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Artificial Baroreflex

Clinical Application of a Bionic Baroreflex System

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Background—We proposed a novel therapeutic strategy against central baroreflex failure: implementation of an artificial baroreflex system to automatically regulate sympathetic vasomotor tone, ie, a bionic baroreflex system (BBS), and we tested its efficacy in a model of sudden hypotension during surgery.

Methods and Results—The BBS consisted of a computer-controlled negative-feedback circuit that sensed arterial pressure (AP) and automatically computed the frequency (STM) of a pulse train required to stimulate sympathetic nerves via an epidural catheter placed at the level of the lower thoracic spinal cord. An operation rule was subsequently designed for the BBS using a feedback correction with proportional and integral gain factors. The transfer function from STM to AP was identified by a white noise system identification method in 12 sevoflurane-anesthetized patients undergoing orthopedic surgery involving the cervical vertebrae, and the feedback correction factors were determined with a numerical simulation to enable the BBS to quickly and stably attenuate an external disturbance on AP. The performance of the designed BBS was then examined in a model of orthostatic hypotension during knee joint surgery (n=21). Without the implementation of the BBS, a sudden deflation of a thigh tourniquet resulted in a 17 ± 3 mm Hg decrease in AP within 10 seconds and a 25 ± 2 mm Hg decrease in AP within 50 seconds. By contrast, during real-time execution of the BBS, the decrease in AP was 9 ± 2 mm Hg at 10 seconds and 1 ± 2 mm Hg at 50 seconds after the deflation.

Conclusions—These results suggest the feasibility of a BBS approach for central baroreflex failure. (*Circulation*. 2006; 113:634-639.)

Key Words: baroreceptors ■ blood pressure ■ computers ■ electrical stimulation ■ nervous system, sympathetic

The arterial baroreflex acts to maintain cerebral perfusion by quickly attenuating the effect of an external disturbance, such as the assumption of an upright position, on arterial pressure (AP).¹⁻⁴ Therefore, functional restoration of dynamic properties of the arterial baroreflex is essential for the treatment of patients with various syndromes of baroreflex failure,⁵ including Shy-Drager syndrome,⁶⁻⁹ baroreceptor deafferentation,^{10,11} and traumatic spinal cord injuries.^{12,13} However, most commonly used interventions, including salt loading,^{14,15} cardiac pacing,^{16,17} and adrenergic agonists,^{18,19} can neither restore nor reproduce the functioning of the native vasomotor center, and most affected patients remain bedridden.

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We recently developed a framework for identifying an operational rule of the vasomotor center and a prototype of a bionic baroreflex system (BBS) in rats.²⁰⁻²² The BBS consisted of a negative-feedback system controlled by a computer (ie, the artificial vasomotor center) that sensed AP and automatically computed the frequency of a pulse train re-

quired to stimulate sympathetic efferent nerves through a pair of wire electrodes placed in the celiac ganglion. Previous experimental work demonstrated that the BBS restored native baroreflex function in rats with central baroreflex failure; however, an applicable neural interface with quick and effective controllability of AP is required for application of this technology in the clinical setting. The goal of the present study was to determine the efficacy of a novel bionic technology for the intraoperative restoration of AP in the context of central baroreflex failure and to validate this technology in a clinical model of orthostatic hypotension.

Methods

All studies were approved by the institutional review committee, and all subjects gave informed consent.

Theoretical Considerations

As previously described,²⁰⁻²² the principle of the BBS is based on a negative-feedback mechanism (Figure 1). The instantaneous AP is measured by a pressure transducer connected to a computer that functions as a controller or artificial vasomotor center. Instead of the disabled native vasomotor center, the controller automatically exe-

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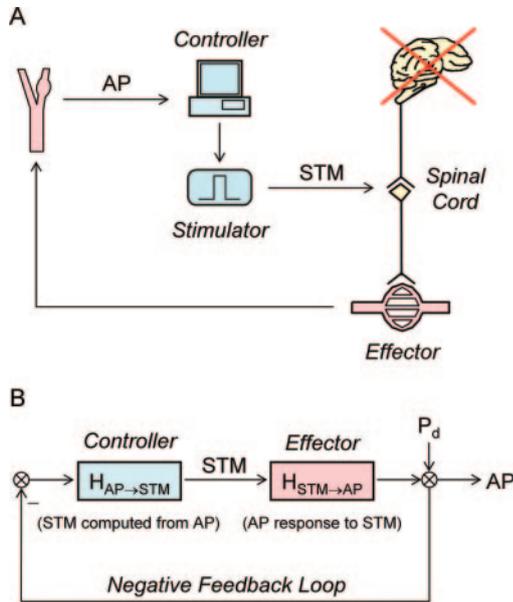


Figure 1. Schematic illustration (A) and block diagram (B) of a BBS. In the context of central baroreflex failure, the BBS automatically computes the frequency (STM) of a pulse train to stimulate sympathetic nerves through an epidural catheter placed at the level of lower thoracic spinal cord, while simultaneously sensing the change in AP. $H_{AP \rightarrow STM}$ denotes a transfer function for the controller functioning as an artificial vasomotor center. $H_{STM \rightarrow AP}$ is a transfer function showing the dynamic response of AP to STM. The overall transfer function of the BBS is given by $H_{AP \rightarrow STM} \times H_{STM \rightarrow AP}$. Therefore, the effect of an external disturbance (P_d) on AP is attenuated to $1/(1 + H_{AP \rightarrow STM} \times H_{STM \rightarrow AP})$.

cutes real-time operations that determine the frequency of electrical stimulation (STM) required to minimize the effect of an external disturbance (P_d) on AP and then commands an electrical stimulator to deliver a stimulus of the same frequency to the vasomotor sympathetic nerves via epidural-catheter electrodes placed at the lower thoracic level of the spinal cord. The lower thoracic level was selected as the site for the neural interface of the BBS because the abdominal splanchnic vascular bed is a major effector mechanism for the arterial baroreflex.^{23–25}

According to a classic feedback-control theory, ie, feedback correction with proportional and integral gain factors,^{26,27} the following algorithm was used to program the controller for the calculation of STM in the frequency domain:

$$(1) \quad H_{AP \rightarrow STM} = K_p + \frac{K_i}{2\pi f j}$$

where $H_{AP \rightarrow STM}$ is a transfer function from AP to STM, K_p is the proportional correction factor, K_i is the integral correction factor, and j is the imaginary unit. The proportional factor determines the feedback amplification based on the absolute value of the instantaneous control error due to P_d , and the integral factor adjusts the feedback amplification based on the cumulative value of the instantaneous control error. Therefore, STM is computed as follows:

$$(2) \quad STM = -AP \cdot H_{AP \rightarrow STM}$$

and AP is also expressed as follows:

$$(3) \quad AP = STM \cdot H_{STM \rightarrow AP} + P_d$$

where $H_{STM \rightarrow AP}$ denotes the frequency response of AP to STM. From Equations 2 and 3, the effect of P_d on AP is estimated as follows:

$$(4) \quad AP = \frac{1}{1 + H_{AP \rightarrow STM} \cdot H_{STM \rightarrow AP}} P_d$$

Thus, if $H_{AP \rightarrow STM} \cdot H_{STM \rightarrow AP}$ is far larger than unity, the BBS can nullify the effect of P_d on AP.

Subjects and Experimental Protocols

A total of 33 patients (46 to 84 years old, 19 males) who underwent orthopedic operations were enrolled in the present study. Ten patients had hypertension, and 4 had diabetes mellitus. None of the subjects had frequent ectopic beats or atrial fibrillation. After induction anesthesia with propofol, an endotracheal tube was introduced orally. The patients were mechanically ventilated with 67% nitrous oxide and 1.5% to 2% end-tidal sevoflurane in oxygen during experimental protocols, while end-tidal carbon dioxide was maintained at 35 to 38 mm Hg. An arterial catheter was placed in the radial artery for AP measurement. To record central venous pressure (CVP), a central venous catheter was placed in the femoral vein, and the tip of the catheter was advanced into the inferior vena cava just above the diaphragmatic level. Furthermore, an epidural catheter was placed percutaneously, and the tip, which contained a pair of electrodes (Unique Medical, Tokyo; interelectrode distance 15 mm), was placed at the level of Th_{9-11} . Placement of the central venous catheter and the epidural catheter was verified by chest radiograph.²⁸

Before making an incision of affected areas, we performed 2 different protocols in separate groups of patients. In the first group of patients ($n=12$, 46 to 76 years old, 7 males) undergoing operations for cervical spondylosis and canal stenosis, the averaged $H_{STM \rightarrow AP}$ was estimated and the $H_{AP \rightarrow STM}$ was designed parametrically with Equation 1 to minimize the effect of P_d on AP. After we programmed the designed $H_{AP \rightarrow STM}$ into the computer, the efficacy of the BBS was tested against the rapid progressive hypotension induced by use of a thigh tourniquet^{29–31} in the second group of patients ($n=21$, 64 to 84 years old, 12 males) undergoing operation for knee joint osteoarthritis. During each protocol, the muscle twitches induced by spinal cord stimulation were prevented by the intravenous administration of vecuronium bromide. Analgesia for the pain provoked by spinal cord stimulation and tourniquet inflation was provided by intravenous injection of fentanyl citrate. In a preliminary study, the validity of the analgesic preparation was confirmed for the experimental protocols, and the safety of spinal cord stimulation for 20 minutes was verified.

Estimation of Transfer Function From STM to AP

To characterize the dynamic nature of the AP response to STM, ie, $H_{STM \rightarrow AP}$, the lower thoracic sympathetic nerves were randomly stimulated for 15 minutes while we recorded AP. According to a white noise method for system identification, the STM was altered between 0 and 20 Hz every 4 seconds. The pulse width of electrical stimuli was fixed at 0.1 ms. The stimulation current was adjusted for each patient so as to produce a pressor response of ≈ 10 mm Hg at 20 Hz. This resulted in an average current of 15 ± 4 (mean \pm SD) mA. The electrical signals of STM and AP were digitized at 100 Hz. As described previously,^{20–22} the transfer function from STM to AP, $H_{STM \rightarrow AP}$, was estimated with a fast Fourier transform algorithm. Finally, the average of $H_{STM \rightarrow AP}$ among 12 patients was calculated.

Design of Artificial Vasomotor Center

With substitution of the averaged $H_{STM \rightarrow AP}$ for Equation 4, the instantaneous AP response to P_d was simulated numerically, and a stepwise decline with an amplitude of 20 mm Hg was imposed on the BBS. While the feedback parameters of $H_{AP \rightarrow STM}$, ie, K_p and K_i , were altered, the effect of the parameters on the AP response was investigated. Finally, the parameters that enabled the BBS to quickly and stably minimize the effect of P_d on AP were determined.

Efficacy of BBS in a Clinical Model of Transient Hypotension

The performance of the BBS was evaluated in a clinical model of rapid transient hypotension ($n=21$). Rapid hypotension was evoked by the sudden deflation of a thigh tourniquet, which is widely used to achieve bloodless dissection during total knee arthroplasty.^{29–31} Acute hypotension immediately after tourniquet release is a well-

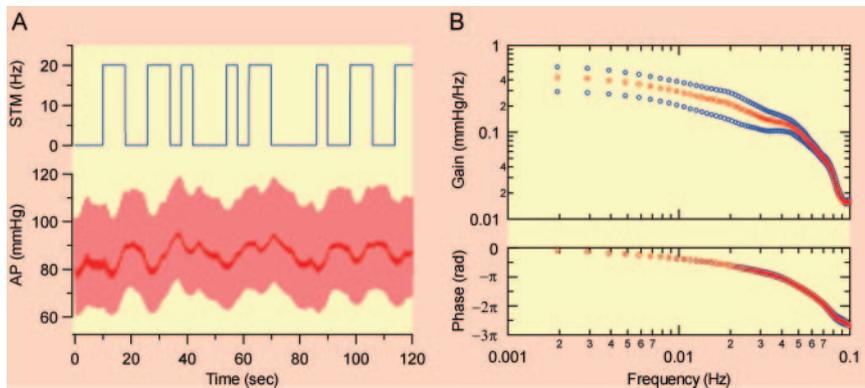


Figure 2. A, Representative example of time series data of the response of AP to random stimulation of the lower thoracic spinal cord. According to quasi-white noise, the STM was randomly altered between 0 and 20 Hz. The AP seems to slowly respond to STM with a delay. B, Transfer function of the AP response to the STM change. Data are expressed as mean \pm SD for 12 patients. rad indicates radians. See text for explanation.

known phenomenon that results from a rapid decrease in peripheral vascular resistance and an increase in venous pooling in the affected limb.²⁹ The degree of hypotension can be potentiated by the use of volatile anesthetic agents such as sevoflurane, which are central depressants of arterial baroreflex function.^{32,33} Therefore, tourniquet-related hypotension during sevoflurane anesthesia can be used as a model of orthostatic hypotension in central baroreflex failure.

Briefly, a tourniquet was applied to the upper femur and inflated at 300 mm Hg for 60 minutes and then quickly deflated for 10 minutes. The procedure was then repeated. The BBS was activated during 1 of the 2 trials of tourniquet-related hypotension, and the electrical signals of STM, CVP, and AP were digitized at 100 Hz.

Statistical Analysis

The hemodynamic responses to tourniquet release were measured for each subject while the BBS was being activated and inactivated. The effects of the BBS execution on the hemodynamic changes at 10, 50, and 100 seconds after tourniquet release were analyzed by paired *t* tests with Bonferroni adjustment. Differences were considered significant at overall $P < 0.05$.

Results

A representative example of original tracings of STM and AP during random stimulation of the spinal cord is shown in Figure 2A. Random on-off change in STM produced a delayed and slow change in AP. The relationship between STM and AP was quantitatively characterized by the frequency domain analysis (Figure 2B). The averaged transfer

function from STM to AP, $H_{STM \rightarrow AP}$, had low-pass characteristics with a corner frequency of 0.06 Hz. The gain factor was 0.43 ± 0.13 mm Hg \cdot Hz⁻¹ at the steady state (lowest frequency) and gradually decreased with input frequency. The phase spectrum showed that the input-output relationship was in phase and that the phase delay increased toward higher frequencies. The squared coherence, a measure of linear dependence between STM and AP, was >0.9 in the frequency range of interest (data not shown).

The results of simulation for the design of the artificial vasomotor center, $H_{AP \rightarrow STM}$, are presented in Figure 3. The AP responses to the external disturbance P_d were simulated under 12 different combinations with feedback correction factors. Without feedback compensation, ie, when both feedback correction factors were zero, there was no attenuation of the effect of the external disturbance on AP. Therefore, AP fell by 20 mm Hg immediately after the imposition of P_d (Figure 3A, black line). By contrast, if either or both of the correction factors were too large, the underdamped oscillatory response of AP appeared, and the BBS became unstable. On the basis of these results, K_p was set at 1, and K_i was set at 0.1, so that the BBS could quickly and effectively attenuate the effect of the external disturbance (Figure 3B, red line).

A representative example of the results of the performance tests of the BBS is shown in Figure 4A. A sudden

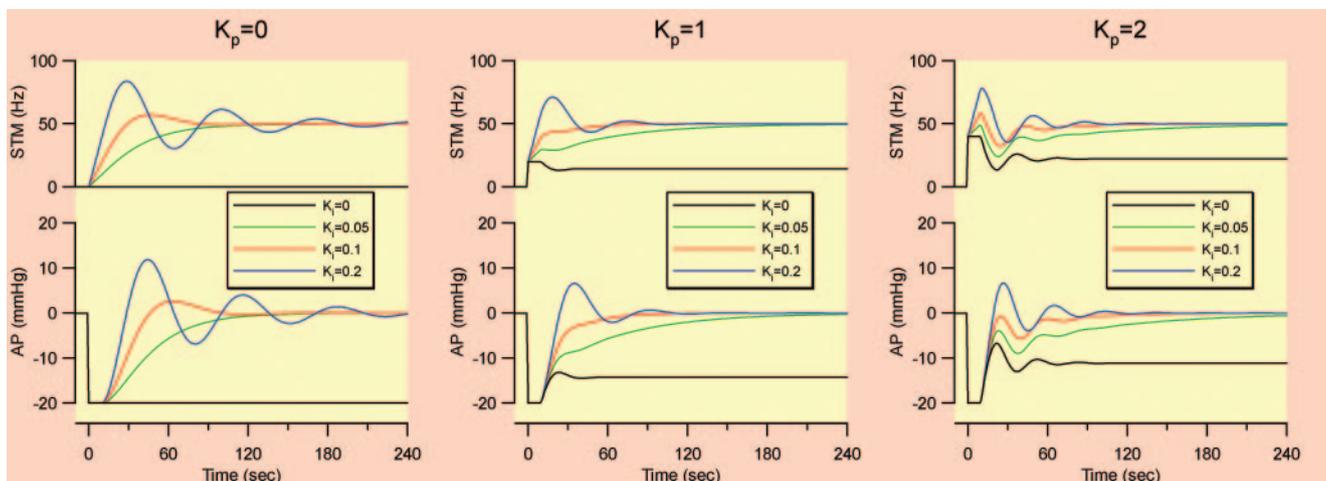


Figure 3. Numerical simulations of a feedback controller of the BBS. A stepwise pressure decline with an amplitude of 20 mm Hg is assumed to be imposed. Results are shown for 12 combinations of proportional (K_p) and integral (K_i) correction factors. See text for explanation.

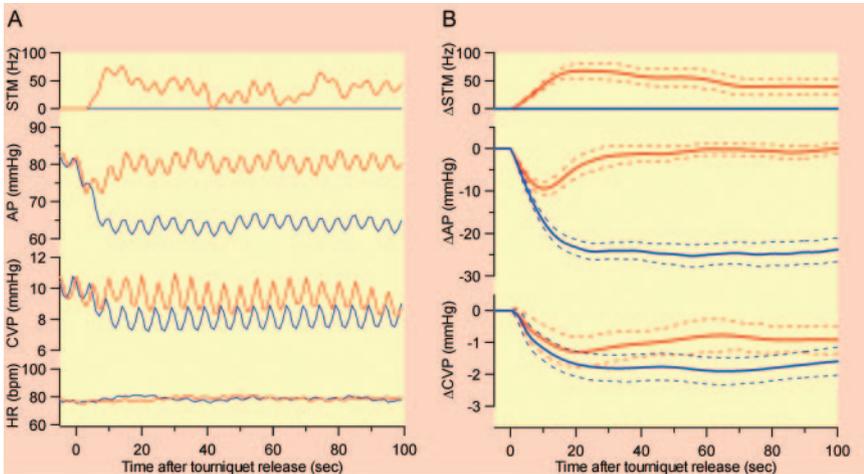


Figure 4. A, Representative example of original tracings of STM, AP, CVP, and heart rate (HR) during 2 episodes of rapid progressive hypotension induced by sudden deflation of a thigh tourniquet in a patient. When the BBS was inactive (blue line), AP decreased immediately after tourniquet release and did not return to baseline level. By contrast, when the BBS was activated (red line), the artificial vasomotor center automatically computed STM and drove an electrical stimulator to restore AP. B, Plots showing averaged changes in STM, AP, and CVP after tourniquet release among 21 patients. Data are expressed as mean (solid line)±SD (dotted line). See text for explanation.

deflation of the thigh tourniquet produced a rapid progressive fall in AP of ≈ 20 mm Hg within 10 seconds, while lowering CVP by 2 mm Hg. By contrast, when the BBS was activated, STM was computed automatically, and the spinal cord was stimulated appropriately to quickly and effectively attenuate the drop in AP and CVP. Figure 4B summarizes the results obtained from 21 patients, demonstrating effectiveness of the BBS performance in buffering the AP fall in response to the sudden release of the tourniquet. As demonstrated in Figure 5, tourniquet release resulted in an AP decrease of 17 ± 3 mm Hg at 10 seconds, 25 ± 2 mm Hg at 50 seconds, and 24 ± 3 mm Hg at 100 seconds. By contrast, during real-time execution of the BBS, the decrease in AP was 9 ± 2 mm Hg at 10 seconds, 1 ± 2 mm Hg at 50 seconds, and 0 ± 1 mm Hg at 100 seconds after the deflation. These data indicated that the BBS significantly attenuated the decrease in AP at these 3 time points and nullified the hypotensive effect of tourniquet release within 50 seconds. Similarly, the BBS significantly suppressed the decrease in CVP within 50 seconds after the release of the tourniquet.

Discussion

Design of BBS

On the basis of knowledge and technology of bionics, we previously developed an artificial feedback control system for automatic regulation of sympathetic vasomotor tone in animal models of central baroreflex failure.^{20–22} As a crucial first step to clinical application, we tested its feasibility and efficacy in a clinical model of orthostatic hypotension. A percutaneous epidural catheter approach

was established for the monitoring of spinal function during surgery and for pain management,²⁸ and the lower thoracic level was selected for spinal cord stimulation based on earlier reports that the abdominal splanchnic vascular bed is a major effector mechanism for arterial baroreflex in animals^{23,24} and humans.²⁵ Although the percutaneous epidural approach is less invasive than implantation surgery, spinal cord stimulation excites motor and sensory nerves^{12,22,28} in addition to sympathetic vasomotor efferents. Therefore, administration of sufficient doses of muscle relaxants and analgesics was required during experimental protocols. Under these conditions, the dynamic response of AP to STM was easily characterized by the white noise system identification method. Furthermore, the quantitatively estimated results of transfer function analysis (Figure 2B) enabled simulation of the effects of feedback correction factors²⁷ on performance of the BBS. As demonstrated in Figure 3, the simulation results suggested that the specific combination of feedback correction factors could optimize the performance of the BBS. On the basis of these results, the feedback correction factors were determined to allow the BBS to quickly stabilize AP against the external disturbances.

Efficacy of BBS

The present study utilized a tourniquet-related model of hypotension^{29–31} during general anesthesia^{32,33} to approximate orthostatic hypotension due to central baroreflex failure. Except for the change in peripheral vascular resistance, the hemodynamic changes after tourniquet deflation are similar to those achieved after upright tilt-

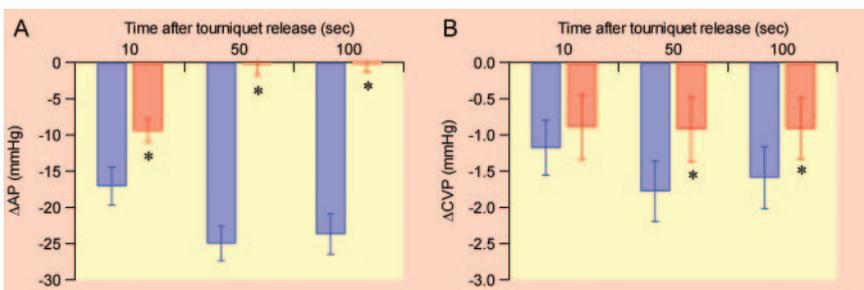


Figure 5. Bar graphs showing changes in AP (A) and CVP (B) at 10, 50, and 100 seconds after tourniquet release. Implementation of the BBS (red column) significantly attenuated tourniquet-related falls (blue column) in AP and CVP. Data are expressed as mean±SD for 21 patients. *Overall $P < 0.05$.

ing.^{29,31} For example, tourniquet release results in a rapid increase in venous pooling in the affected limb with a subsequent decrease in venous return and cardiac output. Under general anesthesia with volatile gases such as sevoflurane,^{32,33} arterial baroreflex function is inhibited, and the hemodynamic disturbance produced by the tourniquet inevitably results in abrupt hypotension. In rare instances, tourniquet deflation can also trigger fatal circulatory collapse.²⁹

Despite the fact that the BBS was implemented with fixed values of feedback correction factors for all patients, the BBS successfully stabilized AP against the hemodynamic challenge induced by sudden tourniquet release (Figure 4). These data indicate that the BBS may compensate for some individual differences in the dynamic response of AP to STM.

Finally, the CVP response to STM (Figure 4) in the present study suggests that the BBS attenuated a decrease in venous return. Previous studies have demonstrated that the baroreflex-mediated vasoconstriction in the splanchnic vascular bed is a major mechanism for recruitment of venous return during head-up tilting.^{23,25} Therefore, the BBS may functionally mimic the baroreflex control of venous return and control of AP.

Study Limitations

This study possessed several limitations. First, based on the previous results^{20–22} obtained from animal studies, the stimulation electrodes were placed in the epidural space at the level of the lower thoracic cord; however, further study to determine the optimal site of electrode placement would be of benefit. Second, it is unclear whether or not the feedback controller designed in the present study is universally applicable to other cases. Although preset parameters for feedback correction were used in the present study, other approaches based on a robust control theory could yield a better result. Finally, the epidural catheter method for sympathetic nerve stimulation is associated with significant pain and discomfort. Thus, practical use of the BBS requires an appropriate method for stimulating only efferent sympathetic nerves.

Clinical Implications

The present study confirmed the efficacy of the BBS in a clinical setting and suggests that the BBS has tremendous potential as a new therapeutic modality for treatment of severe orthostatic intolerance in patients with various syndromes of central baroreflex failure, including Shy-Drager syndrome, baroreceptor deafferentation, and traumatic spinal cord injuries.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Central baroreflex failure due to Shy-Drager syndrome, baroreceptor deafferentation, and traumatic spinal cord injuries results in severe orthostatic hypotension. However, most commonly used interventions, such as salt loading, cardiac pacing, and pharmacological approaches, can neither restore nor reproduce the functioning of a native vasomotor center. Here, we proposed a novel therapeutic strategy against central baroreflex failure and developed a bionic baroreflex system (BBS). The BBS consisted of a pressure sensor, computer, electrical stimulator, and epidural catheter with sympathetic nerve stimulation electrodes. While automatically calculating the frequency of a pulse train in response to a change in arterial pressure, the computer drove the stimulator at the appropriate frequency to stabilize arterial pressure against an external disturbance. According to a parametric negative-feedback control theory, we designed an algorithm of the computer functioning as an artificial vasomotor center. The efficacy of the BBS was tested in a clinical model of orthostatic hypotension during knee joint surgery. Without the implementation of the BBS, a sudden deflation of a thigh tourniquet resulted in rapid progressive hypotension. By contrast, during real-time execution of the BBS, arterial pressure was quickly restored to the baseline level before tourniquet release. These results suggest the technical feasibility of functional restoration of arterial baroreflex with the BBS.