Novel Therapeutic Strategy Against Central Baroreflex Failure : A Bionic Baroreflex System

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Novel Therapeutic Strategy Against Central Baroreflex Failure

A Bionic Baroreflex System

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Background—Central baroreflex failure in Shy-Drager syndrome and traumatic spinal cord injuries results in severe orthostatic hypotension and often confines the patient to the bed. We proposed a novel therapeutic strategy against central baroreflex failure: implementation of an artificial feedback control system able automatically to regulate sympathetic vasomotor tone, that is, a bionic baroreflex system (BBS). With the use of a rat model of central baroreflex failure, we developed the BBS and tested its efficacy.

Methods and Results—Our prototype BBS for the rat consisted of a pressure sensor placed into the aortic arch, stimulation electrodes implanted into the greater splanchnic nerve, and a computer-driven neural stimulator. By a white noise approach for system identification, we first estimated the dynamic properties underlying the normal baroreflex control of systemic arterial pressure (SAP) and then determined how the BBS computer should operate in real time as the artificial vasomotor center to mimic the dynamic properties of the native baroreflex. The open-loop transfer function of the artificial vasomotor center was identified as a high-pass filter with a corner frequency of 0.1 Hz. We evaluated the performance of the BBS in response to rapid-progressive hypotension secondary to sudden sympathetic withdrawal evoked by the local imposition of a pressure step on carotid sinus baroreceptors in 16 anesthetized rats. Without the BBS, SAP rapidly fell by 49 ± 8 mm Hg in 10 seconds. With the BBS placed on-line with real-time execution, the SAP fall was suppressed by 22 ± 6 mm Hg at the nadir and by 16 ± 5 mm Hg at the plateau. These effects were statistically indistinguishable from those of the native baroreflex system.

Conclusions—These results suggest the feasibility of a BBS approach for central baroreflex failure. (***Circulation***. 1999;100:299-304.)

Key Words: baroreceptors ■ nervous system ■ reflex ■ blood pressure

The sympathetic limb of the arterial baroreflex is the most important negative feedback control system functioning physiologically to attenuate the effects of rapid daily perturbations in arterial pressure.[1–4] The change in posture from lying to standing, for example, is associated with a fall in blood pressure sensed by arterial baroreceptors located within the walls of the aortic arch and internal carotid arteries. This fall in pressure is neurally encoded and relayed through afferent pathways to a brain stem vasomotor center that processes the incoming signals, then through activation of efferent sympathetic pathways immediately causes an appropriate degree of compensatory vasoconstriction. Without such compensation, the simple act of standing would cause the arterial pressure responsible for perfusing the brain to inevitably fall, resulting potentially in loss of consciousness. In short, the arterial baroreflex is essential to the buffering of variations in perfusion pressure to the head and upper body during postural tilting.[4]

Patients with neurological disorders such as Shy-Drager syndrome,[5–8] baroreceptor deafferentation,[9,10] and traumatic spinal cord injuries[11,12] have central baroreflex failure and a severely impaired quality of life as a consequence. In Shy-Drager syndrome, idiopathic neurodegeneration affects the vasomotor center in the brain stem; however, peripheral sympathetic neurons are assumed to be relatively spared and able to release norepinephrine in response to excitatory outflow. Iatrogenic baroreceptor deafferentation could be induced by irradiation and surgical resection of head and neck tumors. In spinal cord injuries, sympathetic traffic to preganglionic neurons can be interrupted permanently. In either case, peripheral sympathetic neurons have the potential ability to release norepinephrine in response to direct electrical stimuli. Unfortunately, although various interventions such as salt loading,[13,14] cardiac pacing,[15,16] and adrenergic agonists[17,18] have been attempted to treat orthostatic hypotension,
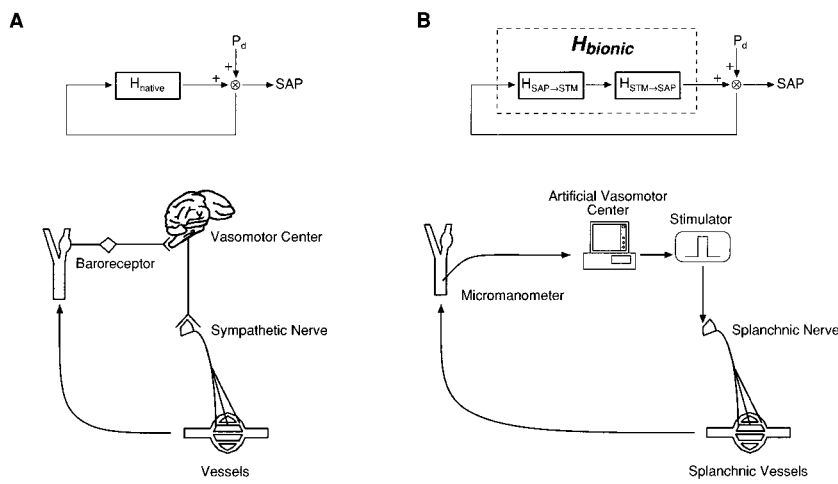
A   B

Figure 1. Block diagrams of native (A) and bionic (B) baroreflex systems. In native baroreflex system, change in SAP induced by external disturbance in pressure (P_d) is sensed by arterial baroreceptors. The change in pressure initiates a reflex change in vasomotor sympathetic outflow and is thereby buffered. Primary reflex center is located in brain stem. In BBS, a catheter-tipped micromanometer functions as the baroreceptor, a computer as the vasomotor center, and an electrical stimulator as the preganglionic sympathetic neuron. H_{native} denotes open-loop transfer function of native baroreflex system. $H_{SAP \to STM}$ and $H_{STM \to SAP}$ are open-loop transfer functions from SAP to STM and from STM to SAP, respectively. Overall open-loop transfer function of BBS is given by $H_{SAP \to STM} \times H_{STM \to SAP}$.

most patients nevertheless remain bedridden for a long time. The reason for this unfortunate outcome is that such interventions can neither restore nor reproduce the functioning of the native vasomotor center. We proposed a novel therapeutic strategy against central baroreflex failure that has its basis in bionics and neurocardiology: functional replacement of the vasomotor center with a bionic baroreflex system (BBS). In the present study, we developed the BBS and tested its efficacy in a rat model of central baroreflex failure.

Methods

Framework for BBS Development

A simplified diagram representing characteristics of the native baroreflex system is provided in Figure 1A. The vasomotor center responsively modifies its command over sympathetic vasomotor nerve activity according to changes in arterial pressure sensed by arterial baroreceptors. Efferent sympathetic nerve activity in turn governs the functional properties of various effectors, such as resistive and capacitive vessels, which exert direct influence over systemic arterial pressure (SAP). With the BBS (Figure 1B), by contrast, changes in SAP are sensed by a pressure transducer in the aortic arch and fed into a computer functioning as an artificial vasomotor center. On the basis of measured changes in SAP, the artificial vasomotor center executes real-time operations that determine the frequency of electrical stimulation (STM) necessary for compensatory adjustment of SAP to the desired level and then commands an electrical stimulator to deliver a stimulus of the same frequency to a sympathetic vasomotor nerve. To enable the BBS to effectively mimic the functioning of the native baroreflex system, it is necessary quantitatively to identify the operating rule that underlies native baroreflex function and to implant it into the BBS. Therefore we first analyzed under open-loop conditions the input-output relation characterizing native baroreflex function (H_{native}) by using a white noise identification method.[19,20] Next, we identified the open-loop transfer function ($H_{STM \to SAP}$) from STM to SAP. Finally, we determined the open-loop transfer function required for the artificial vasomotor center of the BBS, that is, $H_{SAP \to STM}$, by a simple process of division, $H_{native}/H_{STM \to SAP}$. The transfer function $H_{SAP \to STM}$ represents the operating rule characterizing quantitatively the dynamics of how the artificial vasomotor center should operate in its stimulation of the sympathetic vasomotor nerve to mimic the native baroreflex.

Animals and Surgical Procedures

The care of animals was in strict accordance with the guiding principles of the Physiological Society of Japan. A total of 16 male Sprague-Dawley rats weighing 280 to 350 g were used. The rat was

first placed in a glass jar, where it breathed a mixture of 2% halothane (Fluothane, Takeda Pharmaceuticals) in oxygen-enriched air for 5 to 10 minutes. After induction anesthesia, an endotracheal tube was introduced orally and the rat was ventilated artificially by a volume-controlled rodent respirator (model 683, Harvard Apparatus). In accordance with Ono et al,[21] anesthesia was maintained through the use of 1.2% halothane during surgical procedures and 0.6% halothane during data recording. Pancuronium bromide (0.8 mg · kg^{-1} · h^{-1} IV) was administered to eliminate spontaneous muscle activity. Arterial blood gases were monitored with a blood gas analyzer (IL-13064, Instrumentation Laboratory). Polyethylene tubing (PE-10, Becton Dickinson) was inserted into the right femoral vein. For the prevention of dehydration during experiments, physiological saline was continuously infused at a rate of 5 mL · kg^{-1} · h^{-1} with a syringe pump (CFV-3200, Nihon Kohden). For measurement of SAP, a 2F catheter-tipped micromanometer (SPC-320, Millar Instruments) was placed in the aortic arch through the right femoral artery.

To open the feedback loop of the native baroreflex system, we isolated both carotid sinuses from the systemic circulation by our previous method.[22] We cut the vagal and aortic depressor nerves bilaterally. Two short sections of polyethylene tubing (PE-50) were placed into both carotid sinuses and connected to a fluid-filled transducer (DX-200, Viggo-Spectramed) and to a servo-controlled pump system based on an electromagnetic shaker and linear power amplifier (ARB-126, AR Brown).

According to earlier findings that the abdominal splanchnic vascular bed innervated by the greater splanchnic nerve[23] is a major effector mechanism for the arterial baroreflex in animals[24–26] and humans,[11,12] we selected this nerve as the sympathetic vasomotor nerve interface for the BBS. The left greater splanchnic nerve was identified, separated free, and cut at the level of the diaphragm with a retroperitoneal approach through a left flank incision. A pair of Teflon-coated platinum wires (7720, A-M Systems) was looped around and fixed on the distal end of the nerve. The implantation site of the wires was embedded in silicone rubber (Sil-Gel 604, Wacker). The free ends of the wires were connected to an isolated constant-voltage stimulator (SS-202J and SEN-7203, Nihon Kohden) controlled with a personal computer (PC-9801RA21, NEC). An analog-to-digital converter (AD12-16D98H, Contec) was built into the computer. Finally, the flank incision was closed in layers.

Data Recording for Estimation of H_{native}

To estimate the open-loop transfer function H_{native}, we randomly altered carotid sinus pressure (CSP) between 100 to 120 mm Hg with a white bandwidth up to 2 Hz by using the servo-controlled pump system. While the random perturbation was given for an hour, the electrical signals of CSP and SAP were first low-pass filtered with antialiasing filters having a cutoff frequency of 50 Hz (-3 dB) and an attenuation slope of -80 dB · decade^{-1} (ASIP-0260L, Canopus)

and then digitized at a rate of 100 Hz by means of the analog-to-digital converter.

Data Recording for Estimation of $H_{STM \rightarrow SAP}$

To estimate the open-loop transfer function $H_{STM \rightarrow SAP}$, we randomly changed STM between 0 to 10 Hz with a white bandwidth up to 2 Hz while CSP was kept at a constant pressure of 120 mm Hg. The pulse width of the stimulus was fixed at 2 ms. The stimulation voltage was adjusted for each animal to produce a pressor response of 40 mm Hg at 10 Hz. This resulted in an average amplitude of 4.8 ± 0.5 V (mean±SD). While the random perturbation was given for 1 hour, STM and SAP were digitized at a rate of 100 Hz.

Estimation of Transfer Function

The transfer function $H_{x \rightarrow y}$ from input x to output y was estimated with a fast Fourier transform algorithm.[19,20] The digitized data of x and y were resampled at 2 Hz after a moving average to avoid aliasing. The time series of each datum was divided into 50 segments of 256 points each, with 128 points of overlap between segments. The length of each segment was 128 seconds in duration. To suppress spectral leakage, we applied a Hann window to each segment and then computed the raw autospectra of x and y and the raw cross-spectrum between the two. To reduce an error in estimating the spectrum, we calculated the ensemble average of 50 raw spectra. Finally, we computed the transfer function over the frequency range of 0.008 to 1 Hz with a resolution bandwidth of 0.008 Hz as follows:

$$H_{x \rightarrow y} = \frac{S_{xy}}{S_{xx}}$$

where S_{xx} is the ensemble autospectrum of x, and S_{xy} is the ensemble cross-spectrum of x and y. $H_{x \rightarrow y}$ is, in general, a complex quantity and is therefore expressible in polar form as

$$H_{x \rightarrow y} = |H_{x \rightarrow y}| \exp\{j\varphi_{x \rightarrow y}\}$$

where $j^2 = -1$, and $|H_{x \rightarrow y}|$ and $\varphi_{x \rightarrow y}$ are the gain and phase of the transfer function, respectively. The squared coherence function, a measure of linear dependence between x and y, was estimated with the following equation:

$$coh = \frac{|S_{xy}|^2}{S_{xx} \times S_{yy}}$$

where S_{yy} is the ensemble autospectrum of y.

Implantation of $H_{SAP \rightarrow STM}$ Into BBS

The open-loop transfer function required for the artificial vasomotor center, $H_{SAP \rightarrow STM}$, was determined by a simple process of division, $H_{native}/H_{STM \rightarrow SAP}$. To make the BBS computer operate in real time as the artificial vasomotor center, we programmed the computer to automatically calculate instantaneous STM in response to instantaneous SAP change according to a convolution algorithm:[19,20]

$$STM(t) = \int_0^\infty h(\tau) \cdot SAP(t - \tau) d\tau$$

where h (t) is an impulse response function computed by an inverse Fourier transform of $H_{SAP \rightarrow STM}$.

Efficacy of BBS

We evaluated the performance of the BBS in response to rapid progressive hypotension secondary to sudden sympathetic withdrawal. Sympathetic withdrawal was evoked by the imposition on carotid sinus baroreceptors of a pressure step from 110 to 140 mm Hg. The pressure step was maintained for 30 seconds. The sudden sympathetic withdrawal would be expected to produce relatively rapid and progressive hypotension similar to orthostatic hypotension in central baroreflex failure. While being in real time fed into the BBS computer, SAP was recorded during the on-line

real-time execution of the BBS. SAP was also recorded while the BBS was inactivated. For reference, we estimated the SAP response under the closed-loop condition of the native baroreflex from H_{native}.

Statistical Analysis

The SAP responses to the sudden sympathetic withdrawal were analyzed by a mixed model of ANOVA. A post hoc analysis for multiple comparisons was performed by a Scheffé procedure. Differences were considered significant at $P < 0.05$. Values are expressed as mean±SD.

Results

Shown in Figure 2 is a representative example of a process for determining the operating rule of the artificial vasomotor center. The SAP response to random CSP perturbation appeared to be sluggish and opposite (Figure 2A). Clearly, the estimated transfer function indicated low-pass dynamic characteristics for H_{native} (Figure 2B). The gain spectrum reveals a steady-state (lowest frequency) gain of ≈ 2 that is fairly constant up to 0.1 Hz. Toward higher frequencies, the gain decreased rapidly as a function of frequency. The phase spectrum shows that the input-output relation was out of phase at steady state and that the phase delay increased with frequency. The squared coherence values were found to be close to unity, indicating that the input-output relation was governed by nearly linear dynamics and that the transfer function well described the input-output relation in the frequency domain. Because the closed-loop gain[4] is given by $1/(1 + |H_{native}|)$, the native baroreflex system in this case would be expected at steady state to suppress the effect of an external disturbance in pressure to one-third the magnitude of the disturbance after a significant transient response. The SAP response to random electrical stimulation of the greater splanchnic nerve also seemed to be sluggish (Figure 2C). Similar to H_{native}, the transfer function $H_{STM \rightarrow SAP}$ had low-pass characteristics with a corner frequency of 0.1 Hz (Figure 2D). Across the higher range of frequencies, however, its rate of gain attenuation was faster than that of H_{native}. The transfer function $H_{SAP \rightarrow STM}$ was determined by $H_{native}/H_{STM \rightarrow SAP}$. $H_{SAP \rightarrow STM}$ is a high-pass filter with a corner frequency of 0.1 Hz that essentially compensates for the relatively faster gain attenuation in $H_{STM \rightarrow SAP}$ as compared with H_{native} (Figure 2E). The phase spectrum indicates that the input-output relation was out of phase at steady state.

The significance of our investigation is most readily suggested by a representative example in Figure 3A, where we evaluated the performance of the BBS in response to rapid progressive hypotension secondary to sudden sympathetic withdrawal. Sensing the rapid fall in SAP, the BBS automatically computed STM and appropriately stimulated the sympathetic nerve to prevent SAP from falling $>25\%$ in 10 seconds. Figures 3B and 3C summarize results obtained for 16 rats, demonstrating effectiveness of BBS performance in buffering SAP fall in response to sympathetic withdrawal. With normal operation of the native baroreflex prevented and without bionic compensation (no baroreflex), SAP fell by 49 ± 8 mm Hg in ≈ 10 seconds in response to sympathetic withdrawal. However, with the BBS placed on-line with real-time execution (bionic baroreflex), the SAP fall was suppressed by 22 ± 6 mm Hg at the nadir and by 16 ± 5 mm Hg at the plateau. These effects were statistically indistinguishable from those of the native baroreflex system.
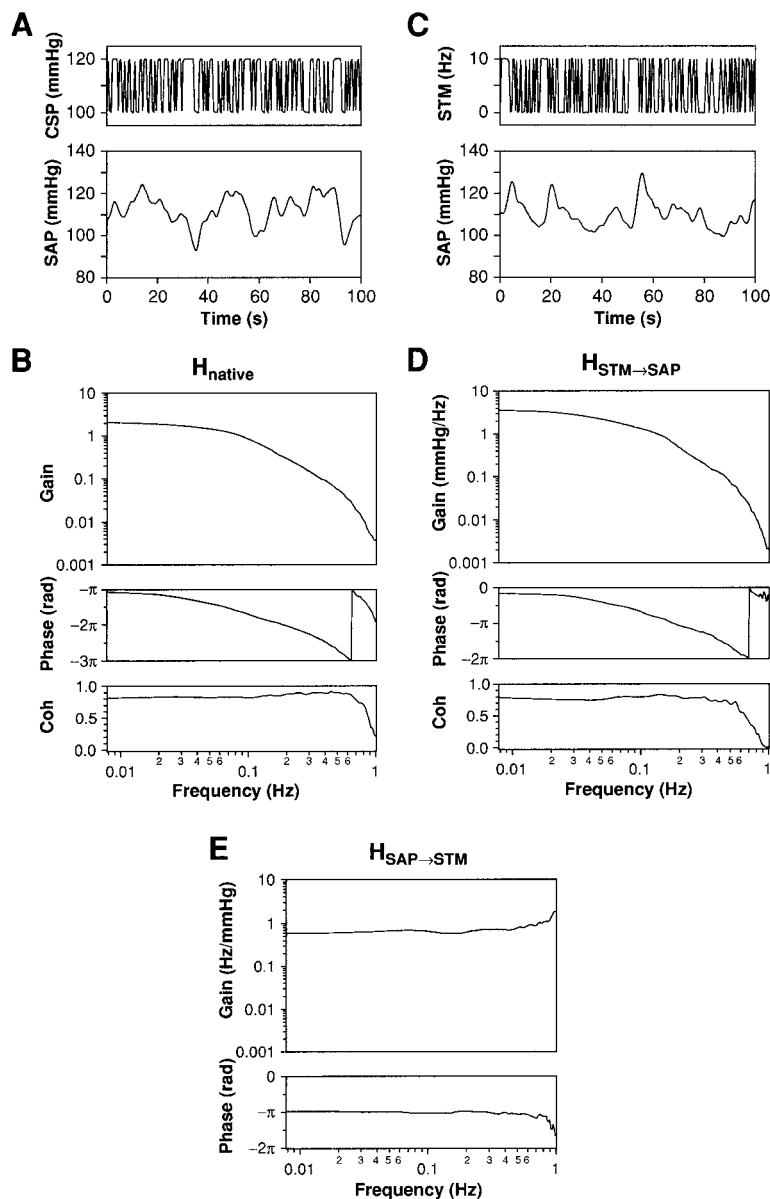
Figure 2. Framework for determination of an operating rule for BBS. A, Native baroreflex response of SAP to random pressure disturbance to carotid sinus baroreceptor regions (CSP). B, Open-loop transfer function (H_{native}) of native baroreflex system. C, SAP response to random electrical stimulation of greater splanchnic nerve (STM). D, Open-loop transfer function ($H_{STM \rightarrow SAP}$) from STM to SAP. Squared coherence values were found to be close to unity in both H_{native} and $H_{STM \rightarrow SAP}$, indicating that input-output relation was governed by nearly linear dynamics and that transfer function well described the input-output relation in the frequency domain. E, Open-loop transfer function ($H_{SAP \rightarrow STM}$) required for artificial vasomotor center of BBS was given by $H_{native}/H_{STM \rightarrow SAP}$.

Discussion

The present results indicate that with the use of the BBS, we have been able to reproduce the dynamic functioning of the native baroreflex control of SAP. The fact that our BBS could mimic the native baroreflex would suggest the importance of our framework in developing the BBS and a new therapeutic strategy against central baroreflex failure.

System Identification by White Noise Approach

To develop an artificial device for functional replacement of a physiological system, we should clarify and identify its function quantitatively. Therefore we described the native arterial baroreflex control of SAP in terms of system physiology by using the white noise technique. Compared with the traditional approach of testing dynamic properties of the physiological system with step and sine wave stimuli, the white noise approach has definite advantages as follows.[19] First, if a step stimulus is applied, we learn the response of the system to this step and have little notion of the response of the system to any other type of stimulus. If a sinusoidal pulse is applied, then we know the response of the system to such a stimulus and little else. The same applies for any other specific waveform. In the white noise approach, the system is tested with every possible stimulus. The white noise stimulus is a very rich stimulus. It should be emphasized that the white noise method is perfectly suited to the analysis of linear systems. As shown in Figures 2B and 2D, high coherence values close to unity indicate the validity of our method for system identification. Second, the identification of the physiological system through the white noise technique is largely unaffected by the types of contaminating noise usually present in such a system. Our study provides the first and quantitative description of the dynamic properties of the arterial baroreflex control in rats.

Dynamic Characteristics of BBS

As shown in Figure 2E, the artificial vasomotor center of the BBS had a high-pass or derivative nature. Although the dynamic characteristics from CSP to sympathetic vasomotor
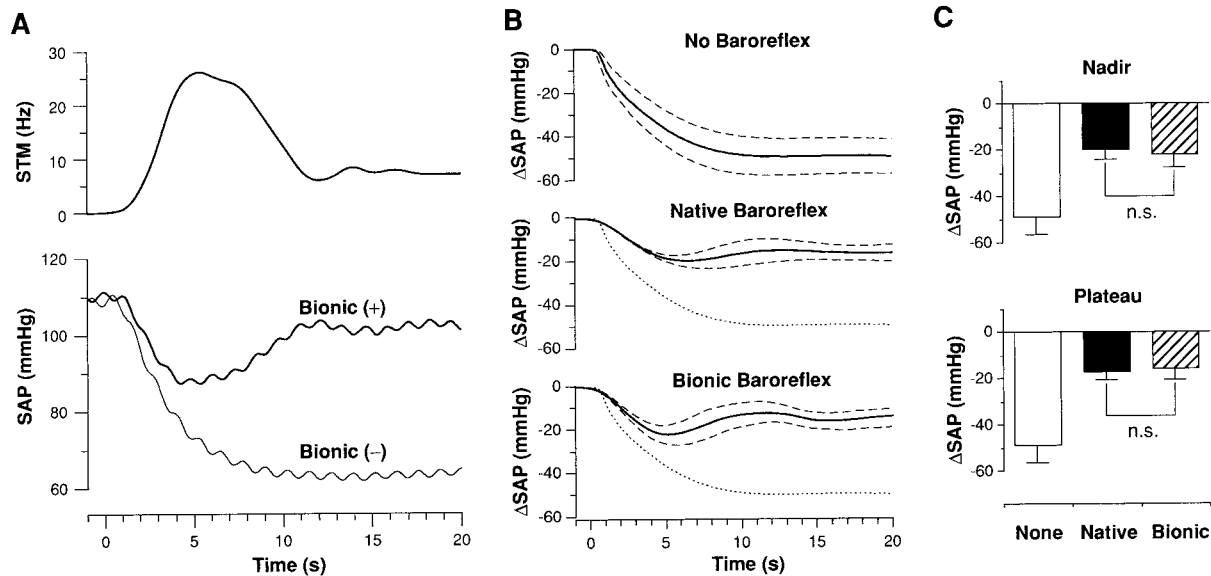
Figure 3. Efficacy of BBS during rapid progressive hypotension induced by sudden sympathetic withdrawal. A, Representative example of online real-time operation of BBS. While sensing changes in SAP, the BBS automatically computed the frequency of STM of the greater splanchnic nerve and drove a stimulator. When BBS was inactive, SAP fell rapidly and severely. Fine regular oscillation observed in SAP was ascribed to respiration. B, Time courses of changes in SAP. Data are expressed by mean (solid line) ±SD (broken line) for 16 rats. For comparison, mean data during no baroreflex are also shown by dotted lines. When no baroreflex system was active, SAP fell monotonically and reached a minimum in 10 seconds. On the other hand, when native baroreflex was active, SAP reached a nadir in ≈5 seconds and then increased to a plateau. A similar time course of SAP change by the native baroreflex system was well reproduced by the BBS. C, Comparison of changes in SAP at nadir and plateau. No significant difference between native and bionic baroreflex systems was found at nadir or plateau.

nerve activity in rats have never been analyzed in the frequency domain, our previous study[27] characterized the transfer functions from CSP to sympathetic nerve activity (mechanoneural arc) and from sympathetic nerve activity to SAP (neuromechanical arc) in rabbits. The high-pass characteristics of the mechanoneural arc up to 1 Hz compensated for the low-pass characteristics of the neuromechanical arc and thus we speculated that the native baroreflex would be optimized and achieve its quickness and stability. Whereas effector organs in the BBS were limited to the abdominal vascular bed innervated by the greater splanchnic nerve, the high-pass characteristics of the mechanoneural arc in the BBS, that is, $H_{SAP \rightarrow STM}$, would contribute toward compensating for the relatively sluggish response of the neuromechanical arc in the BBS, that is, $H_{STM \rightarrow SAP}$.

Clinical Implications

Two important challenges accompany the prospect of future development of the BBS for central baroreflex failure: (1) Hardware for clinical use is required, that is, a pressure sensor, an electrical stimulator, and stimulating electrodes. (2) A standardized software paradigm prescribing precisely how the bionic vasomotor center should determine STM in response to changes in SAP must be established. Fortunately, certain difficulties posed by these challenges have been addressed in other areas of clinical practice to some degree and may be readily adaptable for use with the BBS. For example, a tonometer[28] has been developed as a noninvasive continuous monitor of SAP. Implantable pulse generators such as cardiac pacemakers can serve as permanent electrical stimulators. Also, implantable wire leads for nerve stimulation[29,30] and epidural catheters for percu-

taneous spinal stimulation[31,32] have been approved for the long-term treatment of some neurological disorders and for long-term therapy of pain control. Finally, inasmuch as our present study establishes a solid framework for the necessary software development to implement the approach, we enthusiastically affirm not only that we can but that we should develop the BBS as a new therapeutic modality for treatment of severe orthostatic intolerance in central baroreflex failure such as Shy-Drager syndrome, baroreceptor deafferentation, and traumatic spinal cord injuries.

Study Limitations

In the present study, for the sake of simplicity, we cut the vagal nerves bilaterally to exclude the vagally mediated effect on the arterial baroreflex. The dynamic properties of the arterial baroreflex may be different from the present results when vagally mediated effects are present. Anesthetic agents used in the present study could also affect the dynamic properties of arterial baroreflex control of SAP. Although we used a linear approach for estimating the dynamic properties of arterial baroreflex, the nonlinear nature of the arterial baroreflex system such as threshold and saturation phenomena[4,20,22] has been well known. Therefore our results should be interpreted carefully. However, the fact that the present framework enabled us to restore arterial baroreflex function suggests that the linear approximation of the central baroreflex arc is reasonable, at least under our experimental conditions.

The vasomotor center of the arterial baroreflex[33] is affected by higher-order centers such as the limbic-hypothalamic systems and receives various afferents from the periphery such as sympathetic afferent cardiac and splanchnic fibers.[34,35] In the

present study, we ignored these components. Thus further investigation concerning the effects of these components on the arterial baroreceptor reflex is needed for clarifying the native baroreflex and developing the truly "bionic" baroreflex system.

In summary, we proposed a novel therapeutic strategy against central baroreflex failure with the BBS. Our prototype of the BBS consisted of a pressure sensor, stimulation electrodes implanted into a peripheral sympathetic nerve, and a computer-driven neural stimulator. In rats, we first estimated the dynamic properties underlying the normal baroreflex control of arterial pressure. We then determined how the BBS computer should operate as the artificial vasomotor center to mimic the native baroreflex. The BBS could indeed reproduce the native barore-flex in a model of central baroreflex failure.

Acknowledgments

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