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# Effects of L-type $Ca^{2+}$ Channel Blocker Nifedipine on Dynamic Arterial Blood Pressure Control

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*Abstract*— **Dynamic characteristics of arterial pressure (AP) regulation are important components in our understanding of rapid AP restoration by the arterial baroreflex system. The present study examined the effects of an L-type $Ca^{2+}$ channel blocker nifedipine on baroreflex-mediated dynamic AP regulation. In anesthetized and vagotomized rats, carotid sinus pressure was externally perturbed using a Gaussian white noise signal, and the neural arc transfer function from pressure input to efferent sympathetic nerve activity (SNA) and the peripheral arc transfer function from SNA to AP were identified. The peripheral arc transfer function approximated a second-order low-pass filter with pure dead time. Intravenous administration of nifedipine significantly decreased the steady-state gain and increased the damping ratio of the peripheral arc without affecting the dynamic characteristics of the neural arc. When the step response of AP was calculated based on the peripheral arc transfer function alone, nifedipine prolonged 80% rise time by 26%. When the closed-loop AP response was simulated based on both the neural arc and peripheral arc transfer functions and the dynamic gain of the baroreflex total loop was assumed to be 2.0, nifedipine prolonged 80% recovery time by 107%. In conclusion, L-type $Ca^{2+}$ channel blockade may compromise the baroreflex-mediated AP control not only in the magnitude but also in the speed of AP restoration.**

## I. Introduction

The arterial baroreflex is one of the most important negative feedback systems that stabilize arterial pressure (AP) against pressure disturbance such as that occurs during postural change. Rapid AP restoration is essential to maintain appropriate blood supply for vital organs. Investigation of the dynamic characteristics of the arterial baroreflex is a key to our understanding of rapid AP restoration. The baroreflex dynamic characteristics may be analyzed by dividing the system into two principal subsystems: a baroreflex neural arc and a baroreflex peripheral arc [1]. The neural arc represents the pathway from baroreceptor pressure input to efferent sympathetic nerve activity (SNA), and can be regarded as a controller subsystem. The peripheral arc represents the pathway from SNA to AP, and acts as a controlled subsystem. A previous study has demonstrated that the fast neural arc compensates for the slow peripheral arc to improve the overall performance of dynamic AP regulation attained by the arterial baroreflex [1].

Although L-type $Ca^{2+}$ channel blockers are widely used to reduce AP in hypertensive patients [2], their effects on baroreflex-mediated dynamic AP control remain to be quantitatively analyzed. Norepinephrine is released in response to SNA, which acts on $\alpha_1$-adrenergic receptors and contracts vascular smooth muscles. Because smooth muscle contraction requires $Ca^{2+}$ influx though L-type $Ca^{2+}$ channels, L-type $Ca^{2+}$ channel blockade interferes with vascular smooth muscle contraction and reduces vascular resistance to decrease AP. At the same time, it is also likely that L-type $Ca^{2+}$ channel blockade would compromise the AP regulation associated with SNA. To test the hypothesis that L-type $Ca^{2+}$ channel blockade affects the rapidness of AP regulation, the present study examined the effects of an L-type $Ca^{2+}$ channel blocker nifedipine on the baroreflex-mediated dynamic AP regulation. To identify the dynamic characteristics of the carotid sinus baroreflex, we employed an open-loop systems analysis using a Gaussian white noise input [3].

## II. Materials and Methods

The study was performed on five anesthetized and vagotomized Wistar Kyoto rats. The 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. The experimental protocols were reviewed and approved by the Animal Subjects Committee at National Cerebral and Cardiovascular Center.

### A. Animal Preparation

The rats were anesthetized with intraperitoneal injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/ml). Supplemental anesthetic mixture was continuously administered from a venous catheter inserted from the right femoral vein. Another venous catheter was inserted from the left femoral vein for later administration of nifedipine. An arterial catheter was inserted from the right femoral artery to measure AP. The postganglionic branch of the splanchnic sympathetic nerve was exposed through a left flank incision, and a pair of stainless steel wire electrodes (AS633, Cooner Wire, USA) was attached to record multifiber SNA [3]. At the end of the experiment, a ganglionic blocker hexamethonium bromide (60 mg/kg) was intravenously administered in bolus, and the noise level of SNA was measured.

Bilateral vagal and aortic depressor nerves were sectioned at the neck to avoid reflexes from the cardiopulmonary regions

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and aortic arch. Carotid sinus baroreceptor regions were isolated from the systemic circulation according to previously reported procedures [4, 5]. The isolated bilateral carotid sinuses were filled with warmed Ringer's solution through catheters inserted from the common carotid arteries, and the intra-carotid sinus pressure (CSP) was controlled by a servo-controlled piston pump.

### B. Protocols

To identify dynamic characteristics of the carotid sinus baroreflex, CSP was perturbed according to a Gaussian white noise signal with a mean of 120 mmHg and standard deviation of 20 mmHg [3]. The switching interval of the input signal was set to 500 ms so that the input power spectrum was relatively flat up to 1 Hz. After acquiring the SNA and AP responses under control conditions for 15 min, an L-type $Ca^{2+}$ channel blocker nifedipine was intravenously administered in bolus (100 μg/kg), followed by a continuous infusion (300 $\mu g \cdot kg \cdot h^{-1}$). The dose was determined from a preliminary study so that the hypotensive effect persisted throughout the experiment. Thirty minutes after the initiation of the nifedipine administration, the SNA and AP responses to the dynamic CSP perturbation were examined for 15 min.

### C. Data Analysis

Data were sampled at 1,000 Hz using a 16-bit analog-to-digital converter. To estimate the dynamic characteristics of the baroreflex neural arc, CSP was treated as the input and SNA was treated as the output of the system. To estimate the dynamic characteristics of the baroreflex peripheral arc, SNA was treated as the input and AP was treated as the output of the system.

The input-output data pairs were resampled at 10 Hz. The data were then divided into 10 half overlapping bins of 1,024 data points each. In each segment, a linear trend was subtracted and a Hanning window was applied. The input power spectra, $S_{XX}(f)$, output power spectra, $S_{YY}(f)$, and cross spectra, $S_{YX}(f)$, were calculated over the 10 segments, where $f$ denotes frequency. The transfer function from the input to output was calculated as:

$$H(f) = S_{YX}(f)/S_{XX}(f)$$

The magnitude squared coherence function between the input and output was calculated as:

$$Coh(f) = |S_{YX}(f)|^2/S_{XX}(f)/S_{YY}(f)$$

### D. Modeling of Transfer Functions

Because the magnitude of SNA differed among animals depending on recording conditions, SNA was normalized in each animal and expressed in arbitrary units (a.u.). The normalization was such that the average of dynamic gain values below 0.03 Hz became unity in the neural arc transfer function under control conditions. The reciprocal of the normalization factor was applied to the peripheral arc transfer function. The same normalization factor was used to normalize the transfer functions during nifedipine administration. The total-loop transfer function, which is a product of the neural arc and peripheral arc transfer functions in the frequency domain, was not affected by the normalization of SNA.

According to previous studies [3, 6], the neural arc transfer function was modeled as:

$$H_N(f) = K_N \frac{1 + \frac{f}{f_{C1}} j}{\left(1 + \frac{f}{f_{C2}} j\right)^2} \exp(-2\pi f L_N j)$$

where $j$ represents the imaginary units. $K_N$ is the steady-state gain of the neural arc (in a.u./mmHg), $f_{C1}$ is the corner frequency determining the derivative characteristics (in Hz), $f_{C2}$ is the corner frequency determining the high-cut characteristics (in Hz), and $L_N$ is the pure dead time (in s).

According to previous studies [1, 3, 6], the peripheral arc transfer function was modeled by a second-order low-pass filter as:

$$H_P(f) = \frac{K_P}{1 + 2\zeta \frac{f}{f_N} j + \left(\frac{f}{f_N} j\right)^2} \exp(-2\pi f L_P j)$$

where $K_P$ is the steady-state gain of the peripheral arc (in mmHg/a.u.), $f_N$ is the natural frequency (in Hz), $\zeta$ is the damping ratio (unitless), and $L_P$ is the pure dead time (in s).

### E. Statistical Analysis

Mean AP and SNA values during the CSP perturbation and transfer function parameters were compared between before and during nifedipine administration by paired-t test with a significance level set to $P < 0.05$.

### F. Open-Loop and Closed-Loop Simulations

After obtaining mean values of transfer function parameters from the five animals, the following simulations were performed to understand the effects of nifedipine on the rapid AP response by the baroreflex system. First, an AP step response to a unit change in SNA was calculated from the

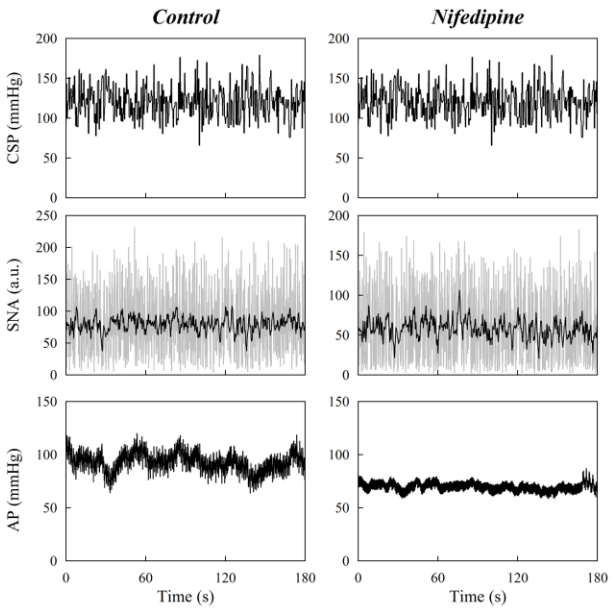


Fig. 1. Typical recordings of carotid sinus pressure (CSP), sympathetic nerve activity (SNA), and arterial pressure (AP). In the SNA plot, the gray lines indicate 10-Hz resampled signal, and the black lines indicate 2-s moving averaged signal. CSP and AP were resampled at 10 Hz.

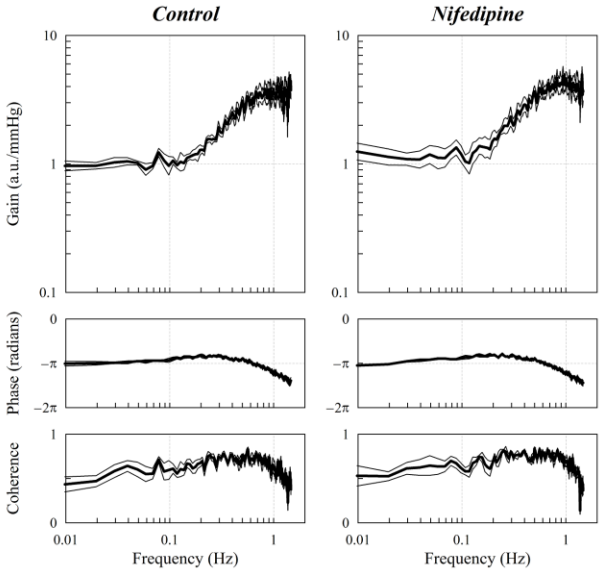


Fig. 2. Neural arc transfer function from carotid sinus pressure to sympathetic nerve activity obtained before (left) and during (right) intravenous nifedipine administration. The lines are means ± SE.

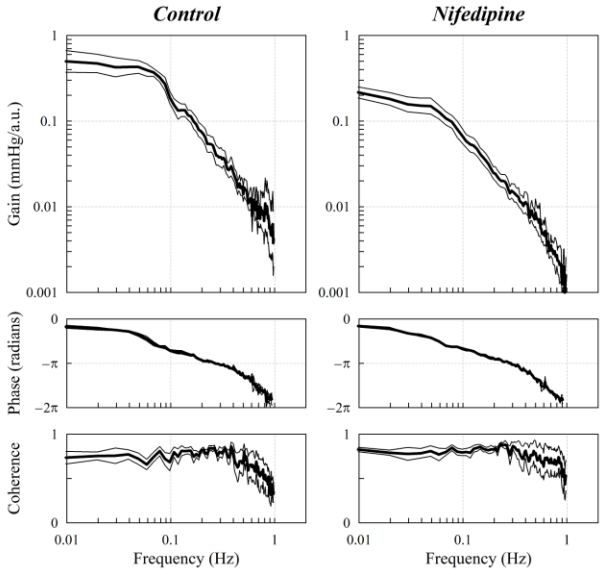


Fig. 3. Peripheral arc transfer function from sympathetic nerve activity to arterial pressure obtained before (left) and during (right) intravenous nifedipine administration. The lines are means ± SE.

peripheral arc transfer function. The effect of nifedipine on 80% rise time was examined. Next, a closed-loop AP response to an exogenous step perturbation was simulated by using both the neural arc and peripheral arc transfer functions. The effect of nifedipine on the time for AP to recover to 80% of the steady-state recovery (80% recovery time) was examined.

## III. Results and Discussion

Typical experimental recordings are shown in Fig. 1. CSP was perturbed according to a Gaussian white noise signal. SNA and AP were changed dynamically in response to the CSP perturbation. The averaged data from the five rats indicated that mean AP during CSP perturbation was significantly decreased by nifedipine from 91.0 ± 5.4 to 66.4 ± 6.0 mmHg (P = 0.001). In contrast, mean SNA during CSP perturbation was not different before and during nifedipine administration (93.3 ± 16.8 vs. 89.7 ± 15.6 a.u., P = 0.75).

### A. Effects of Nifedipine on Neural Arc Transfer Function

Fig. 2 depicts the neural arc transfer function from CSP to SNA before (left) and during (right) nifedipine administration. The dynamic gain of the neural arc increased as the frequency increased beyond 0.1 Hz, suggesting derivative characteristics of the neural arc. The phase was close to $-\pi$ radians at the lowest frequency, reflecting negative feedback nature of the neural arc. Administration of nifedipine did not affect the transfer function parameters of the neural arc (Table I), suggesting that central effects of intravenous nifedipine were minimal as far as the baroreflex-mediated regulation of splanchnic SNA was concerned.

### B. Effects of Nifedipine on Peripheral Arc Transfer Function

Fig. 3 depicts the peripheral arc transfer function from SNA to AP before (left) and during (right) nifedipine administration. The dynamic gain of the peripheral arc decreased as the frequency increased, suggesting low-pass characteristics of the peripheral arc. The phase tended to zero radians at the lowest frequency, indicating a positive AP response to an increase in SNA at the steady state. Administration of nifedipine moved the gain plot downward over the all frequencies tested. The steady-state gain was significantly decreased and the damping ratio was significantly increased by nifedipine (Table II). The natural frequency and the dead time were not changed significantly. These results conform to the prediction that L-type $Ca^{2+}$ channel blockade reduces the contraction of vascular smooth muscles in response to sympathetic activation.

### C. Effects of Nifedipine on Open-Loop and Closed-Loop AP Response

Fig. 4A illustrates mathematical models for the neural arc and peripheral arc transfer functions. The parameter values were derived from the mean values shown in Tables I and II. As can be seen, although the damping ratio of the peripheral arc transfer function was significantly increased by nifedipine, its effect on the phase plot was apparent only in the frequencies above 0.8 Hz. Fig. 4B illustrates the open-loop

TABLE I. Neural Arc Parameters

| | *Control* | *Nifedipine* |
|---|---|---|
| $K_N$, a.u./mmHg | 0.95 ± 0.02 | 1.13 ± 0.15 |
| $f_{C1}$, Hz | 0.18 ± 0.01 | 0.16 ± 0.01 |
| $f_{C2}$, Hz | 1.52 ± 0.21 | 1.34 ± 0.17 |
| $L_N$, s | 0.12 ± 0.01 | 0.12 ± 0.01 |

Data are means ± SE (n = 5). There were no significant differences in the parameters.

TABLE II. Peripheral Arc Parameters

| | *Control* | *Nifedipine* |
|---|---|---|
| $K_P$, mmHg/a.u. | 0.65 ± 0.17 | 0.25 ± 0.04 * |
| $f_N$, Hz | 0.08 ± 0.01 | 0.09 ± 0.01 |
| $\zeta$ | 2.43 ± 0.31 | 3.17 ± 0.29 * |
| $L_P$, s | 0.45 ± 0.03 | 0.53 ± 0.03 |

Data are means ± SE (n = 5). *P < 0.05 by paired-t test.

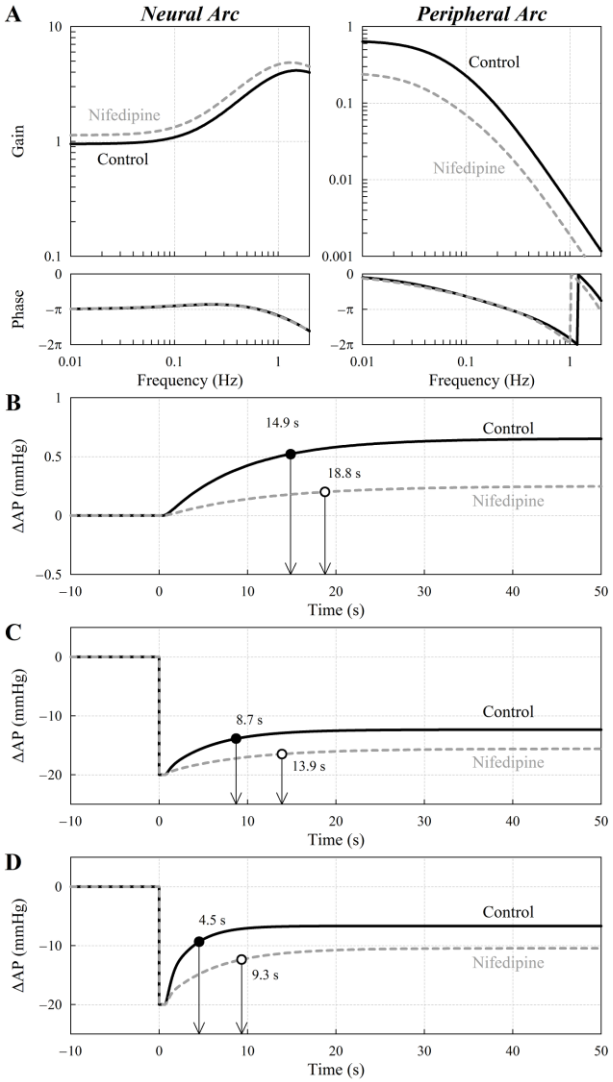


Fig. 4. A: Mathematical models for the neural arc and peripheral arc transfer functions. B: Open-loop step responses of arterial pressure (AP) derived from the peripheral arc transfer functions under conditions of control (black line) and nifedipine administration (gray dotted line). The closed and open circles represent 80% rise times in the respective step responses. C: Simulation results of closed-loop AP response to a stepwise pressure disturbance of –20 mmHg imposed at time 0. The closed and open circles indicate time points of 80% recovery relative to the steady-state AP recovery. D: Simulation results of closed-loop AP response when dynamic gain of the total-loop baroreflex was adjusted to 2.0 under control conditions (see discussion for details).

step response of AP derived from the peripheral arc transfer function alone. Nifedipine attenuated the steady-state step response and delayed the 80% rise time by 26% (from 14.9 to 18.8 s). Fig. 4C depicts the closed-loop AP response against a stepwise disturbance of –20 mmHg. In the closed-loop simulation, both the neural arc and peripheral arc transfer functions were implemented in the negative feedback loop. Nifedipine prolonged the 80% recovery time by 60% (from 8.7 to 13.9 s). Therefore, the delay in the AP response was exaggerated under the closed-loop conditions compared to the open-loop conditions, because the attenuation of the steady-state gain contributed to the prolongation of the response time under the closed-loop conditions.

Large amplitude perturbations in CSP causes underestimation of the baroreflex gain due to the saturation of the SNA response associated with sigmoidal nonlinearity of the baroreflex neural arc [7]. When the baroreflex static characteristics were examined by a staircase-wise CSP input, the maximum gain of the carotid sinus baroreflex was approximately 1.6 [5]. Further, because the arterial baroreflex from the aortic arch exists under physiological conditions, the maximum gain of the total-loop baroreflex might be greater than 1.6. To examine the effects of nifedipine under conditions of higher baroreflex gain, the baroreflex gain of the total loop was assumed to be 2.0 under the control conditions (Fig. 4D). The percent reduction of the baroreflex gain by nifedipine was the same as that for Fig. 3C. In Fig. 4D, nifedipine prolonged the 80% recovery time by 107% (from 4.5 to 9.3 s). These results suggest that even though the natural frequency and the dead time of the peripheral arc transfer function were not changed significantly by nifedipine, the decreased steady-state gain and the increased damping ratio may yield a negative impact on the rapidness of closed-loop AP control.

## IV. Conclusion

L-type $Ca^{2+}$ blockers are widely used for the treatment of hypertension. Although lowering AP is essential to prevent cardiovascular events, an overdose of $Ca^{2+}$ channel blockers can occur, for instance, as a consequence of concomitant use of macrolide antibiotics in elderly patients [8], which induces hypotention. There is a possibility that an overdose of L-type $Ca^{2+}$ channel blockers may compromise the baroreflex-mediated rapid AP control and prolong hypotensive events. Careful management of drug administration may be required to prevent such adverse effects associated with an overdose of L-type $Ca^{2+}$ channel blockers.

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