Bionic epidural stimulation restores arterial pressure regulation during orthostasis

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Yanagiya, Yusuke, Takayuki Sato, Toru Kawada, Masashi Inagaki, Teiji Tatewaki, Can Zheng, Atsunori Kamiya, Hiroshi Takaki, Masaru Sugimachi, and Kenji Sunagawa. Bionic epidural stimulation restores arterial pressure regulation during orthostasis. J Appl Physiol 97: 984–990, 2004. First published May 7, 2004; 10.1152/japplphysiol.00162.2004.—A bionic baroreflex system (BBS) is a computer-assisted intelligent feedback system to control arterial pressure (AP) for the treatment of baroreflex failure. To apply this system clinically, an appropriate efferent neural (sympathetic vasomotor) interface has to be explored. We examined whether the spinal cord is a candidate site for such interface. In six anesthetized and baroreflex-deafferentiated cats, a multielectrode catheter was inserted into the epidural space to deliver epidural spinal cord stimulation (ESCS). Stepwise changes in ESCS rate revealed a linear correlation between ESCS rate and AP for ESCS rates of 2 pulses/s and above ($\tau^2$, 0.876–0.979; slope, 14.3 ± 5.8 mmHg·pulses$^{-1}$·s$^{-1}$·s; pressure axis intercept, 35.7 ± 25.9 mmHg). Random changes in ESCS rate with a white noise sequence revealed dynamic transfer function of peripheral effectors. The transfer function resembled a second-order, low-pass filter with a lag time (gain, 16.7 ± 8.3 mmHg·pulses$^{-1}$·s$^{-1}$; natural frequency, 0.022 ± 0.007 Hz; damping coefficient, 2.40 ± 1.07; lag time, 1.06 ± 0.41 s). On the basis of the transfer function, we designed an artificial vasomotor center to attenuate hypotension. We evaluated the performance of the BBS against hypotension induced by 60° head-up tilt. In the cats with baroreflex failure, head-up tilt dropped AP by 37 ± 5 mmHg in 5 s and 59 ± 11 mmHg in 30 s. BBS with optimized feedback parameters attenuated hypotension to 21 ± 2 mmHg in 5 s ($P < 0.05$) and 8 ± 4 mmHg in 30 s ($P < 0.05$). These results indicate that ESCS-mediated BBS prevents orthostatic hypotension. Because epidural stimulation is a clinically feasible procedure, this BBS can be applied clinically to combat hypotension associated with various pathophysiological conditions.

baroreceptors; blood pressure; autonomic nervous system; Shy-Drager syndrome; orthostatic hypotension

THE ARTERIAL BAROREFLEX SYSTEM configures a negative feedback system and reduces arterial pressure (AP) disturbances from external influences (9, 15, 22, 23). Sudden onset of hypotension by orthostatic change occurs as a result of baroreflex failure, despite normal functioning of the cardiovascular system and efferent sympathetic nervous system. This condition is seen in multiple-system atrophy (Shy-Drager syndrome) (21, 22, 30) as well as spinal cord injuries (7, 17). Current treatments, such as salt loading (19, 33), cardiac pacing (1, 14), and pharmacological interventions (2, 3, 12, 20), fail to prevent the orthostatic hypotension. These therapies often result in an unwanted increase in AP in the supine position and neither restore nor reproduce the function of the feedback system that forms the basis of AP control (See DISCUSSION).

Previously, our laboratory developed a bionic baroreflex system (BBS) that substitutes the defective vasomotor center with an artificial controller (i.e., an artificial vasomotor center) to restore the native baroreflex function (24, 26). In these animal studies, the celiac ganglion was exposed by laparotomy and stimulated directly as the efferent neural interface in the BBS. However, for clinical application of the BBS, a less invasive and more stable electrical stimulation method is required.

In the present study, we examined the hypothesis that the spinal cord is a candidate site for the efferent neural interface in our bionic strategy. Epidural spinal cord stimulation (ESCS) has been used for the management of patients with malignant neoplasm, angina pectoris, and peripheral ischemia (6, 29). Stimulating the dorsal part of the spinal cord changes sympathetic nerve activity, AP in animals (11, 32) and heart rate in humans (18). If we can delineate how ESCS affects AP quantitatively, then this may lead to clinical application of the BBS. We studied the feasibility of ESCS-mediated BBS using an animal model of central baroreflex failure.

MATERIALS AND METHODS

Study design. BBS is a negative feedback system and consists of two components: peripheral effectors and the artificial vasomotor center (Fig. 1). Peripheral effectors change AP in response to ESCS. The artificial vasomotor center (controller) determines the ESCS rate in response to changes in AP. Using BBS, we computer programmed the artificial vasomotor center and substituted the defective vasomotor center with an artificial vasomotor center. For this purpose, we first characterized the static as well as dynamic responses of the peripheral effectors. With this knowledge, we then designed an artificial vasomotor center using simulation to delineate the parameters for obtaining optimal AP response. Finally, we evaluated the performance of the ESCS-mediated BBS in cats during orthostatic AP changes.

Animals and surgical procedures. Animals were cared for 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 adult cats of either sex, weighing...
The spinal levels were selected to be computer programmed as needed. Pd, pressure disturbance to AP.

1.6 pulses/s and above, there is a linear relationship (r = 0.979 (median, 0.959) slope, 14.3–26, 31). The following protocols were performed by sending ESCS command to the stimulator, as calculated by the transfer function from ESCS rate to AP was calculated as a quotient of the rate power. The transfer function was calculated up to 0.5 Hz with a resolution of 0.0098 Hz. We parameterized the transfer function by using an iterative, nonlinear, least squares fitting technique (10).

**Results**

Figure 2A is a representative example of static AP response to stepwise ESCS changes. Stepwise increases of ESCS rate produced a depressor response initially at low-ESCS rate and a pressor response at higher rates, and subsequent decreases of ESCS rate produced almost perfect reversal of AP changes. The relationship between AP and ESCS rate appeared nonlinear as a whole (Fig. 2B, top). However, for ESCS rates of 2 pulses/s and above, there is a linear relationship (r² = 0.964, AP = 16.0 × ESCS + 44.0, so = 3.2 pulses/s; Fig. 2B). A linear relationship during ESCS was found in all animals (r², 0.876–0.979 (median, 0.959) slope, 14.3 ± 5.8 mmHg; pulses⁻1; pressure axis intercept, 35.7 ± 25.6 mmHg; so, 4.9 ± 2.5 pulses/s). The following protocols were performed by using this linear ESCS range.

Figure 3A is a representative example of dynamic AP response to ESCS. We selected low- and high-stimulation rates that produced depressor and pressor responses, respectively.
and stimulated the spinal cord, according to a binary white noise sequence. AP did not respond to fast changes in ESCS rate, but appeared to respond to slower changes, increasing with high-rate stimulation and decreasing with low-rate stimulation. The estimated transfer function indicated low-pass filter characteristics. Figure 3B shows the averaged transfer function from ESCS rate to AP in six animals. The gain decreased as the frequency increased and was attenuated to one-tenth of the lowest frequency at 0.1 Hz. The phase approached zero radian at the lowest frequency, reflecting in-phase changes of ESCS rate and AP. The parameters obtained by the least squares fitting to the second-order, low-pass filter model are as follows: dynamic gain = 16.7 ± 8.3 mmHg·pulses⁻¹·s, natural frequency = 0.022 ± 0.007 Hz, damping coefficient = 2.40 ± 1.07, and lag time = 1.06 ± 0.41 s. The dynamic gain was much higher than the gain at the lowest frequency in the transfer function (Fig. 3A) but comparable to the slope obtained in the static protocol. The coherence function was close to unity between 0.01 and 0.4 Hz, indicating that the input-output relation was governed by almost linear

Fig. 3. A: representative example of dynamic AP response to ESCS. B: averaged transfer functions from ESCS rate to AP, i.e., G_{p} (gain and phase) and coherence function (Coh). C: estimated step response (resp) computed from the transfer function. Data are expressed as means ± SD for 6 cats.
dynamics in this range. To facilitate better understanding of the dynamic AP response to ESCS, the step functions were calculated by time integral of the inverse Fourier transform of the transfer functions. The estimated step functions are averaged and shown in Fig. 3C. An initial time lag and overdamped slow AP response to unit step ESCS are evident. The time courses of the estimated step functions were almost identical to but smoother than those of the actually observed AP responses to stepwise ESCS changes, indicating the ability to cancel out noises by the white noise method.

Figure 4 is a representative example of how we designed the vasomotor center transfer function. The steady-state gain is determined simply to match a total baroreceptor gain of 3.8-fold and reassessed the efficacy of BBS. As a result, AP returned to the predetermined target (Fig. 5, right; AP fall, 19 mmHg in 5 s, 7 mmHg in 30 s).

Figure 6 summarizes the results obtained from six cats, demonstrating the effectiveness of the BBS performance. In the cat model of baroreflex failure, HUT decreased AP by 37 ± 5 mmHg in 5 s and by 59 ± 11 mmHg in 30 s. In animals with simulation-based vasomotor center, the initial attenuation (AP fall: 32 ± 7 mmHg in 5 s) was not significant, and the steady-state attenuation (17 ± 8 mmHg in 30 s) did not satisfy the predetermined target. On the other hand, in animals with gain-adjusted vasomotor center (2.4 ± 1.1-fold increase), the BBS achieved both initial and the steady-state targets (21 ± 2 mmHg in 5 s, P < 0.05; 8 ± 4 mmHg in 30 s, P < 0.05).

**DISCUSSION**

The present results indicate that AP can be controlled by ESCS and that ESCS-mediated BBS prevents orthostatic hypotension in anesthetized cats. Although the BBS based on simulation alone did not work as predicted during HUT gain adjustments of the vasomotor center achieved quick and stable restoration of AP.

**Necessity of BBS for treatment of central baroreflex failure.** Conventional treatments for central baroreflex failure aim at increasing AP. Although they alleviate the hypotension to the extent of preventing syncope, they have adverse effects of causing supine hypertension and enhancing the risk of hypertensive organ disease. Recently, Shannon et al. (28) suggested well-timed water consumption as a treatment for orthostatic hypotension in patients with autonomic failure. Their strategy is superior to conventional treatments because it prevents AP fall if predicted in advance. However, at least a few minutes are necessary for their method to increase AP. This time lag makes it impossible to control AP against sudden or unpredictable AP

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**Figure 4.** Representative example of designing the \( G_c \).

**A:** schematic diagram of the method of designing the \( G_c \). AP changes in the presence of \( P_d \) were simulated by changing the corner frequency \( f_c \) for derivative characteristic in the \( G_c \). **B:** simulation results of this example. A vasomotor center with \( f_c \) of 0.02 Hz restores AP with sufficient speed and stability (center).

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fall. None of the treatments attempted so far can prevent sudden orthostatic hypotension because the dynamics of the baroreflex remain impaired.

In contrast, the BBS continuously monitors and controls AP to achieve quick restoration of AP. Because AP is increased via sympathetic pathways, the AP response to the BBS vasomotor center command is as fast as that to the native vasomotor center control. Therefore, the quick, adequate, and stable nature of the native baroreflex system can be restored by the BBS with appropriate settings of the artificial vasomotor center.

Designing the vasomotor center transfer function and parameter adjustments. In a negative feedback system, closed-loop responses to external perturbation are dependent on the dynamic characteristics of the total open-loop transfer function. We assumed that the derivative characteristics in cats are identical to those in rabbits or rats, which have been delineated previously (10, 13, 25). We optimized gain and derivative parameters for each cat so that both speed and stability were achieved.

In animal experiments, however, the simulation results were not fully reproduced. Gain adjustments of the vasomotor center were necessary to attain quick and sufficient attenuation of the AP fall. This discrepancy cannot be explained without considering a possible slope decrease or nonlinearity in peripheral effector characteristics (AP-ESCS relationship) caused by the HUT, or both. Pooling of blood volume in the splanchnic and hindlimb circulation would be a cause for such attenuated AP response. If AP responses during posture change can be de-

Fig. 5. Representative example of real-time application of the BBS during head-up tilt (HUT). Left: in the cat with baroreflex failure, ESCS rate was fixed at 5.0 pulse/s. HUT produced a rapid and then progressive fall in AP. Middle: simulation-based BBS (BBS-sim) attenuated the AP fall but did not attain the predetermined target. Right: gain adjustment of the vasomotor center (BBS-adj) resulted in quick and sufficient attenuation of AP fall (see text for detail). Vertical bars indicate the ranges of predetermined targets.

Fig. 6. Summarized results of HUT obtained from 6 cats. A: averaged time courses of AP responses to HUT in cats with baroreflex failure (top) and with BBS (middle and bottom). Using the parameters determined from simulation, we found that the BBS (BBS-sim) did not adequately attenuate hypotension in all cats (middle). Appropriate gain increase (BBS-adj) was necessary for quick and sufficient attenuation of hypotension (bottom). B: changes in AP produced by HUT. Data are expressed as means ± SD. *P < 0.05 compared with baroreflex failure.
fined quantitatively, then a more elaborate artificial vasomotor center can be developed that automatically adjusts the parameters. Automated adjustments may also be accomplished with adaptive control systems that execute real-time system identification and self-tuning of controller. The present study suggests the necessity of such manipulation of the vasomotor center settings.

**Pressor and depressor responses by ESCS.** We demonstrated both depressor and pressor responses in AP to ESCS with a linear range (Fig. 2). Earlier studies have shown that dorsal column stimulation produces pressor and depressor responses. Depressor response is produced by a group of dorsal column fibers that project to the dorsal nuclei at the level of C₈ to L₁ and transmit to the fibers that ascend through the dorsal spinocerebellar tracts (4, 27, 32). Pressor response is produced by another group of fibers that ascend or descends through the terminal zone and enter the gray matter. Some of these fibers project to the intermedial lateral columns to activate sympathetic presynaptic fibers. AP responses to ESCS observed in the present study are the results of compound responses in these multiple pathways. Nevertheless, controllability of AP by the BBS is ascertained by a clear linearity between ESCS and AP response in both static and dynamic relationships.

Although we have not confirmed it in the closed-loop condition, depressor response shown in the open-loop condition indicates that ESCS-mediated BBS can attenuate hypertension as well as hypotension. Because an offset ESCS rate (sₒ) is applied in the absence of pressure disturbance, lowering ESCS rate would attenuate hypertension to some extent. AP in conscious animals fluctuates between hypertension and hypotension, even in a quiet position (5). The speed of AP restoration is considered sufficient to control these fluctuations.

**Future step for clinical application.** Clearly, the next step toward clinical application is to demonstrate the safety and the effectiveness of the ESCS-mediated BBS during orthostasis in conscious patients and animals. To study BBS in conscious animals, we have been developing an implantable hardware that enables BBS. Elaboration of such devices is mandatory for its future clinical application by searching the optimal stimulating site and condition that do not cause uncomfortable sensation and muscle twitch. A control algorithm must be developed that overcomes the problem revealed in the present study. The developing implant would be as small and low power as a pacemaker, with the aid of recent LSI technologies, and would be telemetrically programmable. In parallel, we began collaboration with a clinical group to develop ESCS-mediated BBS to suppress sudden hypotension in anesthetized humans during surgery. This study would prove the feasibility of human BBS.

Finally, new methods for long-term manometry are definitely required. Intravascular manometry can be achieved only with long-lasting antithrombotic material. Other indirect methods should be used until we are confident in antithrombotic ability.

**Conclusions.** As a step toward clinical application of BBS, we demonstrated that AP could be controlled with ESCS. We designed the artificial vasomotor center based on the dynamic characteristics of AP response to ESCS. Although there was a dissociation between the predicted and actual attenuation of AP fall, ESCS-mediated BBS with appropriate gain adjustment was capable of preventing HUT-induced hypotension rapidly, sufficiently, and stably.

**APPENDIX**

**Simulation of AP Restoration and Implementation by the Artificial Vasomotor Center**

We modeled the vasomotor center transfer function (Gₚ) as

\[ Gₚ(f) = KCₑ \left( \frac{1 + \frac{f}{f_c}}{1 + \frac{f}{f_d}} \right) \exp(-2\pi fLₑ) \]

(A1)

where \( f \) is frequency, \( K \) is the steady-state gain of the artificial vasomotor center, \( f_c \) is \( f \) for derivative characteristics, \( f_d \) and \( f_{c3} \) are corner frequencies for high-cut characteristics, \( j \) is an imaginary unit, and \( Lₑ \) is a pure delay. The value \( f_c \) was set to 10 × \( f_c \), and \( f_{c3} \) was set to 1 Hz. These settings attenuate AP pulsation and preserve total baroreflex gain (13). \( Lₑ \) was introduced to simulate the possible time delay of 0.1 s in transforming AP to ESCS rate but was excluded in real-time application to improve AP stability.

The simulation was performed as follows. The block diagram in Fig. 4A is represented as

\[ AP = Gₑ \cdot ESCS + Pₛ \]

where \( Gₑ \) is transfer function of the peripheral effectors, and \( Pₛ \) is pressure disturbance to AP. Rearranging these formula yields

\[ AP = Gₑ \cdot Gₑ \cdot AP + Pₛ \]

(A2)

The time domain representation of Eq. A2 is

\[ ΔAP(t) = fg(τ) \cdot ΔAP(t - τ)dτ + Pₛ(t) \]

(A3)

where \( ΔAP(t) \) is AP change from control value, and \( g(τ) \) is the impulse response function of the total open-loop transfer function \( Gₑ(Gₑ-Gₑ) \). To simulate orthostatic hypotension, \( P₅(t) \) is set as an exponential AP fall to −60 mmHg with a time constant of 5 s rather than a stepwise fall (see Fig. 6A, top). We simulated the transient AP response to depressor stimulus while changing \( f_{c1} \) in the presence of the negative feedback system.

To implement the designed vasomotor center transfer function, we programmed the artificial vasomotor center to calculate ESCS rate in response to AP changes, according to the following equation:

\[ ESCS(t) = fh(τ) \cdot ΔAP(t - τ)dτ + sₒ \]

where \( h(τ) \) is the impulse response function of the designed vasomotor center transfer function, \( ΔAP(t) \) is AP change from the control value, and \( sₒ \) is the offset ESCS rate obtained from the static parameterization.

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