New analytic framework for understanding sympathetic baroreflex control of arterial pressure

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Sato, Takayuki, Toru Kawada, Masashi Inagaki, Toshiaki Shishido, Hiroshi Takaki, Masaru Sugimachi, and Kenji Sunagawa. New analytic framework for understanding sympathetic baroreflex control of arterial pressure. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H2251–H2261, 1999.—The sympathetic baroreflex is an important feedback system in stabilization of arterial pressure. This system can be decomposed into the controlling element (mechanoneural arc) and the controlled element (neuromechanical arc). We hypothesized that the intersection of the two operational curves representing their respective functions on an equilibrium diagram should define the operating point of the arterial baroreflex. Both carotid sinuses were isolated in 16 halothane-anesthetized rats. The vagi and aortic depressor nerves were cut bilaterally. Carotid sinus pressure (CSP) was sequentially altered in 10-mmHg increments from 80 to 160 mmHg while sympathetic efferent nerve activity (SNA) and systemic arterial pressure (SAP) were recorded simultaneously under various hemorrhagic conditions. The mechanoneural arc was characterized by the response of SNA to CSP and the neuromechanical arc by the response of SAP to SNA. We parametrically analyzed the relationship between input and output for each arc using a four-parameter logistic equation model. In baseline states, the two arcs intersected each other at the point at which the instantaneous gain of each arc attained its maximum. Severe hemorrhage lowered the gain and offset of the neuromechanical arc and moved the operating point, whereas the mechanoneural arc remained unchanged. The operating points measured under the closed-loop conditions were indistinguishable from those estimated from the intersections of the two arc curves on the equilibrium diagram. The average root mean square errors of estimate for arterial pressure, venous return, and cardiac output. This diagram enables us to quantitatively and analytically understand how the unique value of the cardiac output is determined by the cardiovascular system. Similarly, the arterial baroreflex system has been extensively studied by the open-loop approach (14, 15, 24). Many earlier studies revealed the baroreceptor-mediated control of sympathetic nerve activity (SNA) (4, 8, 9, 16, 19, 23) and the sympathetically mediated control of heart rate and cardiovascular mechanics (2, 7, 18, 26, 29). However, an analytic approach for identifying an operating point of the arterial baroreflex has not been developed. Such an approach is needed for an integrative understanding of the mechanism by which the arterial pressure at the operating point is determined under the closed-loop conditions of the feedback system. The purpose of this investigation was to develop a new analytic framework for the sympathetic arterial baroreflex. The results indicate that the decomposition of the baroreflex loop into mechanoneural and neuromechanical arcs allows us to analytically determine the operating point by equilibrating respective function curves.

METHODS

Theoretical Consideration: Coupling of Mechanoneural and Neuromechanical Arcs

Figure 1A is a simplified diagram representing characteristics of the sympathetic arterial baroreflex system. The vaso-
motor center responsively modifies its command over sympathetic vasomotor nerve activity according to the changes in arterial pressure produced by an external disturbance to the cardiovascular system. The changes in arterial pressure are immediately sensed by arterial baroreceptors. Efferent SNA in turn governs heart rate and the mechanical properties of the heart and vessels, which themselves exert direct influence over systemic arterial pressure (SAP). The effect of external disturbance on arterial pressure, therefore, is attenuated by the arterial baroreflex. However, this circular nature resulting from the feedback makes it difficult to analytically characterize the system behavior (6). To overcome this problem, we opened the feedback loop and divided the system into the controlling element and the controlled element (Fig. 1B). We denoted the controlling element as a mechanoneural arc and the controlled element as a neuromechanical arc. In the mechanoneural arc, the input is the pressure sensed by the arterial baroreceptors and the output is SNA. In the neuromechanical arc, the input is SNA and the output is SAP. Because the variables characterizing the functions of the two arcs are common, we superimposed the two curves and analytically identified the operating point, i.e., the point defined by the arterial pressure and SNA under the closed-loop conditions of the feedback system (C).

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 280–350 g was used. The rat was first placed in a glass jar, in which it inspired a mixture of 2% halothane (Fluothane; Takeda Pharmaceuticals, Tokyo, Japan) in oxygen-enriched air for 5–10 min. After induction of anesthesia, an endotracheal tube was introduced orally and the rat was ventilated artificially via a volume-controlled rodent respirator (model 683; Harvard Apparatus, South Natick, MA). In accordance with Ono et al. (20), anesthesia was maintained through the use of 1.2% halothane during surgical procedures and 0.6% halothane during data recording. Polyethylene tubing (PE-10; Becton Dickinson, Parsippany, NJ) was inserted into the right femoral vein and the left common carotid artery. 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, Lexington, MA). 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, Tokyo, Japan). For measurement of SAP, a 2-Fr catheter-tip micromanometer (SPC-320; Millar Instruments, Houston, TX) was placed in the aortic arch through the right femoral artery.

To open the feedback loop of the arterial baroreflex system, we cut the vagi and the aortic depressor nerves and isolated the carotid sinus baroreceptor regions by our previously described method (24). Briefly, the external carotid artery was ligated at the root of the bifurcation of the common carotid artery, and then the internal carotid and pterygopalatine arteries were embolized with two ball bearings of 0.8-mm diameter (Fig. 2). Two short polyethylene tubes (PE-50) were placed into both carotid sinuses and connected to a fluid-filled...
transducer (DX-200; Viggo-Spectramed, Singapore) and to a custom-made servo-controlled pump system (24, 25) based on an electromagnetic shaker and power amplifier (ARB-126; AR Brown, Osaka, Japan). We used the servo-controlled pump to impose various pressures on the carotid sinus baroreceptor regions.

To record SNA, we identified the left renal nerve branch from the aorticorenal ganglion via a retroperitoneal approach through a left flank incision. The nerve branch was isolated and carefully dissected free. A pair of Teflon-coated platinum wires (7720; A-M Systems, Everett, WA) was looped around and fixed on the nerve branch. The implantation site of the wires was embedded in silicone rubber (Sil-Gel 604; Wacker, Munich, Germany). Finally, the flank incision was closed in layers. The nerve activity was amplified and band-pass filtered in the frequency range between 150 and 3,000 Hz (JB-610J and AB-610J; Nihon Kohden). The root mean square (RMS) waveform of SNA was generated through a custom-made RMS-DC converter with a cutoff frequency of 100 Hz.

Data Recording

Protocol 1: Characterization of two arcs under open-loop conditions. To characterize the mechanoneural and neuromechanical arcs, we examined the relationship between carotid sinus pressure (CSP) and SNA and that between SNA and SAP under open-loop conditions of arterial baroreflex system. After a stabilization period during which CSP was kept at 100 mmHg for 30 min, we altered CSP sequentially in 10-mmHg step increments from 80 to 160 mmHg, and then in 10-mmHg decrements from 160 to 80 mmHg by the servo-controlled pump. Each step was maintained for 1 min. The command signal to the servo-controlled pump was generated by a dedicated laboratory computer (PC-9801RA21; NEC, Tokyo, Japan) through a digital-to-analog converter (DA12–4–98; Contec, Osaka, Japan). The same cycle of sequential changes in CSP was repeated three times over a 1-h period.

The electrical signals of CSP, SNA, 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 (ASIP-0260L; Canopus, Kobe, Japan) and then digitized at a rate of 2 kHz by means of an analog-to-digital converter (AD12–16D-98H; Contec).

Protocol 2: Measurement of operating points under closed-loop conditions. To measure the operating points under the closed-loop conditions of the arterial baroreflex system, we closed the feedback loop of the system with our servo-controlled pump system. As shown in Fig. 2, while digitizing SAP at a rate of 2 kHz through the analog-to-digital converter, the computer in real time commanded the power amplifier to make CSP identical with SAP. Using this technique, we were able to impose the same pressure waveform as SAP on the carotid sinus baroreceptor in the frequency range up to 10 Hz. CSP, SNA, and SAP were recorded for 3 min under the closed-loop conditions.

Protocol 3: Effects of hemorrhage on two arcs and operating points. To examine the effects of loss of blood on the two arcs and the operating point, we also characterized the two arcs and measured the operating points in various hemorrhagic states. We randomly allocated any two volumes of blood loss to each rat in the range of 0.5–2% of body weight by drawing and returning blood through the polyethylene tubing placed into the left common carotid artery.

Data Analysis

For purposes of data reduction, digitized data were resampled at 1 Hz after a moving average was applied. A preliminary study indicated that the responses of SAP and SNA to each pressure step imposed on bilateral carotid sinus baroreceptors reached steady state within 30 s (unpublished observation). Each steady-state value of the responses was therefore obtained by the averaging of the latter 30-s values during each pressure step of CSP. For each rat, SNA was normalized.
by the values at the minimum and maximum of CSP in protocol 1 after the background noise level averaged for 10 min was subtracted. Finally, the responses of SNA or SAP to the same level of CSP were averaged for each rat.

To parametrically characterize the relationship between the input and output, we analyzed the data using a four-parameter logistic equation model (15)

\[ y = p_4 + p_1 / (1 + \exp(p_2(x - p_3))) \]

where \( y \) is the output and \( x \) is the input. The four parameters are defined as follows: \( p_1 \) is the range of change in \( y \) (i.e., maximum minus minimum values of \( y \)); \( p_2 \) is the coefficient for calculation of gain; \( p_3 \) is the value of \( x \) corresponding to the midpoint over the range of \( y \); and \( p_4 \) is the minimum value of \( y \). The instantaneous gain is also calculated from the first derivative of the logistic function, and the maximum gain is \( -p_1 p_2 / 4 \) at \( x = p_3 \). After the parametric characterization, we identified the intersection of the two curves as the estimated operating point on the equilibrium diagram (Fig. 1C).

We obtained the actual operating points under the closed-loop conditions of the arterial baroreflex in baseline and various hemorrhagic states as means of a 3-min data period during which CSP was controlled to be identical with SAP.

Statistical Analysis

Paired measurements were analyzed by a linear regression analysis. The effects of blood loss on the operating points of the arterial baroreflex and on the four parameters for curve fitting were analyzed by analysis of variance with repeated measures. For each animal, the data were categorized into baseline, mild hemorrhage (0.5–1% of body weight), and severe hemorrhage (1–2% of body weight) according to the volume of blood loss. A post hoc analysis for multiple comparisons was performed by a Scheffe procedure. Differences were considered significant at \( P < 0.05 \). Values are expressed as means ± SD.

RESULTS

Shown in Fig. 3A is a representative example of original tracings of CSP, SNA, and SAP during the open-loop carotid sinus baroreflex control of SNA and SAP in the baseline state. The responses of SNA and SAP to a given level of CSP were consistent and reproducible throughout the 1-h recording protocol. The fact that SAP appears to be a mirror image of CSP indicates that the arterial baroreflex is a negative feedback system. Figure 3, B and C, displays the relationship between CSP and SNA and that between SNA and SAP of the example. Both of the curves characterizing the mechanoneural and neuromechanical arcs were sigmoidal and could be well described by the four-parameter logistic equation models; the RMS error of estimate for the mechanoneural arc was 1.8% and that for the neuromechanical arc was 0.3%.

Figure 4 demonstrates the effect of severe hemorrhage on the two arcs in the rat for which baseline data were presented in Fig. 3. As can be seen in Fig. 4A, severe hemorrhage did not affect the SNA response but attenuated the SAP response to CSP; severe hemorrhage seemed to affect only the neuromechanical arc. The differential effect of hemorrhage becomes even clearer if we draw the function curves of the two arcs as shown in Fig. 4, B and C. The blood loss markedly reduced the slope of the neuromechanical arc curve and...
shifted the curve downward, whereas the mechanoneural arc curve was similar to that in the baseline state.

To show how the operating point estimated from the two arc curves moved after severe hemorrhage, we plotted the two curves of Fig. 3 or Fig. 4 on the equilibrium diagram (Fig. 5). The pressure and SNA at the intersection in the baseline state (Fig. 5A) were computed to be 123 mmHg and 0.501 arbitrary units (a.u.), respectively, whereas the measured pressure and SNA at the true operating point under the closed-loop conditions of the arterial baroreflex were 122 mmHg and 0.502 a.u., respectively. On the other hand, pressure and SNA at the intersection after severe hemorrhage (Fig. 5B) were calculated to be 69 mmHg and 1.02 a.u., respectively, whereas the measured pressure and SNA at the true operating point were 68 mmHg and 1.02 a.u., respectively. A good agreement between the operating points estimated and measured was observed even after severe hemorrhage. In the baseline state, the two arc curves appeared to intersect each other near the midpoint, i.e., $p_3$, of each arc where each arc gain was maximum by definition (see METHODS). After severe hemorrhage, on the other hand, the intersection was located on the outlying portion of both curves.

The relationships between the operating points estimated by the equilibrium diagram analysis and those measured for 48 cases in 16 rats are illustrated in Fig. 6. For both arterial pressure and SNA, the estimated values are very close to the measured ones. The RMS
error of estimate for arterial pressure was 2% and that for SNA was 3%.

The multiple-comparison test indicated that hemorrhage significantly reduced arterial pressure and significantly increased SNA under the closed-loop conditions of the arterial baroreflex according to the severity of blood loss (Table 1). Hemorrhage did not affect any of the four parameters characterizing the mechanoneural arc curve, but reduced $p_1$, $p_2$, and $p_3$ of the neuromechanical arc curve.

**DISCUSSION**

We have shown that the operating point of the sympathetic arterial baroreflex estimated from the open-loop operational curves of the mechanoneural and neuromechanical arcs was in good agreement with that measured under the closed-loop conditions in various hemorrhagic states. These results indicate the validity of our framework for the analytic estimation of the operating point of the sympathetic baroreflex control of arterial pressure.

**Importance of Analytic Approach in Estimating Operating Point of Feedback System**

Although many earlier studies of arterial baroreflex elucidated its particular features, such as baroreceptor transduction properties (1, 25), central mechanisms (4, 8, 20, 23), and effector organ contributions (2, 7, 27, 29), few efforts have been made to functionally synthesize the individual components into an overall behavior of arterial baroreflex. Accumulation of detailed knowledge of fragmentary components does not allow us to analytically predict the unique value of arterial pressure determined by the arterial baroreflex or integratively understand how the arterial baroreflex is capable of attenuating external perturbation to the circulatory system.

The proposed framework made it possible to describe the integrative behavior of the sympathetic arterial baroreflex system. As shown in Fig. 7A, the controlled variable of the system, arterial pressure, is fed back into the mechanoneural arc. For the sake of simplicity, we linearized both functional curves. In the mechanoneural arc, a set-point pressure is displayed as reference. The functional meaning of the set-point pressure is the pressure that nullifies SNA on the mechanoneural arc curve (Fig. 7B). The manipulated variable SNA, then, affects the characteristics of the neuromechanical arc. In the neuromechanical arc, we assume an offset value of pressure as $P_0$. The functional meaning of $P_0$ is shown as the pressure that is generated by the cardiovascular system at the null SNA (Fig. 7B). Under the closed-loop conditions of the feedback system, the controlled and manipulated variables should converge on their respective values at the operating point. This framework allows us to explain analytically and show graphically the effect of hemorrhage on the arterial pressure and SNA under closed-loop conditions. Loss of blood volume, the external disturbance that we used in the present study, reduced both the gain and the offset of the neuromechanical arc curve and lowered the operating pressure and increased the operating SNA simultaneously (Fig. 7B).

**Fig. 6. Relationships between values analytically estimated and actually measured for arterial pressure (A) and SNA (B) at operating points of closed-loop conditions of arterial baroreflex among 48 cases in 16 rats. RMS, root mean square.**

**Table 1. Effects of hemorrhage on arterial pressure and sympathetic nerve activity under closed-loop conditions of arterial baroreflex and on 4 parameters of logistic equation model analysis for mechanoneural and neuromechanical arcs**

<table>
<thead>
<tr>
<th></th>
<th>Mild Hemorrhage (0.5–1% of BW)</th>
<th>Severe Hemorrhage (1–2% of BW)</th>
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<tbody>
<tr>
<td>Arterial pressure, mmHg</td>
<td>119 ± 5</td>
<td>74 ± 7†</td>
</tr>
<tr>
<td>Sympathetic nerve activity, a.u.</td>
<td>0.515 ± 0.044</td>
<td>0.941 ± 0.060†</td>
</tr>
<tr>
<td>Mechanoneural arc</td>
<td></td>
<td></td>
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<tr>
<td>$p_1$, a.u.</td>
<td>1.09 ± 0.02</td>
<td>1.11 ± 0.04</td>
</tr>
<tr>
<td>$p_2$, mmHg</td>
<td>0.078 ± 0.005</td>
<td>0.078 ± 0.008</td>
</tr>
<tr>
<td>$p_3$, mmHg</td>
<td>121 ± 2</td>
<td>121 ± 2</td>
</tr>
<tr>
<td>$p_4$, a.u.</td>
<td>−0.08 ± 0.009</td>
<td>−0.09 ± 0.010</td>
</tr>
<tr>
<td>Neuromechanical arc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$p_1$, mmHg</td>
<td>154 ± 6</td>
<td>78 ± 12†</td>
</tr>
<tr>
<td>$p_2$, a.u.</td>
<td>−2.9 ± 0.1</td>
<td>−1.8 ± 0.7†</td>
</tr>
<tr>
<td>$p_3$, a.u.</td>
<td>0.51 ± 0.05</td>
<td>0.50 ± 0.10</td>
</tr>
<tr>
<td>$p_4$, mmHg</td>
<td>58 ± 5</td>
<td>40 ± 11†</td>
</tr>
</tbody>
</table>

Values are means ± SD. BW, body weight; a.u., arbitrary unit. See METHODS for detailed explanation of procedure for normalization of value of sympathetic nerve activity and definition of 4 parameters of logistic equation model analysis. *P < 0.05 from baseline; †P < 0.05 from mild hemorrhage.
As shown in Fig. 7B, the set-point pressure and operating-point pressure are obviously different. The operating-point pressure is always lower than the set-point pressure. From Fig. 7A, according to the feedback control theory (6), ignoring $P_0$ yields the operating-point pressure as

$$P_{operating} = P_{set} \frac{G}{1 + GH}$$

where $P_{set}$ is the set-point pressure, $G$ is the gain of the mechanoneural arc, and $H$ is the gain of the neuromechanical arc. The operating-point and set-point pressures match only when the open-loop gain, i.e., $GH$, is infinitely large. The fact that the loop gain of the carotid sinus baroreflex is on average $2-3$ (6, 10, 15, 24) suggests that the operating-point pressure should be $65-75\%$ of the set-point pressure. Kent et al. (15) estimated the carotid sinus baroreflex characteristics in terms of the CSP-SAP relation and defined the set-point pressure as the pressure at which CSP equals SAP (Fig. 7C). However, this pressure is the operating-point pressure and thus should not be confused with the set-point pressure in our definition. The importance of the distinction between the operating-point and set-point pressures is supported by the fact that hemorrhage (34) lowered $P_{operating}$ by $23 \text{ mmHg}$ despite same MN arc curve and value of maximum gain of NM arc as those in Fig. 7A. If MN arc curve has an infinite gain, $P_{operating}$ matches with value at set point ($P_{set}$). Note that hemorrhage did not affect $P_{set}$ but lowered $P_{operating}$. In contrast to our framework, an earlier diagram (C) proposed by Kent et al. (15) described operating point as “set point.” They reported that intersection of CSP-SAP curve (solid line) and line of identity (dashed line) was termed “set point.” See text for detailed explanation.

Fig. 8. Equilibrium diagrams between 1 MN arc (solid line) and 2 NM arcs before (dotted line) and after (dashed line) imposition of external disturbance to NM arc. Effects of external disturbance that shifts NM arc only downward by 40 mmHg are simulated in 3 conditions of baroreflex system. C, Operating points before and after external disturbance, respectively. In normal conditions similar to Fig. 5A, effect of external disturbance is attenuated to $-10 \text{ mmHg}$ (A). If NM arc curve before external disturbance is shifted at lower left (B), effect of external disturbance results in a pressure fall by 23 mmHg despite same MN arc curve and value of maximum gain of NM arc as those in A. If NM arc curve is shifted at lower left and MN arc curve is shifted upward before the external disturbance (C), effect of external disturbance is not attenuated at all, even if values of maximum gains of two arcs should be same as those in A.
rhage greatly affected the operating-point pressure but did not affect the mechanoneural arc and, thereby, the set-point pressure. Although such an argument may seem a matter of semantics, we believe that clear distinction between the set-point and operating-point pressures in the framework of control theory is crucial for in-depth understanding of the physiological mechanism determining arterial pressure through the baroreflex system.

**Baroreflex Gain and Function**

Although the effect of external disturbance of the cardiovascular system on arterial pressure is attenuated by the arterial baroreflex system, the magnitude of attenuation depends on the baroreflex gain (6). Because the baroreflex gain itself also depends on the operating point, the quantitative analysis of the magnitude of attenuation is complex. To clarify the importance of the relationship between the gain of each arc and the operating point in attenuating the effect of the external disturbance, we give a few examples of simulation.

Three cases are simulated, in which the effect of the external disturbance is assumed to shift the neuromechanical arc only downward by 40 mmHg. In the first case (Fig. 8A), the two curves of the mechanoneural and neuromechanical arcs before the imposition of the external disturbance are assumed to be similar to those of the baseline state shown in Fig. 5A. In such a case, the two curves intersect each other at the point at which the instantaneous gain of each arc is peaked, and thus the instantaneous gain of the total baroreflex loop becomes maximal at the operating point of the closed-loop conditions. These factors determine the operating point after the imposition of the external disturbance and thus contribute toward attenuating the effect of external disturbance to $\Delta P = 10$ mmHg. In the second case (Fig. 8B), the neuromechanical arc before the external disturbance is assumed to be shifted at the lower left on the equilibrium diagram, whereas the characteristics of the mechanoneural arc are the same as those of Fig. 8A. Although the maximum gain of each arc is the same as that of Fig. 8A, the external disturbance could result in a pressure fall by 23 mmHg. In the third case (Fig. 8C), we suppose that the mechanoneural arc curve is shifted upward and that the neuromechanical arc curve is shifted as much as that of Fig. 8B. These conditions deviate the operating point toward the outlying portion of both curves. The effect of external disturbance, therefore, could not be reduced at all by such an ill-conditioned baroreflex system, even if the maximum gain of each arc remained unchanged. Thus it is fair to say that the arterial baroreflex system displays its role to the full if the instantaneous gain of each arc is

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**Fig. 9.** A: equilibrium diagram of MN (solid line) and NM (dotted line) arcs and graph showing instantaneous gains of MN arc ($\Delta SNA/\Delta CSP$) at various levels of CSP and NM arc ($\Delta SAP/\Delta SNA$) at various levels of SAP. In example simulated, arterial pressure at operating point (●) is 130 mmHg and total-loop gain at operating point is product of gain of MN arc at 130 mmHg of CSP (−0.017 a.u./mmHg, ○) and gain of NM arc at 130 mmHg of SAP (90 mmHg/a.u., ○). On other hand, maximum gain ($G_{max}$) of MN arc is given at 140 mmHg of CSP (−0.02 a.u./mmHg, ×), and $G_{max}$ of NM arc is given at 100 mmHg of SAP (120 mmHg/a.u., ×). Therefore, optimization index is calculated to be 64%. B: frequency distribution of optimization index of arterial baroreflex in baseline states for 16 rats. In every animal, optimization index was >90%. See text for definition of optimization index.
peaked at the operating point of the closed-loop conditions.

To examine whether the actual baroreflex system is optimized in terms of the gain, we reanalyzed the baroreflex gain of the experimental data obtained during the baseline states. Here we define an optimization index for a total-loop gain of the baroreflex system as follows

\[
\text{Optimization index (\%) } = \frac{G_{\text{Total,operating}}}{G_{\text{MN,\text{max}}} \times G_{\text{NM,\text{max}}}} \times 100
\]

where \(G_{\text{Total,operating}}\) is the total-loop gain at the operating point of the closed-loop conditions, \(G_{\text{MN,\text{max}}}\) is the maximum gain (\(G_{\text{max}}\)) of the mechanoneural arc, and \(G_{\text{NM,\text{max}}}\) is \(G_{\text{max}}\) of the neuromechanical arc. As illustrated in Fig. 9A, if the gains of both arcs were not maximal at the operating point, the total-loop gain should not be maximal at the operating point. In such a case, the optimization index should not attain 100%. Interestingly, in the baseline state, the optimization index was >90% (96 ± 2%) for all of the animals studied (Fig. 9B), indicating that the gain at the operating point is well optimized.

Many experimental studies of the sympathetic arterial baroreflex system with a variety of hypertensive (16, 20) or heart failure (4, 19) animal models and clinical studies of hypertension (22) and heart failure (17, 21) conclude that “baroreflex dysfunction” plays an important role in hypertension or heart failure. However, most of the studies did not strictly or accurately define what baroreflex dysfunction was. For example, some studies interpreted the low value of the baroreflex sensitivity (BRS) as baroreflex dysfunction and then concluded that this dysfunction contributed to a high level of arterial pressure in hypertensive patients (22) or an increased SNA in heart failure animals (19). On the basis of our framework, the BRS is equivalent to the maximum gain of the mechanoneural arc (\(G_{\text{MN,\text{max}}}\)). However, even if the animal model has a low value of \(G_{\text{MN,\text{max}}}\), it has a high value of \(G_{\text{NM,\text{max}}}\) and the normal value of \(G_{\text{Total,operating}}\), the animal should display a normal baroreflex function to attenuate the effect of external disturbance on arterial pressure. Moreover, as discussed in Importance of Analytic Approach in Estimating Operating Point of Feedback System, the arterial pressure and SNA at the operating point depend not only on the maximum gain of the mechanoneural arc but also on many other factors such as the set-point pressure and the characteristics of the neuromechanical arc (Fig. 7). Therefore, the low value of BRS is not directly linked to baroreflex dysfunction or a high level of arterial pressure or SNA. We should carefully interpret the experimental and clinical findings of the baroreflex studies and consider their functional meanings on the basis of an integrative framework. Our framework would be useful for a comprehensive understanding of baroreflex function.

Clinical Implications

A patient with Shy-Drager syndrome is destined to fall victim to idiopathic neurodegeneration of the vasomotor center in the brain stem (5, 30). Although the common clinical symptom of frequent orthostatic syncope attacks is well explained by central sympathetic baroreflex failure, a mechanism for the supine hypertension observed in some patients remains unclear. A recent study by Jordan et al. (12) reported that a relatively high level of muscle SNA in the supine position and unresponsiveness of muscle SNA to positional tilting were observed in some patients with supine hypertension and orthostatic hypotension. They also pointed out that the pressure fall caused by positional tilting was relatively large in the patient with supine hypertension. On the basis of these findings, the mechanism of supine hypertension and orthostatic hypotension in such central baroreflex failure could be explained graphically as illustrated in Fig. 10. We assume that the effect on the neuromechanical arc of standing is similar to that of hemorrhage, i.e., standing lowers the gain and offset of the neuromechanical arc. In contrast to a normal subject (Fig. 10A), in central baroreflex failure the mechanoneural arc curve is assumed not to be able to respond to a change in arterial pressure (11, 13, 28), and thereby the mechanoneural arc curve becomes a vertical line on the equilibrium diagram (Fig. 10B). Our framework shows that...
the pressure fall induced by standing could not be attenuated at all in central baroreflex failure and clearly suggests that both the level of supine pressure and the magnitude of pressure fall should be considered functions of the level of sympathetic vasomotor activity. Therefore, if the sympathetic activity unresponsive to standing is constant at the higher level, the patient could display orthostatic hypotension with supine hypertension and the magnitude of pressure fall could be larger. Although these suggestions are entirely speculative, such an analytic framework gives us a systematic tool for understanding the pathophysiology of baroreflex failure.

Limitations

In the present study, we excluded the efferent effect of vagally mediated arterial baroreflex and used an anesthetic agent. This could affect the properties of the two arcs, and then the estimated parameters for the two arcs could be biased. The two arc curves that we characterized in the present study would be specific to the renal bed because SNA was recorded from the renal sympathetic fiber. In summary, we propose an analytic framework for understanding the sympathetic baroreflex control of arterial pressure. We divided the feedback system into two arcs, mechanoneural and neuromechanical. We characterized the mechanoneural arc by the response of SNA to baroreceptor pressure and the neuromechanical arc by the response of SAP to SNA. The intersection between the two functional curves on the equilibrium diagram gives the operating arterial pressure. Such an approach could help us analytically understand the integrative function of the sympathetic baroreflex system.

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