Servo-Controlled Hind-Limb Electrical Stimulation for Short-Term Arterial Pressure Control

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Background: Autonomic neural intervention is a promising tool for modulating the circulatory system thereby treating some cardiovascular diseases. Methods and Results: In 8 pentobarbital-anesthetized cats, it was examined whether the arterial pressure (AP) could be controlled by acupuncture-like hind-limb electrical stimulation (HES). With a 0.5-ms pulse width, HES monotonically reduced AP as the stimulus current increased from 1 to 5 mA, suggesting that the stimulus current could be a primary control variable. In contrast, the depressor effect of HES showed a nadir approximately 10 Hz in the frequency range between 1 and 100 Hz. Dynamic characteristics of the AP response to HES approximated a second-order low-pass filter with dead time (gain: \(-10.2\pm1.6\text{mmHg/mA}\), natural frequency: \(0.040\pm0.004\text{Hz}\), damping ratio: \(1.80\pm0.24\), dead time: \(1.38\pm0.13\) s, mean±SE). Based on these dynamic characteristics, a servo-controlled HES system was developed. When a target AP value was set at 20 mmHg below the baseline AP, the time required for the AP response to reach 90% of the target level was 38±10 s. The steady-state error between the measured and target AP values was 1.3±0.1 mmHg.

Conclusions: Autonomic neural intervention by acupuncture-like HES might provide an additional modality to quantitatively control the circulatory system. (Circ J 2009; 73: 851–859)

Key Words: Autonomic neural intervention by acupuncture-like HES; Proportional-integral controller; Transfer function

Because abnormality in the autonomic nervous system is often associated with cardiovascular diseases, treating cardiovascular diseases by autonomic neural interventions have attracted many researchers. Recently, autonomic neural interventions using electronic devices have again gained the focus of attention as a potential modality for treating cardiovascular diseases resistant to conventional therapeutics. To name a few, chronic vagal nerve stimulation dramatically improves the survival of chronic heart failure after myocardial infarction in rats. Chronic baroreceptor activation enhances the survival of pacing-induced heart failure in dogs. A recent version of a device-based treatment of hypertension in human is reported. A framework of electrical neural intervention is also effective to elevate arterial pressure (AP) against hypertensive events.

Aside from direct neural stimulation, electroacupuncture can modify autonomic balance, thereby treating cardiovascular diseases. Although one feature of the electroacupuncture might be its long-lasting effects, immediate cardiovascular responses to acupuncture-like stimulation are also observed in several experimental settings. For example, a 60-s manual acupuncture-like stimulation of a hind limb reduces renal or cardiac sympathetic nerve activity, causing hypotension and bradycardia in anesthetized rats. We have shown that electrical stimulation of a hind limb using acupuncture needles immediately resets the arterial baroreflex and reduces sympathetic nerve activity in anesthetized rabbits. Acupuncture-like hind-limb electrical stimulation (HES) induces immediate hypotension with changes in the relationship between cardiac and renal sympathetic nerve activities in anesthetized cats.

In the present study, we hypothesized that AP could be controlled by HES. Quantification of the dynamic input-output relationship between a given stimulus and the AP response is essential for artificially controlling AP. Accordingly, the first aim was to identify the dynamic input-output relationship between HES and the AP response. The second aim was to develop a feedback controller system that could reduce AP at a prescribed target level using HES.

Methods

Surgical Preparation

Animal care was provided 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. All protocols were approved by the Animal Subject Committee of the National Cardiovascular Center. Eight adult cats weighing from 2.3 to 4.3 kg were
anesthetized by an intraperitoneal injection of pentobarbital sodium (30–35 mg/kg) and ventilated mechanically via a tracheal tube with oxygen-supplied room air. The depth of anesthesia was maintained with a continuous intravenous infusion of pentobarbital sodium (1–2 mg·kg⁻¹·h⁻¹) through a catheter inserted into the right femoral vein. Vecuronium bromide (0.5–1.0 mg·kg⁻¹·h⁻¹, iv) was given continuously to suppress muscular activity. AP was measured using a catheter-tip manometer inserted from the right femoral artery and advanced into the thoracic aorta.

HES

In the supine position, both hind limbs were lifted to obtain a better view of the lateral sides of the lower legs. An acupuncture needle with a diameter of 0.2 mm (CE0123, Seirin-Kasei, Shimizu, Japan) was inserted into a point below the knee joint just lateral to the tibia. A 23-gauge needle was inserted into the skin behind the ankle as the ground. HES was applied bilaterally via 2 independent isolators connected to an electrical stimulator (SEN 7203, Nihon Kohden, Tokyo, Japan) as shown in Figure 1. The pulse width was changed manually whereas the stimulus frequency and the stimulus current were controlled by a dedicated laboratory computer system. The electrical stimulation was started after the hemodynamic effects of needle insertion had disappeared, and the acupuncture needle remained inserted during each protocol.

Protocols

Protocol 1 (n=8) To quantify the AP response to HES as a function of stimulus current and pulse width, we fixed the stimulus frequency at 10 Hz and changed the stimulus current stepwise from 0 to 5 mA in 1-mA increments every minute. The 6-min current test was repeated with an intervening interval of 3–5 min using different pulse widths (0.1, 0.2, 0.5 and 1 ms). The order of the pulse-width settings was randomized across the animals.

Protocol 3 (n=8) To identify the dynamic input–output relationship between HES and the AP response, we randomly turned HES on and off every 2 s according to a binary white noise sequence for 30 min. The HES setting (0.5-ms pulse width, 10 Hz, 3 mA) was chosen to induce effective hypotension based on the preliminary results obtained from Protocols 1 and 2.

Protocol 4 (n=8) Based on the result of Protocol 3, we designed a feedback controller that could automatically adjust the stimulus frequency and the stimulus current for HES. The pulse width was fixed at 0.5 ms. To examine the performance of the feedback controller, we set a target AP value at 20 mmHg below the baseline AP and activated the feedback controller for 10 min.

The following 2 supplemental protocols were performed in 3 of the 8 cats: (1) we inserted 2 acupuncture needles into the triceps surae muscle with a distance of approximately 2.5 cm, and examined if changes in AP was associated with direct muscle stimulation (0.5-ms pulse width, 10 Hz, 3 mA). Both hind limbs were stimulated simultaneously using 2 independent isolators; and (2) we exposed the sciatic nerve after finishing Protocols 1 through 4, and examined if sectioning the sciatic nerve abolished the hemodynamic effects of HES. Unilateral HES was performed (0.5-ms pulse width, 10 Hz, 3 mA) before and after sectioning the ipsilateral sciatic nerve.

Data Analysis

In Protocols 1 and 2, the AP value was obtained by averaging the last 10-s data at each stimulus condition. In Protocol 1, the effect of stimulus current was assessed by changes in AP from the 0-mA stimulus condition for each pulse width. The order of the pulse-width settings was randomized across the animals.

In Protocol 3, the transfer function from HES to AP was estimated by means of an analysis for one-input, one-output systems. Data were first resampled at 10 Hz and segmented into 8 sets of 50%-overlapping bins of 4,096 points each. For each segment, a linear trend was subtracted and a
Hanning window was applied. Frequency spectra of the input and output were obtained via fast Fourier transformation. Next, the ensemble averages of input power spectral density \( S_{XX}(f) \), output power spectral density \( S_{YY}(f) \), and cross spectral density between the input and output \( S_{XY}(f) \) were calculated over the 8 segments. Finally, the transfer function from input to output \( H(f) \) was calculated as:

\[
H(f) = \frac{S_{XY}(f)}{S_{XX}(f)} \tag{1}
\]

To quantify the linear dependence between the input and output signals in the frequency domain, a magnitude-squared coherence function \( Coh(f) \) was also calculated as:

\[
Coh(f) = \frac{|S_{XY}(f)|^2}{S_{XX}(f)S_{YY}(f)} \tag{2}
\]

In Protocol 4, the performance of the feedback controller was evaluated by the time required for the AP response to reach 90\% of the target AP decrease and by the standard deviation of the steady-state error between the target and measured AP values during the last 5 min of the 10-min feedback control. These 2 values were calculated based on the 2-s moving averaged data of AP.

### Statistical Analysis

All data are presented as mean and SE values. In Protocol 1, changes in AP were examined by 2-way repeated-measures analysis of variance (ANOVA) using the stimulus current as one factor and the pulse width as the other factor. In Protocol 2, changes in AP were examined by 2-way repeated-measures ANOVA using the stimulus frequency as one factor and the pulse width as the other factor. Differences were considered significant when \( P < 0.05 \).
Results

Relationship Between Stimulus Intensity and AP Response

Typical time series of Protocols 1 and 2 obtained from one animal are shown in Figures 2A and B, respectively. The pulse width was set in a random order. In Protocol 1, baseline AP obtained at the 0-mA stimulus condition was 118.4 ± 5.4 mmHg across the animals. Changes in mean AP as a function of stimulus current are summarized in Figure 2C. The decrease in AP became greater as the stimulus current increased. The overall statistical analysis indicated that the effect of the stimulus current on the magnitude of AP decrease was significant whereas that of pulse width was not. There was no significant interaction effect between the stimulus current and the pulse width.

In Protocol 2, baseline AP at the 0-Hz stimulus condition was 117.6 ± 5.9 mmHg across the animals. Changes in mean AP as a function of stimulus frequency are summarized in Figure 2D. The decrease in AP became greater as the stimulus frequency increased from 1 to 10 Hz but it became smaller when the stimulus frequency exceeded 10 Hz. At the pulse width of 1 ms, the stimulus frequency of 100 Hz even increased AP. The overall statistical analysis indicated that the effect of stimulus frequency on the magnitude of AP decrease was significant whereas that of pulse width was not. There was no significant interaction effect between the stimulus frequency and the pulse width.

Dynamic Characteristics of AP Response to HES

Figure 3A depicts a typical time series obtained from Protocol 3. HES was turned on and off randomly, which decreased the mean level of AP and also caused intermittent AP variations. When HES was finally turned off at 30 min, AP began to increase toward the prestimulation value. A long-lasting effect of HES was not observed in the present protocol. The white line in the AP trace represents the 2-s moving averaged data of AP.

The results of transfer function analysis are depicted in Figure 3B. In the gain plot, the magnitude of AP response relative to the HES input was plotted in the frequency domain. The gain value became smaller as the frequency increased, indicating the low-pass characteristics of the AP response to HES. In the phase plot, AP showed an out-of-phase relationship with HES at the lowest frequency (0.0024 Hz). The phase delayed more with increasing the frequency of modulation. The coherence value was approximately 0.7 in the frequency range below 0.06 Hz. The
coherence value became smaller in the frequency range above 0.1 Hz but still retained a value of 0.5, indicating that approximately half of the AP variation was explained by the HES input.

The general feature of the dynamic characteristics of the AP response to HES approximated what is known as a second order low-pass filter with a pure dead time. When we set the proportional gain at zero. Under this condition, the AP response was transformed into the stimulus current and the stimulus frequency (in Hz) by a factor of 10 (Figure 4B, Right). The stimulation was turned off when the HES command became negative.

Several sets of simulations were conducted using the model transfer function. The target AP was set at 20 mmHg below the baseline AP. To mimic the pulse pressure in AP, a 3-Hz sinusoidal wave (corresponding to the HR of 180 beats/min) with an amplitude of 15 mmHg (corresponding to the pulse pressure of 30 mmHg) was added to the AP signal. To avoid pulsatile variation in the HES command, we set the proportional gain at zero. Under this condition, when the integral gain was set at 0.001, AP decreased gradually and it took more than 3 min to reach the target AP (Figure 4C, Left). When the integral gain was set at 0.005, AP decreased more promptly and reached the target AP in less than 1 min (Figure 4C, Center). When the integral gain was set at 0.01, the AP response occurred more rapidly but showed significant oscillations before settling (Figure 4C, Right). Based on these simulation results, we set the proportional gain at zero and the integral gain at 0.005 for the actual feedback-control experiment in Protocol 4.

**Performance of the Feedback Controller**

Figure 5A demonstrates the AP regulation by HES obtained from 2 typical animals. The proportional and integral gains of the controller were not altered among the animals (ie, \( K_P=0, K_I=0.005 \)). The white line in the AP trace indicates 2-s moving averaged data. The target AP was set at 20 mmHg below the AP value just before the application of HES. The feedback controller was activated for 10 min, which decreased AP at the target level. The HES command was individualized via the feedback mechanism. In the left panel of Figure 5A, the HES command gradually increased throughout the 10-min regulation. In the right panel of Figure 5A, the HES command was less than unity.
from 1 to 7 min of the 10-min regulation. In this time period, the HES command altered the stimulus frequency rather than the stimulus current.

Mean and mean±SE values of the HES command averaged from 8 animals are shown in the top panel of Figure 5B. There was a large variance in the HES command among the animals, suggesting inter-individual differences in the responsiveness to HES. The target AP was 102.5±5.6 mmHg across the animals. The error signal between the target AP and measured AP disappeared in less than 1 min (Figure 5B, 5B). In each cat, the target AP was set at 20 mmHg below the baseline AP value. The current and frequency of HES were automatically adjusted to keep the AP at the target level.

(B) HES command and the error signal between the target AP and measured AP averaged from 8 cats. The thick and thin lines indicate mean±SE values, respectively.

Figure 5. (A) Results of 10-min feedback control of arterial pressure (AP) by hind-limb electrical stimulation (HES) obtained from 2 cats. The current and frequency of HES were automatically adjusted to keep the AP at the target level.

(B) Effects of sectioning the ipsilateral sciatic nerve on the HES-induced changes in AP. After the severance of the ipsilateral sciatic nerve, HES no longer produced significant hypotension.

Figure 6. (A) Effects of electrical stimulation of the triceps surae muscle (MS) in comparison to hind-limb electrical stimulation (HES). Although muscle twitching was observed, there was no change in arterial pressure (AP) during MS. (B) Effects of sectioning the ipsilateral sciatic nerve on the HES-induced changes in AP. After the severance of the ipsilateral sciatic nerve, HES no longer produced significant hypotension.
Arterial Pressure Control by Hind-Limb Stimulation

The strength and rapidity of the neural effect or the spinal cord in anesthetized cats.

Figure 4B. Right). A similar strategy of selecting the monotonous input–output portion was used in a previous study.12

We quantified the dynamic AP response to HES using a transfer function analysis (Figure 3B), and modeled it by a second-order low-pass filter with a pure dead time (Figure 3C). Once the transfer function is modeled, we could construct a numerical simulator for the feedback controller design (Figure 4A). Because the optimization of control parameters usually requires a number of trials, even if the initial values are selected via classical methods such as the Ziegler–Nichols’ method23 it is impractical to determine optimal parameter values without using the simulator. The simulation results indicated that the integral gain value of 0.005 would provide rapid and stable AP regulation (Figure 4C). Because the controller was designed via intensive simulations, AP was actually controlled at the target level with a small variance (Figure 5B, Bottom). Note that the current and frequency of HES were automatically adjusted and individualized via the feedback mechanism (Figure 5A).

Bionic Strategies Using Neural Interfaces

A framework of treating cardiovascular diseases using neural interfaces is intriguing because the autonomic nervous system exerts powerful influences on the circulatory system. In previous studies, we identified the dynamic characteristics of the arterial baroreflex system and used them to design an artificial vasomotor center. The artificial vasomotor center was able to control AP by stimulating the celiac ganglia in anesthetized rats10,11 or the spinal cord in anesthetized cats12. The strength and rapidity of the neural effect on the cardiovascular system compared with that of the

Discussion

We identified the dynamic input–output relationship between HES and the AP response. By using the model transfer function from HES to AP, we were able to develop a servo-controller that automatically adjusted the HES command to reduce AP at a prescribed target level.

Development of the Feedback Controller

The stimulus current-AP response relationship showed a monotonous decreasing slope (Figure 2C). Because the effect of the pulse width was statistically insignificant, we chose the stimulus current as a primary control variable. The problem with using the stimulus current for the control variable was that a certain threshold current existed between 0 and 1 mA where the AP response to HES became discontinuous. If the stimulus current happened to be feedback controlled near the threshold current, AP showed significant oscillation around the target level (Figure 7, see Appendix B for details). To avoid such a problem related to the threshold current, we set the minimum current to 1 mA (above the threshold current) and used the stimulus frequency as a secondary control variable (Figure 4B).

The stimulus frequency-AP response relationship revealed a valley-shaped curve with the nadir of approximately 10 Hz (Figure 2D). The result is similar to that obtained by stimulating hamstring muscle afferent nerves.26 From the viewpoint of controller design, the valley-shaped input–output relationship is troublesome because the proportional-integral controller only assumes a monotonous input–output relationship.21 To avoid the problem of the valley-shaped input–output relationship, we limited the stimulus frequency to the range from 0 to 10 Hz (Figure 4B, Right). A similar strategy of selecting the monotonous input–output portion was used in a previous study.12

Figure 7. Typical recordings showing failure of controlling the intensity of the hind-limb electrical stimulation during the course of controller development. In this experimental run, only the stimulus current was controlled with a fixed stimulus frequency at 10 Hz. The controller showed on–off type controller behavior once the arterial pressure (AP) approached the target level. The horizontal dashed line indicates the target AP level.

Bottom). The time required for the AP response to reach 90% of the target AP decrease was 38±10 s. Thereafter, the error remained very small until the end of the 10-min regulation. The standard deviation of the steady-state error was 1.3±0.1 mmHg. After the end of the feedback regulation, the error signal gradually returned to approximately 20 mmHg.

Figure 6 represents typical results of the supplemental protocols. Electrical stimulation of the triceps surae muscle (denoted as “MS”) did not change AP significantly in spite of visible twitching of the stimulated muscle, suggesting that the depressor response to HES was not the outcome of the direct muscle stimulation (Figure 6A). Sectioning the ipsilateral sciatic nerve abolished the depressor effect of HES, suggesting that somatic afferent signals were delivered through the sciatic nerve to the central nervous system during HES (Figure 6B).
humoral effect make the neural interventions desirable for the rapid and stable restoration of AP against acute disturbances such as those induced by postural changes. Gotoh et al demonstrated that a direct neural interface to the rostral ventrolateral medulla also enabled rapid and stable restoration of AP during nitroprusside-induced hypotension in conscious rats. The bionic system to control AP has also been applied in human subjects.

Although the aforementioned bionic systems aimed to maintain AP against acute hypotension by increasing sympathetic nerve activity and sympathoinhibition might also be required for the treatment of cardiovascular diseases accompanying sympathetic overactivity. Baroreceptor activation is one of the potential sympathoinhibitory neural modulations. In the present study we only demonstrated a framework of short-term AP control by HES. With a development of proper implanting electrodes, however, we might be able to control AP chronically using HES. Although carotid sinus baroreceptor stimulation has a potential to treat drug-resistant hypertension it could activate peripheral chemoreflex by stimulating carotid bodies. HES might circumvent such unintentional chemoreflex activation. Another clinical implication will be the treatment of chronic heart failure. Although the vagal effect of HES was not evaluated in the present study, acupuncture stimulation might facilitate cardiac vagal activity. Because chronic intermittent vagal nerve stimulation increased the survival of chronic heart failure rats, chronic intermittent HES might be used as an alternative method of direct vagal nerve stimulation for the treatment of chronic heart failure.

Study Limitations

First, we did not identify the mechanism of HES. Because sectioning of the ipsilateral sciatic nerve abolished the AP response to HES (Figure 6B), somatic afferent is involved in the effect of HES. In a series of studies, Chao et al and Li et al demonstrated that electroacupuncture-activated group III and IV fibers in the median nerves and inhibited sympathetic outflow via activation of µ- and δ-opioid receptors in the rostral ventrolateral medulla. Whether a similar mechanism underlies in the rapid-onset and short-lasting effect of HES awaits further studies.

Second, we used pentobarbital anesthesia. Although peripheral neurotransmissions of norepinephrine and acetylcholine can be assessed under the same anesthesia because pentobarbital can suppress many neurotransmitters in the central nervous system, anesthesia might compromise the HES effect. Further studies are required to establish the utility of HES in awake conditions.

Third, we set the proportional gain of the controller at zero to avoid pulsatile changes in the HES command. However, other approaches such as that using a low-passed signal of measured AP as a controlled variable might also be effective to avoid the pulsatile variation in the HES command.

Finally, a development of implanting electrodes is the prerequisite for chronic use of HES. Intramuscular electrodes used in functional electrical stimulation might be used for HES but further refinements are clearly needed regarding the positioning of electrodes including the depth of implantation.

In conclusion, we identified the dynamic characteristics of the AP response to acupuncture-like HES and demonstrated that a servo-controlled HES system was able to reduce AP at a prescribed target level. Although further studies are required to identify the mechanism of HES to reduce AP, acupuncture-like HES would be an additional modality to exert a quantitative depressor effect on the cardiovascular system.

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References


Appendix A
Framework of the Feedback Controller
Figure 4A is a simplified block diagram of the feedback controller system used in the present study. The controller was based on a proportional-integral controller\textsuperscript{23–25}. \( G(f) \) represents the transfer function of the controller.
\[
G(f) = -K_p \frac{1}{1 + j \omega T} \text{ (A1)}
\]
where \( K_p \) and \( T \) denote proportional and integral gains, respectively. \( j \) represents the imaginary unit. Negative signs for the proportional and integral gains compensate for the negative input–output relationship between HES and the AP response. \( H(f) \) represents a model transfer function from HES to AP determined from Protocol 3. The measured AP can be expressed as:
\[
AP_{measured}(f) = H(f)HE(f) + AP_{noise}(f) \text{ (A2)}
\]
where \( AP_{noise}(f) \) is the AP fluctuation such as that associated with changes in animal conditions. The controller compares the measured AP with the target AP, and adjusts the HES command to minimize the difference between them according to the following equation:
\[
HES(f) = G(f)[AP_{target}(f) - AP_{measured}(f)] \text{ (A3)}
\]
By eliminating \( HES(f) \) from the equations A2 and A3, the overall controller characteristics are described as:
\[
AP_{measured}(f) = \frac{G(f)H(f)}{1 + G(f)H(f)} \text{AP}_{target}(f) + \frac{1}{1 + G(f)H(f)} \text{AP}_{noise}(f) \text{ (A4)}
\]
The equation A4 indicates that if \( G(f) \) is properly selected so that \( G(f)H(f) \) becomes by far greater than unity, the measured AP approaches the target AP whereas the noise term is significantly attenuated over the frequency range of interest.

Appendix B
Problem with the Threshold Current
We tried to adjust the intensity of HES by the stimulus current alone. When the stimulus current happened to be feedback controlled near a threshold current, however, the controller showed an on–off type controller behavior around the target AP level, as shown in Figure 7. At time zero, the controller was activated. The stimulus current increased to approximately 2.7 mA in the beginning and then decreased to a value below 1 mA, accompanying the AP reduction around a target level (a horizontal dashed line). However, the stimulus current and AP did not stabilize. Because the AP response was discontinuous at the threshold current (ie, the depressor effect of HES was abruptly turned on and off), the controller could not adjust the stimulus current in a continuous manner. To avoid this kind of on–off type controller behavior, we introduced the stimulus frequency as the secondary control variable (Figure 4B).