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Consideration on Parameter Determination of a New Model Describing Dynamic Vagal Heart Rate Control in Rats

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Abstract— **The dynamic characteristics of vagal heart rate control can be approximated by a first-order low-pass filter with pure dead time in rabbits. However, this model may not necessarily be the best approximation of the vagal transfer function of the heart rate control in rats, because a flatter portion exists in the gain plot above approximately 0.3 Hz. We developed a new model that includes a frequency-independent gain term to reproduce the flatter portion of the gain plot seen in the vagal transfer function in rats. The inclusion of the new term increased the coefficient of determination in an external validation of the linear regression relationship between measured and predicted heart rate responses to vagal stimulation, and made the slope of the regression line closer to unity. The parameters of mathematical transfer functions were determined in both the frequency and time domains. The frequency-domain fitting provided a set of parameters that was also able to reproduce the time-domain step response reasonably well. In contrast, the time-domain fitting provided a set of parameters that reproduced the frequency-domain transfer function only up to 0.2 Hz. Determination of proper model parameters was crucial for the development of a new model to describe the dynamic heart rate response to vagal stimulation in rats.**

I. Introduction

Dynamic heart rate control is important to adjust cardiac function to meet demands in daily activity. Both sympathetic and vagal systems are involved in the control of heart rate. Our previous study showed that dynamic characteristics of vagal heart rate control could be approximated by a first-order low-pass filter with pure dead time in rabbits [1]. However, a first-order low-pass filter with pure dead time is not necessarily the best approximation for the vagal transfer function of heart rate control in rats, because the transfer gain does not fall off smoothly above the corner frequency [2]. The gain plot exhibits a flatter portion in the frequency-domain around 0.3 Hz and above, which makes the transfer function deviate from a simple first-order low-pass filter with pure dead time. To describe the flatter portion in the gain plot, we propose a new model that includes a frequency-independent gain term in addition to the terms describing the low-pass nature of the dynamic heart rate control. The parameters of the proposed model were determined by the frequency-domain and time-domain methods.

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II. Methods

A. Animal Preparation

The study was performed on 6 anesthetized Sprague-Dawley rats. Animals were cared for in strict accordance with the Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences, which has been approved by the Physiological Society of Japan. All experimental protocols were reviewed and approved by the Animal Subjects Committee at National Cerebral and Cardiovascular Center.

The rats were anesthetized with an intraperitoneal injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/ml), and ventilated mechanically with oxygen-supplied room air. Supplemental anesthetic mixture was administered continuously. Arterial pressure was monitored through a catheter inserted into the right femoral artery. Heart rate was measured from body surface electrocardiogram using a cardiotachometer. In order to minimize systemic changes in sympathetic nerve activity, baroreceptor regions at bilateral carotid sinuses were isolated from the systemic circulation, and the intracarotid sinus pressure was maintained at 120 mmHg using a servo-controlled piston pump [3], [4], [5]. The aortic depressor nerves and vagi were sectioned bilaterally at the neck. A pair of stainless steel wire electrodes (Bioflex wire, AS633, Cooner Wire, CA, USA) was attached to the sectioned distal end of the right vagus for electrical stimulation.

To estimate dynamic characteristics of the vagal heart rate control, the right vagus was stimulated for 15 min according to a binary white noise signal. The command signal was assigned to either 0 or 20 Hz every 0.5 s. As a result, the input power spectrum was relatively constant up to 1 Hz.

B. Data Analysis

Experimental data were stored at 1000 Hz using a 16-bit analog-to-digital converter. To avoid the possibility that the initial transition from zero stimulation to the binary white noise stimulation biasing the transfer function estimation, the data were analyzed starting 2 min after the initiation of

stimulation. Input-output data pairs were resampled at 10 Hz, and partitioned into 10 half-overlapping segments consisting of 1024 data points each. In each segment, the linear trend was subtracted and a Hanning window was applied. Frequency spectra of the input [$X(f)$] and the output [$Y(f)$] were obtained via the fast Fourier transform. The input power [$S_{XX}(f)$], output power [$S_{YY}(f)$], and the cross spectra between the input and output [$S_{YX}(f)$] were calculated over the 10 segments. Finally, the transfer function from vagal stimulation to the heart rate response was calculated using the following equation [6]:

$$H(f) = \frac{S_{YX}(f)}{S_{XX}(f)}$$

To quantify the linear dependence of the heart rate response to the vagal stimulation, the magnitude squared coherence function was calculated using the following equation:

$$Coh(f) = \frac{\left|S_{YX}(f)\right|^2}{S_{XX}(f)S_{YY}(f)}$$

To help intuitive understanding of the system behavior, the system step response was calculated from a time integral of the system impulse response which was derived from the inverse Fourier transform of the transfer function. Hereafter in this paper, this step response is referred to as an "nonparametric" step response.

In the original model (Model A) we used a first-order low-pass filter with pure dead time as described below [1].

$$M_A(f) = \frac{K}{1 + \frac{f}{f_C} j} \exp(-2\pi f L j)$$

where K is the steady-state gain, f_C is the corner frequency (in Hz), and L is the pure dead time (in s). j represents the imaginary units. The step response corresponding to Model A is as follows.

$$\begin{cases} S_A(t) = 0 & (t < L) \\ S_A(t) = K\left[1 - \exp\left(-\dfrac{t-L}{\tau}\right)\right] & (L \le t) \end{cases}$$

$$\tau = \frac{1}{2\pi f_C}$$

Our newly proposed model (Model B) is a combination of the first-order low-pass filter and a frequency-independent gain term as follows.

$$M_B(f) = K\left(\frac{\dfrac{1-R}{1 + \dfrac{f}{f_C} j} + R}\right) \exp(-2\pi f L j)$$

where R ($0 \le R < 1$) represents the fraction of the frequency-independent gain relative to the steady-state gain. Although other models could be possible, Model B is thought to be most convenient because it provides the steady-state gain by K as in Model A. When $R > 0$ Model B can be rewritten as:

$$M_B(f) = K\left(\frac{1 + \dfrac{f}{f_R} j}{1 + \dfrac{f}{f_C} j}\right) \exp(-2\pi f L j)$$

where $f_R = f_C/R$. Because R is defined as a value less than unity, f_R is greater than f_C. The step response corresponding to Model B is as follows.

$$\begin{cases} S_B(t) = 0 & (t < L) \\ S_B(t) = K\left[1 - (1-R)\exp\left(-\dfrac{t-L}{\tau}\right)\right] & (L \le t) \end{cases}$$

The model parameters were estimated in both the frequency domain and the time domain. In the time-domain fitting, the sum of squared errors between the model step response and the nonparametric step response was minimized using a nonlinear iterative least square fitting. In the frequency-domain fitting, the following error function was employed.

$$E = \sum_{k=1}^{N} \frac{\left[\log\left(H(f_k)\right) - \log\left(M(f_k)\right)\right]^2}{k} = \sum_{k=1}^{N} \frac{1}{k}\left[\log\left(\frac{H(f_k)}{M(f_k)}\right)\right]^2$$

$$f_k = f_0 \times k$$

where f_0 is the fundamental frequency of the Fourier transform, k is an index of the frequency, and f_k is the k-th frequency. N represents the frequency index up to which the error was considered. In the present study, N was set at 120, which corresponded to 1.17 Hz. $H(f)$ and $M(f)$, which are both complex values, represent the experimental and model transfer functions, respectively. The error function took the logarithmic representation of the system dynamic characteristics on the Bode plot into account. In this context, there was no difference whether the natural or common logarithm were used, as the task of fitting was to find a set of parameters to minimize the error function.

After the model parameters were estimated, the dynamic heart rate response to vagal stimulation was predicted from the convolution of the command signal with the impulse response derived from the model transfer function. The regression analysis for the measured versus the predicted heart rate response was performed using a data set that was obtained externally to the segments used for the estimation of the transfer function (i.e., external validation). The output signal of 2048 points was predicted.

III. Results and Discussion

Figure 1 illustrates a typical example of the transfer function from vagal stimulation to the heart rate response obtained in one animal (solid lines). In the gain plot, the transfer gain decreased as the frequency increased above 0.02 Hz, suggesting low-pass characteristics of the heart rate response to vagal stimulation. The transfer gain, however, did not fall off smoothly beyond 0.3 Hz, creating a flatter portion in the higher frequency range. In the phase plot, the phase was close to $-\pi$ radians at the lowest frequency, and delayed with increasing frequency. These phase characteristics suggest that the heart rate response to vagal stimulation should be negative

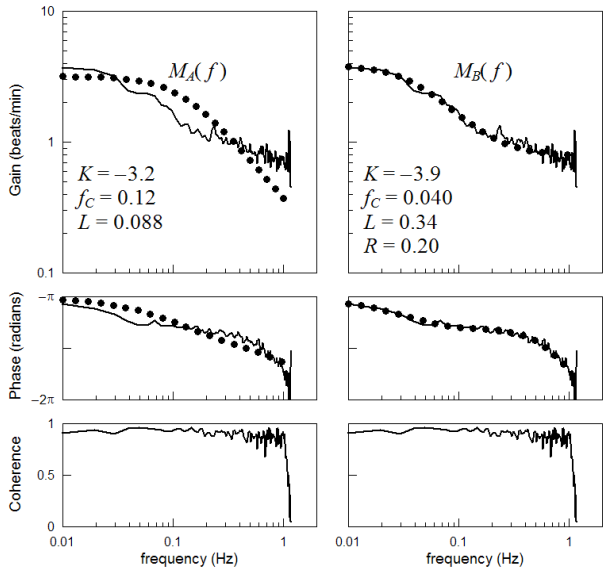

Figure 1. Transfer function from vagal stimulation to the heart rate response (solid lines) and model tranfer functions (circled lines).

at steady state. The coherence was high up to 1 Hz, suggesting that the heart rate response can mostly be described by linear dynamics in the present experimental settings. Therefore, the flatter portion observed in the gain plot is not likely the result of a reduction in the accuracy of the transfer function estimation in the higher frequency range.

The circles in the left panels of Figure 1 represent the transfer function of Model A with its parameters determined by the frequency-domain fitting. There was a significant deviation between Model A and experimental transfer functions such that the steady-state gain was estimated to be lower in Model A compared with the experimental transfer function. The corner frequency was estimated to be higher in Model A than in the experimental transfer function. Therefore, frequency-domain parameter determination does not work well when a given model does not have the degree of freedom

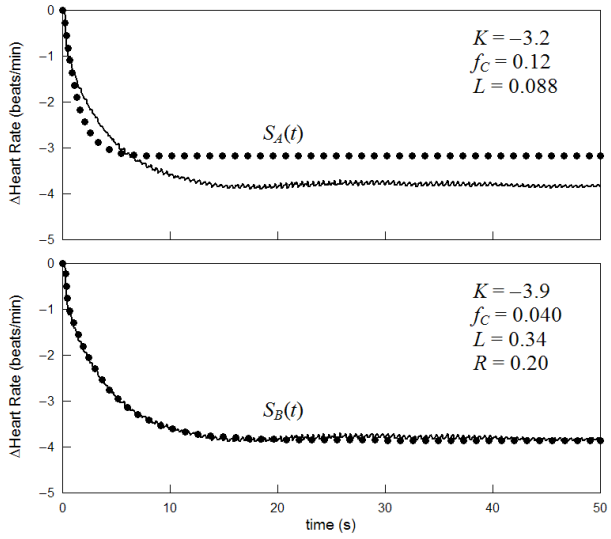

Figure 2. Step response of the heart rate response to vagal stimulation (solid lines) and model step responses based on the frequency-domain parameter determination (circles).

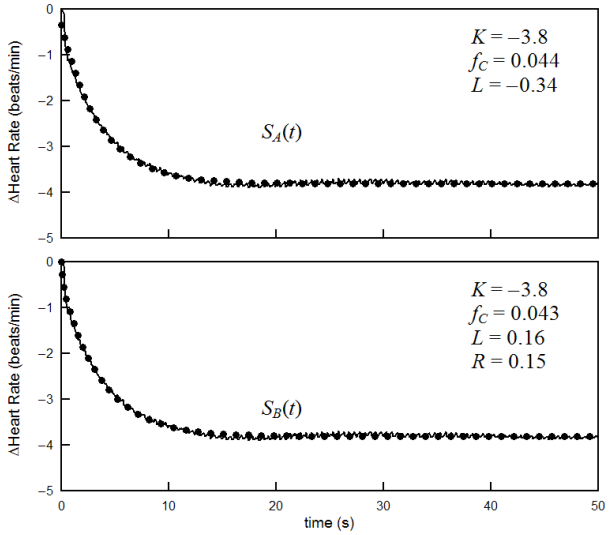

Figure 3. Step response of the heart rate response to vagal stimulation (solid lines) and model step responses based on the time-domain parameter determination (circled lines).

to reproduce an experimental transfer function.

The circles in the right panels of Figure 1 indicate the transfer function of Model B with its parameters determined by the frequency-domain fitting. The model transfer function reproduced the characteristics of the experimental transfer function reasonably well in the frequency range from 0.01 to 1 Hz.

Figure 2 depicts the step responses corresponding to the transfer functions shown in Figure 1. In the top panel, the step response of Model A underestimated the steady-state response relative to that of the nonparametric step response. The time constant was estimated to be shorter, which is equivalent to the higher corner frequency in the frequency domain. In the bottom panel, the step response of Model B reproduced the nonparametric step response well.

While Model A did not reproduce the experimental step response well when parameters were determined in the frequency domain, both models A and B were able to mimic the nonparametric step response when parameters were determined in the time domain (Figure 3). However, the lag time was estimated to be negative in Model A, which is physically unrealizable.

Figure 4 illustrates the transfer function from vagal stimulation to the heart rate response (solid lines) and the model transfer functions (circles) with their parameters determined in the time domain to minimize the error between the model and nonparametric step responses. While both models A and B reproduced the experimental transfer function up to 0.2 Hz, the model transfer functions deviated from the experimental transfer function in the frequency range above 0.2 Hz. Therefore, even though the model step response appeared to mimic the nonparametric step response, there can be a significant deviation in the higher frequency range when examined in the frequency domain. In the present case, because the fraction of the frequency-independent gain relative to the steady-state gain was approximately 0.2, the

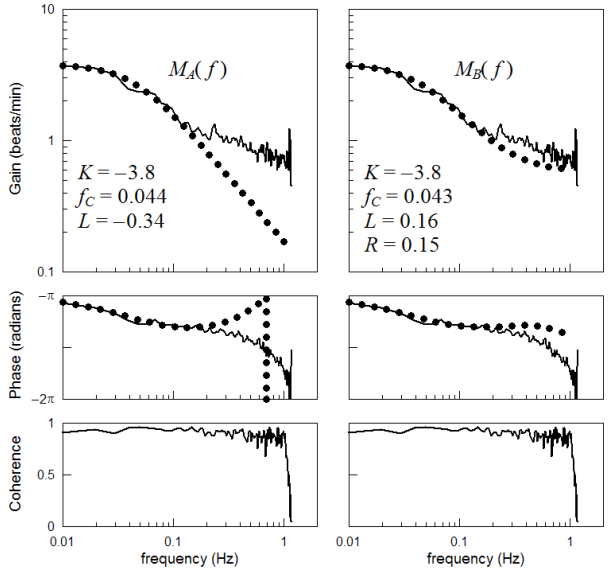

Figure 4. Transfer function from vagal stimulation to the heart rate response (solid lines) and model tranfer functions based on the time-domain parameter determination (circles).

majority of the step response could be described by the parameters relating to the first-order low-pass filter.

Figure 5 illustrates the actually measured dynamic heart rate response to vagal stimulation versus the heart rate responses predicted by Model A (top panel) and Model B (bottom panel). Close inspection of the figure indicates that Model A was not able to reproduce sharp rises in the heart rate response (marked with asterisks) in contrast with Model B. The scatter plots of the measured versus the predicted heart rate are shown in the right panels of Figure 5. The coefficient of determination was higher for the prediction when using Model B compared with Model A.

The regression analysis on data obtained from 6 rats shows that the slope of the regression line was 0.81±0.05 for the heart rate prediction by Model A, and was 0.94±0.03 for the heart rate prediction by Model B. In all six animals, the coefficient of determination was higher in the prediction by Model B (ranged from 0.71 to 0.91) than in the prediction by Model A (ranged 0.56 to 0.90). While the increment of the number of model parameters itself should increase the coefficient of determination, because the regression analysis was performed on a data set that was not used for the estimation of the transfer function (i.e., external validation), it may be fair to say that Model B provided a better prediction of the heart rate response compared with Model A.

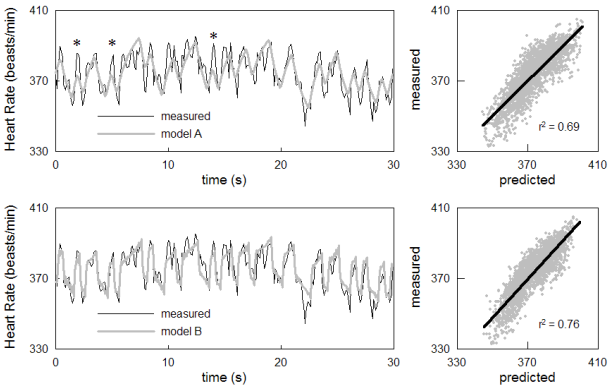

Figure 5. Measured (solid lines) and model-predicted (gray lines) of the heart rate response to vagal stimulation. The top panels are the results ofmodel A and the bottom panels are the results of model B. The coefficient of determination was higher for the prediction by model B.

There are several limitations to the present study. First, the heart rate of the anesthetized rats was 300–400 beats/min (5–6.7 Hz), which indicates that the Nyquist frequency may be as low as 2.5 Hz for the heart rate data. The heart rate signal cannot reproduce frequency components above this frequency. Although we included a frequency-independent gain term to explain the flatter portion in the gain plot observed in the experimental transfer function, there is an inherent upper frequency limit to the heart rate control, above which the model is likely to deviate from the experimental transfer function. Second, the frequency-independent gain term suggests the presence of a rapid responding system parallel to the low-pass system in the vagal heart rate control in rats. While the inclusion of the frequency-independent gain term improved the prediction of the dynamic heart rate response to vagal stimulation, the mechanisms for the rapid responding system are largely unknown. Further studies are required to identify the mechanisms and the physiological significance for the rapid responding system observed in rats but not in rabbits.

REFERENCES

[1] T. Kawada, Y. Ikeda, M. Sugimachi, T. Shishido, O. Kawaguchi, T. Yamazaki, et al. "Bidirectional augmentation of heart rate regulation by autonomic nervous system in rabbits," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 271, pp. H288-H295, 1996.

[2] M, Mizuno, T. Kawada, A. Kamiya, T. Miyamoto, S. Shimizu, T. Shishido, et al. "Dynamic characteristics of heart rate control by the autonomic nervous system in rats," *Exp. Physiol.*, vol. 95, pp. 919-925, 2010.

[3] A. A. Shoukas, C. A. Callahan, J. M. Lash, E. B. Haase. "New technique to completely isolate carotid sinus baroreceptor regions in rats," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 260, pp. H300-H303, 1991.

[4] T. Sato, T. Kawada, H. Miyano, T. Shishido, M. Inagaki, R. Yoshimura, et al. "New simple methods for isolating baroreceptor regions of carotid sinus and aortic depressor nerves in rats," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 276, pp. H326-H332, 1999.

[5] T. Kawada, M. Li, A. Kamiya, S. Shimizu, K. Uemura, H. Yamamoto, et al. "Open-loop dynamic and static characteristics of the carotid sinus baroreflex in rats with chronic heart failure after myocardial infarction," *J. Physiol. Sci.*, vol. 60, pp. 283-298, 2010.

[6] P. Z. Marmarelis, V. Z. Marmarelis. Analysis of Physiological Systems. The White-Noise Approach. New York and London: Plenum Press, 1978, pp. 131-178.