High-cut characteristics of the baroreflex neural arc preserve baroreflex gain against pulsatile pressure

TORU KAWADA, CAN ZHENG, YUSUKE YANAGIYA, KAZUNORI UEMURA, TADAYOSHI MIYAMOTO, MASASHI INAGAKI, TOSHIKAI SHISHIDO, MASARU SUGIMACHI, AND KENJI SUNAGAWA

Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Osaka 565-8565, Japan

Received 21 August 2001; accepted in final form 12 November 2001

The carotid sinus baroreflex is one of the most important negative feedback systems that stabilizes arterial pressure (AP) against exogenous pressure perturbation. The dynamic characteristics of the carotid sinus baroreflex may be divided into two subsystems: the neural arc and peripheral arc components. The neural arc transfer function represents the dynamic characteristics from pressure input to sympathetic nerve activity (SNA), whereas the peripheral arc transfer function represents those from SNA to AP. In previous studies (4, 6–8, 14), we demonstrated that the neural arc shows derivative characteristics, i.e., the magnitude of the SNA response becomes greater as the frequency of baroreceptor pressure input increases. On the other hand, the peripheral arc shows low-pass characteristics, i.e., the magnitude of the AP response becomes smaller as the frequency of SNA modulation increases. A numerical simulation with a nonpulsatile signal indicates that the fast neural arc compensates for the slow peripheral arc to achieve quick and stable AP regulation (4). In previous studies (4, 6–8, 14) in rabbits, we focused on the baroreflex dynamic characteristics in the frequency range between 0.01 and 1 Hz. Because the open-loop gain of the total baroreflex above 1 Hz is less than 1/10 of that at 0.01 Hz, the neural arc transfer characteristics above 1 Hz appear to be unimportant in regulating AP.

Notwithstanding the above-mentioned viewpoint, the baroreceptors are normally exposed to higher frequency pressure input mainly associated with the frequency of heart rate (HR) (3–5 Hz in rabbits) and its harmonics. Although pulsatile pressure input is known to affect baroreflex gain in both baroreceptor transduction (2) and the total baroreflex loop (5, 9), the exact transfer characteristics of the neural arc in the frequency range above 1 Hz remain to be elucidated. A previous study (4) only documented the baroreflex dynamic characteristics up to 1 Hz, allowing no conclusion regarding the system characteristics in the higher frequency range. If we simply extrapolated the neural arc derivative characteristics beyond 1 Hz and modeled them by an all-zero filter with a zero at 0.1 Hz, a 10-mmHg pulsatile input at 4 Hz required a baroreflex dynamic range equivalent to that processing a 400-mmHg pressure input at 0.01 Hz. Because such a large dynamic range is physiologically unlikely, we hypothesized that the neural arc possesses high-cut characteristics to attenuate HR-related high-frequency components. To test this hypothesis, we extended the frequency range of the transfer function analysis up to 10 Hz in anesthetized rabbits. The results of the present study indicate that the neural arc effectively attenuated the HR-related high-frequency components, hence probably preserving baroreflex gain against pulsatile pressure inputs.
MATERIALS AND METHODS

Surgical preparations. Animals were cared in strict accordance with the "Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences" approved by the Physiological Society of Japan. Six Japanese White rabbits weighing 2.6–3.5 kg were anesthetized by intravenous injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/ml) and mechanically ventilated with oxygen-enriched room air. Supplemental anesthetics were injected as necessary (0.5 ml/kg) to maintain an appropriate level of anesthesia. AP was measured using a high-fidelity pressure transducer (Millar Instruments; Houston, TX) inserted via the right femoral artery. We isolated the bilateral carotid sinuses from the systemic circulation by ligating the internal and external carotid arteries and other small branches originating from the carotid sinus regions. The isolated carotid sinuses were filled with warmed physiological saline through catheters inserted via the common carotid arteries. The intra-carotid sinus pressure (CSP) was controlled by a servo-controlled piston pump (model ET-126A, Labworks; Costa Mesa, CA). Bilateral vagal nerves and aortic depressor nerves were sectioned at the middle of the neck to eliminate baroreflexes from the cardiopulmonary region and the aortic arch. We exposed the left cardiac sympathetic nerve through a midline thoracotomy and attached a pair of stainless steel wire electrodes (Bioflex wire AS633, Cooner Wire) to record SNA. The nerve fibers peripheral to the electrodes were sectioned to eliminate afferent signals from the heart. To insulate and secure the electrodes, the nerve and electrodes were covered with a mixture of silicone gel (Semicosil 932A/B, Wacker Silicones) and white petrolatum (Vaseline). The preamplified nerve signal was band-pass filtered at 150–1,000 Hz. It was then full-wave rectified and low-pass filtered at 30 Hz to quantify the nerve activity. The cutoff frequency was sufficiently higher than the frequency range of interest in the present study (up to 10 Hz). Pancuronium bromide (0.3 mg/kg) was administered to prevent artifacts of muscular activity from appearing in the SNA recording. Body temperature was maintained at ~38°C with a heating pad.

Protocol. After the surgical preparation was completed, the baroreflex negative feedback loop was closed by adjusting CSP to AP. Mean AP (and thus mean CSP) at the steady state was treated as the operating pressure. To estimate the baroreflex dynamic characteristics, we randomly assigned CSP at 20 mmHg either above or below the operating pressure every 50 ms according to a binary white noise sequence. The input power spectrum of CSP was reasonably flat up to 10 Hz. We recorded CSP, SNA, and AP for 10 min at a sampling rate of 200 Hz using a 12-bit analog-to-digital converter. The data were stored on the hard disk of a dedicated laboratory computer system for later analysis.

Data analysis. To estimate the neural arc transfer function, we treated CSP as the input and SNA as the output of the system. To estimate the peripheral arc transfer function, we treated SNA as the input and AP as the output. We also estimated the total loop transfer function by treating CSP as the input and AP as the output. We segmented the 200-Hz input-output data pairs into 20 sets of 50% overlapping bins of 21st data points each. The segment length was 41 s, which yielded the lowest frequency bound of 0.024 Hz. For each segment, a linear trend was subtracted and a Hanning window was applied. We then performed fast Fourier transform to obtain frequency spectra of the input and output. We ensemble averaged the input power \(S_{xx}(f)\), output power \(S_{yy}(f)\), and cross power between the input and output \(S_{yx}(f)\) over the 20 segments. Finally, we calculated the transfer function \(H(f)\) from the input to output using Eq. 1 (12) as follows

\[
H(f) = \frac{S_{yx}(f)}{S_{xx}(f)}
\]

To quantify the linear dependence between the input and output signals in the frequency domain, we calculated a magnitude-squared coherence function \(\text{Coh}(f)\) using Eq. 2 (11) as follows

\[
\text{Coh}(f) = \frac{|S_{yx}(f)|^2}{S_{xx}(f)S_{yy}(f)}
\]

The coherence value ranges from zero to unity. A unity coherence indicates a perfect linear dependence between the input and output signals, whereas zero coherence indicates total independence of the two signals.

RESULTS

Typical time series of CSP, SNA, and AP are shown in Fig. 1. CSP was perturbed according to a binary white noise sequence. SNA showed burst activities with a random interval. AP did not change perceivably in this time window.

Power spectra of CSP, SNA, and AP averaged from all animals are shown in Fig. 2. CSP showed a relatively flat power spectrum up to 10 Hz. SNA showed a power spectrum centered between 0.3 and 1 Hz. Peaks around 0.5 Hz indicate the respiratory frequencies in respective animals. Note that HR-related peaks were not observed in the power spectrum of SNA, because we imposed the white noise input on CSP. AP showed a power spectrum that decreased as the frequency increased except for peaks associated with the frequencies of respiration (~0.5 Hz) and HR (~4 Hz).

Figure 3 shows the neural arc (A), peripheral arc (B), and total loop (C) transfer functions averaged from all animals; gain plots (top), phase plots (middle), and coherence functions (bottom) are presented. In the neural arc transfer function, the transfer gain increased as the frequency increased at frequencies below 0.8 Hz, whereas it decreased above 0.8 Hz at a rate of approx-
imately −20 dB/decade. The phase approached −π radians in the lowest frequency range, reflecting the negative feedback in the baroreflex neural arc. Starting with −π radians, the phase slightly lead at frequencies below 0.3 Hz and lagged above 0.3 Hz as the frequency increased. The continuous phase shift could be traced up to 5 Hz, although the variation became greater as the frequency approached 5 Hz. The coherence was ~0.3 at frequencies below 0.1 Hz, increased to 0.5 in the frequency range between 0.1 and 1 Hz, and decreased above 1 Hz. The coherence approached zero at frequencies above 3 Hz, indicating that the baroreflex-mediated components of SNA relative to noise components were minimal in this frequency range.

In the peripheral arc transfer function, the transfer gain decreased in the frequency range from 0.05 to 1 Hz as the frequency increased. The average slope of decline in the transfer gain approximated −40 dB/decade. The phase approached zero radians at the lowest frequency, reflecting the fact that an increase in SNA increased AP. However, the phase did not reach zero radians, indicating an insufficient length of the analyzed segment. The phase delayed as the frequency increased up to 1 Hz. The coherence was ~0.3 at frequencies below 0.1 Hz, increased to 0.5 in the frequency range between 0.1 and 0.4 Hz, and decreased above 0.4 Hz. The coherence approximated zero at frequencies above 1 Hz, indicating that SNA-related components of AP fluctuation were minimal in this frequency range.

In the total loop transfer function, the transfer gain decreased as the frequency increased. The average slope of decline in the transfer gain below 0.5 Hz was shallower than that in the peripheral arc transfer function. The phase approached −π radians at the lowest frequency, reflecting the negative feedback produced by the total loop baroreflex. The coherence was between 0.3 and 0.5 at frequencies below 0.5 Hz. The coherence decreased to zero at frequencies above 0.5 Hz.

**DISCUSSION**

The present study demonstrates that the neural arc transfer function of the carotid sinus baroreflex in rabbits showed derivative characteristics in the frequency range below 0.8 Hz, as consistent with previous results (4, 6–8, 14). At the same time, the neural arc
transfer function showed high-cut characteristics (or integrative characteristics) at frequencies above 0.8 Hz. The declining slope of the transfer gain approximated −20 dB/decade. The continuous phase shift could be traced up to 5 Hz in the neural arc transfer function.

Importance of high-cut characteristics of the neural arc. In a previous study, Ikeda et al. (4) emphasized the importance of derivative characteristics of the neural arc in achieving a quick and stable AP regulation based on a simulation using a nonpulsatile signal. As shown in Fig. 3, the decreasing slope of the transfer gain in the frequencies up to 0.5 Hz was less in the total loop transfer function than in the peripheral arc transfer function, suggesting an improved frequency response of the total loop baroreflex by the neural arc. The absolute gain value under physiological conditions, however, would be greater than that described in the total loop transfer function, because we sectioned the aortic depressor nerves and because the isolation procedure would have damaged the carotid sinus baroreflex function to a variable extent. Therefore, gain and phase margins in the total loop transfer function should be carefully interpreted.

The derivative characteristics of the neural arc improved the frequency response of the total loop baroreflex. However, if the derivative characteristics hold beyond 1 Hz, the transfer gain of the neural arc at 4 Hz (an example of HR frequency) will become as much as 40 times that at 0.01 Hz. Consequently, the dynamic range required to process a 10-mmHg pulsatile signal at 4 Hz would theoretically be equivalent to that processing a 400-mmHg pressure input at 0.01 Hz. The actual neural arc transfer function, however, demonstrated high-cut characteristics at frequencies above 0.8 Hz (Fig. 3, left). By virtue of these high-cut characteristics, the transfer gain of the neural arc at 4 Hz was within two times that at 0.01 Hz. Thus the dynamic range required to process a 10-mmHg pulsatile signal at 4 Hz was less than that processing a 20-mmHg pressure input at 0.01 Hz. These high-cut characteristics would be beneficial to avoid a saturation of signal transduction when the baroreflex dynamic range is finite.

The effects of pulsatile pressure on the baroreflex gain compared with nonpulsatile pressure have been extensively documented. Chapleau et al. (2) demonstrated that the pulsatile pressure decreases the maximum gain of baroreceptor transduction from pressure input to afferent nerve activity. Derivative characteristics followed by a nonlinear threshold element would explain the operating point dependency of the pulsatile effect on the baroreflex gain (18). The pulsatile pressure decreases the open-loop gain of the total baroreflex around the middle of the operating range (5, 9). These previous studies focused on the pulsatile effect on the baroreflex gain. On the other hand, the present study suggests that high-cut characteristics of the neural arc would attenuate the amplitude of the pulsatile signal in the baroreflex central pathways. As a result, the high-cut characteristics would minimize the effect of pulsatility on the baroreflex gain, thereby preserving the baroreflex open-loop gain against pulsatile pressure inputs.

Simulation of high-cut characteristics in the neural arc. To demonstrate the effect of high-cut characteristics in the neural arc on the baroreflex function more quantitatively, we performed a mathematical simulation described below. Figure 4A illustrates a simulator consisting of a neural arc transfer function ($H_N$), a nonlinear limiter element (NL), and a peripheral arc transfer function ($H_P$) (see APPENDIX for details). Estimating linear transfer functions followed by an introduction of NL does not make sense in general. However, we carefully set the saturation value of NL so that the nonlinearity did not interfere with the signal transduction by the actual transfer functions with the input amplitude of 20 mmHg. In addition, the dynamic range for NL was larger than the actual dynamic range of the baroreflex as determined from the static sigmoidal relationship between CSP and SNA (8, 16). If we assign a smaller dynamic range to NL, the effect of pulsatility on the baroreflex gain will be more pronounced.

Figure 4B shows a diagram of signal transduction when $H_N$ is simulated by derivative characteristics alone. $H_N$ inverts the sign of the signal and augments the pulsatile component while not affecting the amplitude of stepwise component. Before the stepwise change in CSP occurs, NL causes a symmetric saturation of signal transduction (solid arrows in Fig. 4B). $H_P$ filters out the pulsatile component, leaving no deviations in AP from the baseline value. On the other hand, after the stepwise change in CSP occurs, NL causes an asymmetric saturation of signal transduction (open arrows in Fig. 4B). $H_N$ and $H_P$ are nonlinear elements that determine the frequency response of the total loop baroreflex, NL, a nonlinear limiter element (see APPENDIX for details). Solid and open arrows indicate the magnitude of a saturation in signal transduction before and after the initiation of stepwise change in $\Delta$CSP, respectively. Horizontal dashed lines indicate a dynamic range determined by NL and a midpoint of operation.

AJP-Heart Circ Physiol • VOL 282 • MARCH 2002 • www.ajpheart.org
The magnitude of saturation is greater in the direction of the step response in SNA. As a result, the step response in AP is attenuated when HP filters out the pulsatile component.

Figure 5A, left, shows \( H_N \) simulated with derivative characteristics alone (dashed line) and \( H_N \) with derivative plus high-cut characteristics (solid line). Figure 5A, right, shows \( H_P \) simulated with second-order low-pass characteristics. The dynamic gain at the lowest frequency was set at unity for both \( H_N \) and \( H_P \); hence, the total baroreflex gain determined from steady-state AP response to CSP perturbation should be unity if the baroreflex signal transduction is not saturated. Figure 5B, top, presents changes in AP (\( \Delta AP \)) obtained from simulations using a nonpulsatile signal. The simulation results for the nonpulsatile signal were identical for \( H_N \) with derivative characteristics alone and \( H_N \) with both derivative and high-cut characteristics. The steady-state \( \Delta AP \) was \(-5\) mmHg in response to a 5-mmHg stepwise input of CSP \([u(t)]\), which yielded the total baroreflex gain of unity. Figure 5B, bottom, presents \( \Delta AP \) obtained from simulations using a pulsatile signal. The amplitude and frequency of the pulsatile input \([p(t)]\) were set at 10 mmHg and 4 Hz, respectively. The pulsatility itself did not appear in \( \Delta AP \) due to the low-pass filtering by the peripheral arc. However, the steady-state \( \Delta AP \) was attenuated to \(-0.8\) mmHg and the open-loop gain reduced to 0.16 when \( H_N \) was simulated with derivative characteristics alone (dashed line in Fig. 5B, bottom). In contrast, the steady-state \( \Delta AP \) was \(-5\) mmHg and the open-loop gain remained at unity when \( H_N \) was simulated with both derivative and high-cut characteristics (solid line in Fig. 5B, bottom).

Figure 6 summarizes the effects of pulse amplitude and pulse frequency on the baroreflex open-loop gain determined by the simulation (see APPENDIX for details). When \( H_N \) had derivative characteristics alone (Fig. 6A), an increase in pulse amplitude or pulse frequency easily attenuated the open-loop gain. When the pulse frequency was 4 Hz, considerable attenuation of the open-loop gain was noted even at the pulse amplitude of 10 mmHg (thick lines in Fig. 6A). In contrast, when the high-cut characteristics were added to \( H_N \) with derivative characteristics (Fig. 6B), the open-loop gain was well preserved at all the pulse frequencies examined as long as the pulse amplitude was \( \leq 20\) mmHg. Increasing the pulse amplitude beyond 20 mmHg decreased the open-loop gain when the pulse frequency was \( \sim 0.8\) Hz even when the high-cut characteristics of \( H_N \) were operating. Because \( H_N \) revealed a peak transfer gain near 0.8 Hz (Fig. 5A, left, solid line), the pulsatile signal around this frequency most easily caused a saturation of signal transduction when the pulse amplitude became too large. Although a pulse amplitude of 50 mmHg (i.e., pulse pressure of 100 mmHg) at a pulse frequency of 0.8 Hz reduced the open-loop gain to 0.3, these conditions are nonphysiological and would have little significance in terms of AP regulation.

**Neural arc transfer function above 1 Hz.** HR-synchronized activity is one of the hallmarks of SNA (11, 19). The present study indicates that the transfer gain of the neural arc decreased as the frequency increased above 0.8 Hz (Fig. 3, left). Thus the amplitude of HR-synchronized SNA is expected to decrease as HR increases. Although Suzuki et al. (19) demonstrated that changes in HR by propranolol and isoproterenol administrations resulted in a frequency-dependent decrease in HR-synchronized SNA, the input pressure and frequency were not exactly controlled due to the closed-loop nature of their study. In contrast, CSP was controlled independently of AP in the present study, validating application of the conventional open-loop analysis using transfer functions (6). Thus the present study would provide an analytic basis for the results by Suzuki et al. (19).
Several mechanisms may explain the high-cut characteristics of the neural arc. First, dynamic transduction properties of baroreceptors from pressure input to afferent nerve activity may contribute to high-cut characteristics (17). However, the baroreceptor transduction properties show a declining gain of approximately −12 dB/decade in the frequency range between 1 to 5 Hz. Thus the baroreceptor transduction properties alone cannot account for high-cut characteristics of −20 dB/decade in the neural arc. Second, the differences in conduction velocity among fibers that make up the baroreflex central pathways may produce some low-pass effect on the multifiber recording of SNA (8). Finally, frequency-dependent depression (FDD) of synaptic transmission in the baroreflex central pathways may be related to the high-cut characteristics. FDD is the phenomenon that the probability of excitatory postsynaptic potentials progressively reduces as the frequency of afferent input increases beyond 1 Hz (3, 10, 13). The input frequency of CSP perturbation corresponded to the modulation frequency of afferent fiber stimulation, whereas the input frequency of FDD is defined as the frequency itself of afferent fiber stimulation. Thus FDD and the decline in transfer gain should be discriminated in theory. However, interactions between FDD and transfer gain may occur when the modulation frequency of afferent fiber stimulation approached the frequency range of FDD. For instance, if we assume that multiple fibers are excited synchronously, reduction in the probability of synaptic transmission would result in a decrease in the amplitude of multifiber recording at that frequency.

Limitations. There are several limitations in this study. First, we investigated the carotid sinus baroreflex in anesthetized rabbits. Because anesthesia affects SNA, the results might have differed had the experiment been performed in conscious animals. For instance, HR-synchronized SNA reportedly decreases under anesthesia (19).

Second, coherence values associated with transfer functions were lower than those demonstrated in our previous studies (4, 7, 8, 14, 15). One possible reason for the low coherence values is that we expanded the upper frequency bound of the CSP perturbation from 1 to 10 Hz without increasing the input amplitude. As a result, an effective input power at each frequency decreased to ~1/10, reducing the signal-to-noise ratio in the system identification process. Although the low coherence values would confound the estimation of transfer functions, the estimated transfer functions below 1 Hz were consistent with those estimated in previous studies showing higher coherence values. Because the input power was relatively flat up to 10 Hz (Fig. 2, left), we believe that our system identification process was valid.

Third, we lumped the nonlinearities in the baroreflex central pathways into a single NL element in the simulation (Fig. 4A). The postulated importance of high-cut characteristics in preserving baroreflex gain against pulsatile pressure input could be applicable to anywhere in the baroreflex signal transduction if a
NEURAL ARC HIGH-CUT PROPERTIES

H1155

derivative linear element is followed by a nonlinear limiter element, although we have not identified the exact number and location of such a combination of subsystems. Moreover, because not only the number and location but also the type of nonlinear elements would affect overall system characteristics, the simulation results should be carefully interpreted.

Finally, we filled the isolated carotid sinuses with warm physiological saline. Because ionic content affects the sensitivity of the baroreceptors (1), it might also affect dynamic characteristics of the neural arc. Further studies are clearly required to elucidate the effects of ionic content on dynamic characteristics of the neural arc.

In conclusion, we found high-cut characteristics of the baroreflex neural arc in the frequency range above 0.8 Hz. By virtue of these high-cut characteristics of the neural arc, a pulsatile signal at a frequency of typical HR did not saturate the baroreflex signal transduction. In the absence of high-cut characteristics, the pulsatile signal would have caused a considerable reduction in the baroreflex open-loop gain even with the small amplitude of pulsatility.

Appendix

Figure 4A illustrates a simulator used to demonstrate the significance of high-cut characteristics in determining the baroreflex open-loop gain. The simulation was performed with Matlab Simulink toolbox (Math Works; Natick, MA). ΔCSP, ΔSNA, and ΔAP indicate changes in CSP, SNA, and AP, respectively. We modeled the neural arc transfer function (H₆₅) using Eq. 3 as follows

\[ H₆₅(f) = - \frac{1 + \frac{j}{f_c_1}}{1 + \frac{j}{f_c_2}} \exp(-2\pi f L) \]  \hspace{1cm} (3)

where \( f \) and \( j \) represent the frequency (in Hz) and imaginary units, respectively; \( f_c_1 \) and \( f_c_2 \) (\( f_c_1 < f_c_2 \)) are corner frequencies (in Hz) for derivative and high-cut characteristics, respectively; and \( L \) is a pure delay (in s). In a transfer function, a zero and a pole provide maximum phase shifts of 0.5π and –0.5π radians, respectively. Because \( H_N \) consists of one zero and two poles, the maximum phase shift attained by \( H_N \) without \( L \) is –0.5π radians on top of –π radians derived from a negative sign. Accordingly, introducing the pure delay \( L \), was indispensable to add the progressive phase shift and to simulate the maximum phase shift in the neural arc transfer function beyond –1.5π radians. The pure delay in the neural arc would represent the sum of delays in the sympathetic ganglion.

When \( f_c_2 \) is set greater than \( f_c_1 \), dynamic gain increases in the frequency range from \( f_c_1 \) to \( f_c_2 \) and decreases above \( f_c_2 \). When \( f_c_2 \) is set far greater than the frequency range of interest, \( H_N \) approximates a derivative or the high-pass filter used in our previous studies (4, 6, 14).

To model the neural arc transfer function with derivative characteristics alone, we set \( f_c_1, f_c_2, \) and \( L \) at 0.1 Hz, 100 Hz, and 0.5 s, respectively. Although the model transfer function mimicked the actual neural arc transfer function in the frequency range between 0.01 and 0.5 Hz, the transfer gain progressively deviated from the actual transfer gain in the frequencies above 0.5 Hz (Fig. 5A, left, dashed line). To model the neural arc transfer function with both derivative and high-cut characteristics, we set \( f_c_1, f_c_2, \) and \( L \) at 0.1 Hz, 0.8 Hz, and 0.2 s, respectively. The model transfer function mimicked the actual transfer function in the frequency range between 0.01 and 5 Hz (Fig. 5A, left, solid line). The pure delay was set shorter than that used to model the derivative characteristics alone, because the high-cut characteristics yielded an additional phase delay. The overall phase delay attained by the derivative plus high-cut characteristics approximated the actual phase delay reasonably well.

We modeled the peripheral arc transfer function (Hₗ₇) using the second-order low-pass filter (Eq. 4) according to our previous studies (4, 6, 15)

\[ Hₗ₇(f) = \frac{1}{1 + 2i \frac{f}{f_{N}} j + \left( \frac{f}{f_{N}} \right)^2} \exp(-2\pi f L) \]  \hspace{1cm} (4)

where \( f_{N} \) and \( \zeta \) indicate a natural frequency (in Hz) and a damping ratio, respectively. \( L \) is a pure delay (in s), which was required to add a progressive phase shift and to simulate maximum phase shift beyond –π radians in the peripheral arc transfer function. The pure delay in the peripheral arc would represent the sum of delays in the sympathetic transmission at neuroeffector junctions and the intracellular signal transduction in the effector organs.

To simulate the actual peripheral arc transfer function, we set \( f_{N}, \zeta, \) and \( L \) at 0.07 Hz, 1.2, and 1 s, respectively. The model peripheral arc transfer function mimicked the actual peripheral arc transfer function in the frequency range between 0.01 and 1 Hz (Fig. 5A, right). Although the actual transfer gain showed several peaks associated with the frequency of HR and its harmonics, we ignored the transfer characteristics in the frequencies above 1 Hz. This is because the zero coherence values as well as the dispersed phase values indicated a very low signal-to-noise ratio of the transfer function estimation at frequencies above 1 Hz.

To model the presence of a dynamic range in the baroreflex central pathways, we inserted a nonlinear limiter element (NL) between \( H_{N} \) and \( H_{P} \). NL limits the absolute value of the signal to a given saturation value. Equation 5 gives the mathematical description of NL as follows

\[ \text{NL}(x) = \begin{cases} a & (x > a) \\ x & (-a \leq x \leq a) \\ -a & (x < -a) \end{cases} \]  \hspace{1cm} (5)

where \( x \) and \( a \) represent the input and saturation values, respectively. The saturation value was set at 100 so as to provide a dynamic range of ±100 units for ΔSNA. Because dynamic gain in the lowest frequency was set at unity for both \( H_{N} \) and \( H_{P} \), the dynamic range of ±100 units for ΔSNA corresponded to a dynamic range of ±100 mmHg for both ΔCSP and ΔAP.

We used a stepwise input [\( u(t) \)] to calculate the open-loop gain of the baroreflex. The pressure change of \( u(t) \) was set at 5 mmHg so that \( u(t) \) itself did not saturate the signal transduction at all. The simulation continued up to 60 s after the initiation of the stepwise input. The open-loop gain was calculated from the ratio of ΔAP to ΔCSP averaged from the last 10 s of the simulation. Although the open-loop gain was calculated to be a negative value due to a negative feedback nature in the neural arc, we omitted the negative sign of the open-loop gain in the present study for convenience.

We imposed a sinusoidal input [\( p(t) \)] on top of the stepwise input to examine the effects of pulsatile signal on the open-
loop gain. The zero to peak amplitude of $p(t)$ was varied in the range between 0 (nompulsatile) and 50 mmHg with increments of 1 mmHg. The frequency of $p(t)$ was varied in the range between 0 and 6 Hz with increments of 0.1 Hz (Fig. 6).

This study was supported by Ministry of Health and Welfare of Japan Research Grants for Cardiovascular Diseases 9C-1, 11C-3, and 11C-7, by a Health Sciences research grant for Advanced Medical Technology from the Ministry of Health and Welfare of Japan, by a Ground-Based research grant for Space Utilization promoted by National Space Development Agency of Japan and the Japan Space Forum, by Ministry of Education, Science, Sports and Culture of Japan Grants-In-Aid for Scientific Research, B-11694337, C-11680862, and C-11670730 and Grant-in-Aid for Encouragement of Young Scientists 13770378, by the Research and Development for Applying Advanced Computational Science and Technology from Japan Science and Technology Corporation, and by the Program for Promotion of Fundamental Studies in Health Science from the Organization for Pharmaceutical Safety and Research.

REFERENCES