

The influence of mean heart rate on measures of heart rate variability as markers of autonomic function: a model study

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Abstract

Some studies have demonstrated that the assessments of autonomic activities from the alterations of heart rate variations (HRVs) after autonomic blockade and during exercise of high intensity by the spectral analysis of HRV seemed inconsistent with actual situation. The inconsistency is probably caused by the contributions of fluctuating magnitudes and mean levels of autonomic activities on HRV having not been clarified. The alterations of HRV after autonomic blockade and during exercise of high intensity using a mathematical model were simulated. The autonomic activity in normal condition was assumed first according to some experimental evidence. Then autonomic activities after sympathetic blockade, vagal blockade and during exercise of high intensity were appropriately adjusted accordingly. The HRVs in response to these given autonomic activities were simulated. We found that the effect on HRV influenced by the mean level of autonomic activity is helpful to explain alterations of HRV in these conditions. After vagal blockade, a largely reduced low frequency (LF) power could be caused by the reduced mean heartbeat interval induced by a decreased mean level of vagal activity. Increased low and high frequency powers after sympathetic blockade could be caused by the increased mean heartbeat interval induced by a decreased mean level of sympathetic activity. A decreased LF power during exercise of high intensity, in addition to the withdrawal of vagal activity, could also be caused by the decreased mean heartbeat interval induced by an increased mean level of sympathetic activity.

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1. Introduction

Power spectral analysis of heart rate variation (HRV) has been widely used for assessing the autonomic nervous system (ANS) function [1–3]. Generally, the power spectra of HRV can be divided into low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz) components. The LF power is modulated by both sympathetic and vagal controls [4,5], while the HF power mainly reflects the vagal influence [2,5,6]. A physiological basis for such assessment is that cardiac response to vagal activity is more rapid than to sympathetic activity [7,8]. However, measures of HRV for assessment of ANS after autonomic blockade and during exercise of

high intensity have generated inconsistent results. Both LF and HF powers were slightly increased after sympathetic blockade [9]. After vagal blockade, the LF power was largely reduced in supine posture [5,9] and also in standing posture [5]. Previous studies have shown that during low and medium exercise intensities heart rate was increased primarily by the withdrawal of vagal activity, the increase in sympathetic tone was minimal. However, with high exercise intensity the increase in heart rate was due to increased sympathetic tone. Although the sympathetic activity was enhanced during exercise of high intensity, the LF power was dramatically decreased [10–13]. Some investigators have pointed out that the spectral powers of HRV reflect periodic fluctuations in autonomic activity rather than autonomic tones [14,15]. On the other hand, the transfer function behavior of atrial rate response to autonomic regulation depended on the mean level of vagal or sympathetic tone [16]. Hence, the mean autonomic tone also

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makes a contribution to HRV. The spectral powers of HRV may simultaneously reflect the contributions of the fluctuating magnitude and the mean level of autonomic activity. Recently, a mathematical model has been developed to examine the relationship between autonomic activity and beat-to-beat heartbeat interval variation [17]. The contributions of the fluctuating magnitude and the mean level of autonomic activity to the spectral powers of HRV were studied. In this study, the influences of the fluctuations and mean tones of autonomic activities on alterations of HRV after autonomic blockade and during high intensity exercise were explored by using the same model.

2. Methods

2.1. Characteristics of autonomic activity

Generally, autonomic nervous activity is a spike-type signal. The firing rate of spikes is called the ‘tone.’ Many studies have used the number of spikes over a time interval to represent an instantaneous neural activity for analysis [7,14,18–20] and thus neural activities have the unit of spikes/s. A sinusoidal oscillation form is the widely used expression for a periodic fluctuating signal. Considering the instantaneous neural activity as a sinusoidal form, the amplitude of oscillation and the DC value can be quantitative representations for the fluctuating magnitude and the mean level of autonomic activity, respectively. Fig. 1 shows some sinusoidal forms of neural signals and the spike-type neural activities that they represented. In every part figure, the spike train of neural activity is plotted below the corresponding sinusoidal signal. Comparing with the sinusoidal oscillation in the left top of Fig. 1(A), the signal has larger oscillation amplitude in the left bottom of Fig. 1(B), higher oscillation frequency in the right top of Fig. 1(C) and larger mean level in the right bottom of Fig. 1(D).

2.2. Model

The mathematical model, as shown in Fig. 2, is described in detail in Ref. [17] and will be briefly summarized. The model consists of a set of equations that describe the kinetics of concentration of neurotransmitters proposed by Warner and Cox [21] (Warner model) and an integral pulse frequency modulation (IPFM) model [22] that determines the timings of heartbeats. The inputs of this model are the sympathetic and vagal activities. The concentrations of neurotransmitters, acetylcholine (Ach) and norepinephrine (NE), in response to the corresponding vagal and sympathetic inputs, respectively, are obtained from the Warner model. By a linear transformation, $G(t)$, the concentrations of Ach and NE are combined to be the modulating input, $m(t)$, of the

IPFM model. A constant, m_0 , determines the intrinsic pulse rate of IPFM model. The output of the IPFM model is the heartbeat intervals generated by the input, $m_0 + m(t)$. The model can simulate HRV response to combined sympathetic and vagal regulations.

The dynamic characteristics, cardiac response to vagal control being more rapid than to sympathetic control [7,8], were performed by the Warner model. The mean level of autonomic activity determined the mean heartbeat interval. HRV was induced by the fluctuations in autonomic activities. The spectral power of HRV was directly proportional to the fluctuating magnitude of autonomic activities, either sympathetic activity or vagal activity. With regard to the influence of mean level of autonomic activity on HRV [16], the IPFM model demonstrated that the fluctuation in heartbeat interval decreased as the mean heartbeat interval decreased under the same fluctuating magnitude of autonomic activity, and vice versa. Thus, an increased mean sympathetic (vagal) tone decreased (increased) the mean heartbeat interval and concurrently decreased (increased) the fluctuating magnitude of heartbeat interval. The characteristics of the model are summarized in Table 1.

2.3. Autonomic activities after autonomic blockade and during exercise of high intensity

In order to demonstrate changes of HRVs after autonomic blockade and during exercise of high intensity compared with normal condition, the autonomic activities in these conditions and normal condition must be determined. Some findings on autonomic activities in normal condition were considered as the reference for assuming an appropriate autonomic input for simulation. Malliani et al. [6] recorded the preganglionic sympathetic neural discharge from third left thoracic sympathetic ramus communicans, and recorded the efferent vagal neural discharge in an artificially ventilated decerebrate cat. They found that both LF and HF fluctuations were present in instantaneous sympathetic and vagal activities. An inverse relationship exists between vagal and sympathetic activities modulated by respiration [19,23,24] and baroreflex [20,25].

According to the above characteristics, we assumed that vagal activity in normal condition oscillates at the respiration frequency and at the LF. Sympathetic activity in normal condition was assumed to have a pattern similar to that of vagal activity but out of phase at all times. Therefore, the instantaneous sympathetic activity ($s(t)$) and the instantaneous vagal activity ($v(t)$) for the simulation of a normal HRV were set as follows:

$$s(t) = [A_{\text{sif}} \sin(2\pi f_{\text{if}} t)] + [A_{\text{shf}} \sin(2\pi f_{\text{hf}} t)] + M_{\text{s}}, \quad (1)$$

$$v(t) = [A_{\text{vif}} \sin(2\pi f_{\text{if}} t - \pi)] + [A_{\text{vhf}} \sin(2\pi f_{\text{hf}} t - \pi)] + M_{\text{v}}, \quad (2)$$

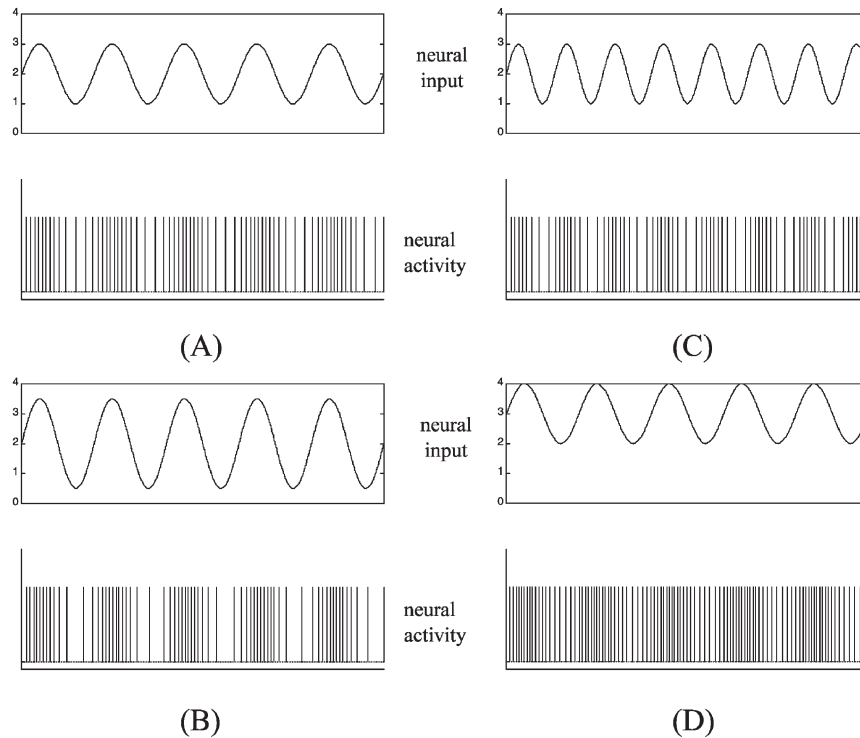


Fig. 1. Four sinusoidal signals and the neural activities that they represent. In every part figure, a sinusoidal oscillation (top) and the corresponding spike train of the neural activity (bottom) are plotted. Compared with the signal in (A), the signal in (B) has the larger oscillation amplitude, the signal in (C) has higher oscillation frequency and the signal in (D) has larger mean value.

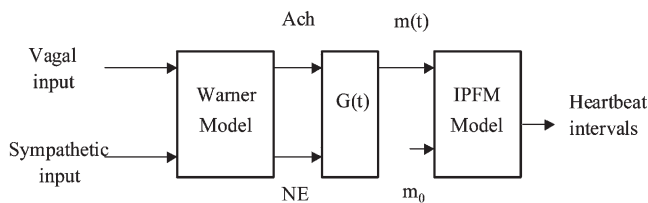


Fig. 2. Block diagram of the mathematical model. The concentrations of NE and Ach in response to sympathetic and vagal activities, respectively, are generated by the Warner model. They are linearly combined to form a modulating signal $m(t)$ for the IPFM model. Then the IPFM model generates a heartbeat interval series accordingly.

where f_{lf} and f_{hf} are the main frequencies at LF and HF bands, respectively. A_{slf} and A_{vlf} are the oscillating amplitudes of sympathetic and vagal activities at frequency f_{lf} , respectively. A_{shf} and A_{vhf} are the oscillating amplitudes of sympathetic and vagal activities at frequency f_{hf} , respectively. M_s and M_v are the mean levels of sympathetic and vagal activities, respectively.

For a normal subject at rest with a controlled respiration of 15 breath/min, the f_{lf} was chosen as 0.09 Hz and f_{hf} was 0.25 Hz. The intrinsic heartbeat interval is 600–750 ms for 20–40 years healthy humans [26,27]. m_0 was chosen as 1.4 in the IPFM model to let the intrinsic heartbeat interval be about 700 ms in our model. By trial and error and referring to a previous investigation [6], we assumed that $A_{slf} = 0.3$ spikes/s, $A_{shf} = 0.2$ spikes/s, $A_{vlf} = 0.6$ spikes/s, $A_{vhf} = 0.7$ spikes/s keep HRV in

a normal range [3]. Moreover, $M_s = 1.5$ spikes/s and $M_v = 1.8$ spikes/s were assumed to keep the autonomic activities positive at all times, and to keep the mean heartbeat interval in a normal range [26,27].

Once autonomic activities in normal condition were determined, the autonomic activities after vagal blockade, sympathetic blockade and during exercise of high intensity could be determined accordingly. After complete vagal blockade, the cardiac response to vagal activity is reduced to zero. We assumed vagal activity to be zero to simulate such a situation. It is reasonable that blockade in one branch of nervous system would not affect the activity of the other branch of the nervous system. Hence, the sympathetic activity after vagal blockade could be the same as that in normal condition. Similarly, we assumed that sympathetic input was zero and vagal input was the same as that in normal condition to mimic the complete sympathetic blockade condition. During high exercise intensity, M_s in Eq. (1) was assumed to become 7.7 spikes/s in order to simulate an increased mean sympathetic activity [27,28]. The high frequency (f_{hf}) was shifted to 0.35 Hz due to the increased respiration rate [12,13]. Other parameters were kept unchanged from those in normal condition. Although vagal activity should be withdrawn during exercise of high intensity [28,29], we did not make such an assumption in this study in order to reveal the contribution of the increased sympathetic tone to HRV. The

Table 1
Summary of the influences of autonomic activities on HRV in our mathematical model

Nerves	Change of autonomic activity		Change of HRV		
	Mean level	Fluctuating magnitude	Mean heartbeat interval	Spectral power	
				Induced by sympathetic fluctuation	Induced by vagal fluctuation
Sympathetic activity	↑	—	↓	↓	↓
	—	↑	—	↑	—
Vagal activity	↓	—	↑	↑	↑
	—	↓	—	↓	—
	↑	—	↑	↑	↑
	—	↑	—	—	↑
	↓	—	↓	↓	↓
	—	↓	—	—	↓

↑: increased; ↓: decreased; —: remained unchanged.

chosen parameters in different conditions are summarized in Table 2.

2.4. Power spectrum of heartbeat intervals

In each simulation, 256 consecutive heartbeat intervals were generated by our model. The fast Fourier transform (FFT) method was used to compute their power spectra. Because the generated heartbeat interval series is a function of heartbeat number rather than time, we used averaged heartbeat interval as the sampling interval of this series in order to obtain spectra with the correct frequency [22]. The LF and HF powers were estimated by integrating the spectral power in the LF band (0.04–0.15 Hz) and in the HF band (0.15–0.4 Hz) respectively.

3. Results

Fig. 3 shows the simulated heartbeat interval tachograms and their power spectra in normal condition, after

vagal blockade, after sympathetic blockade and during high exercise intensity. Mean heartbeat interval, LF power and HF power, were computed and are listed in Table 3. The power spectrum in normal condition (Fig. 3(A)) illustrates that two significant frequency components appeared at 0.09 and 0.25 Hz, respectively. The mean heartbeat interval, LF and HF powers were 714 ms, 2243 and 1675 ms², respectively. This result was compatible with measurements in humans [3,27]. The simulation result for vagal blockade is shown in Fig. 3(B). It is apparent that the mean heartbeat interval was shorter and both LF and HF powers were largely reduced compared with those in normal condition. In contrast, sympathetic blockade (Fig. 3(C)) showed a marked increase in the mean heartbeat interval and an increase in both LF and HF powers of the HRV spectrum compared with normal condition. Fig. 3(D) shows the simulated HRV during exercise of high intensity. The location of HF power was shifted to 0.35 Hz due to the HF fluctuations of sympathetic and vagal activity signals that were set to 0.35 Hz to simulate an increased breathing rate as shown in Table 2. In addition to the shorten-

Table 2
Parameters of autonomic activities in Eqs. (1) and (2) to simulate HRV in normal condition, after vagal blockade, after sympathetic blockade and during exercise of high intensity

Parameters	Normal condition	Vagal blockade	Sympathetic blockade	High intensity exercise
f_{lf}	0.09	0.09	0.09	0.09
f_{hf}	0.25	0.25	0.25	0.35
A_{slf}	0.3	0.3	0	0.3
A_{shf}	0.2	0.2	0	0.2
A_{vlf}	0.6	0	0.6	0.6
A_{vhf}	0.7	0	0.7	0.7
M_s	1.5	1.5	0	7.5
M_v	1.8	0	1.8	1.8

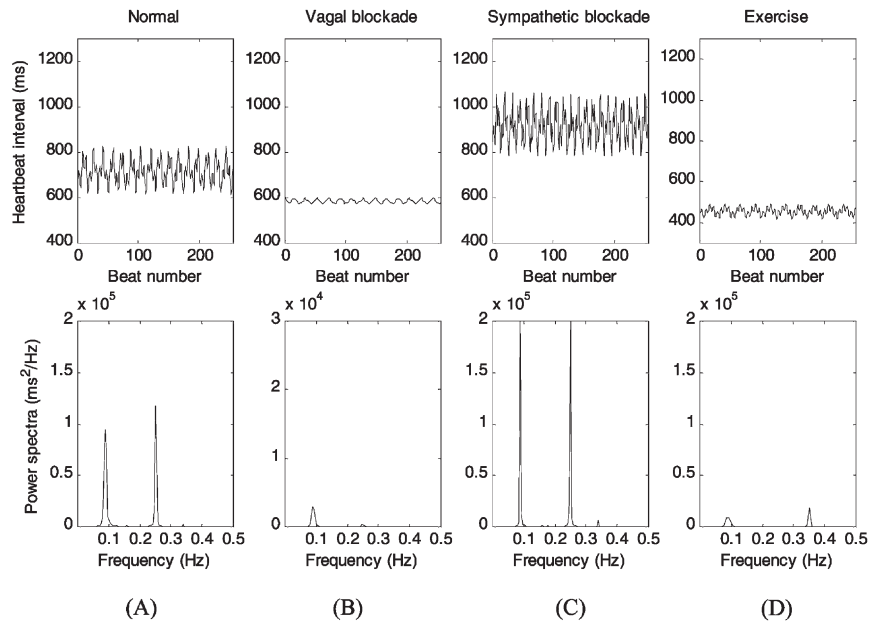


Fig. 3. Simulations for normal condition, vagal blockade, sympathetic blockade and exercise of high intensity. Top panels are the tachograms of 256 heartbeat intervals. Bottom panels show the power spectra of these heartbeat interval series obtained by the FFT method. Note the different scale in the y-axis of (B), indicating the decreased power compared with normal. See text for comparisons between different conditions with normal condition.

Table 3
Estimated mean values, LF and HF powers of the heartbeat intervals shown in Fig. 3

	Heartbeat intervals		
	Mean (ms)	LF power (ms ²)	HF power (ms ²)
Normal	714	2243	1675
Vagal blockade	585	89	12
Sympathetic blockade	918	2822	2936
High intensity exercise	455	374	357

ing of the mean heartbeat interval, both LF and HF powers also decreased compared with normal condition.

4. Discussion

4.1. Autonomic blockade

Several authors have investigated the effect of autonomic blockade on HRV. They revealed that both LF and HF powers were largely reduced after vagal blockade [1,5,9] and were slightly raised after sympathetic blockade [5,9] comparing with normal condition. Our simulations for vagal blockade and sympathetic blockade, as shown in Fig. 3(B) and (C), respectively, demonstrated similar results. Moreover, the mean heartbeat interval was reduced to 585 ms after vagal blockade and increased to 918 ms after sympathetic blockade. These

results are similar to the findings of several studies [26,27].

Most investigators have tended to seek physiological explanations for the alterations of HRV after autonomic blockade [5,9]. Pomeranz et al. [5] explained that an 84% reduction of LF power after vagal blockade in supine posture was due to the predominance of vagal control in this posture. However, they did not explain the 72% reduction of LF power after vagal blockade in standing posture in which heart rate control should be dominated by sympathetic control. Moreover, it was suggested that the slight increase of LF power after sympathetic blockade was likely a result of vagal nerve activation [9].

In this study, we attempted to mathematically explain the alterations of HRV. Our assumptions for the autonomic activities were that autonomic activities contain two parts, the mean level and the fluctuating magnitude. Recalling the characteristics of the model in Table 1, the mean level of autonomic activity determines the mean heartbeat interval. Moreover, HRV is caused by the fluctuation of autonomic activity and its quantity could be influenced by both the fluctuating magnitude and the mean level. After autonomic blockade, the mean level and the fluctuating magnitude of autonomic activities were reduced to zero. With regard to vagal blockade, a decreased vagal fluctuating magnitude caused a decrease of HRV. A decreased mean level of vagal activity caused a decrease of mean heartbeat interval that further decreased the HRV induced by sympathetic modulation. Hence, the LF and HF powers of HRV were largely

reduced. Thus, the 72% reduction of LF power in standing posture after vagal blockade [5] could be explained reasonably.

With regard to sympathetic blockade, similarly according to Table 1, a decreased sympathetic fluctuating magnitude caused a decrease of HRV. But a decreased mean level of sympathetic activity increased the mean heartbeat interval that increased the HRV induced by vagal modulation. When the reduction of HRV due to the reduction of fluctuation in sympathetic activity is smaller than the increase of HRV due to the increase of mean heartbeat interval, the LF and HF powers will be raised after sympathetic blockade consequently. The results from Jokkel et al. [9] and our simulation showed this case. Alternatively, if the effect of the reduced fluctuation in sympathetic activity is greater than that of the reduced mean sympathetic activity, the result will be reversed. Such a possibility cannot be neglected in actual experiment. Therefore, the increase of LF and HF powers after sympathetic blockade could not be statistically significant [5].

4.2. High intensity exercise

Although the increase in sympathetic tone was minimal during exercise of low to medium intensities, the reduction of both LF and HF powers has been demonstrated in several studies [10–13]. It is suggested that the decreased spectral powers might result from a withdrawal of the vagal activity or some non-neural mechanisms [10,13]. However, it is difficult to explain the decrease of LF power during exercise of high intensity with increased sympathetic tone. Some investigators have suggested that high-level saturation of sympathetic activity during exercise of high intensity might be a main cause [6,12]. In the present study, we increased the mean level of sympathetic activity to simulate HRV during exercise of high intensity. The result, shown in Fig. 3(D), is similar to those of previous studies, even though we did not assume a withdrawal of vagal activity. The main cause for the reduction of LF and HF powers was the decrease of the mean heartbeat interval (455 ms). This might suggest that if the increase of sympathetic activity during high exercise intensity is mainly contributed by the mean level rather than the fluctuating magnitude, the LF power will be reduced rather than increased. Thus, the decrease of LF power can be explained. However, the proportion of the decrease of spectral powers in this simulation was smaller than that in actual experiments. Hence, the withdrawal of vagal activity still plays another important role in the changes of HRV during exercise of high intensity [10,13,28].

5. Conclusion

In this study, we successfully simulated and interpreted changes of HRV after autonomic blockade and during exercise of high intensity based on the individual contribution of the fluctuating magnitude and the mean level of autonomic activity. In currently used HRV analysis, the contributions of the fluctuation and mean level of autonomic activity have been mixed and resulted in some controversial assessments of autonomic activity. To obtain a more precise assessment, the spectral power of HRV has been normalized in different ways [3,6,12]. Our results show that the mean heartbeat interval may play an important role on HRV analysis. How to interpret the HRV by taking mean heart rate into account could be an important issue.

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