ESTIMATION OF TOTAL BAROREFLEX GAIN USING AN EQUILIBRIUM DIAGRAM BETWEEN SYMPATHETIC NERVE ACTIVITY AND ARTERIAL PRESSURE

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Abstract- **The arterial baroreflex system may be divided into the mechano-neural arc from pressure input to sympathetic nerve activity (SNA) and the neuro-mechanical arc from SNA to arterial pressure (AP). We explored a new strategy to estimate total baroreflex gain (G_{baro}) using an equilibrium diagram between the mechano-neural and neuro-mechanical arcs. In 8 anesthetized rabbits, a neck suction procedure (NS) was simulated by shifting isolated carotid sinus pressure above AP by 30 mmHg. NS shifted the mechano-neural arc alone, yielding the slope of the neuro-mehcnaical arc around the operating point. A lower body negative pressure procedure (LBNP) was simulated by 5-ml/kg hemorrhage. LBNP shifted the neuro-mechanical arc alone, yielding the slope of the mechano-neural arc around the operating point. By multiplying the slopes of the neuro-mechanical and mechano-neural arcs, we obtained G_{baro} under baroreflex closed-loop conditions. We also estimated G_{baro} from the relationship between isolated carotid sinus pressure and AP under baroreflex open-loop conditions. G_{baro} estimated by the equilibrium diagram matched reasonably well with that estimated by the open-loop method ($y=1.06x-0.09$, $r^2=0.96$, SEE=0.15). In conclusion, G_{baro} could be estimated using the equilibrium diagram without opening the baroreflex negative feedback loop when data obtained from NS and LBNP were combined in a given subject.**

Keywords- **open-loop analysis, closed-loop analysis**

I. INTRODUCTION

Estimation of open-loop baroreflex gain (G_{baro}) in terms of pressure output relative to pressure input is essential for evaluating the total buffering effect of the arterial baroreflex. Although estimation of G_{baro} based on the open-loop systems analysis is theoretically straightforward, it has a practical drawback that an isolation technique of the baroreceptor regions is not applicable to clinical settings. Accordingly, baroreflex sensitivity (BRS) of heart rate is widely used as the substitute for G_{baro} in clinical settings. Although BRS has shown to be of clinical importance, information on BRS alone is not sufficient for thorough characterization of the arterial baroreflex system as a negative feedback system. As an example, the extent of attenuation of exogenous disturbance by the arterial baroreflex could not be assessed by BRS. In contrast, the extent of the attenuation is calculated to be $1/(1+G_{baro})$ if G_{baro} is specified. The aim of the present study was to develop a new strategy to estimate G_{baro} without opening baroreflex negative feedback loop. To achieve this, we applied the framework of equilibrium diagram analysis between sympathetic nerve activity (SNA) and arterial pressure (AP) [1, 2] to the data obtained from animal models for neck suction (NS) [3] and lower body negative pressure (LBNP).

This study was supported by Grants-in-Aid for Scientific Research (B 11694337, B 12557066, C 12670716) and for Encouragement of Young Scientists (13770378, 13770379) from the Japan Society for the Promotion of Science, by Research Grants for Cardiovascular Diseases (11C-3) and a Health Sciences Research Grant for Advanced Medical Technology from the Ministry of Health and Welfare of Japan, Research and Development Grant for Applying Advanced Computational Science and Technology from Japan Science and Technology Corporation, Program for Promotion of Fundamental Studies in Health Science of the Organization for Pharmaceutical Safety and Research, Ground-Based Research Grant for the Space Utilization from National Space Development Agency of Japan and Japan Space Forum.

II. THEORETICAL CONSIDERATION

The arterial baroreflex system may be divided into two principal arcs: a mechano-neural arc representing the relationship between AP input and SNA output, and a neuro-

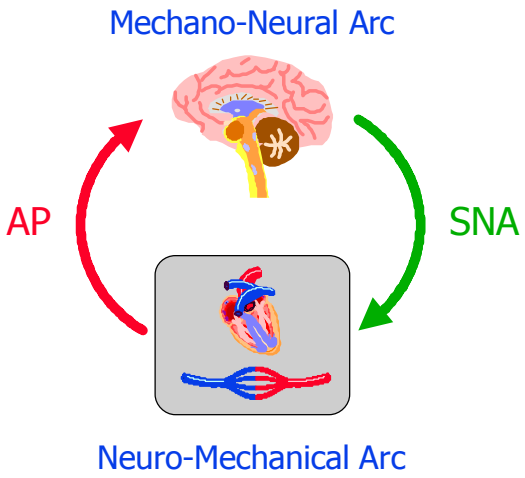

Fig. 1. Closed-loop operation of the circulatory system. Arterial pressure (AP) alters sympathetic nerve activity (SNA) via the mechano-neural arc, whereas SNA in turn affects AP via the neuro-mechanical arc.

Report Documentation Page

Report Date	Report Type	Dates Covered (from... to)
25 Oct 2001	N/A	-

Title and Subtitle Estimation of Total Baroreflex Gain Using An Equilibrium Diagram Between Sympathetic Nerve Activity and Arterial Pressure	**Contract Number**
	Grant Number
	Program Element Number
Author(s)	**Project Number**
	Task Number
	Work Unit Number
Performing Organization Name(s) and Address(es) Department of Cardiovascular Dynamics National Cardiovascular Center Research Institute Japan	**Performing Organization Report Number**
Sponsoring/Monitoring Agency Name(s) and Address(es) US Army Research, Development & Standardization Group (UK) PSC 802 Box 15 FPO AE 09499-1500	**Sponsor/Monitor's Acronym(s)**
	Sponsor/Monitor's Report Number(s)

Distribution/Availability Statement
Approved for public release, distribution unlimited

Supplementary Notes
Papers from 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, October 25-26, 2001 held in Istanbul, Turkey. See also ADM001351 for entire conference on cd-rom., The original document contains color images.

Abstract

Subject Terms

Report Classification unclassified	**Classification of this page** unclassified
Classification of Abstract unclassified	**Limitation of Abstract** UU

Number of Pages
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mechanical arc representing the relationship between SNA input and AP output (Fig. 1). Changes in AP alter SNA via the mechano-neural arc, whereas changes in SNA, in turn, affect AP. AP is maintained against exogenous perturbation by this closed-loop negative feedback of the arterial baroreflex system.

With respect to the static characteristics of the two arcs, we can construct an equilibrium diagram for the two arcs as shown in Figure 2. The intersection between the two arcs gives an operating point of the arterial baroreflex [1, 2]. In the equilibrium diagram, G_{baro} around the operating point can be calculated by multiplying the slope of the neuro-mechanical arc (∠NM) and that of the mechano-neural arc (∠MN). Estimation of G_{baro} using the equilibrium diagram is comprised of the following steps.

First, suppose that NS is applied to test the circulatory system. Since NS increases effective pressure to the carotid sinus baroreceptors, SNA at a given AP decreases, thereby shifting the mechano-neural arc leftward. Because the neuro-mechanical arc is unaffected by NS, the operating point moves from point "a" to point "b" during NS (Fig. 2). ∠NM is then estimated by the slope of a line "a-b" relative to the horizontal axis.

Second, suppose that LBNP is applied to test the circulatory system. Since LBNP causes the redistribution of blood volume toward the lower body, AP at a given SNA decreases during LBNP. Thus, the neuro-mechanical arc shifts downward during LBNP, whereas the mechano-neural arc remains unchanged. The operating point would move from point "a" to point "c" during LBNP (Fig. 2). ∠MN is then estimated by the slope of a line "a-c" relative to the vertical axis.

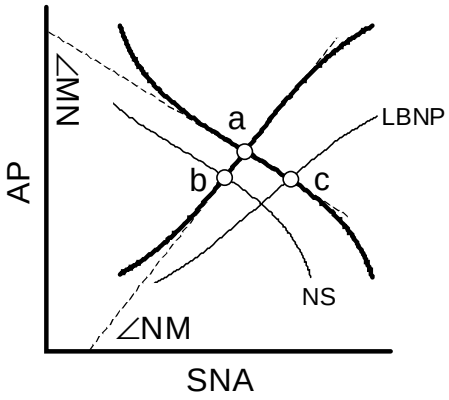

Fig. 2. Equilibrium diagram between sympathetic nerve activity (SNA) and arterial pressure (AP). Thick curves indicate normal equilibrium. a: normal operating point. b: operating point during neck suction (NS). c: operating point during lower body negative pressure (LBNP). ∠NM: slope of the neuro-mechanical arc. ∠MN: slope of the mechano-neural arc.

Finally, G_{baro} is calculated by multiplying ∠NM by ∠MN.

III. METHODS

In order to validate the strategy described in the previous section, we performed an animal experiment as follows. Eight Japanese white rabbits were anesthetized via intravenous injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/kg). Bilateral carotid sinuses were isolated from the systemic circulation and intracarotid sinus pressure (CSP) was servo-controlled. Bilateral vagi and aortic depressor nerves were sectioned to eliminate the effects of cardiopulmonary and aortic arch baroreflexes. The stainless steel wire electrodes were attached to the left cardiac sympathetic nerve to record SNA. CSP, SNA, and AP data were digitized at 200 Hz and stored on the hard disk of a dedicated laboratory computer system for later analyses.

Protocol 1 (*open-loop protocol*). CSP was changed stepwise from 60 to 140 mmHg with an increment of 20 mmHg. Each pressure step was maintained for 60 s, and the AP response was measured by averaging the last 10-s data during each pressure step. G_{baro} around the operating point was estimated from the least-squared fit of a logistic function to the CSP-AP data pairs [4].

Protocol 2 (*NS model protocol*). CSP was adjusted to AP in order to close the baroreflex negative feedback loop. After the steady state of AP was reached, CSP was raised above AP by 30 mmHg for 60 s to mimic NS (positive CSP deviation) [3]. CSP was also dropped below AP by 30 mmHg for 60 s to mimic positive pressure around the neck (negative CSP deviation). ∠NM around the operating point was calculated from the slope of linear regression for the SNA-AP data pairs obtained before and during the CSP deviations.

Protocol 3 (*LBNP model protocol*). CSP was adjusted to AP in order to close the baroreflex negative feedback loop. After the steady state of AP was obtained, hemorrhage of 5 ml/kg was performed to mimic LBNP. AP-SNA data pair was obtained 60-s after the completion of the hemorrhage. The blood was then restored. ∠MN around the operating point was calculated from the slope of linear regression for the CSP (and thus AP) and SNA data pairs obtained before, during, and after the hemorrhage.

After estimating ∠NM and ∠MN in *Protocols 2* and *3*, G_{baro} around the operating point was calculated from ∠NM×∠MN. To expand the range of G_{baro} to be tested, the three protocols were repeated using unilateral CSP input.

IV. RESULTS

Figure 3 shows typical recordings obtained from *Protocols 1*, *2* and *3*. In *Protocol 1*, CSP was increased stepwise from 60 to 140 mmHg. SNA and AP decreased in response to the increment in CSP. In *Protocol 2*, CSP was adjusted to AP for 0-1 min, then increased above AP by 30 mmHg for 1-2 min. CSP was again adjusted to AP during 2-3 min, then decreased below AP by 30 mmHg for 3-4 min. SNA and AP decreased in response to the positive CSP deviation, whereas increased in response to the negative CSP deviation. In *Protocol 3*, CSP was adjusted to AP throughout the protocol. AP (and CSP) was decreased by the hemorrhage. SNA increased via the arterial baroreflex. The opposite responses in AP and SNA were observed during the restoration of blood.

Figure 4 shows a representative equilibrium diagram between SNA and AP obtained from one animal. The solid and open circles represent the neuro-mechanical and mechano-neural arcs, respectively, obtained from *Protocol 1*. The solid triangles represent the SNA-AP data pairs obtained from *Protocol 2*. ∠NM indicates the slope of liner regression for the SNA-AP data pairs. The open triangles represent the AP-SNA data pairs obtained from *Protocol 3*. ∠MN indicates the slope of liner regression for the AP-SNA data pairs. G_{baro} was estimated by multiplying ∠NM and ∠MN together.

G_{baro} estimated using the equilibrium diagram between SNA and AP (*Protocols 2* and *3*) matched reasonably well with G_{baro} estimated by the open-loop method (*Protocol 1*) across the 8 animals ($y = 1.06x - 0.09$, $r^2 = 0.96$, SEE = 0.15).

V. DISCUSSION

Mohrman and Heller first proposed the concept of equilibrium in the arterial baroreflex system based on the negative feedback nature of the arterial baroreflex system [1]. We confirmed that the operating point of AP was well determined by the intersection between the mechano-neural and neuro-mechanical arcs using a baroreflex open-loop experiment in a previous study [2]. The equilibrium diagram of the arterial baroreflex system indicates that G_{baro} can be estimated by multiplying the slope of the neuro-mechanical arc and that of the mechano-neural arc around the operating point. If we intentionally disturb one of the arcs, the slope of the other undisturbed arc can be estimated around the operating point as shown in Figure 2. Once the disturbances on the two arcs are combined in a given subject, G_{baro} can be estimated from ∠NM×∠MN. We confirmed this framework of estimating G_{baro} in the anesthetized rabbit model for NS and LBNP.

Neck suction is frequently used to estimate baroreflex function in clinical settings. However, because of the counteraction by the aortic baroreflex, NS alone does not allow us to estimate G_{baro} in terms of pressure output relative to the pressure input [3]. However, the equilibrium diagram method is not flawed by the counteraction by the aortic baroreflex during NS. Since the counteraction by the aortic baroreflex takes place in the mechano-neural arc, the neuro-mechanical arc remains unchanged during NS even in the presence of the aortic baroreflex. The aortic baroreflex merely attenuates the amount of leftward shift in the mechano-neural arc induced by NS. Therefore, we can obtain ∠NM using NS by simply ignoring the counteracting effect of the aortic baroreflex.

We assumed that LBNP would shift the neuro-mechanical arc downward via blood volume redistribution

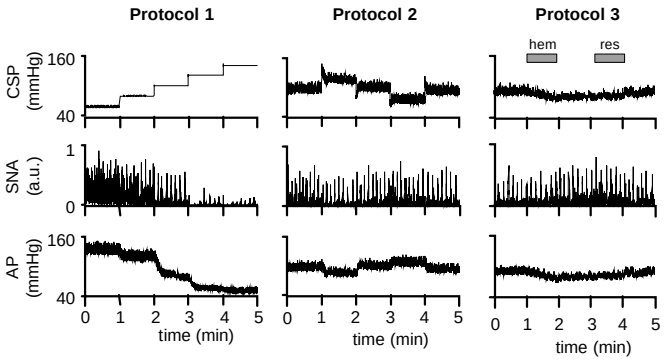

Fig. 3. Typical recordings of carotid sinus pressure (CSP), sympathetic nerve activity (SNA), and arterial pressure (AP) obtained from *Protocols 1*, *2*, and *3*. hem: hemorrhage, res: restoration.

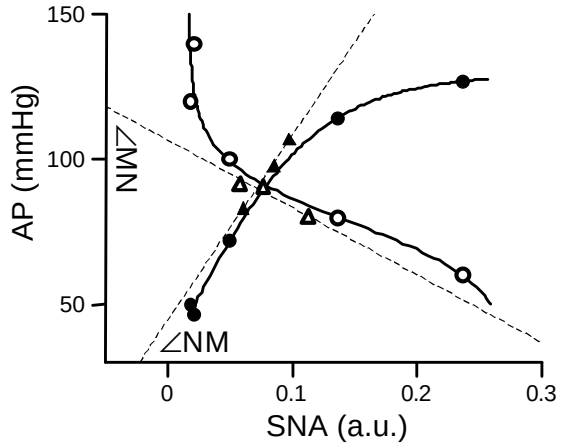

Fig. 4. Typical equilibrium diagram and estimated slopes of the mechano-neural and neuro-mechanical arcs. The open circles indicate AP-SNA data pairs obtained from *Protocol 1*. The solid circles indicate SNA-AP data pairs obtained from *Protocol 1*. The solid triangles indicate SNA-AP data pairs obtained from *Protocol 2*. The open triangles indicate AP-SNA data pairs obtained from *Protocol 3*.

without affecting the mechano-neural arc (Fig. 2). With vagal nerves kept intact, however, LBNP would affect SNA not only via the arterial baroreflex but also via cardiopulmonary low-pressure baroreflexes. To integrate the low-pressure baroreflexes into the equilibrium diagram method, characterization of the vagally mediated low-pressure baroreflexes by treating AP as a system variable would become necessary. This formulation has rationale in that the central role of the baroreflex systems is the maintenance of AP but not of central venous pressure. As an example, Hosomi et al. analyzed interactions between high- and low-pressure baroreflexes during mild hemorrhage by treating AP as a system variable [5]. Nevertheless, further studies are clearly required to determine whether the equilibrium diagram method is truly valid when low-pressure baroreflexes are operative.

VI. CONCLUSION

G_{baro} can be estimated without opening the baroreflex negative feedback loop using the equilibrium diagram of the arterial baroreflex system. We assume that NS and LBNP can be used to shift the mechano-neural and neuro-mechanical arcs, respectively. Although further studies are clearly required before actual application of the equilibrium diagram method in clinical settings, the presented framework would be a new step toward estimating G_{baro} in terms of pressure output relative to pressure input in clinical settings.

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