

Differential Control of Adrenal and Renal Sympathetic Nerve Activity During Hemorrhagic Hypotension in Rats

Ronald G. Victor, Peter Thorén, Donald A. Morgan, and Allyn L. Mark

The reflex mechanisms that produce the neurocirculatory adjustments to hemorrhagic hypotension are incompletely understood. The goal of this study was to determine if hemorrhagic hypotension in rats produces differential effects on sympathetic outflow to the adrenal gland and kidney and if the two sympathetic nerve responses are governed by different reflex mechanisms. We performed simultaneous multifiber recordings of adrenal and renal sympathetic nerve activity (SNA) during 8 minutes of sustained hemorrhagic hypotension to a mean arterial pressure of 50 mm Hg in chloralose-anesthetized Sprague-Dawley rats with a) baroreceptors intact, b) cervical vagotomy, c) sinoaortic baroreceptor denervation, and d) combined vagotomy plus sinoaortic denervation. During hemorrhagic hypotension in rats with intact baroreceptors, renal SNA decreased by $31 \pm 10\%$ (mean \pm SEM, $p < 0.05$ vs. control) and heart rate decreased from 384 ± 13 to 365 ± 16 beats per minute ($p < 0.05$), but adrenal SNA increased by $69 \pm 10\%$ over control ($p < 0.05$). The decreases in renal SNA and heart rate were reversed by cervical vagotomy but not by atropine, which indicates vagal afferent mediation. In contrast, the increases in adrenal SNA during hemorrhage were not affected by vagotomy alone or by sinoaortic denervation alone but were markedly attenuated by combined sinoaortic denervation and vagotomy, which indicates redundancy in the baroreflex control of adrenal SNA. The major new conclusions from this study are 1) that hemorrhagic hypotension in rats produces directionally opposite reflex changes in renal and adrenal SNA with sympathoinhibition in the kidney but sympathoexcitation in the adrenal gland, and 2) that both of these reflex responses are mediated by vagal afferents. Differential reflex control of regional sympathetic outflow by vagal afferents is an important factor in producing a complex and highly differentiated pattern of autonomic response to this form of hypotension. (*Circulation Research* 1989;64:686–694)

Hemorrhagic hypotension is well known to produce reflex changes in heart rate and vascular resistance that are related in part to profound alterations in sympathoadrenal activity.^{1–3} However, the precise mechanisms that produce the specific autonomic adjustments to hemorrhagic hypotension are incompletely understood.

Heesch and Bishop⁴ provided evidence that plasma concentrations of adrenomedullary catecholamines are under tonic restraint by both arterial and

cardiac (vagal afferent) baroreceptor activity. However, Fater et al⁵ concluded that arterial baroreceptors have minimal physiologic effects on adrenal release of catecholamines during the hypotension produced by hemorrhage or by vasodilators. These previous studies relied on measurements of plasma catecholamines and did not measure adrenal sympathetic nerve activity (SNA) directly.

In contrast, several recent studies have examined the regulation of renal SNA during hemorrhage. Surprisingly, in many species renal SNA does not increase and may actually decrease during hypotensive hemorrhage.^{6–8} In rats the inhibitory effect of severe hemorrhage on renal SNA appears to be caused in part by paradoxical activation of cardiac vagal afferents,⁷ whereas in dogs this effect is not dependent on either cardiac or arterial baroreceptors.⁶ Thus, the sympathetic responses to hypotensive hemorrhage may be regulated by highly specific reflex pathways that differ greatly not only between the different species but even between two

From the Veterans Administration Medical Center and Department of Medicine, University of Iowa College of Medicine, Iowa City, Iowa

This research was supported by Clinical Investigator Award HL-01362 (to R.G.V.) and Program Project Grant HL-14388, both from the National Heart, Lung, and Blood Institute, by research funds from the Veterans Administration, and by a travel grant (to P.T.) from the Swedish Medical Research Council.

Address for correspondence: Dr. Ronald G. Victor, Cardiology Division, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75235-9034

Received June 2, 1987; accepted September 6, 1988.

organs that are in close anatomic proximity (e.g., the adrenal gland and kidney) in the same animal. Differential regulation of sympathetic nerve discharge to different organs might contribute to the complicated pattern of regional blood flow distribution during graded hemorrhage.³

In the present study, we performed simultaneous recordings of SNA from adrenal and renal nerves in rats to determine if hemorrhagic hypotension produces contrasting effects on sympathetic outflow to the adrenal gland and kidney. Based on the previous studies of plasma catecholamines, we hypothesized that this form of hypotension would stimulate sympathetic drive to the adrenal gland while inhibiting sympathetic drive to the kidney. We examined effects of sinoaortic deafferentation and cervical vagotomy on the responses to hemorrhagic hypotension to determine if the two sympathetic responses are governed by different reflex mechanisms.

Materials and Methods

Experiments were performed in 31 Sprague-Dawley rats in accordance with the guiding principles of the American Physiological Society for animal experimentation.

In all experiments, anesthesia was induced with methohexital sodium (Brevital, Eli Lilly Co, Indianapolis, Indiana) (75 mg/kg i.p.) and sustained with α -chloralose (50 mg/kg i.v. initially followed by 25 mg/kg/hr i.v.). Polyethylene catheters were inserted into the femoral artery for measurement of arterial pressure, into the tail artery for hemorrhage, and into the femoral vein for administration of fluids and drugs. In some experiments, a polyethylene catheter was inserted into the left ventricle (via the right common carotid artery) to monitor left ventricular end-diastolic pressure (LVEDP). LVEDP was used as a measure of left heart filling pressure and the mechanical stimulus to cardiac vagal afferents. The trachea was cannulated and animals were allowed to breathe oxygen-enriched air. Body temperature was maintained at 38° C.

Sinoaortic Denervation

Sinoaortic denervation (SAD) was performed according to the technique of Krieger⁹ by cutting the aortic depressor nerves at the junction with the superior laryngeal nerves and by stripping the arterial walls in the carotid sinus region and painting them with 10% phenol. The cervical sympathetic chains and superior laryngeal nerves were also cut. The effectiveness of SAD was confirmed by demonstration of the failure of phenylephrine-induced increases in mean arterial pressure (+20 to +40 mm Hg) to decrease heart rate and sympathetic nerve traffic.

Vagotomy

The cervical vagi were sectioned bilaterally to remove vagal afferent input. The effectiveness of vagotomy was demonstrated by the finding that

graded blood transfusion caused graded decreases in SNA before but not after vagotomy.

Recordings of Sympathetic Nerve Activity

The left kidney and adrenal gland were exposed with a retroperitoneal dissection. The sympathetic nerve branch to the kidney close to the aorta and the adrenal nerve branch between the celiac ganglion and adrenal medulla were dissected free, placed on thin bipolar platinum electrodes, and covered with silicone rubber (Wacker Sil-gel 604, Wacker-Chemie, Munich, FRG) according to the technique of Schad and Seller.¹⁰

Each electrode was connected to a high-impedance probe. Action potentials were amplified 20–50 $\times 10^3$ times by bandpass amplifier (model P511, Grass Instrument, Quincy, Massachusetts) with a bandwidth of 100–1,000 Hz. For monitoring during the experiment, the filtered neurogram was routed through an oscilloscope (model 5111, Tektronix, Beaverton, Oregon) and an amplitude discriminator to an audio amplifier. For permanent recording and analysis, the filtered neurogram was fed through a nerve-traffic analyzer (model 706C, University of Iowa Bioengineering, Iowa City), which counted nerve spikes exceeding a threshold voltage set just above the noise level. The counter's time bin was set at 1 second, so that impulse frequency was displayed on a Beckman RM Dynograph recorder (Beckman Instruments, Fullerton, California) as the number of spikes detected each second (Hz) on a time-frequency histogram.

Experimental Protocols

Animals were allowed to stabilize for at least 1 hour after surgery before the experimental protocols were begun. In each animal, adrenal and renal SNA were recorded simultaneously.

Protocol I: Hemorrhage

A: Responses to hypotensive hemorrhage before and after vagotomy (n=10). The purpose of this protocol was to compare effects of hemorrhagic hypotension on renal and adrenal SNA and to examine the role played by vagal afferents in causing these responses. Rats were bled rapidly so that mean arterial pressure fell to approximately 50 mm Hg within 2 minutes; small additional amounts of blood were either withdrawn or infused in order to maintain arterial pressure at that level for 6 additional minutes. The SNA was averaged at consecutive 30-second intervals during the 2-minute control period and the 8-minute period of hemorrhagic hypotension. The blood was then reinfused and the cervical vagi were sectioned bilaterally. When arterial pressure had stabilized after vagotomy, the hemorrhage was repeated.

B: Responses to hemorrhagic hypotension after atropine (n=5). To determine if effects of vagotomy were due to interruption of vagal afferents or to interruption of vagal efferents, we compared responses

to hemorrhage under three conditions: 1) after injection of vehicle (5% dextrose in water), 2) after administration of atropine methylnitrate (0.25 mg/kg i.v.), and 3) after bilateral cervical vagotomy. Efficacy of muscarinic blockade was demonstrated by failure of acetylcholine (0.5 μ g i.v.) to produce decreases in arterial pressure and heart rate.

C: Responses to hemorrhagic hypotension after SAD alone and after combined SAD plus vagotomy (n=8). Our goal in performing these experiments was to examine the role of the sinoaortic baroreceptors in the control of adrenal and renal SNA during hemorrhagic hypotension and to search for an interaction between arterial and cardiac baroreflex in control of adrenal SNA during hemorrhage. In eight rats with bilateral SAD, we studied responses to hemorrhage with the vagi intact (i.e., SAD alone) and then again after bilateral vagotomy (i.e., SAD plus vagotomy).

Protocol II: Arterial Baroreflex Control of Adrenal and Renal SNA During Increases in Arterial Pressure (n=10)

To compare arterial baroreflex control of adrenal and renal SNA, we recorded changes in SNA in the 10 rats from Protocol IA during arterial baroreceptor stimulation produced by infusion of the α -adrenergic agonist phenylephrine. The drug was diluted in 5% dextrose in water (1:50 dilution of a 1 μ g/ml solution) and infused intravenously to produce ramp increases in mean arterial pressure up to 160 mm Hg. For each animal, the gain of the arterial baroreflex was expressed as the percent decrease in SNA per millimeter of mercury increase in mean arterial pressure over the linear portion of the baroreflex curve.

Protocol III: Vagal Afferent Control of Adrenal and Renal SNA During Volume Expansion (n=8)

To compare vagal afferent regulation of adrenal and renal SNA, we recorded graded increases in LVEDP and decreases in SNA in eight additional rats with SAD during activation of vagal afferents with repeated intravenous infusions of 0.5 ml of whole blood (from a donor rat) to a total infusion of 3.5 ml. The maximal increases in LVEDP and corresponding reflex changes in SNA were averaged over 15 cardiac cycles during each step infusion.

In summary, we studied 10 rats in Protocol IA and II, five rats in Protocol IB, eight rats in Protocol IC, and eight rats in Protocol III.

Data Analysis

In Protocols I and II, on-line acquisition and data analysis were performed with a software routine and an IBM PC. Analog values of arterial pressure, heart rate, and SNA were digitized on a second-by-second basis during each experimental intervention. In Protocol III, values of LVEDP and SNA were measured by inspection of the polygraph record.

The data were entered into the Statistical Analysis System of Weeg Computing Center at the University

of Iowa. Statistical analysis was performed using repeated measures analysis of variance with the Bonferroni adjustment for multiple comparisons.¹¹ Results are expressed as mean \pm SEM. Values of $p < 0.05$ were considered statistically significant.

Results

Protocol I: Hemorrhage

The volume of blood removed by hemorrhage was 2.27 ± 0.76 , 2.39 ± 0.79 , 2.88 ± 1.01 , and 2.47 ± 0.89 ml in rats with intact baroreceptors, with vagotomy, with SAD, and with combined SAD plus vagotomy, respectively. There were no statistical differences between these values. Body weights were 264 ± 6 g for the 10 rats studied before and after vagotomy and 245 ± 6 g for the eight rats with SAD.

Responses to hemorrhagic hypotension with intact arterial baroreceptors and cardiac vagal afferents (Table 1 and Figures 1 and 2). At the onset of hemorrhage, heart rate, renal SNA, and adrenal SNA all tended to increase. However, during sustained hypotension heart rate decreased from 384 ± 13 to 365 ± 16 beats/min ($p < 0.05$) and renal SNA progressively decreased to a value $31 \pm 10\%$ below control ($p < 0.05$). In contrast, adrenal SNA progressively increased to a value $67 \pm 18\%$ above control ($p < 0.05$). Thus, sustained hemorrhagic hypotension produced directionally opposite effects on renal and adrenal SNA.

Arterial pressure, heart rate, and renal and adrenal SNA returned to control values after reinfusion of blood (Figure 1). Ganglionic blockade with chlorisondamine (5 mg/kg i.v.) abolished SNA in the postganglionic renal nerve but did not decrease and indeed caused a small increase in SNA in the preganglionic adrenal nerve (Figure 1).

A: Effects of vagotomy on responses to hemorrhagic hypotension (Table 1 and Figure 3). Cervical vagotomy reversed the bradycardic and renal sympathoinhibitory responses to hypotensive hemorrhage. After vagotomy, heart rate increased from 443 ± 14 to 459 ± 16 beats/min ($p < 0.05$) and renal SNA increased by $28 \pm 13\%$ after 8 minutes of hypotension ($p < 0.05$ vs. control). In contrast, adrenal SNA responses to hemorrhage were not affected by vagotomy alone; increases in adrenal SNA with hemorrhage were $67 \pm 18\%$ before and $61 \pm 19\%$ after vagotomy ($p < 0.1$).

B: Effects of atropine on responses to hemorrhagic hypotension. Whereas cervical vagotomy abolished and reversed the decreases in renal SNA during hypotensive hemorrhage (Table 1 and Figure 3), muscarinic blockade with atropine had no effect on the renal SNA response to hemorrhage. During hemorrhagic hypotension, renal SNA decreased by $55 \pm 10\%$ before atropine and by $49 \pm 13\%$ after atropine ($p < 0.1$).

C: Responses to hemorrhagic hypotension after SAD alone and after combined SAD plus vagotomy (Table 1 and Figure 4). In rats with SAD, bilateral

TABLE 1. Responses to Hemorrhagic Hypotension in Rats

	Control value	Value 30 seconds after onset of hemorrhage	Value during eighth minute of hemorrhagic hypotension
Mean arterial pressure (mm Hg)			
Intact	108±4	85±7	51±1
VGX	112±6	83±11	53±2
SAD	120±7	95±6	53±1
SAD+VGX	103±5	75±5	53±1
Heart rate (beats/min)			
Intact	384±13	388±13	365±16*
VGX	443±14	452±14*	459±16*
SAD	406±17	404±17	397±24
SAD+VGX	436±25	437±25	432±28
Renal SNA (% of control)			
Intact	100	115±5	69±10*
VGX	100	121±6*	128±13*
SAD	100	95±5	90±8
SAD+VGX	100	105±2	119±12*
Adrenal SNA (% of control)			
Intact	100	125±8*	167±18*
VGX	100	119±6*	161±19*
SAD	100	115±8*	157±15*
SAD+VGX	100	108±2*	117±5*

VGX, bilateral cervical vagotomy; SAD, bilateral sinoaortic denervation.

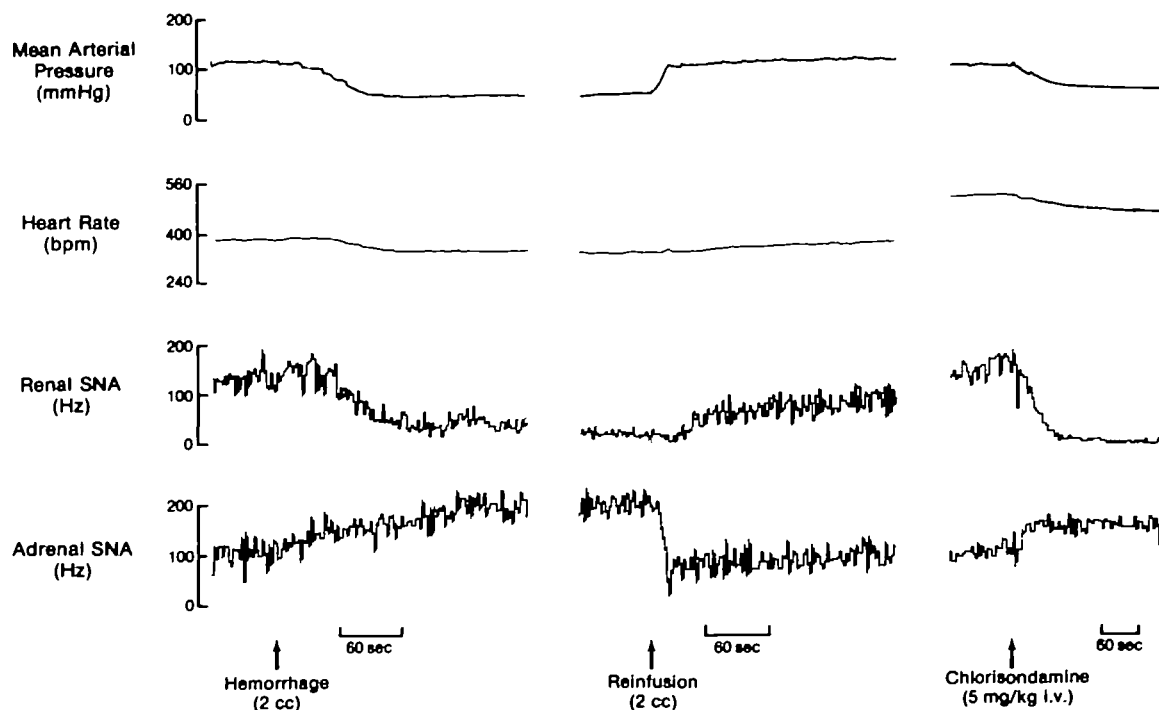
* $p < 0.05$ vs. control.

FIGURE 1. Segments of an illustrative record showing responses of mean arterial pressure, heart rate, and renal and adrenal sympathetic nerve activity (SNA) (displayed as a time-frequency histogram) during hypotensive hemorrhage, reinfusion of blood, and ganglionic blockade with chlorisondamine. Hemorrhagic hypotension decreased renal SNA and heart rate but increased adrenal SNA; these variables returned toward control values after retransfusion. Ganglionic blockade abolished SNA in postganglionic renal nerve but did not decrease and even tended to increase SNA in preganglionic adrenal nerve.

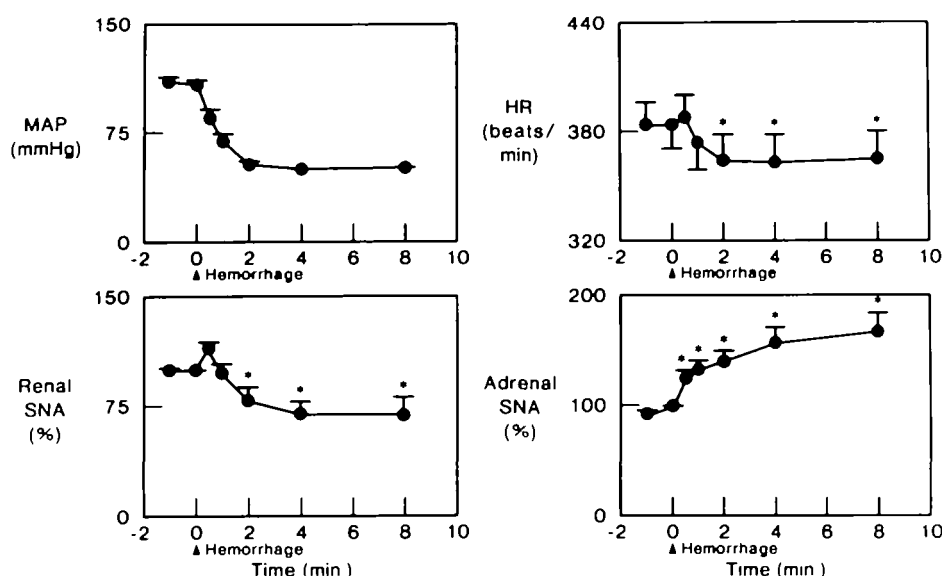


FIGURE 2. Average responses to hemorrhagic hypotension. Data are mean \pm SEM for 10 rats. Asterisks (*) indicate significant changes from control values ($p < 0.05$). Hemorrhagic hypotension produced directionally opposite changes in renal and adrenal sympathetic nerve activity (SNA). Changes in heart rate (HR) paralleled changes in renal SNA. MAP, mean arterial pressure.

vagotomy reversed the renal sympathoinhibitory response to hypotensive hemorrhage. Most importantly, the adrenal sympathoexcitatory response to the sustained hypotension was not attenuated by SAD alone but was sharply attenuated by a combination of SAD plus vagotomy (Figure 4).

Protocol II: Comparison of Arterial Baroreflex Control of Adrenal Versus Renal SNA (Figure 5)

Ramp increases in arterial pressure during an infusion of phenylephrine produced graded decreases in SNA in both adrenal and renal nerves. The baroreflex gain (Δ SNA in %/ Δ MAP in mm Hg) was comparable in the two nerves: 1.67 ± 0.29 for renal SNA and 2.21 ± 0.28 for adrenal SNA ($p > 0.1$). At the highest level of mean arterial pressure (160 mm Hg), the maximal decrease in adrenal SNA ($76 \pm 6\%$ below control) was greater ($p < 0.05$) than the maximal decrease in renal SNA ($60 \pm 9\%$).

Protocol III: Comparison of Vagal Afferent Control of Adrenal and Renal SNA During Volume Expansion (Table 2 and Figures 6 and 7)

Rats in this group weighed 260 ± 4 g. During the first four steps of volume infusion in rats with SAD, increases in LVEDP (values between 5.8 and 19.5 mm Hg) were associated with significantly greater decreases in adrenal than renal SNA. Thus, 1 ml of blood increased LVEDP by 6.4 ± 1.5 mm Hg over control values and decreased adrenal SNA by $28 \pm 8\%$ ($p < 0.05$ vs. control) but did not decrease renal SNA. However, with greater increments in infused volume, the decreases in renal and adrenal SNA per unit increase in LVEDP were comparable; infusion of 2.5 ml of blood increased LVEDP by 13.7 ± 1.3 mm Hg and produced equivalent decreases in adrenal and renal SNA ($46 \pm 10\%$ vs. $32 \pm 16\%$; $p > 0.1$). The SNA responses to volume expansion were abolished by vagotomy (Table 2).

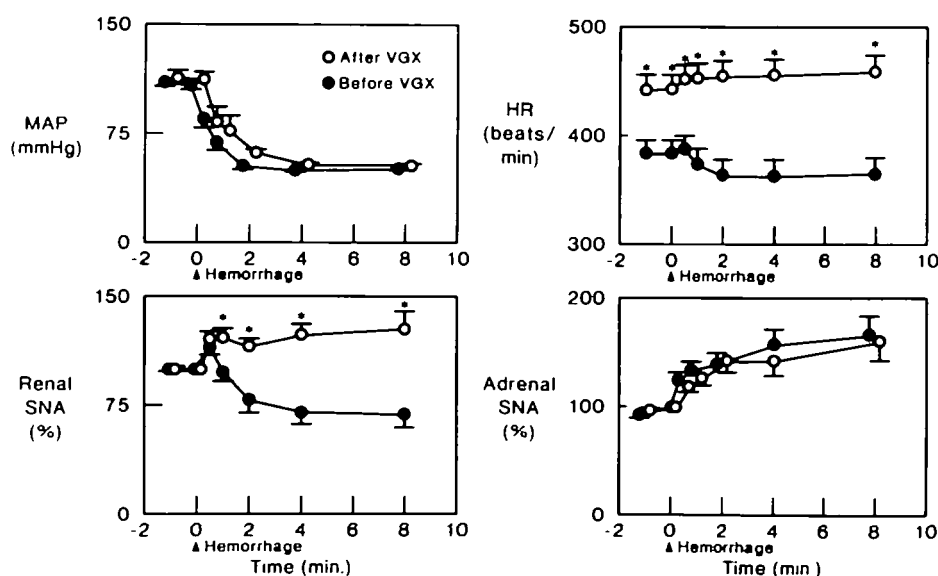


FIGURE 3. Effects of vagotomy (VGX) on responses to hemorrhage in 10 rats (mean \pm SEM). Asterisks (*) indicate significant effect of VGX ($p < 0.05$ before VGX vs. after VGX). Bilateral cervical vagotomy reversed heart rate (HR) and renal sympathetic nerve activity (SNA) responses to hemorrhagic hypotension but did not affect responses in adrenal SNA.

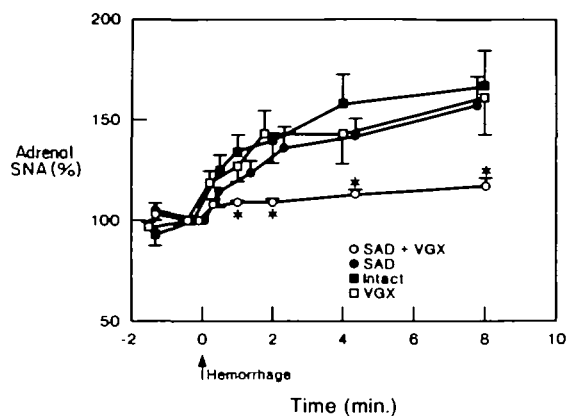


FIGURE 4. Effects of sinoaortic denervation (SAD) and vagotomy (VGX) alone and in combination on adrenal sympathetic nerve activity (SNA) during hemorrhagic hypotension. Data are mean \pm SEM for 10 rats with intact baroreceptors, 10 rats with VGX alone, eight rats with SAD alone, and eight rats with SAD plus VGX. Asterisks (*) indicate significant differences from rats with intact baroreceptors ($p < 0.05$). Adrenal sympathoexcitatory response to hemorrhagic hypotension was not affected by SAD alone or by VGX alone but was sharply attenuated by combined SAD plus VGX.

Discussion

This study demonstrates the comparative reflex effects of hemorrhagic hypotension on sympathetic nerve discharge to the adrenal gland and to the kidney in chloralose-anesthetized rats. The major new conclusions are twofold. First, hemorrhagic

hypotension produces directionally opposite changes in renal and in adrenal sympathetic outflow with renal sympathoinhibition but adrenal sympathoexcitation. Second, both responses are reflexly mediated by vagal afferents. Although many previous studies have shown that vagal afferents exert a nonuniform influence on various regional circulations in many species,¹² this study provides the first direct evidence that when stimulated by hemorrhagic hypotension, afferents in the cervical vagus elicit directionally opposite reflex changes in sympathetic discharge to the adrenal gland and kidney. Differential reflex control of regional sympathetic outflow by vagal afferents is an important factor in producing a complex and highly differentiated pattern of autonomic response to this form of hypotension.

The finding that hemorrhage failed to produce sustained reflex increases in renal SNA and heart rate is not an artifact produced by chloralose anesthesia. Hemorrhagic hypotension recently has been shown to cause decreases in renal SNA and heart rate in chloralose-anesthetized rats comparable with those in conscious rats.¹³

We should consider the possibility that an impairment in ganglionic transmission during severe hemorrhage could have decreased postganglionic renal SNA but would not have decreased adrenal SNA that was preganglionic. This explanation is improbable because the renal sympathetic nerve response to hemorrhage was reversed by cervical vagotomy. This effect of vagotomy was due to interruption of vagal afferents and not to interruption of vagal efferents because the decreases in renal SNA during

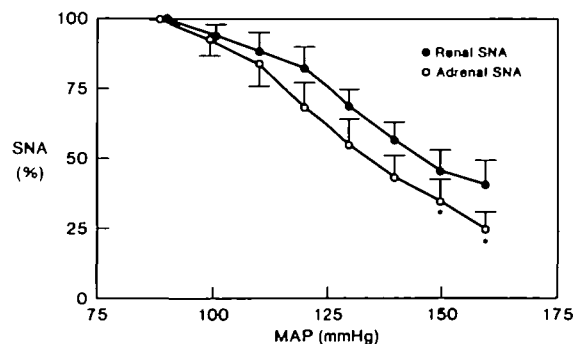
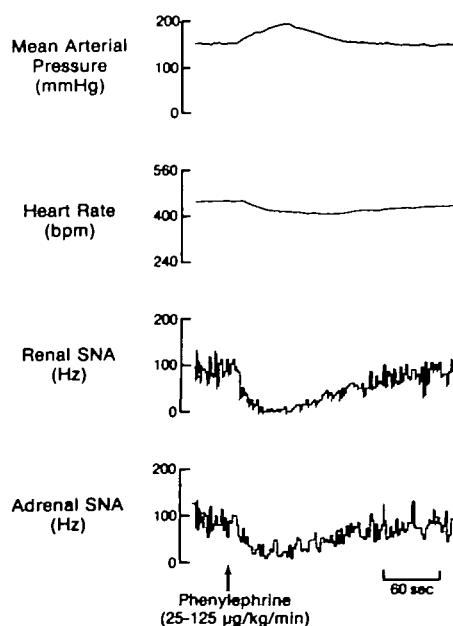


FIGURE 5. Arterial baroreflex-mediated decreases in renal and adrenal sympathetic nerve activity (SNA) during increases in arterial pressure produced by intravenous infusion of phenylephrine. Left panel shows segments from an illustrative record in one rat. Right panel shows average responses in 10 rats (mean \pm SEM). Asterisks (*) indicate significant differences between adrenal and renal SNA ($p < 0.05$). During arterial baroreceptor stimulation, decreases in adrenal SNA were the same as or larger than decreases in renal SNA. MAP, mean arterial pressure.

TABLE 2. Responses to Volume Expansion After Sinoaortic Denervation

Step	Infusion		Vagi intact			Vagi cut		
	(ml)	(ml/100 g body wt)	Δ LVEDP (mm Hg)	Δ Renal SNA (%)	Δ Adrenal SNA (%)	Δ LVEDP (mm Hg)	Δ Renal SNA (%)	Δ Adrenal SNA (%)
1	0.5	0.19 \pm 0.01	2.7 \pm 0.3	+13 \pm 6	-8 \pm 4	1.6 \pm 0.3	-8 \pm 12	-2 \pm 5
2	1.0	0.37 \pm 0.02	6.4 \pm 1.5*	-2 \pm 13	-28 \pm 8*†	3.5 \pm 0.9*	+10 \pm 2	-7 \pm 6
3	1.5	0.56 \pm 0.02	11.5 \pm 1.3*	-9 \pm 13	-39 \pm 5*†	5.7 \pm 1.1*	+4 \pm 6	-3 \pm 6
4	2.0	0.74 \pm 0.03	12.6 \pm 1.4*	-11 \pm 13	-38 \pm 9*†	8.5 \pm 1.8*	+10 \pm 10	+2 \pm 6
5	2.5	0.93 \pm 0.04	13.7 \pm 1.3*	-32 \pm 16*	-46 \pm 10*	10.9 \pm 2.0*	+8 \pm 8	0 \pm 6

Data are mean \pm SEM for eight rats. Δ LVEDP, change in left ventricular end diastolic pressure over control values; Δ SNA, percentage change in sympathetic nerve activity over control values during graded volume expansion with whole blood.

* p <0.05 vs. control.

† p <0.05 for differences between renal and adrenal SNA.

hemorrhage were unaffected by muscarinic blockade with atropine.

Our data, however, do not provide insight into either the location of or the precise stimulus to the vagal afferent endings whose discharge reflexly decreases renal sympathetic activity and heart rate during hemorrhagic hypotension in the rat. In cats and rabbits, hypotension and bradycardia during severe hemorrhage have been attributed in part to stimulation of unmyelinated vagal afferents arising in the left ventricle.^{14,15} One possibility is that these

ventricular endings are activated by mechanical deformation of the myocardium when the heart contracts forcefully around an almost empty ventricular chamber.^{14,16}

Another possibility is that cardiac vagal afferents are activated or sensitized by chemical factors, such as vasopressin^{8,17,18} and catecholamines, that are released into the circulation during severe hemorrhage. In this regard, recent studies in our laboratory have shown that phenyl diguanide, which is known to stimulate chemosensitive vagal afferents,¹⁹

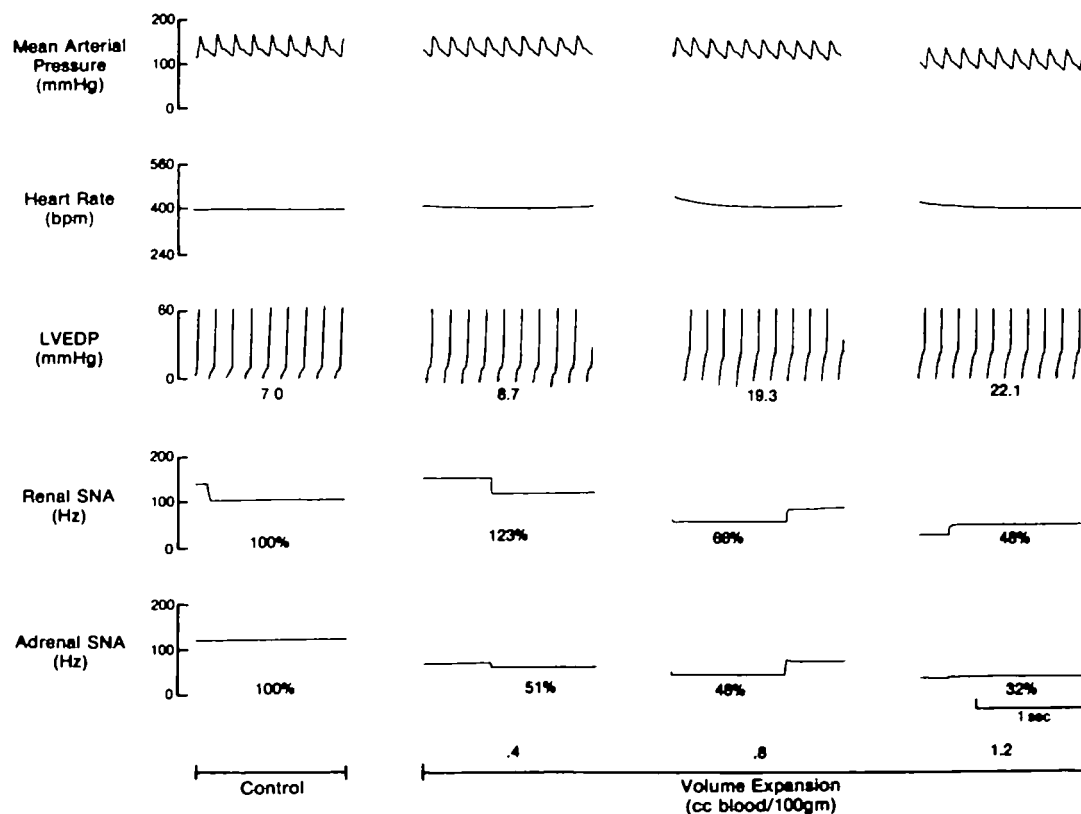


FIGURE 6. Segments of an original record from one rat showing sympathoinhibitory response to stimulation of cardiac baroreceptors by graded volume expansion after bilateral sinoaortic denervation. From top to bottom, arterial pressure, heart rate, left ventricular end-diastolic pressure (LVEDP), and renal and adrenal sympathetic nerve activity (SNA) are displayed as a time-frequency histogram. Values of SNA expressed as a percentage of control value are also shown. Panel labeled LVEDP is a tracing of left ventricular pressure recorded at high gain (0–60 mm Hg) to measure LVEDP, the values of which are shown below the pressure tracings.

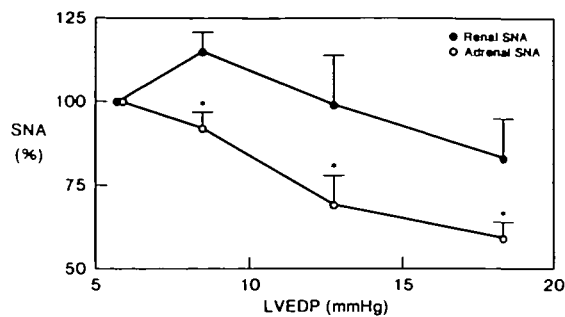


FIGURE 7. Average responses of renal and adrenal sympathetic nerve activity (SNA) expressed as a percentage of control value plotted as a function of absolute levels of left ventricular end-diastolic pressure (LVEDP) in mm Hg during graded volume in eight rats with sinoaortic denervation (mean \pm SEM). Asterisks (*) indicate significant differences between renal and adrenal SNA ($p < 0.05$). Stimulation of cardiac vagal afferents during volume expansion produced greater decreases in adrenal SNA than in renal SNA.

elicits the same pattern of sympathetic response as that produced by hypotensive hemorrhage.²⁰ When injected into the pericardium of rats, phenyl diguanide also decreases renal and increases adrenal sympathetic outflow.

We found that increases in adrenal sympathetic outflow evoked by hemorrhage were not altered by cervical vagotomy alone or by sinoaortic denervation alone but were greatly attenuated by combined sinoaortic and vagal deafferentation. These observations indicate that there is a high degree of redundancy in the control of adrenal sympathetic activity by cardiac and arterial baroreceptors and that neural occlusion may be operative.²¹ This interpretation is consistent with the findings of Heesch and Bishop,⁴ who demonstrated a similar interaction between carotid and cardiac baroreflex restraint of adrenomedullary catecholamine secretion in cats.

Sympathetic nerve responses to increases in arterial pressure produced by phenylephrine infusion and to increases in left ventricular filling pressure produced by volume expansion provide additional insight into the regulation of adrenal and renal sympathetic activity by arterial and cardiac baroreceptors. Previously, the role of sinoaortic baroreceptors in the control of adrenal sympathetic outflow and catecholamine release has been controversial. In cats and dogs, bilateral carotid occlusion did not increase plasma levels of adrenal catecholamines if the vagi were intact.^{4,5} Fater et al⁵ reported that the hypotension induced by hemorrhage or by infusion of nitroglycerin did not increase plasma catecholamines, whereas Glaviano et al²² found that hemorrhage markedly stimulated catecholamine secretion from the adrenal medulla.

This study provides direct evidence that arterial baroreceptor stimulation reflexly decreases sympathetic outflow to the adrenal gland as well as to the

kidney. The present data are consistent with those of Ito et al,²³ who found a close relationship between adrenal SNA and adrenal vein epinephrine during baroreceptor stimulation and inhibition. Our finding that the gain of arterial baroreflex control of sympathetic activity was comparable for adrenal and renal SNA suggests that differences in these two sympathetic outflows during hemorrhagic hypotension are not due to regional differences in arterial baroreflex regulation.

We also found that progressive volume expansion produced graded decreases in both adrenal and renal sympathetic activity in rats with sinoaortic denervation. These reflex responses were caused by vagal afferents because they were abolished by cervical vagotomy. Thus, an important feature of this study is the suggestion that adrenal and renal sympathetic outflows are coupled when vagal afferents are activated by increases in cardiac filling pressure over the physiologic range but are dissociated when vagal afferents are activated by the pathophysiologic condition of hemorrhagic hypotension.

Speculation: Pathophysiologic Significance

Increased sympathetic drive to the adrenal medulla most likely provides the stimulus to adrenal catecholamine secretion during hemorrhagic hypotension. In addition, recent studies by Breslow et al²⁴ and Traystman et al²⁵ indicate that adrenal sympathetic nerve discharge stimulates adrenal medullary blood flow, which would increase the rate of catecholamine release. Adrenergic stimulation of the cardiovascular system by circulating catecholamines is thought to be an important mechanism for maintaining circulatory function during severe hemorrhage. Withdrawal of sympathetic vasoconstrictor drive to the kidney might provide a protective mechanism for minimizing renal ischemia and acute tubular necrosis. Renal sympathoinhibition has been shown to be sustained when hemorrhagic hypotension is prolonged for more than 30 minutes.⁷ Reflex bradycardia may serve to reduce myocardial oxygen demands and thus minimize myocardial ischemia during this form of hypotension. Hemorrhagic hypotension is frequently accompanied by bradycardia not only in the experimental setting in animals but also in the clinical setting in patients.^{26–28}

Acknowledgments

The authors thank Ms. Cindy Lawson and Ms. Pamela Kay Maass for expert secretarial assistance.

References

1. Bedford EA, Jackson HC: The epinephrine content of the blood in conditions of low blood pressure and "shock." *Proc Soc Exp Biol Med* 1916;13:85–87
2. Abboud FM: Shock, in Wyngaarden JB, Smith LH Jr (eds): *Cecil Textbook of Medicine*. Philadelphia, WB Saunders Co, 1985, pp 211–225

3. Vatner SF: Effects of hemorrhage on regional blood flow distribution in dogs and primates. *J Clin Invest* 1974; 54:225-235
4. Heesch CM, Bishop VS: Cardiovascular reflex modulation of plasma catecholamine concentrations in the anesthetized cat. *Circ Res* 1982;52:391-399
5. Fater DC, Sundet WD, Schultz HD, Goetz KL: Arterial baroreceptors have minimal physiological effects on adrenal medullary secretion. *Am J Physiol* 1983;244:H194-H200
6. Morita H, Vatner S: Effects of hemorrhage on renal nerve activity in conscious dogs. *Circ Res* 1985;57:788-793
7. Skoog P, Monsson J, Thorén P: Changes in renal sympathetic outflow during hypotensive hemorrhage in rats. *Acta Physiol Scand* 1985;125:655-660
8. Undesser KP, Hasser EM, Trapani AJ, Bishop VS: The effect of vasopressin on renal sympathetic nerve activity responses to hemorrhage in conscious rabbits (abstract). *Circulation* 1985;72(suppl III):III-17
9. Krieger EM: Neurogenic hypertension in the rat. *Circ Res* 1964;15:511-521
10. Schad H, Seller P: A method for recording autonomic nerve activity in unanesthetized, freely moving cats. *Brain Res* 1975;100:425-430
11. Miller RJ Jr: *Simultaneous Statistical Inference*, ed 2. New York, Springer-Verlag, 1981, pp 67-70
12. Bishop VS, Malliani A, Thorén P: Cardiac mechanoreceptors, in Shepherd JT, Abboud FM (eds): *Handbook of Physiology, Section 2: The Cardiovascular System, Vol III, Part 2*. Bethesda, Md, American Physiological Society, 1983, pp 497-555
13. Morgan DA, Thorén P, Staudt SM, Mark AL: Differential effects of anesthesia on heart rate, renal, and lumbar sympathetic nerve activity in the rat. *FASEB J* 1988;2:A1690
14. Oberg B, Thorén P: Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat. A possible cause of the vaso-vagal reaction. *Acta Physiol Scand* 1972;85:164-173
15. Chen HI, Stinnett HO, Peterson DF, Bishop VS: Enhancement of vagal restraint on systemic blood pressure during hemorrhage. *Am J Physiol* 1978;234:H192-H198
16. Pearce JW, Henry JP: Changes in cardiac afferent nerve-fiber discharges induced by hemorrhage and adrenalin (abstract). *Am J Physiol* 1955;183:650
17. Abboud FM, Aylward PE, Floras JS, Gupta BN: Sensitization of aortic and cardiac baroreceptors by arginine vasopressin in mammals. *J Physiol (Lond)* 1986;377:251-265
18. Peuler JD, Schmidt PG, Morgan DA, Mark AL: Lack of renal sympathoinhibition during severe hemorrhage in Brattleboro rats (abstract). *Circulation* 1986;74(suppl II):II-436
19. Coleridge HM, Coleridge JCG, Dangel A, Kidd C, Tuck JC, Sleight P: Impulses in slowly conducting vagal fibers from afferent endings in the veins, atria, and arteries of dogs and cats. *Circ Res* 1973;33:87-97
20. Higuchi S, Morgan DA, Mark AL: Contrasting reflex effects of chemosensitive and mechanosensitive vagal afferents. *Hypertension* 1988;11:674-679
21. Keele CA, Neil E, Joels NA: Reflex action, in *Samson Wright's Applied Physiology*, ed 13. New York, Oxford University Press, Inc, 1982, pp 265-267
22. Glaviano VV, Bass N, Nykeil F: Adrenal medullary secretion of epinephrine and norepinephrine in dogs subjected to hemorrhagic hypotension. *Circ Res* 1960;8:561-571
23. Ito K, Sato A, Shimamura K, Swenson RS: Reflex changes in sympatho-adrenal medullary functions in response to baroreceptor stimulation in anesthetized rats. *J Auton Nerv Syst* 1984;10:295-303
24. Breslow MJ, Mennen A, Koehler RC, Traystman RJ: Adrenal medullary and cortical blood flow during hemorrhage. *Am J Physiol* 1986;250:H954-H960
25. Traystman RJ, Breslow MJ, Jordan DA: Neurally mediated adrenal medullary vasodilation during hemorrhagic hypotension. *Blood Vessels* 1986;23:103
26. Secher NH, Jensen KS, Werner C, Warberg J, Bie P: Bradycardia during severe but reversible hypovolemic shock in man. *Circ Shock* 1984;14:267-274
27. Rørsgaard S, Secher NH: Slowing of the heart during hypotension in major abdominal surgery. *Acta Anaesthesiol Scand* 1986;30
28. Sander-Jensen R, Secher NH, Bie P, Warberg J, Schwartz TW: Vagal slowing of the heart during haemorrhage: Observations from 20 consecutive hypotensive patients. *Br Med J [Clin Res]* 1986;292:365-366

KEY WORDS • sympathetic nerve activity • hemorrhage • hypotension • vagal afferents • arterial baroreceptors