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Attenuation of Arterial Baroreceptor Reflex Response to Acute Hypovolemia During Induced Hypotension

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Preservation of the arterial baroreflex response is important to restore cardiac output and blood pressure by reflex sympathetic nerve activation in the event of sudden hypotension caused by acute blood loss during surgery. However, the arterial baroreflex may be significantly attenuated by both anesthetics and hypotensive agents. In isoflurane-anesthetized dogs, the authors investigated the arterial baroreflex response 1) to bolus injections of sodium nitroprusside (SNP), prostaglandin E_1 (PGE_1) and trimethaphan (TM); and 2) to rapid blood loss (5 ml/kg) before and during induced hypotension with SNP, PGE_1, and TM by measuring mean arterial pressure (MAP), heart rate (HR), and renal sympathetic nerve activity (RSNA). Hypotension produced by both SNP and PGE_1 was accompanied by an increase in RSNA and HR. The increase in RSNA and HR following the SNP bolus injection was significantly greater than that following injection of PGE_1 ($P < 0.05$). Trimethaphan was associated with a decrease in RSNA and HR. Rapid blood loss resulted in the same degree of MAP reduction (20 ± 2 mmHg) before and during induced hypotension. Sensitivities of baroreflex, as evaluated by ratios of maximum changes in RSNA or HR to MAP (ΔRSNA/ΔMAP, ΔHR/ΔMAP), in response to rapid blood loss, were significantly suppressed during continuously induced hypotension, as compared with responses before induced hypotension. Despite the same degree of induced hypotension (70 ± 5 mmHg of MAP), ΔRSNA/ΔMAP and ΔHR/ΔMAP in response to rapid blood loss were significantly greater with PGE_1 than those with SNP ($P < 0.05$). Because of its sympathetic ganglion blocking action, arterial baroreflex sensitivity was suppressed by rapid blood loss during TM infusion. The authors conclude that induced hypotension with PGE_1 provides a greater margin of safety than that associated with SNP when acute blood loss occurs during isoflurane anesthesia. Trimethaphan is inferior to both PGE_1 and SNP in this respect. (Key words: Anesthetic techniques, deliberate hypotension: sodium nitroprusside; prostaglandin E_1; trimethaphan. Blood pressure: baroreceptor reflexes, hypovolemia. Sympathetic nervous system: renal sympathetic nerve activity.)

INDUCING ARTERIAL HYPOTENSION with vasodilators is used to reduce surgical blood loss and to facilitate surgical procedures. During induced hypotension, compensatory general reflex sympathetic activation is elicited, which is manifested as tachycardia and peripheral vasoconstriction, to maintain cardiac output and arterial blood pressure. It has been shown, however, that the arterial baroreflex is impaired by anesthetic agents as well as by vasodilators.[1–9]** Under these circumstances, acute blood loss during surgery can cause a precipitous reduction of arterial blood pressure and cardiac output.

Sodium nitroprusside (SNP), a commonly used hypotensive agent, has been found not to attenuate arterial baroreflex responses.[10,11] However, the effects of other hypotensive agents, such as prostaglandin E_1 (PGE_1) and trimethaphan (TM), have not been established. The purpose of this study was twofold: 1) To investigate arterial baroreflex response, during isoflurane anesthesia, to a bolus injection of SNP, PGE_1, and TM by measuring heart rate and renal sympathetic nerve activity as indices of overall sympathetic activity; and 2) to investigate arterial baroreflex response to rapid blood loss during continuously induced hypotension with these agents during isoflurane anesthesia.

Materials and Methods

This study was approved by the Kansas University Institutional Animal Care and Use Committee, and appropriate guidelines for the use of animal were observed during all aspects of this study.

General Preparation

Adult mongrel dogs of either sex, weighing between 17.2 and 25.0 kg, were anesthetized using intravenous pentobarbital sodium (10 mg/kg) and thiopental sodium (10 mg/kg). After tracheal intubation with a cuffed endotracheal tube, the lungs were ventilated with a Harvard animal ventilator (Millis, MA) using oxygen in nitrogen (fractional inspired O_2 concentration [FI_{O_2}]: 0.4) at a tidal volume of 10–15 ml/kg and a frequency of 15–20 cycles/min to maintain Pa_{CO_2} within 35 and 45 mmHg. Isoflurane was used to control mean arterial pressure at 120 ± 10 mmHg in the absence of vasodilators throughout the experiment. The animals were paralyzed with pancuronium bromide (0.1 mg/kg intravenously [iv]) to avoid artifacts secondary to muscular movement. Polyethylene

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catheters were inserted into a femoral vein for iv administration of vasodilators, and in both femoral arteries, for measurement of arterial pressure and to perform rapid exsanguination. Arterial blood pressure was monitored *via* a pressure transducer (DTX Spectramed, Oxnard, CA) and recorded continuously. Mean arterial pressure (MAP) was derived by electronic integration of the pulsatile pressure signal. Heart rate (HR) was calculated from lead II of the electrocardiogram using a cardiotachometer (1321 San-ei, Japan).

Recording of Renal Sympathetic Nerve Activity (RSNA)

The left kidney was exposed retroperitoneally by a left flank incision. Renal sympathetic nerves along the renal artery were isolated using a microscope. The distal end of the strands were crushed, and then immersed in mineral oil and placed on a bipolar silver electrode for recording the renal nerve discharges. Electrical impulses recorded from the renal sympathetic nerves were amplified using a preamplifier (AVB 10: bandwidth: 50–3,000 Hz; Nihon Kohden, Japan). The amplified nerve discharges were visualized on a dual-beam oscilloscope (VC 11 Nihon Kohden, Japan) and monitored by an audiospeaker. The neurogram was integrated by a resistance–capacitance integrator circuit (time constant, 2.0 s). Because integrated output is dependent on the voltages and frequencies of RSNA, it was used as a measurement of overall RSNA. Nerve activity was recorded after death in all dogs as a measurement of the level of zero "noise." Renal sympathetic nerve activity was continuously measured and recorded on a DAT tape PCM recorder (RD-100T TEAC, Montebello, CA), and played back on a multichannel chart recorder (Omnicorder 8M14; San-ei,. Japan).

Experimental Protocol and Data Analysis

Twenty animals were divided randomly into one of three groups to receive sodium nitroprusside (SNP: n = 6), prostaglandin E_1 (PGE_1: n = 7) and trimethaphan (TM: n = 7). After completion of the surgical preparation, a sufficient time (over 1 h) was allowed for hemodynamic stabilization before study.

Study 1: Baroreflex Response to Bolus Injections of SNP, PGE_1, and TM. Hypotension was induced by a bolus infusion of SNP (10 μg/kg), PGE_1 (1.0 μg/kg), or TM (50 μg/kg). These doses of the three agents were found to decrease MAP to 60–70 mmHg at the same rate in the preliminary study. Renal sympathetic nerve activity and HR were measured with every 10-mmHg decrement of MAP from the preinjection level (120 ± 10 mmHg). Renal sympathetic nerve activity was expressed as percentage change from the resting spontaneous nerve discharge before bolus injection of vasodilators. The relationships between changes of MAP and RSNA or HR after the bolus injection of vasodilators were analyzed, using a nonlinear regression program (SAS, PROC NLIN) with an IBM computer for a sigmoid logistic function described by Kent *et al.*[12] The logistic model was derived from the following formula:

$$\text{RSNA (or HR)} = A_1/(1 + e^{A2(MAP-A3)}) + A_4$$

Using the above four parameters, the following descriptors of the baroreflex function curve were derived: A_1 = range of RSNA (or HR); A_2 = slope of reflex response; A_3 = centering point of the function curve; A_4 = minimum RSNA (or HR); $A_1 + A_4$ = maximum RSNA (or HR). Maximum slope is estimated from the parameters as $(A_1 \times A_2)/4$.

Data were expressed as means ± standard errors of the mean (SEM). Differences between individual means were compared, using a Student's *t* test for paired differences.

Study 2: Baroreflex Response to Rapid Blood Loss Before and During Induced Hypotension. After hemodynamic stabilization following bolus infusion of hypotensive agents (at least 30 min earlier), arterial blood (5 ml/kg) was rapidly withdrawn at the rate of 0.5 $ml \cdot kg^{-1} \cdot s^{-1}$ over 10 s from femoral artery into heparinized glass syringes while measuring RSNA, HR, and MAP. Thereafter, the shed blood was retransfused and a steady state was re-established. Then, continuous infusions of either SNP (10–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$), PGE_1 (0.5–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), or TM (20–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were begun and adjusted to obtain 70 ± 5 mmHg of MAP, and the rapid blood loss study was repeated after 10 min of steady state of induced hypotension. Changes of RSNA were expressed as per cent change from the resting spontaneous nerve discharges before the first rapid blood loss. Sensitivities of arterial baroreflex control of RSNA and HR in response to acute hypotension by rapid blood loss were compared, using the ratios of ΔRSNA/ΔMAP and ΔHR/ΔMAP, respectively, where ΔRSNA was the maximum change in RSNA, ΔHR was the maximum change in HR, and ΔMAP was the maximum decrease in MAP.

All data were expressed as the means ± SEM. Comparisons within experimental protocols were made using a repeated measurement analysis of variance (ANOVA). Multiple comparisons between individual means were performed using Newman-Keul's method. Differences with a statistical probability of less than 0.05 were considered significant.

Results

The inhaled concentration of isoflurane ranged from 1 to 2%, to control MAP at 120 ± 10 mmHg. Arterial

TABLE 1. MAP, RSNA, and HR Before and After Bolus Injection of SNP, PGE_1, and TM

	Vasodilators	Baseline	After Infusion
MAP (mmHg)	SNP	126 ± 1	67 ± 2*
	PGE_1	124 ± 2	68 ± 2*
	TM	122 ± 2	65 ± 3*
RSNA (%)	SNP	100 ± 0	254 ± 10*
	PGE_1	100 ± 0	180 ± 6*
	TM	100 ± 0	13 ± 3*
HR (bpm)	SNP	144 ± 1	191 ± 5*
	PGE_1	142 ± 1	164 ± 3*
	TM	147 ± 2	133 ± 2*

Values are mean ± SEM. MAP = mean arterial pressure; RSNA = renal sympathetic nerve activity; HR = heart rate; SNP = sodium nitroprusside; PGE_1 = prostaglandin E_1; TM = trimethaphan.

* $P < 0.05$, significantly different from baseline values. There are significant differences in RSNA and HR between three groups; SNP *versus* PGE_1 ($P < 0.05$), SNP *versus* TM ($P < 0.01$), PGE_1 *versus* TM ($P < 0.01$).

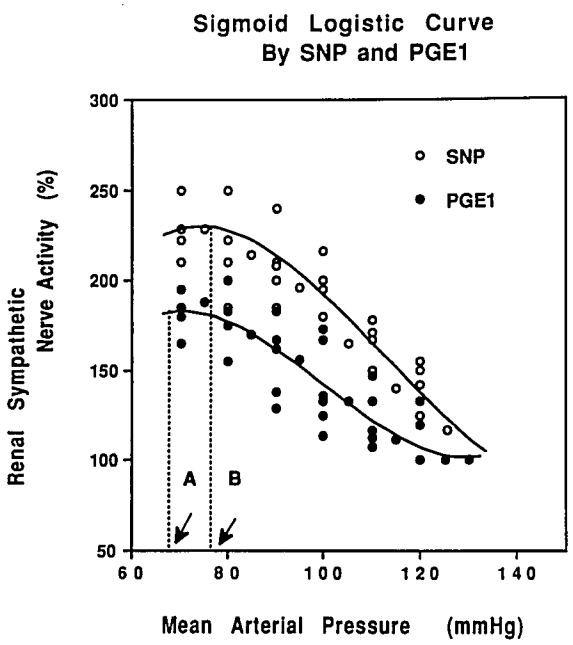
blood gas measurement revealed that Pa_{CO_2} was 40.0 ± 3.5 mmHg, Pa_{O_2}: 205.8 ± 9.5 mmHg, and *p*H: 7.39 ± 0.04 (mean ± SD) before each study.

Study 1: Baroreflex Responses to Bolus Injections of SNP, PGE_1, and TM

The changes in MAP, RSNA, and HR after bolus injections of SNP, PGE_1, and TM are summarized in table 1. There were no significant differences in time (s) to reach MAP at 60–70 mmHg among three agents (SNP: 33 ± 3 s, PGE_1: 31 ± 3 s, TM: 33 ± 4 s; mean ± SEM). Sodium nitroprusside and PGE_1-induced hypotension was accompanied by an increase in RSNA and HR. Despite the same decrease in arterial blood pressure, the increase in RSNA and HR caused by SNP was significantly higher than that produced by PGE_1. Trimethaphan administration was associated with decreases in RSNA and HR. Figure 1 shows the relationship between per cent changes of RSNA and each 10-mmHg decrement of MAP produced by SNP and PGE_1. Renal sympathetic nerve activity range (A_1: $P < 0.02$), slope (A_2: $P < 0.02$), and the maximum slope ($A_1 \times A_2/4$: $P < 0.03$) of the sigmoid logistic curve observed with SNP were significantly greater than those with PGE_1. Renal sympathetic nerve activities reached plateaus at a higher MAP with SNP (point B) than with PGE_1 (point A). Similar results were obtained with HR with respect to MAP changes caused by SNP and PGE_1 (fig. 2). Because RSNA and HR decreased with reduction of MAP, data associated with administration of TM could not fit the sigmoid logistic function using a nonlinear regression curve.

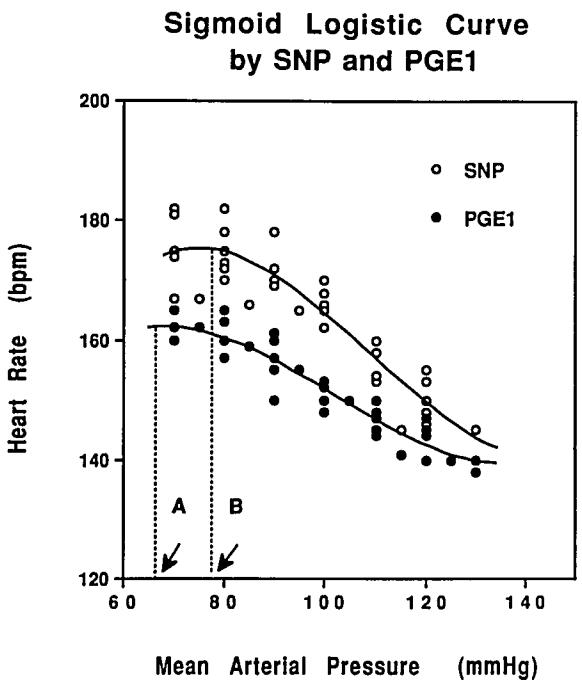
Study 2: Baroreflex Responses Following Rapid Blood Loss Before and During Induced Hypotension

Figure 3 shows the time course of integrated RSNA, HR, and MAP during induced hypotension. After 3–5 min of induced hypotension, RSNA, HR, and MAP became stable, and they remained the same until rapid blood loss was performed (point B). Table 2 shows baseline values of MAP, RSNA, HR, and central venous pressure (CVP) during the normotensive state and during induced hypotension before rapid blood loss. There were no statistical differences in MAP, RSNA, HR, and CVP between the three groups before commencement of induced hypotension. Maximum changes in MAP and RSNA induced by rapid blood loss during the normotensive state, and during induced hypotension with SNP, PGE_1, and TM, are shown in table 3. Despite the same MAP reduction (20 ± 2 mmHg) caused by rapid blood loss, maximum increases in RSNA and HR were significantly attenuated during induced hypotension, as compared with those values before induced hypotension. Figure 4 shows the original recording of RSNA and HR as a baroreflex response to rapid blood loss during induced hypotension with SNP,



	SNP	PGE_1	
A_1	352 ± 75.1	119.9 ± 5.6	p<0.02
A_2	0.106 ± 0.016	0.048 ± 0.014	p<0.02
A_3	120.3 ± 7.6	83.5 ± 15.2	p<0.06
A_4	68.3 ± 8.9	85.9 ± 4.1	p<0.10
$A_1 \times A_2/4$	10.267 ± 3.197	1.512 ± 0.465	p<0.03

FIG. 1. Relationship between renal sympathetic nerve activity (RSNA) and mean arterial pressure (MAP) on sigmoid logistic curve. SNP = sodium nitroprusside; PGE_1 = prostaglandin E_1; A = MAP at maximum RSNA on sigmoid logistic curve of SNP; B = MAP at maximum RSNA on sigmoid logistic curve of PGE_1; A_1 = range of RSNA; A_2 = slope of reflex response; A_3 = centering point of the function curve; A_4 = minimum RSNA; $(A_1 \times A_2)/4$ = maximum slope. Student's *t* test was used for statistical comparison of means for paired difference.



	SNP	PGE_1	
A_1	79.4 ± 12.7	33.2 ± 15.2	p<0.05
A_2	0.284 ± 0.091	0.038 ± 0.013	p<0.03
A_3	125.5 ± 21.3	82.4 ± 13.8	p<0.12
A_4	124.6 ± 12.3	123.1 ± 16.1	p<0.94
$A_1 \times A_2/4$	11.231 ± 3.332	0.316 ± 0.299	p<0.05

FIG. 2. Relationship between heart rate (HR) and mean arterial pressure (MAP) on logistic regression curve. SNP = sodium nitroprusside; PGE_1 = prostaglandin E_1; A = MAP at maximum HR on sigmoid logistic curve of SNP; B = MAP at maximum HR on sigmoid logistic curve of PGE_1; A_1 = range of HR; A_2 = slope of reflex response; A_3 = centering point of the function curve; A_4 = minimum HR; ($A_1 \times A_2$)/4 = maximum slope. Student's *t* test was used for statistical comparison of means for paired difference.

PGE_1, and TM. The increases in RSNA and HR caused by rapid blood loss were greater with PGE_1 than with SNP (fig. 4*A*, *B*), whereas RSNA and HR were not increased by rapid blood loss during TM infusion (fig. 4*C*). Figure 5 shows the ratios of ΔRSNA/ΔMAP and ΔHR/ΔMAP as an index of sensitivity of arterial baroreflex response to rapid blood loss during induced hypotension. ΔRSNA/ΔMAP with PGE_1 (1.84 ± 0.16) was significantly higher ($P < 0.05$) than with SNP (0.84 ± 0.27). ΔHR/ΔMAP with PGE_1 (0.39 ± 0.06) was also significantly higher ($P < 0.05$) than with SNP (0.11 ± 0.03).

Discussion

In the present study, we attempted to create experimental conditions similar to those present clinically. Anesthesia depth was judged by mean arterial pressure (MAP), which was maintained and controlled at 120 ± 10 mmHg by adjusting the inspired isoflurane concentration. The primary role of arterial baroreflex is to adjust blood pressure toward baseline MAP, and baroreflex sensitivity can change, depending on the baseline blood pressure. Therefore, it is important to maintain the same MAP for the study of baroreflex sensitivity. Different inspired isoflurane concentrations (1–2%) might have influenced the outcome of the study by changing baseline sympathetic activity and response to hypotension. However, there were no statistical differences in baseline sympathetic activity (the integrated absolute RSNA, table 2) among three groups during the normotensive state. There were also no statistical differences in the degree of hypotension due to bolus injection of each vasodilator (table 1) and due to acute blood loss among the three groups (table 3). This

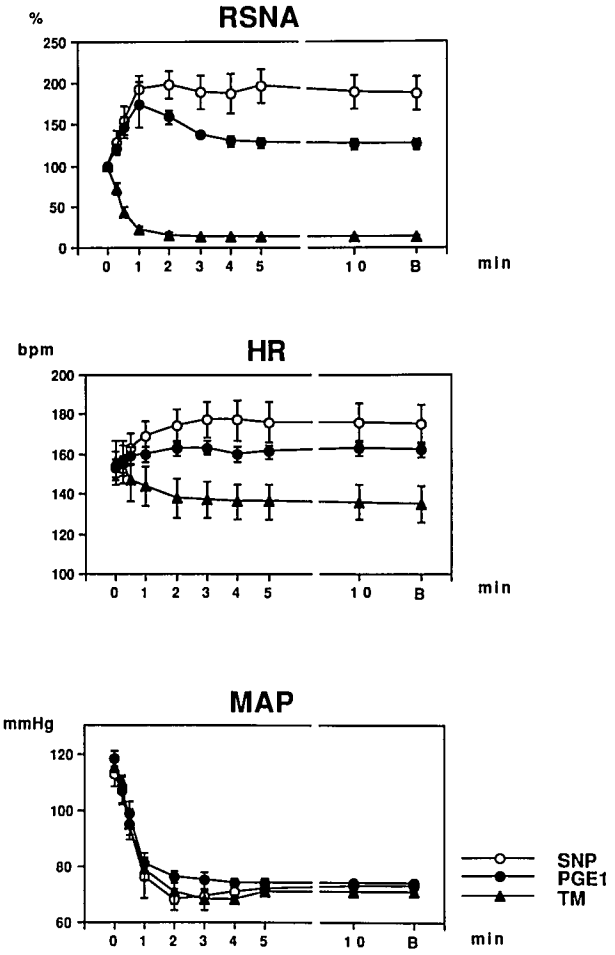


FIG. 3. The time course of renal sympathetic nerve activity (RSNA), heart rate (HR) and mean arterial pressure (MAP) during induced hypotension with sodium nitroprusside (SNP), prostaglandin E_1 (PGE_1), and trimethaphan (TM). B = before rapid blood loss during induced hypotension.

TABLE 2. Baseline values of MAP, RSNA, and HR Before Rapid Blood Loss

Variable	Pre-SNP Control	SNP-induced Hypotension	Pre PGE_1 Control	PGE_1-Induced Hypotension	Pre-TM Control	TM-Induced Hypotension
MAP (mmHg)	114 ± 4	73 ± 1*	119 ± 3	74 ± 1*	115 ± 2	71 ± 1*
IRSNA (μV)	3.1 ± 0.6	5.7 ± 0.9*	3.2 ± 0.4	4.1 ± 0.5*	3.4 ± 0.4	0.8 ± 0.2*
HR (bpm)	154 ± 7	175 ± 10*	153 ± 4	163 ± 3*	156 ± 9	136 ± 9*
CVP (mm Hg)	4.2 ± 0.3	2.9 ± 0.1*	4.4 ± 3.0	3.0 ± 0.3*	4.1 ± 0.6	2.8 ± 0.6*

Values are mean ± SEM.
IRSNA: integrated renal sympathetic nerve activity.
* $P < 0.05$, significantly different from control values.

is probably because the baseline MAP was maintained at 120 ± 10 mmHg and isoflurane inspired concentration varied between 1 and 2%. In this study, we chose isoflurane as a basic anesthetic agent and to control MAP because it depresses baroreceptors in humans, but to a substantially lesser degree than halothane or enflurane.[3,4] Relatively small doses of barbiturates (pentobarbital 10 mg/kg, thiopental 10 mg/kg) were administered intravenously only at the time of induction of anesthesia. The effects of these barbiturates on the baroreflex, therefore, are thought to be minimal, as the actual baroreflex study was performed at least 2 h after induction of anesthesia. This is particularly true for thiopental, which is an ultra short-acting barbiturate. During continuously induced hypotension, MAP was maintained at 71–74 mmHg (fig. 4, table 2). These pressures are often used clinically for deliberate hypotension induced with vasodilators.

The results of this study show that bolus injections of SNP produced the highest increases in RSNA and HR as indicators of arterial baroreflex activity in dogs anesthetized with isoflurane. This is due to the lack of an effect of SNP on the arterial baroreflex, owing to its lack of direct action on the autonomic nervous system.[10] Therefore, SNP has been used as a standard agent to examine baroreflex sensitivity to reduction of arterial pressure.[11] Although several investigators have reported[13–15] that PGE_1 caused a similar baroreflex increase in HR following SNP in humans and dogs, Brunsting *et al.*[16] and Goto *et al.*[17] observed that HR was not significantly increased by the infusion of PGE_1, even though arterial pressure decreased significantly. Feniuk[18] and Hedqvist and Wennmalm[19] also demonstrated that PGE_1 inhibited the tachycardia produced by electric or chemical sympathetic nerve stimulation in animals. They suggested that this inhibitory effect of PGE_1 on sympathetic nerve activity is associated with a reduction of the neurotransmitter in preganglionic or postganglionic neurons. Furthermore, some prostaglandins (PGE_2 and PGI_2) and arachidonic acid, a precursor of prostaglandins, attenuate the arterial baroreflex in response to hypotension.[20–22] Our observation that PGE_1, one of the derivatives of arachidonic acid, attenuates the arterial baroreflex is in agreement with these findings. Our study was the first to compare differences between PGE_1 and SNP by constructing the MAP and RSNA or HR response curves. The slope of the sigmoid logistic curve following PGE_1 is less steep than that following SNP, indicating clearly that PGE_1 attenuates baroreflex control of RSNA and HR when the same level of hypotension is produced (figs. 1. 2).

Because of the ganglion-blocking effect, RSNA was depressed significantly by TM bolus injection, even though the arterial baroreceptors must have been unloaded because of arterial hypotension. This finding indicates that a reflex vasoconstrictive response to arterial hypotension after bolus injection of TM does not occur. Heart rate also decreased despite the acute arterial hypotension produced by TM bolus injection. This is in agreement with the observation by Wang *et al.*[23] that sympathetic ganglion blocking effect produces a gradual slowing of HR during a brief infusion of TM infusion. Conversely, several investigators[24,25] observed increases of HR after TM infusion. They suggest that HR may increase or decrease, depending on sympathetic or parasympathetic balance before and during TM infusion.

It has been recognized that the arterial baroreceptor possesses a characteristic set point, and it is reset so that

TABLE 3. Maximum Changes in MAP (ΔMAP), RSNA (ΔRSNA), and HR (ΔHR) Induced by Rapid Blood Loss Before and During Induced Hypotension by SNP, PGE_1, and TM

Variable	Pre-SNP Control	SNP-Induced Hypotension	Pre-PGE_1 Control	PGE_1-Induced Hypotension	Pre-TM Control	TM-Induced Hypotension
ΔMAP (mmHg)	−19 ± 2	−19 ± 3	−21 ± 2	−21 ± 1	−20 ± 2	−21 ± 2
ΔRSNA (%)	63 ± 5	15 ± 6*	64 ± 4	37 ± 2*	57 ± 3	−1 ± 1*
ΔHR (bpm)	15 ± 1	2 ± 1*	17 ± 3	9 ± 4*	18 ± 2	1 ± 1*

Values are mean ± SEM. *$P < 0.05$, significantly different from control values.

the equivalent baroreflex response will occur in response to the same degree of hypotension. During induced hypotension, baroreflex sensitivities to rapid blood loss were significantly suppressed as compared with those during the normotensive state (table 3). This indicates that baroreceptor resetting did not take place during induced hypotension. Formerly, several investigators speculated on how soon arterial baroreceptor resetting can take place, *i.e.*, in a matter of hours, days, *or* a week.[26-28] Recently, Dorward *et al.*[29] and Kunze[30] observed the rapid resetting of arterial baroreceptors in a matter of minutes, using animals either conscious or anesthetized with α-chloralose, a drug that does not significantly attenuate the arterial baroreflex.[31-33] If rapid arterial baroreceptor resetting should occur in a matter of minutes, the reduction in MAP by rapid blood loss during induced hypotension should evoke the same increase in RSNA and HR as would occur during the normotensive state. Such a response was not evident in our study. Two factors may have contributed to failure of rapid arterial baroreceptor resetting. First, we examined baroreflex sensitivity within 20 min after induction of induced hypotension, which might have been before the completion of baroreceptor resetting. Second, isoflurane[4] and pentobarbital[8] can impair baroreflex control of RSNA and HR, as they depress the central nervous system in general. Thus, they might have attenuated acute baroreceptor resetting in this study.

Baroreflex response to rapid blood loss was significantly greater during PGE_1 than with SNP-induced hypotension (fig. 5), despite the same baseline-induced hypotension (MAP; 71–74 mmHg, table 2), and the same degree of further hypotension from rapid blood loss. This may be explained by using the sigmoid logistic curve of baroreflex

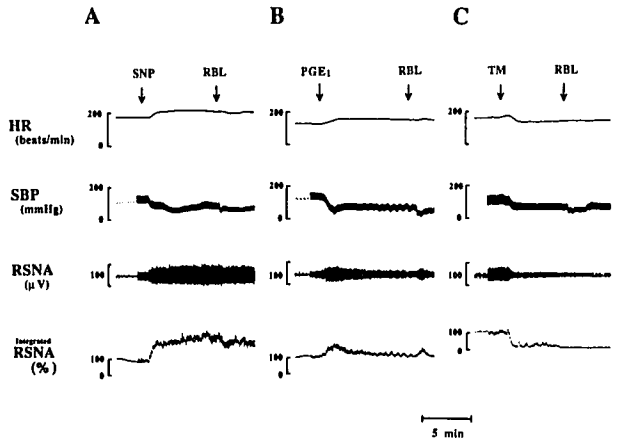


FIG. 4. Original recording showing baroreflex response to rapid blood loss estimated by renal sympathetic nerve activity (RSNA) and heart rate (HR) during induced hypotension with sodium nitroprusside (SNP), prostaglandin E_1 (PGE_1), and trimethaphan (TM). SBP = systemic blood pressure; MAP = mean arterial pressure; RBL = rapid blood loss.

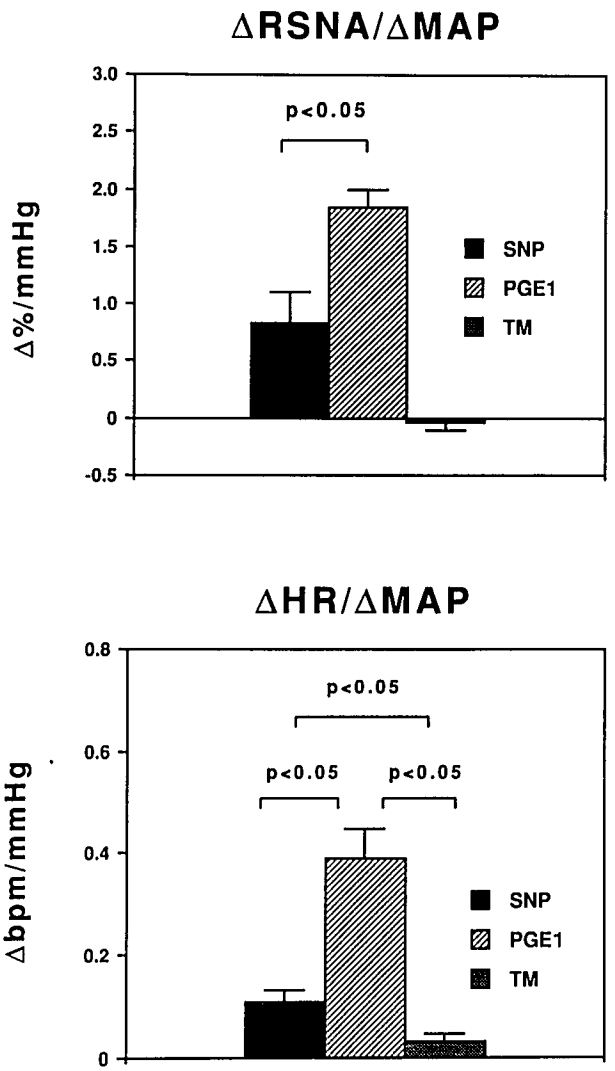


FIG. 5. The sensitivity of arterial baroreflex control of RSNA and HR using the ratios of ΔRSNA/ΔMAP and ΔHR/ΔMAP, which compared the changes in response to acute hypotension caused by rapid blood loss during induced hypotension with sodium nitroprusside (SNP), prostaglandin E_1 (PGE_1), and trimethaphan (TM). ΔRSNA = maximum change in RSNA; ΔHR = maximum change in HR; ΔMAP = maximum change in MAP.

at 120 ± 10 mmHg in response to bolus injections of SNP and PGE_1 (figs. 1, 2). If arterial baroreceptor resetting did not occur during 10 min of induced hypotension, the sigmoidal nature of the reflex curve could produce an apparent decrease in sensitivity because of displacement of the reflex to a flat portion of the sigmoidal curve. Mean arterial pressure at maximum response of RSNA or HR on the sigmoid logistic curve of PGE_1 (figs. 1, 2: point A) is approximately 12 mmHg lower than that of SNP (figs. 1, 2: point B). This indicates that RSNA and HR reach their plateaus at a lower MAP with PGE_1. Renal sympathetic nerve activity and HR during PGE_1-induced hy-

potension, therefore, could still increase in response to further reduction of MAP because of rapid blood loss. Another possible explanation why PGE_1 preserved baroreflex better than SNP during induced hypotension is that the character of the reflex curve might have changed in such a way that the sigmoid logistic curve of PGE_1 becomes steeper than that of SNP at the baseline MAP of 71–74 mmHg.

Arterial baroreflex response to rapid blood loss was severely depressed during induced hypotension with TM, as compared with PGE_1 and SNP (figs. 4, 5). Because of blocking of sympathetic ganglia by TM, increases in RSNA and HR were not observed (figs. 4, 5), even though the baroreceptors must have been unloaded in response to rapid blood loss. The preservation of baroreflex response is believed to be important for cardiovascular stability during anesthesia and surgery. Therefore, TM may not be the ideal hypotensive agent when rapid blood loss is expected.

In conclusion, results from the present study demonstrate that PGE_1 is followed by smaller reflex increases in RSNA and HR than these following SNP. Arterial baroreflex response to acute hypovolemia was better maintained during induced hypotension with PGE_1 than with SNP during isoflurane anesthesia. Reflex sympathetic responses to acute hypovolemic hypotension did not occur during TM infusion. These findings indicate that PGE_1 may attenuate undesirable reflex sympathetic activity such as tachycardia during induced hypotension, and that induced hypotension with PGE_1 provides a greater margin of the safety than that following SNP when rapid bleeding occurs during surgery. Trimethaphan is inferior to both PGE_1 and SNP in this respect.

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