Time-dependent Changes in Open-loop Gains of Baroreflex Systems after Massive Hemorrhage

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Abstract To quantify the effects of massive hemorrhage (5 ml/kg body weight) on the individual arterial baroreflex systems in the dog, changes in the open-loop gains of the intact arterial pressure control system ($G_{\text{intact}}$), the carotid sinus baroreflex system ($G_{CS}$), and the vagally mediated and aortic arch baroreflex systems ($G_{V}$) were measured repeatedly from the response to quick mild hemorrhage (2 ml/kg body weight) before and after massive hemorrhage. Fifteen mongrel adult dogs were divided into 3 groups, i.e., the control, vago-aortic nerve-severed, and carotid sinus-denervated groups. The dogs anesthetized with Nembutal (35 mg/kg body weight) were bled by 2 ml/kg body weight within 2 sec through a catheter inserted into the abdominal aorta. The arterial pressure change after mild hemorrhage was monitored via a catheter placed in the aortic arch. The open-loop gain of the baroreflex system was assessed as $(\Delta AP_I/\Delta AP_S - 1)$, where $\Delta AP_I$ and $\Delta AP_S$ are the immediate and steady-state falls in arterial pressure following mild hemorrhage. The mean values of $G_{\text{intact}}$, $G_{CS}$, and $G_{V}$ before massive hemorrhage were 7.8, 2.0, and 1.8, respectively. Since $G_{\text{intact}}$ is not a simple summation of $G_{CS}$ and $G_{V}$, it is speculated that the carotid sinus baroreflex system interacts in a facilitatory way with the vagally mediated and aortic arch baroreflex systems. After massive hemorrhage, $G_{\text{intact}}$ changed along a time course of parabolic form, whereas $G_{CS}$ did not change and $G_{V}$ decreased. These results suggest that the time-dependent change of $G_{\text{intact}}$ after massive hemorrhage depends on the change in the open-loop gain of the baroreflex system making a facilitatory interaction.

Hemorrhage is a common disturbance of the cardiovascular system. Effects of hemorrhage on the cardiovascular system vary with bled volume. After massive hemorrhage (5 ml/kg body weight), the overall open-loop gain of the rapidly acting arterial pressure control system ($G_{\text{intact}}$) in the cat decreases to 43% at 35 min and then gradually increases up to a control level (Hosomi, 1978). A question arises to which of the following three subsystems of the baroreflex system the change
in $G_{\text{intact}}$ can be attributed: the carotid sinus baroreflex system (CS-system), the vagally mediated and aortic arch baroreflex systems (V-system), or the interacting system between the CS-system and the V-system ($\&$-system) (Hosomi and Sagawa, 1979). The present study attempts to answer this question by estimating the effects of massive hemorrhage on the individual open-loop gains of the CS-system ($G_{\text{CS}}$), the V-system ($G_{V}$), and the $\&$-system ($G_{\&}$). $G_{\text{intact}}$, $G_{\text{CS}}$, and $G_{V}$ are estimated from the mean arterial pressure response to quick mild hemorrhage, which perturbs the arterial pressure control system but does not affect the characteristics of the system, i.e., an open-loop gain, the time constant of arterial pressure response to mild hemorrhage, and so forth. $G_{\&}$ is assumed as $G_{\text{intact}} - G_{\text{CS}} - G_{V}$. Estimation of $G_{\text{intact}}$, $G_{\text{CS}}$, $G_{V}$, and $G_{\&}$ is repeated several times before and after massive hemorrhage. The repeated tests at one level of blood volume allowed identification of a time-dependent variation in $G_{\text{intact}}$, $G_{\text{CS}}$, $G_{V}$, and $G_{\&}$.

MATERIALS AND METHODS

Fifteen mongrel adult dogs of both sexes, weighing 9.3±2.0 (mean±SD) kg, were anesthetized by intravenous injection of Nembutal in a dose of 35 mg/kg body weight and heparinized. The dogs were intubated intratracheally and breathed room air.

Arterial pressure was measured by a catheter-transducer system; the catheter was advanced into the aortic arch via the right omocervical artery. Two ml of blood per kg body weight (quick mild hemorrhage) was withdrawn into a hand-driven syringe within 2 sec through a large-bore catheter inserted into the abdominal aorta via the right femoral artery. Two min later, the bled blood was reinfused into the abdominal aorta through the large-bore catheter.

Displacement of the syringe piston was converted into an electric signal by a sliding resistor attached to the piston shaft. Changes in the bled volume (displacement of the syringe piston), the arterial pressure, and the mean arterial pressure determined by the use of a filter with a time constant of 2 sec were recorded on a strip chart (Fig. 1) (Hosomi and Yokoyama, 1981).

The quick mild hemorrhage and reinfusion procedure (test procedure) were repeated several times at a regular interval of 10 min under the intact condition (Fig. 2 and Fig. 3 (INTACT)). The dogs were then divided into 3 groups, i.e., the control, vago-aortic nerve-severed, and carotid sinus-denervated groups.

In the control group, 5 ml of blood per kg body weight (massive hemorrhage) was withdrawn into a reservoir through the large-bore catheter within 1 min. After stabilization of the arterial pressure, the test procedure was again repeated several times over 2 hr (Fig. 2).

In the vago-aortic nerve-severed group, the vagi and the aortic nerves were sectioned together at the cricocartilage level. After the arterial pressure settled down around the control level, the test procedure was repeated several times (Fig. 3)
Fig. 1. Sample records of arterial pressure response to quick mild hemorrhage and notations. Topmost trace: time in minutes. Second trace: stepwise displacement of the piston, indicating quick mild hemorrhage. Third trace (MAP): mean arterial pressure. $\Delta AP_I$: immediate pressure fall after hemorrhage. $\Delta AP_s$: steady-state pressure fall 1 to 2 min after hemorrhage. Fourth trace (AP): arterial pressure.

Fig. 2. Typical experimental records of mean arterial pressure response to quick mild hemorrhage before and after massive hemorrhage in one dog. The legends for the topmost trace and 2nd trace are the same as those in Fig. 1. Third trace: mean arterial pressure response to quick mild hemorrhage before massive hemorrhage. Fourth and 5th traces: mean arterial pressure responses to hemorrhage 40 and 120 min after massive hemorrhage, respectively.

(V). Massive hemorrhage was then imposed on the dogs. After the arterial pressure stabilized, the test procedure was again repeated several times over 2 hr. In the carotid sinus-denervated group, both carotid sinus nerves were function-
Fig. 3. Typical experimental records of mean arterial pressure responses to quick mild hemorrhage under the intact nerve condition (INTACT) (3rd trace), under the vagotomized and aortic nerve-severed condition (V) (4th trace), under the carotid sinus-denervated condition (CS) (5th trace), and under the carotid sinus-denervated and the subsequently vagotomized and aortic nerve-severed condition (V CS) (6th trace). The legends for the topmost and 2nd traces are the same as those in Fig. 1. Records for INTACT and V were taken in one dog and those for CS and V CS in another.

ally blocked by ligating them between the internal and the external carotid arteries. After the arterial pressure stabilized at a level higher than that of the control level, the test procedure was repeated several times (Fig. 3 (CS)). Massive hemorrhage was then imposed on the dogs. After the subsequent pressure change stabilized, the test procedure was repeated several times over 2 hr. In order to confirm whether the carotid sinus nerves were blocked completely or not, the test procedure was performed after vagotomy (Fig. 3 (V CS)). If elimination of the carotid sinus baroreflex system was incomplete, the data were discarded.

To estimate the open-loop gain ($G$) of the arterial baroreflex system, the following method (Hosomi, 1978) was used. In short, an immediate arterial pressure drop ($\Delta P_1$) after completion of quick mild hemorrhage and a steady-state arterial pressure drop ($\Delta P_s$) 1 to 2 min after quick mild hemorrhage were measured (Fig. 1). According to the linear control theory (Milhorn, 1966), $G$ of the arterial baroreflex system was defined as $\Delta P_1/\Delta P_s - 1$.

RESULTS

Experiment under the intact condition

The mean arterial pressure response to quick mild hemorrhage, observed
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Fig. 4. Changes in $G_{\text{intact}}$ in 5 dogs (#1-#5) and mean $G_{\text{intact}}$ (MEAN) caused by massive hemorrhage. Massive hemorrhage was imposed on each dog at time 0. The perpendicular line in Fig. MEAN is S.D.

before massive hemorrhage, is shown in Figs. 2 and 3 (INTACT). The values of $G_{\text{intact}}$ in 5 dogs were plotted in the respective figures (#1-#5) of Fig. 4.

$G_{\text{intact}}$ in Fig. 4 (#1) decreased from 5.4 (the mean value of $G_{\text{intact}}$ before massive hemorrhage) to 1.6 about 60 min after massive hemorrhage and then increased up to 9.0 about 110 min thereafter. #3, #4, and #5 also show similar time-dependent changes in $G_{\text{intact}}$ to #1 after massive hemorrhage, although the mean value of $G_{\text{intact}}$ before massive hemorrhage, the minimum values of $G_{\text{intact}}$ and the time course of changes in $G_{\text{intact}}$ after massive hemorrhage varied from dog to dog. The mean value ($\pm$ S.D.) of $G_{\text{intact}}$ before massive hemorrhage, first averaged within individual dogs and then again averaged for 5 dogs, was 7.8 ($\pm$ 3.8). The values of $G_{\text{intact}}$ after massive hemorrhage were pooled within every 30 min for each dog and then averaged for 5 dogs. The mean values of $G_{\text{intact}}$ before and after massive hemorrhage were plotted in Fig. 4 (MEAN) (CLEVELAND and KLEINER, 1975). Because of a disparity in the individual characteristics, especially in the time course of changes in $G_{\text{intact}}$ after massive hemorrhage as mentioned before, there was no significant difference among the mean values of $G_{\text{intact}}$ ($P>0.1$ by Wilcoxon’s location test). However, a time-dependent parabolic change in $G_{\text{intact}}$ after massive hemorrhage can be observed in the individual dogs.

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Fig. 5. Changes in $G_{CS}$ in 5 dogs (#6-#10) and mean $G_{CS}$ (MEAN) caused by massive hemorrhage. Massive hemorrhage was imposed on each dog at time 0. The perpendicular line in Fig. MEAN is S.D.

**Experiment under the vago-aortic nerve-severed condition**

The mean arterial pressure response to quick mild hemorrhage, observed before massive hemorrhage, is shown in Fig. 3(V). The remaining arterial baroreflex system after severing the vagi and the aortic nerves is the carotid sinus baroreflex system. Therefore, the open-loop gain estimated under the vago-aortic nerve-severed condition corresponds to that of the carotid sinus baroreflex system ($G_{CS}$). The values of $G_{CS}$ in 5 dogs were plotted in the respective figures (#6-#10) of Fig. 5. #6, #7, and #9 did not show any characteristic change. #8 and #10 showed a slight decrease and increase, respectively. The mean value ($\pm$ S.D.) of $G_{CS}$ before massive hemorrhage, first averaged within individual dogs and then averaged for 5 dogs, was 2.0 ($\pm$0.6). The values of $G_{CS}$ after massive hemorrhage were pooled within every 30 min for each dog and then averaged for 5 dogs. The mean values of $G_{CS}$ before and after massive hemorrhage were plotted in Fig. 5 (MEAN) (CLEVELAND and KLEINER, 1975). The difference between locations of the $G_{CS}$ values before and after massive hemorrhage was not significant at the 10% level for the individual dogs by Wilcoxon’s location test. Therefore, $G_{CS}$ was not affected by massive hemorrhage.

**Experiment under the carotid sinus-denervated condition**

The mean arterial pressure response to mild hemorrhage observed before massive hemorrhage after sectioning the carotid sinus nerves is shown in Fig. 3 (CS). The vagally mediated and aortic arch baroreflex systems remain after sectioning the carotid sinus nerves. Therefore, the open-loop gain estimated under the carotid sinus-denervated condition is the sum of those of the vagally mediated and aortic arch baroreflex systems ($G_{V}$). The values of $G_{V}$ in 5 dogs were plotted in the respective figures (#11-#15) of Fig. 6. The mean value ($\pm$ S.D.) of $G_{V}$ before massive hemorrhage, first averaged within individual dogs and then averaged for 5 dogs,
Fig. 6. Changes in $G_v$ in 5 dogs (#11–#15) and mean $G_v$ (MEAN) caused by massive hemorrhage. Massive hemorrhage was imposed on each dog at time 0. The perpendicular line in Fig. MEAN is S.D.

was 1.8 (± 1.0). The values of $G_v$ after massive hemorrhage were pooled within every 30 min for each dog and then averaged for 5 dogs. The mean values of $G_v$ before and after massive hemorrhage were plotted in Fig. 6 (MEAN) (CLEVELAND and KLEINER, 1975). The mean values of $G_v$ decreased gradually after massive hemorrhage and steadied 60 to 120 min later. The mean values of $G_v$ between 60 and 90 min and between 90 and 120 min after massive hemorrhage are significantly different from the mean value of $G_v$ before massive hemorrhage ($P<0.05$ by Wilcoxon’s location test).

Experiment under the carotid sinus-denervated and vago-aortic nerve-severed condition

The mean arterial pressure response to quick mild hemorrhage after sectioning the carotid sinus nerves, the vagi and the aortic nerves is shown in Fig. 3 (V CS). Arterial pressure was not restored after hemorrhage. Therefore, the open-loop gain of the rapidly acting arterial pressure control system was 0.

DISCUSSION

*The open-loop gains of the arterial baroreflex systems.* The value of $G_{\text{intact}}$ estimated in the present study was 7.8. This is far greater for the overall open-loop gain of the intact arterial baroreflex system in the dog than the simple summation of the reflex gains individually determined for the CS-system (SCHER and YOUNG, 1963; SAGAWA and WATANABE, 1965) and the V-system (ALLISON et al., 1969; ANGELL JAMES and DALY, 1970) by the open-loop experiments. However, it is not a surprising result. VALENTINUZZI et al. (1972) inflated an aortic balloon to stimulate both reflex receptors simultaneously and estimated the overall open-loop gain (22) of the combined reflex control of arterial pressure in the dog. HOSOMI
(1978) estimated the overall open-loop gain (20) of the intact arterial pressure control system of the anesthetized cat by the quick mild hemorrhage method, where an arterial pressure fall caused by hemorrhage stimulated all the arterial baroreceptors simultaneously. Hosomi and Sagawa (1979) withdrew 10% of the total blood volume from the abdominal aorta in the conscious dog with the baroreflex systems intact and estimated the open-loop gain at 9.12. Hosomi and Yokoyama (1980) applied the quick mild hemorrhage method to the anesthetized dog and obtained an open-loop gain of 9.4. In all the methods used in the above-cited papers, the baroreceptors located at the carotid sinus, the aortic arch and the cardiopulmonary region were simultaneously stimulated by a pressure change, that is, with the closed-loop method. The discrepancy in size between $G_{\text{intact}}$ and the sum of $G_{\text{CS}}$ and $G_V$ will be discussed in the following sections.

$G_V$ estimated in the present study was 1.8. $G_V$ estimated by the closed-loop method was 0.9 (Hosomi and Sagawa, 1979). $G_V$'s estimated by the open-loop method were 0.5 (Allison et al., 1969) and 1.0 (Angell James and Daly, 1970). There is a big difference between $G_V$ estimated in the present study and $G_V$'s reported by the other authors. This might depend on differences in the method used for estimating $G_V$. The different point in the method is the size of the input for analyzing the V-system. We used mild hemorrhage which caused an immediate pressure drop of about 15 mmHg. Hosomi and Sagawa (1979) used 10% hemorrhage which caused the arterial pressure change of 67 mmHg. Allison et al. (1969) used a 30 mmHg step change in the aortic arch pressure, and Angell James and Daly (1970) a 17.7 mmHg step change. The size of the input used in the present study is the smallest one. The small input analysis is always preferred to analyze a nonlinear system like the baroreceptor reflex system (Angell James, 1971; Ito, 1969; Katona and Barnett, 1969; Levison et al., 1966; Spickler et al., 1967). Therefore, the estimate of $G_V$ in the present study may be the best one.

$G_{\text{CS}}$ estimated in the present study was 2.0. $G_{\text{CS}}$'s estimated by the closed-loop method were 2.3 (Edis, 1971), 1.3 (Pelletier et al., 1971), 1.64 (Hosomi and Sagawa, 1979), and 1.68 (Hosomi and Yokoyama, 1980). $G_{\text{CS}}$'s estimated by the open-loop method were 2.0 (Scher and Young, 1963), 1.52 (Sagawa and Watanabe, 1965), and 2.0 (Schmidt et al., 1971). Therefore, a $G_{\text{CS}}$ of 2.0 estimated in the present study would be a reasonable value.

The sum of $G_{\text{CS}}$ and $G_V$ estimated in the present study is 3.8. If both baroreflex systems worked independently, this value should have been the same as that of $G_{\text{intact}}$. However, there is a considerably big difference of 4.0 between the sum of both $G_{\text{CS}}$ and $G_V$ and $G_{\text{intact}}$. Therefore, it is a reasonable hypothesis that both the CS-system and the V-system are interacting with each other, as Hosomi and Sagawa (1979) suggested. Kendrick et al. (1979) reported that combined stimulation of both the carotid sinus and the aortic nerves ipsilaterally resulted in systemic arterial depressor responses that were greater than the respective sum of the responses to separate stimulation of these nerves. They also suggested that an interaction be-
between the aortic and the carotid baroreceptor reflexes occurs centrally. A subsystem of the arterial pressure control system which is organized by interaction of the CS-system and the V-system and of which the open-loop gain is 4.0 before massive hemorrhage was named the AND-system (&-system) (Hosomi and Sagawa, 1979).

Effects of the massive hemorrhage on the open-loop gains of the baroreflex systems. A central question in the present study is to which of the following three subsystems of the baroreflex system the time-dependent parabolic change in $G_{\text{intact}}$ is attributable: the CS-system, the V-system, or the &-system. To the best of our knowledge, there is no information in the literature relevant to this question. The lack of information probably resulted from the lack of an appropriate method for estimating $G_{\text{cs}}$ or $G_{\text{v}}$ repeatedly. The quick mild hemorrhage method used in the present study allowed the study on time-dependent changes in the baroreflex system characteristics under a more physiological condition (the closed-loop condition), rather than the open-loop condition.

The results showed that $G_{\text{cs}}$ was not influenced markedly by massive hemorrhage but that $G_{\text{v}}$ decreased to one half of the control and became stable about 60 min after massive hemorrhage. In Fig. 7, the mean values of $G_{\text{v}}$ were laid upon the mean values of $G_{\text{cs}}$. The difference (the shaded area in Fig. 7) between the mean values of $G_{\text{intact}}$ and $G_{\text{v}}$ laid upon $G_{\text{cs}}$ is $G_{\&}$. The decrease in $G_{\text{v}}$ after massive hemorrhage could be attributable to the open-loop gains of the aortic arch baroreflex system, the baroreflex system of which the baroreceptors are located in the cardiopulmonary region, and the interacting system which may exist between the two systems mentioned above, if the aortic nerves and the vagi had been cut separately. It is, however, very difficult to separately cut the aortic nerves and the vagi in the dog (Edis and Shepherd, 1971; Scher, 1977). Therefore, we could not attribute the decrease in $G_{\text{v}}$ after massive hemorrhage to these subsystems, although it is obvious that the vago-aortic baroreflex systems are influenced by massive hemorrhage.

$G_{\text{cs}}$ did not change after massive hemorrhage. Therefore, the CS-system seems to be the fundamental arterial pressure control system which is not influenced by changes in the total blood volume.

The open-loop gain of the &-system ($G_{\&}$), which is assumed as $G_{\text{intact}} - G_{\text{cs}} - G_{\text{v}}$ and in which the changes after massive hemorrhage are expressed as the shaded area in Fig. 7, was 4.0 before massive hemorrhage and decreased down to 0.3 with-
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in 75 min after massive hemorrhage and then increased up to 1.8 during the subsequent 30 min. Thus $G_\&$ changed along a time course of parabolic form after massive hemorrhage. The time-dependent changes in $G_\&$ seem to express the greater part of the changes in $G_{\text{intact}}$ after massive hemorrhage. Therefore, the $\&$-system seems to be influenced by massive hemorrhage more than other systems. Since even the anatomical location or the physiologically functioning site of the $\&$-system has not yet been found, we cannot imagine the physiological meaning of not only the $\&$-system itself but also the time-dependent parabolic change in $G_\&$.

We thank Dr. I. Ninomiya for his critical reading of the manuscript and his suggestions. We also wish to express our thanks to Miss Y. Shimomura, Mr. M. Mori, and Mr. K. Kawaguchi for their wholehearted cooperation in part of this study.

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