardiovasc Res* 1973;7:542–56.
- [17] Teague S, Collins S, Wu D, et al. A quantitative description of normal AV nodal conduction curve in man. *J Appl Physiol* 1976;40:74–8.
- [18] Nayebpour M, Talajic M, Nattel S. Quantitation of dynamic AV nodal properties and application to predict rate-dependent AV conduction. *Am J Physiol* 1991;261:292–300.
- [19] Heethaar RM, Van der Gon JD, Meijler FL. Mathematical model of AV conduction in the rat heart. *Cardiovasc Res* 1973;7:105–14.
- [20] Guevara MR. Iteration of the human atrioventricular (AV) nodal recovery curve predicts many rhythms of AV block. In: Glass L, Hunter P, McCulloch A, editors. *Theory of heart: biomechanics, biophysics, and nonlinear dynamics of cardiac function*. New York, USA: Springer-Verlag; 1991. p. 313–58.
- [21] Meijler FL, Jalife J, Beaumont J, et al. Atrioventricular nodal function during atrial fibrillation: the role of electrotonic modulation of propagation. *J Cardiovasc Electrophysiol* 1996;7:843–61.
- [22] Jorgensen P, Schafer C, Guerra PG, et al. A mathematical model of human atrioventricular nodal function incorporating concealed conduction. *Bull Math Biol* 2002;64:1083–99.
- [23] Zeng W, Glass L. Statistical properties of heartbeat intervals during atrial fibrillation. *Phys Rev E* 1996;54:1779–84.
- [24] Cohen RJ, Berger RD, Dushane TE. A quantitative model for the ventricular response during atrial fibrillation. *IEEE Trans Biomed Eng* 1983;30:769–80.
- [25] Rashidi A, Khodarahmi I. Nonlinear modeling of the atrioventricular node physiology. In: *Atrial fibrillation*. *J Theor Biol* 2005;212:820–5.
- [26] ten Hoopen M. Ventricular response in atrial fibrillation. A model based on retarded excitation. *Circ Res* 1966;19:911–6.
- [27] Stein KM, Walden J, Lippman N, Lerman BB. Ventricular response in atrial fibrillation: random or deterministic? *Am J Physiol* 1999;277:452–8.
- [28] Lewis T, Master AM. Observations upon conduction in the mammalian heart. A-V conduction. *Heart* 1925;12:209–69.
- [29] Liu Y, Zeng W, Delmar M, et al. Ionic mechanisms of electrotonic inhibition and concealed conduction in rabbit atrioventricular nodal myocytes. *Circulation* 1993;88:1634–46.
- [30] Billette J. Anatomy and physiology of concealment in dual atrioventricular nodal pathway. *J Cardiovasc Electrophysiol* 2004;15:150–1.
- [31] Liu S, Olsson B, Yang Y, et al. Concealed conduction and dual pathway physiology of the atrioventricular node. *J Cardiovasc Electrophysiol* 2004;15:144–9.
- [32] Chorro FJ, Kirchhof CJ, Brugada J, Allesie MA. Ventricular response during irregular atrial pacing and atrial fibrillation. *Am J Physiol* 1990;259:1015–21.
- [33] Cohen SI, Lau SH, Berkowitz WD, Damato AN. Concealed conduction during atrial fibrillation. *Am J Cardiol* 1970;25:416–9.
- [34] Langendorf R. Concealed A-V conduction: the effects of blocked impulses on the formation and conduction of subsequent impulses. *Am Heart J* 1948;35:542–52.
- [35] Jalife J, Berenfeld O, Mansour M. Mother rotor and fibrillatory conduction: a mechanism of atrial fibrillation. *Cardiovasc Res* 2002;54:204–16.
- [36] Mandapati R, Skanes A, Chen J, et al. Stable micro-reentrant sources as a mechanism of AF in the isolated sheep heart. *Circulation* 2000;101:194–9.
- [37] Mansour M, Mandapati R, Berenfeld O, et al. Left-to-right gradient of atrial frequencies during acute atrial fibrillation in the isolated sheep heart. *Circulation* 2001;29:2631–6.
- [38] Haissaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–66.
- [39] Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J* 1959;58:59–70.
- [40] Li D, Zang L, Kneller J, et al. Potential ionic mechanism for repolarization differences between canine right and left atrium. *Circ Res* 2001;88:1168–75.
- [41] Shrier A, Raffi A, Munk A. Ionic mechanisms of atrioventricular nodal excitability. In: Zipes DP, Jalife J, editors. *Cardiac electrophysiology: from cell to bedside*. Philadelphia, PA USA: WB Saunders; 1995. p. 164–73.
- [42] Billette J, Shrier A. Atrioventricular nodal activation and functional properties. In: Zipes DP, Jalife J, editors. *Cardiac electrophysiology: from cell to bedside*. Philadelphia, PA USA: WB Saunders; 1995. p. 216–28.
- [43] Billette J, Metayer R, St-Vincent M. Selective functional characteristics of rate-induced fatigue in rabbit atrioventricular node. *Circ Res* 1988;62:790–9.
- [44] Reeves JF, Karp RB, Buttner EE, et al. Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. *Circulation* 1982;66:49–55.