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Sympathetic Nerve Activity-Induced Blood Pressure Fluctuations are Stacked on Linearly: A Simulation Study

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A possible mechanism to fit the empirical relationship between the power spectrum of the variability of sympathetic nerve activity (P_{SNA}) and blood pressure (P_{BP}) is described. Since the BP rise depends on the magnitude of SNA with an S-mode relationship, we assume that a single BP rise is independent of the SNA frequency, while two successive SNA-induced BP fluctuations are stacked on linearly. The damping function was used to model the BP fluctuations caused by SNA, and the box function was used to model the SNA compound action potential. We quantified the logistic relationship ($P_{SNA} = cP_{BP} \cdot 10^{kf}$) between the frequency and power spectrum of these two functions. The simulation data showed the physiological rationality of the empirical relationship between the P_{SNA} and P_{BP} and supported the assumption that the BP stack-on is linear and independent of the SNA frequency.

Keywords: blood pressure, sympathetic nerve activity, simulation, fluctuation, stacking-on.

INTRODUCTION

The relationship between sympathetic nerve activity (SNA) and variability of the blood pressure (BP) has been widely studied and discussed during the past three decades. However, many studies were based only on a statistic comparison and concluded exclusively with a qualitative description. There were few attempts to link these two variables quantitatively. Tsai et al. [1] used an equation to describe the quantitative relationship between the power spectrum of BP variability (P_{BP}) and that of SNA (P_{SNA}). The respective experiments were carried out under simplified conditions; the animals were anesthetized with pentobarbital, paralyzed, and sinoaortic-deafferented. The respiration frequency of the rats was controlled by a respirator, and their cardiac autonomic regulation and angiotensin-converting enzyme were blocked. Experimental results showed that the BP fluctuated at the same frequency as the SNA fluctuations induced by stimulations of the sympathoexcitatory areas of the *medulla oblongata*. The amplitudes of BP fluctuations induced by such successive SNA stimulation were frequency-dependent (the amplitude was the highest at the lowest frequency and rapidly decreased as the stimulation frequency increased). This relationship could be mathematically expressed as $P_{SNA} = cP_{BP} \cdot 10^{kf}$, when the frequency f is between 0.016 and 0.85 Hz. The result holds in spontaneously occurring BP and SNA fluctuations when rats were anesthetized only with pentobarbital [2] or were in a conscious state without additional restrictions [3].

A wavelet-based time-frequency analysis shows a close connection between the fluctuations of BP and SNA at various stimulation frequencies. Only the SNA fluctuations at 0.25-0.4 Hz were proportional to the BP fluctuations over time [4]. These results further suggest that the fluctuations "transmitted" from SNA to the BP are uniform and unaffected by the nature of the vasculature or the lag of the sympathetic action at frequencies ranging from 0.25 to 0.4 Hz. Therefore, if the sympathetic nerve is repeatedly activated at frequencies higher than 0.4 sec^{-1}, the resulting BP fluctuations stack on the previous one before fading out. This would increase the mean BP and decrease the amplitude of oscillations [5]. Previous research has suggested that rostral ventrolateral medullary neurons are involved in generating low-frequency rhythms in SNA and the corresponding BP fluctuations, and that the baroreflex can induce the participation of more

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neurons in generating low-frequency rhythms [6].

Is this empirical relationship for P_{SNA} and P_{BP} only a numerical coincidence or a consequential result owing to some physiological phenomenon? In our study, we used a simulation approach to evaluate the possible physiological mechanism to fit the empirical relationship. Since the BP rise is proportional to the magnitude of SNA through an S-mode relationship [7], we assumed two additional conditions: (i) a single BP rise is independent of the SNA frequency, and (ii) two successional SNA-induced BP fluctuations stack on linearly. Because the BP responds to SNA through a quick rise and a slow decrease, we used the "damping function" as the model. The "box function" was chosen to model the compound action potential of the sympathetic discharges in bursts. We compared the mathematical relationship between the simulated P_{SNA} and P_{BP} with the experimental data to evaluate whether the $P_{SNA} = cP_{BP} \cdot 10^{kf}$ formula conforms to these two assumptions. We also discuss the corresponding changes of the parameters in the formula and the relationship shift between SNA and BP.

METHODS

Models for the BP and SNA

Preprocessing of the Experimental Signals. This study filters out the high-frequency signals recorded from the animal experiments [1] to focus on the frequencies lower than 0.85 Hz, where the relationship between BP and SNA was formulated. To erase the low-frequency noises frequently obtained in the recordings, very low-frequency signals were also ruled out. A fast Fourier transform (FFT) was used to analyze the original signals, and the coefficients were set at frequencies higher than 0.85 Hz or lower than 0.05 Hz to zero. An inverse FFT was then performed to obtain the experimental signals.

The experimental signals produced six BP and SNA waveforms. These waveforms were then used to determine the parameters of the model functions, as described in the next subsections.

Damping Function Model of BP Oscillations. Because the BP responds to SNA with a quick rise and a slow decrease, this study uses the damping function with a vertical shift h to model the BP:

$$S_{BP}(x) = h + \begin{cases} axe^{-bx^n}, & 0 \le x \le T \\ 0, \text{otherwise} \end{cases}$$

where a, b, and n are positive parameters. Six BP waveforms were selected from the experimental signals, as shown by the gray thin curve in Fig. 1A. The waveforms were separated from each other to prevent the stack-on effects. The waveforms showed that S_{BP} starts at a magnitude $h = -2.65$, has a duration of $T = 8.56$ sec and an amplitude of $Y = 7.90$, and reaches its maximum at 1.33 sec after the starting point. The parameters that best fit the criteria are $a = 14.29$, $b = 0.63$, and $n = 1.14$.

The black thick curve in Fig. 1A shows the BP waveforms simulated by six consecutive models. The correlation coefficient between simulated and experimental signals is 0.95.

Box Function Model of SNA. Because SNA discharges in bursts, this study uses the box function with a vertical shift k to model the SNA:

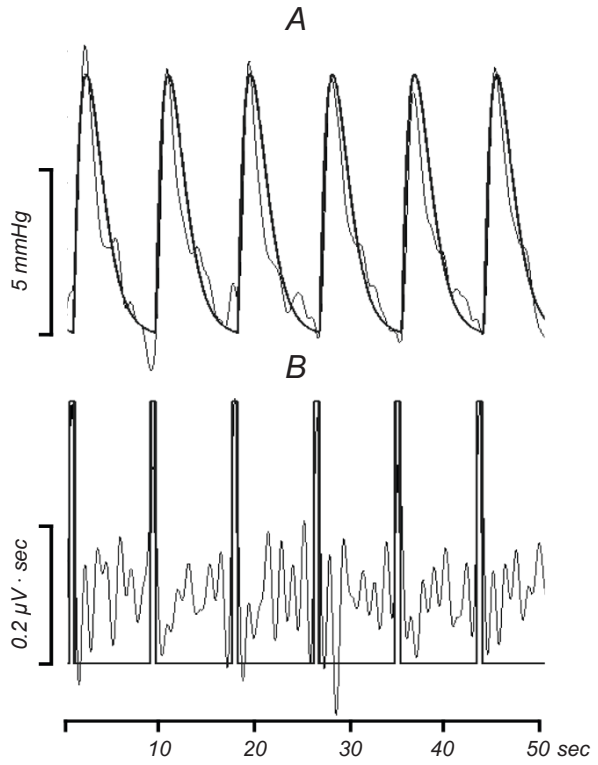
$$S_{SNA}(x) = k + \begin{cases} c, & 0 \le x \le d \\ 0, \text{otherwise} \end{cases}$$

where c and d are positive parameters. The gray thin curve in Fig. 1B shows six SNA waveforms selected from the experimental signals. These waveforms show that S_{SNA} starts at a magnitude $k = 0.15$ and has a duration of $d = 0.50$ and an amplitude $c = 0.38$. The black thick curve in Fig. 1B shows the SNA waveforms simulated by six repeated models; the correlation coefficient between the simulated and experimental signals is 0.82.

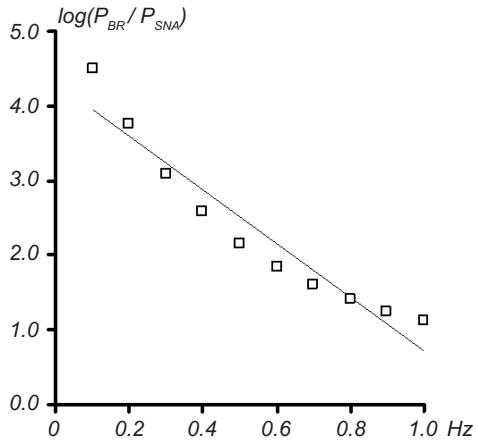
Regression Function for Simulated Signals. This study presents simulation of S_{BP} and S_{SNA} with the same analysis procedure, as was used in the animal experiments published by Tsai et al. [1]. Specifically, the SNA was forced to fluctuate at frequencies of 0.1 Hz, 0.2 Hz, …, 1.0 Hz, and the SNA and the respective BP signals were recorded for 60 sec. The stack-on effect of BP fluctuations caused by SNA is assumed to be linear and independent of the SNA frequency. Throughout the course of linear BP stack-on, the starting BP mean value increases as the SNA stimulation frequency increases and is stabilized after several BP stack-on. The simulations in this study select the periods of stable BP mean value for the analysis.

When the stimulations are presented at the f (sec^{-1}), P_{SNA} and P_{BP} represent the absolute values at each f from the FFT of the simulated SNA and BP signals, respectively. For example, $P_{SNA} = 1.18$ and $P_{BP} = 101.48$ for $f = 0.1$, and $(0.1, \log(P_{BP}/P_{SNA}))$ make up the dots on the scattering plot of Fig. 2. The scattering plot contains ten dots

that are in a clear linear correlation with each other (Fig. 2). The regression line can be represented as $y = -3.53x + 4.25$, and the correlation between the two components is 0.96.



F i g. 1. Comparisons of the experimental and simulated waveforms. Gray lines represent the experimental waveforms of the BP (A) and SNA (B); black lines indicate their simulated models. The experimental and simulated signals have the correlation coefficient of 0.95 for the BP and 0.82 for SNA.



F i g. 2. Simulated scattering plot of $\log(P_{BP}/P_{SNA})$ at the stimulation frequency f (abscissa) with the regression line and correlation coefficient of 0.96.

Simulations on the Effects of Amplitude. Under common physiological conditions, the BP magnitude is related to the amplitude of SNA by an S-mode logistic curve [7]. Specifically, when the SNA amplitude increases or decreases by the factor α, the corresponding BP magnitude is multiplied by $f(\alpha)$, and the graph of $(\alpha, f(\alpha))$ is an S-mode logistic curve:

$$f(x) = \frac{b}{1 + ae^{-k(x-x_0)}} + c$$

where a, b, c, k, and x_0 are constants. We set an S-mode logistic curve passing through point (1,1) with an upper limit of 2.5 and a lower limit of 0.4.

Along the Reference S-Mode Curve. Let $Y = 7.9031$ and $c = 0.38$ be the reference amplitudes of BP and SNA, respectively, as defined in the previous sections. The BP duration was calculated as 8.5 sec. It is assumed that the BP amplitude corresponding to the SNA amplitude of αc is $f(\alpha)Y$, and the duration is unaffected by changes in the amplitude. The simulations described in Section *Regression Function for Simulated Signals* were repeated by applying the regression line shown in Fig. 2.

The proposed mathematical models allow us to run the computational simulations when the magnitudes of SNA decrease or increase by $\alpha = 0.4$ to 1.6. Table 1 shows the regression lines that fit the simulated data. The slope of the regression lines is unaffected by the amplitude changes of SNA and BP waveforms when their relationship is represented by the S-mode, and the vertical positions are proportional to α. The result holds for the cases when the scaling factor α lies within the segment where $f(\alpha)$ increases sharply (i.e., $0.8 \leq \alpha \leq 1.4$), and the Y-intercept increases when α increases. However, when α is out of this range, the vertical positions of the regression lines do not follow this trend.

T a b l e 1. Slopes and Y-Intercepts of the Regression Lines for the Computational Simulated $\log(P_{BP}/P_{SNA})$ when the Amplitudes of SNA and BP are Scaled by α and $f(\alpha)$, respectively

	slope	*Y*-intercept
α = 0.4	–3.59	4.32
α = 0.6	–3.59	3.98
α = 0.8	–3.59	3.94
α = 1.0	–3.59	4.31
α = 1.2	–3.59	4.71
α = 1.4	–3.59	4.80
α = 1.6	–3.59	4.73

Along Other Shapes of S-Mode Curves. The relationship between the amplitudes of the BP and SNA may be changed under conditions of diseases or pharmaceutical interferences in rats. When the BP amplitude sluggishly reacts to SNA fluctuations, a slower increasing rate may appear in the S-mode, and this shifts the curve toward the right. Conversely, when BP is more reactive to SNA fluctuations, a faster increasing rate may appear in the S-mode, and this shifts the curve toward the left.

To investigate the effects of the shifted S-mode on the regression lines, the simulations described in former section were repeated with a faster and slower rate of increase in the BP reactions to SNA fluctuations. These experiments produced results similar to those described in former section. The slope of the regression lines remains the same if a greater BP occurs when induced by SNA stimulation of an unchanged amplitude (i.e., the S-curve shifts toward the left), but the *Y*-intercept tends to increase. Conversely, if a lower BP occurs when induced by sympathetic nerve stimulation of an unchanged amplitude (i.e., the S-curve is shifted toward the right), the *Y*-intercept tends to decrease, whereas the slope of the regression lines remains the same. For example, when the scaling factor $\alpha = 1$, different $f(\alpha)$, 0.6, 0.8 (these two are at the curve shift toward the right), 1 (original), 1.2, and 1.4 (these two are at the curve shift toward the left) were used to produce regression lines. Results showed that the slopes are all –3.59, but the *Y*-intercepts are 3.79, 4.08, 4.31, 4.49, and 4.64, respectively.

Simulations on the Effects of Duration. Because the duration of SNA may vary, it may affect the duration of the corresponding BP wave. The difference between the duration of SNA and BP is not constant and varies with variations of each animal's physiological and pathological conditions. Therefore, we further examined the effects of the duration of SNA and BP on $\log(P_{BP}/P_{SNA})$.

Let T and d be the BP duration (damping function) and SNA (box function), respectively. Assume that $T = d + \beta$, where β is the prolongation time (in seconds) that the corresponding BP wave lasts after the end of SNA. Similarly to those in the above Section, $T = 8.56$ and $d = 0.50$. The following simulations were performed using the reference amplitudes defined above.

First, let us try to input various β with a fixed d. Specifically, set $d = 0.50$, assume that the durations of BP are 7.5, 8, 8.5, and 9 sec (with $\beta = 7.0$, 7.5, 8.0, and 8.5), perform the simulations described in Section *Regression Function for Simulated Signals*. Each value of β outputs a set of points of $\log(P_{BP}/P_{SNA})$ on the scattering plot, and these points in turn determine a regression line. Table 2 shows four regression lines, each of which corresponds to a definite value of β. Each line has a different slope and the line steepens as the prolongation time decreases. The lines are obtained by linear regression analysis considering that the prolongation time varies in the damping function. The lines may rotate around the center frequency point at 0.32 Hz.

T a b l e 2. Effects of the Duration of the SNA and BP on the Regression Lines for the Computational Simulated $\log (P_{BP}/P_{SNA})$

		Regression line
$d = 0.5$	$B = 7.0$	$y = -3.7048(x - 0.32) + 3.16$
	$\beta = 7.5$	$y = -3.6695(x - 0.32) + 3.16$
	$\beta = 8.0$	$y = -3.5887(x - 0.32) + 3.16$
	$\beta = 8.5$	$y = -3.5864(x - 0.32) + 3.16$

RESULTS AND DISCUSSION

The assumption that the stack-on effect of BP fluctuations caused by SNA is linear makes it possible to linearly correlate the relationship between the frequency and simulated logistic power ratio, as was shown in the animal experiments. These results confirm that the empirical mathematical relationship between the P_{SNA} and P_{BP} is physiologically possible and are due to the property of the linear stack-on.

According to our simulation, the following points describe changes in the parameters of the mathematical formula and the relationship shift between the SNA and BP:

(i) When physiologically normal rats remain in an experimentally elevated sympathetic tone, the slopes of the regression lines are unchanged, but these lines are shifted toward the right.

(ii) If a greater BP fluctuation occurs under the same intensity of sympathetic nerve stimulation in rats, the slope of the regression lines remains unchanged, but there is a shift toward the right. Conversely, if the BP reacts less strongly to sympathetic nerve stimulation of the same intensity, the regression lines are shifted toward the left, and the slope remains the same.

(iii) The regression lines may rotate around the center (a frequency point at 0.32 Hz), whereas the prolongation time varies at the same intensity of

sympathetic nerve stimulation, and the slope of the regression lines becomes steeper, as the prolongation time decreases.

Previous animal experiments applied the mathematical relationship between the P_{SNA} and P_{BP} to rats under pentobarbital anesthesia and rats in a conscious state. It was found that the two regression lines may rotate around the center (frequency point of 0.22 Hz), while those representing the conscious state group showed a gentler slope [3]. The relationship between the two regression lines can be inferred, as will be described below. First, the regression line representing the conscious state group may rotate around the center frequency point of 0.32 Hz after the rats were anesthetized, creating a steeper slope (refer to Statement 3 in the preceding paragraph). In other words, the BP prolongation time in response to SNA stimulation may be shorter in anesthetized animals. Second, the rotated regression line may be shifted toward the left and intercept with the line representing the conscious state group at 0.22 Hz (refer to Statement 1 in the preceding paragraph). This suggests a lower SNA tone in the anesthetized state of the animals. Another possibility is that the BP reacts more sluggishly to sympathetic nerve stimulation of the same intensity after anesthesia (refer to Statement 2 in the preceding paragraph).

Pentobarbital can directly provide vasodilation by acting on vascular smooth muscles [8]. It reduces the vascular contraction induced by neurotransmitters released by a single-unit sympathetic nerve activity. Consequently, the degree of BP fluctuations and the value of the prolongation time may decrease accordingly. This agrees with the possibility porposed by Statement 2 that the BP reacts more sluggishly to sympathetic nerve stimulation of the same intensity after anesthesia, and by Statement 3 that the regression line steepens as the prolongation time decreases. These results show a changing trend of the regression lines, which may provide a mechanism to predict how the SNA influences the BP variability.

The baroreflex has for a long time been considered the main factor affecting the frequency spectra of the BP and SNA. However, the linear regression results of previous studies remained the same, and the slope and interception did not change significantly after removing the effects of baroreflex receptors and functions in rats [2]. According to the mathematical models used in our study, the results obtained by Tsai et al. [2] are reasonable because the amplitude relationship between the SNA and BP causes regression shifting, and the BP prolongation time in response to SNA causes regression rotation. These two factors are mainly related to the interaction between neurotransmitters released in the synapses and the receptors located on vascular smooth muscles. At the same time, such interaction is independent of the discharge frequency in the nerve fibers. Despite the possibility that the BP and SNA spectra may vary with the baroreflex variation, the amount of neurotransmitters released by each action potential, the number of the corresponding receptors on smooth muscles, and intracellular signal transduction are not influenced by the baroreflex. Consequently, there is no significant difference in the power ratio between the BP and SNA at the same frequency.

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This theoretical study was not related to any experiments with animals and tests with humans, thus, confirmation of the correspondence of the study to the existing international ethical norms is not necessary.

The authors, W. T. Tseng, W. C. Shann, B. C. Chen, Y. C. Chang, and M. L. Tsai, declare the absence of any conflict in commercial or financial relations, relationships with organizations or persons that in any way could be related to the study, and also in interrelations of the co-authors.

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