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Resetting of Baroreflex Sensitivity after Induced Hypotension

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The effect of sodium nitroprusside (SNP)-induced hypotension on the sensitivity of the baroreflex was studied in 11 informed patients anesthetized with morphine (M) or halothane (H). Pa_{CO_2} was controlled at 28 to 32 mmHg with a respirator. Baroreflex sensitivity was assessed with a depressor test using a small dose of SNP (4–6 μg/kg, iv) to decrease the systolic pressure (SP) rapidly by about 30 mmHg. The slope of the regression line (in ms/mmHg) relating SP and the succeeding pulse interval (PI, R-R interval) was used as an index for the sensitivity of baroreflex control of heart rate. In control measurements, SP-PI slopes were 6.4 ms/mmHg for the morphine group and 3.2 ms/mmHg for the halothane group, indicating that baroreflex sensitivity is greater during morphine than during halothane anesthesia. This diffference in baroreflex sensitivity might explain the differences in dose requirements for SNP in patients anesthetized with either morphine or halothane. Following a control test, SNP was infused at a rate adjusted to maintain the mean arterial pressure between 55 and 60 mmHg. The duration of hypotension was in accordance with surgical needs. SNP infusion was then discontinued and SP was allowed to recover spontaneously. When SP recovered to its control level, PI was significantly prolonged by 18 per cent in patients anesthetized with morphine and by 13 per cent in those anesthetized with halothane over the respective control values. Immediately after the recovery of SP following the discontinuation of SNP infusion, another baroreflex sensitivity test was made; the SP-PI slopes increased markedly by 105 per cent in patients anesthetized with morphine and by 179 per cent in those with halothane over the respective control values, indicating a resetting of the baroreflex. These changes may have significant implications in hemodynamic adjustments following induced hypotension in patients during general anesthesia. (Key words: Anesthetics, intravenous: morphine. Anesthetics, volatile: halothane. Anesthetic techniques: hypotensive; nitroprusside. Blood pressure: control. Reflexes: baroreceptor.

HYPOTENSION induced with sodium nitroprusside (SNP) infusion has been commonly used clinically during general anesthesia to facilitate the surgical procedure and to reduce blood loss.[1,2] Since the baroreceptor reflex is a rapidly acting pressure control mechanism which counteracts acute alterations in arterial pressure,[3] it may serve as a physiologic antagonist to the induced hypotension. The baroreceptor reflex, however, characteristically shows an adaptation phenomenon when exposed to a different pressure level.[4] Persistent hypertension associated with a resetting of the baroreflex functions has been repeatedly shown both in humans[5,6] and in laboratory animals.[7–9] Recently, it also has been demonstrated in rats that the threshold pressure required to produce firing of the baroreceptors is progressively lowered during a 6-h period of moderate hemorrhagic hypotension.[10] Induced hypotension utilized clinically also may alter baroreflex functions. There is, however, a lack of information in this regard. The present investigation was undertaken to study the effect of induced hypotension on the sensitivity of baroreflex control of heart rate in humans during morphine and halothane anesthesia.

Methods

Studies were conducted on 15 patients ranging in age from 20 to 50 years. Eleven patients were to undergo lumbar laminectomies with spinal fusion or intracranial aneurysm surgery in which the use of deliberate hypotension had been planned. To evaluate the effect of a prolonged period of anesthesia on the baroreflex function, four other patients undergoing craniotomies without induced hypotension also were studied. None of these patients had a previous history of cardiovascular disorders. Informed consent regarding the nature and risks of the study, which had been approved by the Institutional Review Board, was obtained from each patient. Morphine (0.1 mg/kg) and secobarbital (1.5 mg/kg) were administered intramuscularly about 1.5 h prior to the induction of general anesthesia. Atropine and scopolamine were excluded from the premedication regimen.

In all patients, general anesthesia was induced with an intravenous injection of thiopental (4 mg/kg) followed by succinylcholine (1 mg/kg) to facilitate endotracheal intubation. Metocurine (0.3 mg/kg) was administered intravenously for muscle relaxation. Pa_{CO_2} was controlled at 28–32 torr with intermittent positive pressure ventilation. Anesthesia was maintained with morphine (0.5 mg/kg), diazepam (10 mg), and N_2O (60 per cent) in five patients (group M) and with halothane (0.5–1 per cent, inspired concentration) in N_2O (60 per cent) in the other ten patients (group H). Halothane was delivered from a calibrated halothane vaporizer (Dräger-Vapor, Drägerweck-AG-Lübeck, Lübeck, Germany). The radial artery was cannulated, and the arterial pressure was measured with the use of a Statham pressure transducer. The airway pressure was monitored through a side-arm

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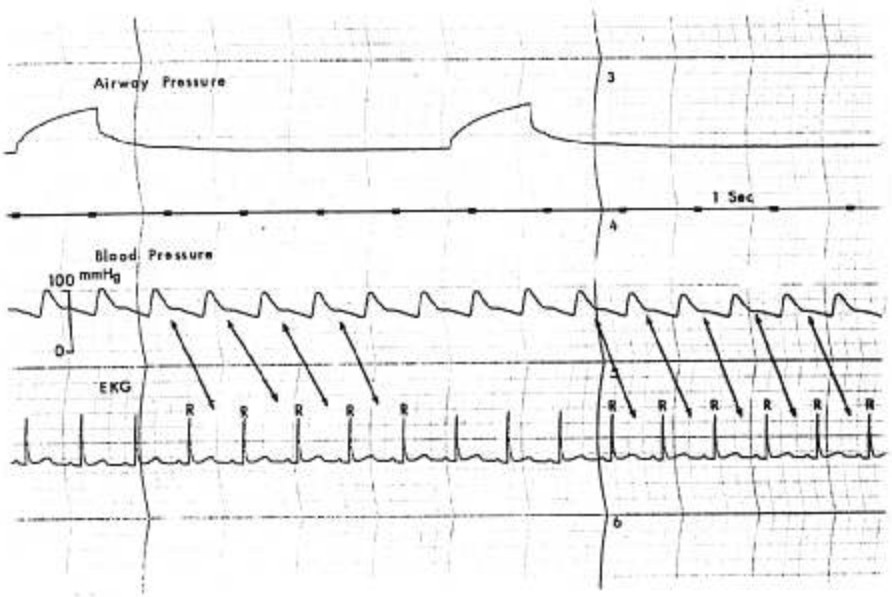

FIG. 1. Portion of the tracings of arterial blood pressure, electrocardiogram (ECG), and airway pressure during the decreasing pressure phase in a pre-hypotension control depressor test in one subject during halothane anesthesia. Arrows indicate the correlation of the systolic pressure with the succeeding pulse interval (R-R interval from the ECG tracing). The heart beats falling in the inspiratory phase are excluded.

connector to the endotracheal tube. Arterial pressure, electrocardiogram (ECG) and airway pressure were recorded simultaneously on a polygraph recorder (Model 7, Grass Instrument Company, Quincy, Massachusetts). The blood gas tensions were determined on freshly drawn arterial blood samples with a blood gas analyzer (Model IL 813, Instrumentation Laboratory, Lexington, Massachusetts).

Induced hypotension with sodium nitroprusside (SNP) infusion usually started 2 to 3 h following the induction of anesthesia. During this period, the anesthetic requirement for each patient was carefully determined so as to maintain the resting arterial pressure and to minimize any increase of blood pressure due to surgical stimulation. Halothane was administered at the same inspired concentration throughout the hypotension period. For those anesthetized with morphine, a dose of morphine (1–2 mg) was administered intravenously at regular intervals (usually 15 to 20 min, as determined prior to induced hypotension) during the hypotension period. Blood loss was replaced with whole blood or an albumin solution. At the beginning of induced hypotension, SNP (approximately 4–6 μg/kg) was rapidly infused to produce a modest decrease in systolic pressure by about 30–50 mmHg within 20 to 30 s. This served as a control depressor test for the sensitivity of the baroreflex control of heart rate. The infusion of SNP was then adjusted to a rate sufficient to maintain the mean arterial pressure between 55 and 60 mmHg. The duration of hypotension was generally determined by surgical needs. However, efforts were made to limit the total dose of SNP to about 1.5 mg/kg for each patient in order to avoid SNP toxicity.[11] At the conclusion of the hypotension procedure, the SNP infusion was discontinued and the arterial pressure was allowed to recover spontaneously to the pre-hypotension level (usually in 3 to 4 min). The sensitivity of the baroreflex was then tested once more with a rapid infusion of SNP (4–6 μg/kg) to produce a fall in systolic pressure of about 30 mmHg.

During the period of hypotension, the SNP infusion rate was increased progressively in order to maintain a

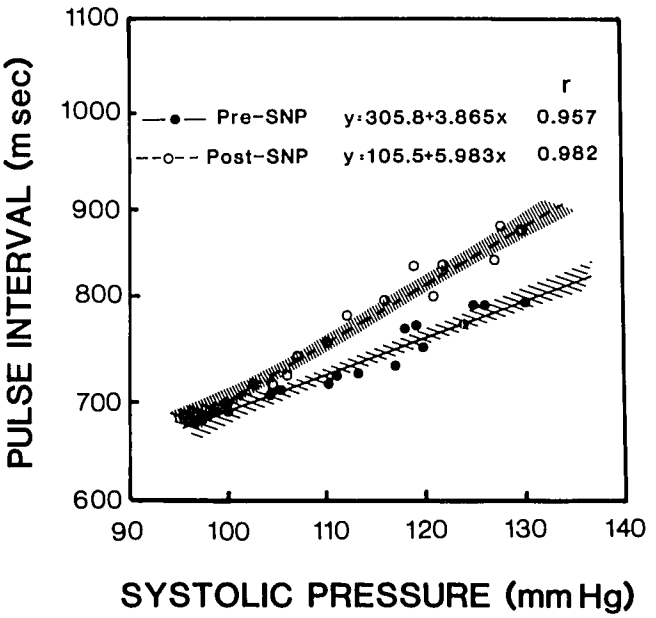

FIG. 2. Correlation of systolic pressure with its succeeding pulse interval in one subject during morphine anesthesia. Solid circles with solid line depict those heart beats taken during the pre-hypotension control depressor test. Open circles with dashed line depict those heart beats taken during the post-hypotension depressor test. The shaded areas indicate 95 per cent confidence limits of the regression lines with the least square method.

TABLE 1. Hemodynamic Variables and Baroreflex Sensitivity in Patients Undergoing Halothane Anesthesia without Nitroprusside-induced Hypotension

Subject	Age (yr)	Time (min)	Halothane Inspired Concentration (per cent)	Hemodynamic Variables Immediately Prior to the Control Test		Baroreflex Sensitivity
				Systolic Pressure (mmHg)	Pulse Interval (ms)	SP-PI Slope (ms/mmHg)
A	24	0	0.5	115	770	2.5
		30	0.5	120	735	2.8
B	32	0	1.0	106	760	1.0
		15	1.0	112	747	1.0
C	41	0	0.5	110	725	2.2
		30	0.5	116	732	2.1
		60	0.5	108	730	2.4
D	50	0	0.5	120	935	1.3
		45	0.5	110	1020	2.0

relatively constant blood pressure. The total dose of SNP infused was determined at the end of the hypotension procedure and the average infusion rate over the period of hypotension was calculated. For the four patients not subjected to induced hypotension, a control depressor test (with 4–6 μg/kg SNP) was performed about 2 h following the induction of anesthesia. The depressor test was repeated at various intervals after the control test while maintaining the same inspired concentration of halothane.

The sensitivity of the baroreflex control of heart rate was assessed by evaluating the quantitative relationship between systolic pressure and the succeeding pulse interval (taken from the R-R interval on the ECG tracing) on a beat-to-beat basis during the phase of decreasing pressure.[12] Those pulse intervals falling on the inspiratory phase were excluded in order to avoid possible sinus arrhythmia effects related to respiration.

The statistical significance between the paired and unpaired data was evaluated by Student's *t* test.

Results

During the depressor test, arterial pressure decreased rapidly and the pulse interval shortened concomitantly following the infusion of SNP (4–6 μg/kg). An example of the changes in these variables during the SNP depressor test is shown in fig. 1. Correlation of the systolic pressure (SP) with its succeeding pulse interval (PI) shows a linear relationship between these two parameters in each of the depressor tests. Figure 2 shows the results of the depressor tests obtained from a patient during morphine anesthesia. The slope of the SP-PI regression line in the post-SNP test was 5.98 ± 0.73 (ms/mmHg, at 95 per cent confidence level) as compared with 3.86 ± 0.74 (ms/mmHg, at 95 per cent confidence level) in the pre-SNP test. The difference between these two slopes was statistically significant ($P < 0.005$). The correlation coefficients for all regression lines obtained in the present study were greater than 0.90. The slope of the SP-PI regression line (in ms/mmHg) is used as an index of the sensitivity of baroreflex control of heart rate.

The effects of the duration of halothane anesthesia on baroreflex sensitivity are shown in table 1. The control depressor test (designated as time zero) was performed about 2 h after the induction of anesthesia. In each patient, the systolic pressure and pulse interval were maintained relatively constant with a constant inspired concentration of halothane. Repeated depressor tests at various intervals following the control test showed that the baroreflex sensitivity remained essentially unchanged during a constant level of anesthesia.

In patients undergoing induced hypotension, the pulse interval immediately prior to the control depressor test (pre-SNP) was comparable between those patients anesthetized with either morphine or halothane (table 2); the pre-SNP systolic pressure, however, was significantly greater during morphine anesthesia (117 ± 6 mmHg) than that during halothane (110 ± 2 mmHg). The baroreflex sensitivity, as indicated by the slope of SP-PI regression line, was substantially greater in those patients anesthetized with morphine (6.4 ± 2.1 ms/mmHg) than those anesthetized with halothane (3.2 ± 1.0 ms/mmHg).

Following the control test in each patient, the SNP infusion rate was adjusted to maintain the systolic pressure at about 70–80 mmHg (mean arterial pressure about 55–60 mmHg). There were wide variations in the duration of induced hypotension and the SNP dose requirements among all patients studied. During hypotension, the infusion rate of SNP usually had to be increased in order to maintain a given level of hypotension, and the pulse interval tended to recover from the initial shortening despite a relatively constant arterial pressure. An

TABLE 2. Hemodynamic Variables, Baroreflex Sensitivity, Duration of Hypotension, and Dosage of SNP in Patients Undergoing Induced Hypotension

Anesthesia	Subject	Age (yr)	Hemodynamic Variables Immediately Prior to the Depressor Test				Baroreflex Sensitivity		Duration of Hypotension (min)	Dose of SNP ($\mu g \cdot min^{-1} \cdot kg^{-1}$)
			Systolic Pressure (mmHg)		Pulse Interval (ms)		SP-PI Slope (ms/mmHg)			
			Pre-SNP	Post-SNP	Pre-SNP	Post-SNP	Pre-SNP	Post-SNP		
Morphine	1	48	121	124	996	1074	5.1	8.0	10	6.9
	2	45	94	96	931	1201	9.0	17.0	70	11.1
	3	24	122	113	784	1005	13.0	25.1	98	16.3
	4	41	130	130	804	880	3.9	6.1	16	4.2
	5	38	118	115	882	1000	1.1	3.6	40	9.7
MEAN			117**	116	879	1032**	6.4**	12.0*	47**	9.6**
SEM			6	6	39	53	2.1	4.0	17	2.0
Post-SNP/Pre-SNP Ratio (Mean ± SEM)			1.00 ± 0.01		1.18 ± 0.05†		2.05 ± 0.32†*			
Halothane	1	50	110	112	906	1032	2.0	4.1	140	4.7
	2	40	110	111	703	760	2.1	7.5	117	8.0
	3	42	107	107	739	977	0.9	3.3	130	3.5
	4	36	118	123	829	934	1.9	7.4	60	4.4
	5	33	109	116	916	996	7.8	11.1	25	8.8
	6	39	105	104	908	914	4.6	9.8	89	10.2
MEAN			110**	112	834	936**	3.2**	7.2*	94**	6.6**
SEM			2	3	38	39	1.0	1.3	18	1.1
Post-SNP/Pre-SNP Ratio (Mean ± SEM)			1.02 ± 0.01		1.13 ± 0.04†		2.79 ± 0.42†*			

Values are means ± SEM.

Comparison between post-hypotension (post-SNP) and Control (pre-SNP) values: †$P < 0.05$.

Comparison between those patients anesthetized with either morphine or halothane: **$P < 0.01$, *$P < 0.05$.

example of such changes in SNP dose requirement and pulse interval during the entire course of induced hypotension in a patient anesthetized with halothane (0.5 per cent, inspired concentration) is illustrated in fig. 3. The SNP infusion rate was increased progressively from 75 μg/min to 500 μg/min during the first 40 min and leveled at approximately 500 μg/min for the remaining period of induced hypotension. Although the systolic pressure was maintained relatively constant at 70–80 mmHg for the 60-min period of induced hypotension, the pulse interval showed a trend to recover about 15 min after the induction of hypotension. Similar tendencies of changes in pulse interval and SNP infusion rate were observed in all patients. The duration of hypotension (table 2) was significantly longer in patients anesthetized with halothane (93.5 ± 18.1 min) than those with morphine (46.8 ± 16.6 min). The average dose of SNP required to maintain the same level of hypotension was greater in patients anesthetized with morphine (9.6 ± 2.0 $\mu g \cdot min^{-1} \cdot kg^{-1}$) than those anesthetized with halothane (6.6 ± 1.1 $\mu g \cdot min^{-1} \cdot kg^{-1}$).

After the termination of SNP infusion, systolic pressure recovered spontaneously to its prehypotension level in approximately 3 to 4 min. At an arterial pressure comparable to that in the control (pre-SNP), the pulse interval was significantly prolonged after induced hypotension (post-SNP) in both groups of patients (Table 2). The post-SNP pulse intervals were increased by about 18 ± 5 (mean ± SEM) per cent in patients anesthetized with morphine and 13 ± 4 per cent in those anesthetized with halothane over the respective pre-SNP control values (table 2). The response of pulse interval to an acute reduction in systolic pressure caused by another testing dose (4–6 μg/kg) of SNP also was markedly increased following the induced hypotension procedure in both groups of patients. Thus, the post-SNP SP-PI slope increased by 105 ± 32 (mean ± SEM) per cent in patients anesthetized with morphine and by 179 ± 42 per cent in those with halothane as compared with the respective control tests. The percentage changes of the SP-PI slope following induced hypotension was found to be significantly greater during halothane than that during morphine anesthesia.

None of the patients studied experienced any adverse effect from SNP. The arterial blood gas tensions and *p*H values were similar in both groups of patients during either morphine or halothane anesthesia before the hypotension procedure. The mean Pa_{O_2} was 150 ± 2 (±SEM) mmHg, Pa_{CO_2} was 29 ± 1 mmHg and arterial *p*H was 7.45 ± 0.05 for all patients during the control measurements. After various periods of induced hypotension, there was no alterations in arterial blood gas tensions and *p*H values in all patients during both forms of anesthesia.

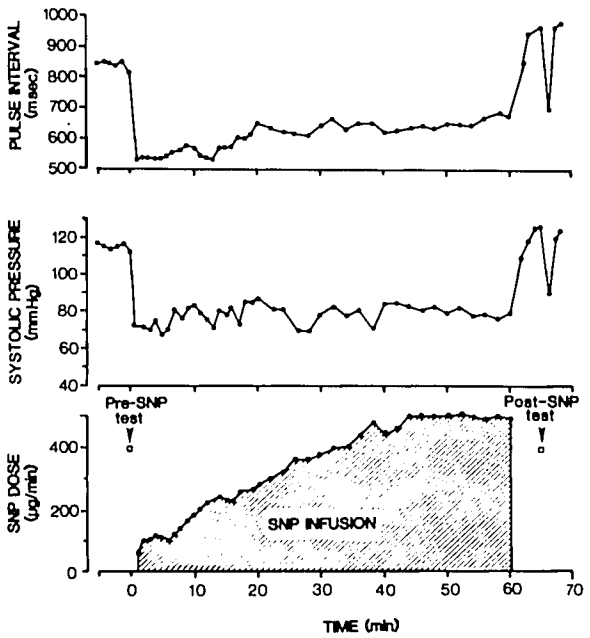

FIG. 3. Pulse interval (upper panel), systolic pressure (middle panel) and dose of SNP infusion (lower panel) during induced hypotension in one subject during halothane (0.5 per cent inspired concentration) anesthesia. The square symbols indicate the time when the depressor tests were performed.

Discussion

Sodium nitroprusside (SNP) is a potent vasodilator which causes arterial hypotension by relaxing vascular smooth muscle and reducing peripheral vascular resistance. Reflex tachycardia associated with SNP-induced hypotension has been repeatedly demonstrated in dogs[13] and in humans.[11] In the present study, the sensitivity of the baroreflex control of heart rate was assessed by a depressor test correlating the systolic pressure with the succeeding pulse interval during the phase of decreasing pressure following the administration of a small dose of SNP (4–6 μg/kg). This approach is based on the same principle as the pressor test which has been utilized for determining baroreflex sensitivity in human subjects with the use of phenylephrine or angiotensin II-induced hypertension.[12] The baroreflex control of heart rate also has been studied using other vasodilating agents, *e.g.*, amyl nitrite and nitroglycerin.[14,15] It is worth noting that the baroreflex sensitivity determined by these methods reflects the overall activity of carotid sinus and aortic baroreceptor reflex pathways.

It has been demonstrated that halothane decreases the sensitivity of the baroreceptor reflex.[16–18] The present results from baroreflex sensitivity during halothane and nitrous oxide (N_2O) anesthesia are in agreement with those of previous reports.[18] In the present study, baroreflex sensitivity was found to be greater in patients anesthetized with morphine-N_2O-metocurine than those with

halothane-N_2O-metocurine (table 2). The relative hypotension found in patients during halothane anesthesia as compared with the systolic pressure found during morphine anesthesia was not associated with shorter pulse intervals. This may reflect the differences in baroreflex sensitivity during these two forms of anesthesia and/or a direct depression of the sinoatrial node by halothane.[19] The finding that the baroreceptor reflex is more active during morphine than during halothane anesthesia might explain why greater doses of SNP are required to induce a given level of hypotension during morphine anesthesia. The differences in the dose requirement of SNP between patients anesthetized with these two forms of anesthesia in the present study were compared in terms of the average dose administered during the entire period of induced hypotension. Since the duration of hypotension was significantly shorter in patients anesthetized with morphine and the dose requirement usually increased with time, the dosage of SNP required in these patients would have been even greater if the induced hypotension had been for the same duration as in those anesthetized with halothane. Halothane is known to depress myocardial contractility and decrease peripheral vascular resistance which may also facilitate SNP-induced hypotension and reduce the dose requirement.[20]

In the control studies without induced hypotension, the baroreflex sensitivity remained relatively constant after varying periods of anesthesia (table 1). Therefore, the observed changes in baroreflex sensitivity can not be attributable to the prolonged period of anesthesia. Rather, the results indicate that there is a resetting of baroreflex sensitivity following SNP-induced hypotension. Similar changes in baroreflex sensitivity have been reported in experimental animals following hemorrhagic hypotension. Thus, Glaviano and Yo[21] showed that after a short period (5–30 min) of hemorrhagic hypotension (mean arterial pressure of 40 mmHg) in dogs, the degree of vasoconstriction in response to carotid occlusion was greatly increased. Following a longer period of hemorrhagic shock, on the other hand, the baroreflex function was depressed,[21] which may have been related to the severe metabolic acidosis and a profound hypocapnia.[22] In the present study, hypotension was induced pharmacologically with SNP and the arterial blood gases remained constant throughout the period of hypotension. The finding of an increased baroreflex sensitivity following SNP-induced hypotension agrees with that observed after a short period of hemorrhagic hypotension without significant metabolic derangement.[21]

The mechanisms responsible for the resetting of the baroreceptor reflex following induced hypotension in humans are not clearly understood and can only be speculated and deduced from available data obtained in animal studies at the present time. An adaptation of carotid sinus and aortic baroreceptors to sustained hemorrhagic hypotension has been demonstrated in rats.[10] The adaptation process of peripheral baroreceptors was found to be progressive during a 6-h period of hypotension. This agrees with our observation that the pulse interval tended to recover toward the control values during hypotension while the systolic pressure was maintained relatively constant (fig. 3). Therefore, the resetting of baroreflex sensitivity after induced hypotension might be attributable to adaptation at the receptor sites. With electric stimulation of the carotid sinus nerve, Seller and Illert[23] also have shown in cats that an adaptation of the baroreceptor reflex can occur centrally at the nucleus tractus solitarii (NTS) within the central synaptic pathway of the baroreflex arc. The time required for this adaptation of synaptic pathway was found to be within 1 min and the degree of adaptation increased with increasing stimulation frequency. Stimulation of certain regions of the central nervous system, *e.g.*, the amygdala or the preoptic, septal, and anterior regions of the hypothalamus, have been shown to facilitate the response evoked from the carotid and aortic baroreceptors.[24,25] The involvement of higher centers in the brain in the resetting of baroreflex sensitivity cannot be excluded in the present investigation. The difference in the increase of baroreflex sensitivity found between morphine and halothane anesthesia (table 2) suggests that anesthetics also may modify the resetting process.

Although recovery of the reset baroreflex sensitivity following induced hypotension was not studied in the present investigation, there is evidence indicating that the resetting of baroreflex sensitivity is reversible and the process of readaptation of the baroreceptors after returning to normotensive state requires several hours.[26] Upon termination of induced hypotension, arterial pressure recovered quickly to the prehypotension control level in 3–4 min. This post-hypotensive pressure level might then be interpreted by the central neurons, which were still adapted to the hypotensive level, as a change toward a hypertensive level. As a result, the same arterial pressure as the control level was accompanied by a relative bradycardia.

Resistance to SNP has been observed during SNP-induced hypotension.[11,27] This phenomenon has been attributed to the elevation of plasma renin activity and catecholamine levels.[28,29] The present results of increased baroreflex sensitivity provide an additional mechanistic explanation for the resistance to SNP during deliberate hypotension. Thus, the elevated baroreflex sensitivity causes an enhancement of sympathetic activity to counteract the hypotension induced by SNP infusion, and a larger dose of SNP would then be required to maintain the same degree of hypotension.

In summary, the present study indicates that deliberate

hypotension causes a resetting of baroreflex function. When the arterial pressure has recovered to the pre-hypotension level at the end of the induced hypotension procedure, the pulse interval is substantially prolonged and the sensitivity of baroreflex control of heart rate is significantly increased. These changes may have significant implications in hemodynamic adjustments following induced hypotension in patients during general anesthesia.

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