Positive Correlation between Heart Rate Variability and Stochastic Nervous Modulation - a Computer Simulation Study

H Zhang[1], JQ Zhang[3], AV Holden[2]

[1]The University of Manchester, Manchester, UK
[2]Anhui Normal University, Wuhu, PR China
[3]The University of Leeds, Leeds, UK

Abstract

Cardiac rhythm is irregular with heart rate varies from time to time. Heart rate variation (HRV) is clinically relevant and indicative of a pathological condition. However, the mechanisms underlying the HRV are still controversial and stochastic nervous modulation may be a major responsible factor. In this study, we implemented a computer simulation study to investigate a causative link between stochastic autonomic nervous modulation and the HRV. It was shown that stochastic activity of parasympathetic nerve system (i.e., by application of acetylcholine) produces varying rate of cardiac pacemaker potentials that presents "chaotic" characteristics although the underlying process is stochastic. A positive correlation between the measured time series of CL and ACh has also been revealed. This study provides a solid evidence to support the hypothesis that stochastic nervous modulation is associated with the HRV, which may be produced by a deterministic system driven by a stochastic process, even though it can show "chaotic" characteristics.

1. Introduction

The normal heart rate is controlled by the primary cardiac pacemaker, the sinoatrial node (SA node), which generates spontaneous and rhythmic action potentials [1]. Heart rate is irregular with high degree of beat to beat variability [2]. Heart rate variability (HRV) is clinically relevant as profoundly depressed HRV has been found in patients with congestive heart failure and in survivors of myocardiac infarction [3-6]. The mechanisms underlying the genesis of HRV are still controversial [2]. One possible mechanism is the intrinsically stochastic nature of ion channels that open and close stochastically [7]. However, irregular ion channel currents arising from stochastic open and close of ion channels are remarkable only if the number of a type of ion channel is less than a few hundreds [2]. As a cardiac cell has at least more than 10^3 ion channels of each channel type, it is therefore arguable that stochastic ionic channels may contribute primarily to the HRV. Another possible mechanism is stochastic modulation of autonomic nervous on sinus nodal discharge rate [8-9]. Though there is a large set of number of experimental data implicating possible involvements of autonomic nervous modulation in producing the HRV [9], the explicit link between the two has not been established yet. The aim of this study is to elucidate a possible correlation between HRV and stochastic nerve activity, by using a biophysically detailed mathematical model of the electrical action potentials of rabbit SA node that incorporates the concentration-dependent effects of acetylcholine (ACh), a neurotransmitter released by parasympathetic neurons, on the pacemaker activity of the heart.

2. Methods

Model of cardiac pacemaking action potentials and effects of acetylcholine: The Zhang et al. models [10] for the electrical action potentials of rabbit SA node cells are used in this study. The models were later modified to incorporate the chronotropic effects of ACh, a neurotransimitter released by parasympathetic nerve system on pacemaking activity [11]. In the model, the chronotropic effect of ACh on cardiac pacemaker action potentials was simulated by including the ACh activated potassium channel current, $i_{K,ACh}$, ACh-induced changes on the channel conductance and kinetics of $i_{Ca,L}$ and i_f [11]. Details of equations and parameters of the Zhang et al. models of SA node cells and actions of ACh are fully documented in Zhang et al. (2000; 2002).

Modeling of stochastic parasympathetic nerve activity. Upon excitation, a firing parasympathetic nerve neuron in the vicinity of cardiac cells releases neurotransmitters, ACh, which bind to several targeted ion channels of SA node cells to modulate their rhythmic and spontaneous

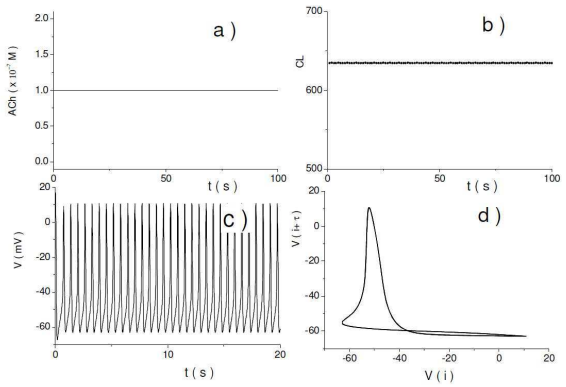

Figure 1. Simulated chronotropic effect of a constant ACh concentration on the pacemaker activity of SA node cells. a) Time course of ACh concentration during simulation (i.e., $1x10^{-7}$ M); b) Time course of measured cycle length of SA node action potentials; c) Time series of simulated action potentials; d) Reconstructed attractor in the phase space by the time-delay method.

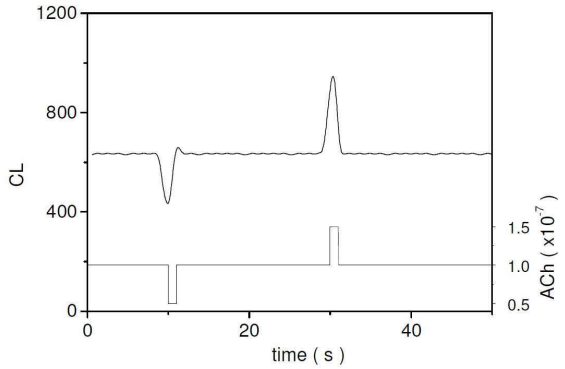

Figure 2. Effects of discrete and pulse-like fluctuation of ACh on the pacemaker action potentials of the SA node. The measured CL (upper panel) varies in response to ACh concentration variation (lower panel).

electrical action potentials [11]. The neurotransmitters are released in discrete and quantal packets that present a stochastic process [12]. In this study, the stochastic time-varying ACh concentration is set by:

$$[ACh] = [ACh]_0 + [ACh]_{\xi(t)} \qquad (1)$$

Where, $[ACh]_0$ is set to be a constant value $1.0x10^{-7}$ M, which is able to produce a noticeable chronotropic effect on the pacemaking action potentials [11]. $[ACh]_{\xi(t)}$ is a random fluctuation term, which is set to:

$$[ACh]_{\xi(t)} = \begin{cases} +[ACh]_0 \times n / n_{\max} & if\ (\text{rand}()/n_{\max} >= 0.5 * n_{\max}) \\ -[ACh]_0 \times n / n_{\max} & else \end{cases} \qquad (2)$$

In Equation (2), n_{max} is an integer constant number and fixed to be 100, the random numbers n ($0 < n < n_{max}$) are generated by the intrinsic function $\text{rand}()/n_{max}$ of the C complier with uniform deviates.

The model equations are numerically integrated by the fourth-order Runge-Kutta method with a time step 0.2 ms, which is sufficiently small for stable solutions [10]. The simulated time series of membrane potentials were used to reconstruct state attractors in the phase space by the time-delayed method, which were then quantified by the maximal Lyapunov exponent (LE) using the method developed by Wolf et al. [13].

The correlation between the time series of ACh and the measured CL of spontaneous action potentials was quantified by a linear correlation coefficient R. For a paired time series of (x_i, y_i), where i indexes discrete time (i=1,…,N), R defined as [14]:

$$R = \frac{\sum_i (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_i (x_i - \bar{x})^2} \sqrt{\sum_i (y_i - \bar{y})^2}} \qquad (3)$$

Where $\bar{x}$ and $\bar{y}$ are the means of the time series of x_i and y_i respectively. The value of R lies between -1 and 1. If x and y are complete positively correlated, R=1 (indicating that x and y increasing together). If x and y are complete negatively correlated, if R=-1 (indicating that y decreases as x increases). A value of R near zero indicates that the variables x and y are uncorrelated.

3. Results

Simulations were performed using both the central and peripheral cell models of for the electrical action potentials of rabbit SA node cells [10]. Due to similar results, data from the central cell model were shown.

Without fluctuation in concentration, (i.e., $[ACh]=1.0x10^{-7}$ M), a constant level of ACh concentration produced a remarkable chronotropic effect on the pacemaking action potentials of the model with a remarkable prolonged measured cycle length (CL=640 ms) compared to the control condition (CL=330 ms). This is consistent with the results of Zhang et al. [12]. During the time course of 100 second simulations, the simulated action potentials are periodic (Fig 1C) and stable, with a constant measured CL (Fig 1B). The reconstructed attractor in the phase space by the time delayed method (i.e., $V_m(t)$ vs $V_m(t+\tau)$; τ=400 ms) presents as a limit cycle (Fig 1D).

A discrete and short period of pulse-like variation in the ACh concentration produces a short-termed but smoothed change in the measured CL of action potentials

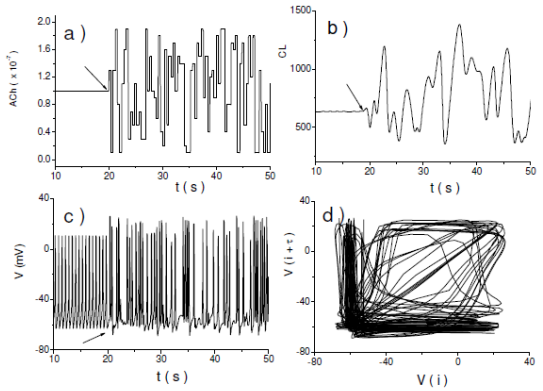

Figure 3. Effects of stochastic variation in [ACh] on the pacemaking action potentials of SA node cells. a) ACh concentration fluctuates around the central level $1.x10^{-7}$ M; b) Measured time series of CL; c) Time series of simulated action potentials; d) Reconstituted state attractor in phase space. The arrow denotes the time when stochastic ACh fluctuation is switched on.

(Fig 2) with the measured CL being either increased when ACh concentration is elevated or decreased when ACh concentration is reduced. However, elevated and reduced ACh concentrations have asymmetric effects on the variation of the measured CL. With the same magnitude of ACh fluctuation (an amplitude of $0.5x10^{-7}$ M and a duration of 400 ms on the basis of $1.0x10^{-7}$ M), an elevated ACh prolonged the measured CL from 640 ms to 948 ms (δCL=308 ms), whilst a reduced ACh shortened the measured CL from 640 ms to 434 ms (δCL=206 ms). Such an asymmetric effect on the variation of the measured CL between an increased and a decreased ACh concentration is due to the nonlinear concentration-dependent response curve of ACh on cardiac pacing rates [12].

It is notable that the measured CL responds rapidly to the onset, but takes some relaxation time to follow the offset of ACh variation. In the result shown in Fig 2, when the variation in ACh concentration is switched off, the cell model takes about additional 2 second to follow before it resumes its original pacing rate.

Effects of a series of stochastic discrete and pulse-like variations in ACh on the pacemaker action potentials of the SA node model are shown in Fig 3. In the first 20 seconds of simulation, the ACh concentration is fixed to a constant level (*i.e.*, $[ACh]=[ACh]_0=1.0x10^{-7}$ M) (Fig 3A). During this period, the pacemaking action potential is periodic (Fig 3B) with a constant measured CL (Fig 3C). When ACh variation is switched on to fluctuate stochastically around the central level $[ACh]_0$, with both the amplitude (either elevated or reduced) and

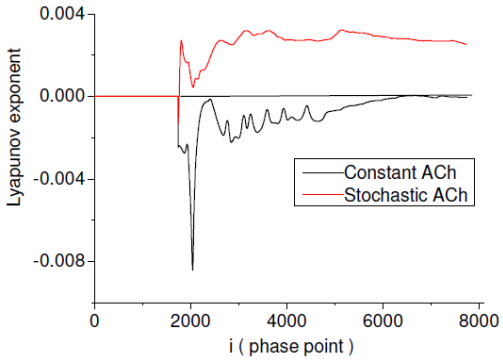

Figure 4. Time series of computed maximal Lyapunov exponent from the reconstructed phase attractors for action potentails with a constant ACh concentration (black) and with stochastic ACh concentration (red).

duration of fluctuation changing randomly, the simulated action potentials become apparently irregular with the measured CL varying remarkably from beat to beat. The reconstructed attractor is the phase space (Fig 3D) appears to be a strange attractor, with nearby trajectories diverging in some regions but converging in some other regions and all trajectories are confined to a limited space.

The reconstructed attractor appears to be a strange attractor, a typical feature of a chaotic deterministic system even though it is produced by a nonlinear deterministic system driven by a stochastic process. To characterize the property of the reconstructed attractor, we computed the maximal Lyapunov exponent by using the Wolf method [13]. Results are shown in Fig 4. With a constant ACh level, the simulated action potentials are periodic. In this case, the computed Lyapunov exponent is always negative and asymptotically approaches zero with the evolution of time. However, with stochastic variation in ACh concentration, the simulated action potentials are chaotic-alike. In this case, the estimated maximal Lyapunov exponent is positive.

Table 1 Averaged correlation coefficient (R) for different numbers of paired [ACh] and CL time series.

Pair numbers	200	300	500	1000
R	0.45	0.46	0.52	0.55

To further quantify the correlation between the stochastic variation in ACh concentration and the fluctuating CL, the coefficient R was estimated from paired time series of [ACh] and CL. Results are summarized in Table-1. It was shown that the computed

R is positive, suggesting that the fluctuating CL can be confidently attributable to the stochastic variation in ACh concentration.

4. Discussion and conclusions

In this study, we have studied the effects of stochastic nervous activities (i.e., stochastic variation in acetylcholine concentration) on cardiac pacemaking action potentials and their rates (i.e., changes in the measured CL). We found that (i) stochastic variation in ACh concentration produces fluctuating CL, which changes from beat to beat; (ii) effects of varying ACh concentration on cardiac pacemaking rates is highly nonlinear with an elevated or reduced ACh concentration having an asymmetrical impact on increasing or decreasing the measured CL; (iii) there is a positive correlation between ACh concentration variation and the measured fluctuating CL, suggesting that stochastic nervous activities is one of major responsible factors underlying the HRV; (iv) the simulated action potentials under the effects of stochastic ACh concentration appears to be chaotic-like with a strange-like phase portrait and positive maximal Lyapunov exponent, though they are produced by a nonlinear system driven by a stochastic process. Thus it should be cautious to interpret data obtained from nonlinear analysis of HRV data. In our simulation, the fluctuating CL is attributable in confidence to stochastic ACh variation. This provides a solid evidence to support the hypothesis that stochastic nervous modulation, especially the parasympathetic modulation, is associated with the HRV.

Acknowledgements

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Address for correspondence

Henggui Zhang
Biological Physics Group
School of Physics & Astronomy
The University of Manchester
Manchester, M13 9PL, UK
E-mail address: Henggui.zhang@manchester.ac.uk