

Subarachnoid Blockade Alters Homeostasis by Modifying Compensatory Splanchnic Responses to Hemorrhagic Hypotension

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To demonstrate that sympathetic responses transmitted by the splanchnic nerve help maintain intravascular stability, 12 mongrel dogs (35–45 kg each), anesthetized with pentobarbital, were given two separate but identical hypotensive stimuli (mean arterial blood pressure of 60 mmHg for 15 min) by the withdrawal of appropriate amounts of blood. The first stimulus was performed in the absence of drug or surgical manipulation. The second stimulus was performed after animals were subjected to no intervention ($n = 4$), bilateral splanchnic nerve section ($n = 4$), or spinal anesthesia ($n = 4$). Before and 10 min after the onset of hypotension, arterial epinephrine concentration and adrenal medullary and abdominal organ blood flow were measured. In the group without intervention, the second hypotensive stimulus (like the first) elicited 3-fold increases in adrenal medullary blood flow, 40-fold increases in arterial epinephrine concentration, and a 61% reduction in abdominal organ blood flow ($P > 0.002$). The volume of blood withdrawn to produce hypotension was similar ($\sim 21 \text{ ml} \cdot \text{kg}^{-1}$). Bilateral splanchnic nerve section attenuated the adrenal medullary blood flow, arterial epinephrine concentration, and abdominal organ blood flow responses to hypotension by 86, 64, and 66%, respectively ($P < 0.008$), and the blood volume withdrawn was reduced by 42% ($P < 0.02$). Spinal anesthesia eliminated the adrenal medullary blood flow response to hypotension, attenuated the arterial epinephrine concentration and abdominal organ blood flow responses by 78 and 57%, respectively ($P < 0.01$), and decreased the blood volume extracted by 55% ($P < 0.01$). To demonstrate further that peripheral sympathetic effector responses transmitted by the splanchnic nerve can augment blood pressure and intravascular volume, four normovolemic animals who were anesthetized with pentobarbital and whose lungs were mechanically ventilated were subjected to unilateral electrical stimulation of the splanchnic nerve. In these animals, nerve stimulation elicited a 4-fold increase in adrenal medullary blood flow, a 200-fold increase in adrenal venous epinephrine concentration, and a 54% reduction in abdominal organ blood flow ($P < 0.002$). In addition, mean arterial blood pressure and pulmonary artery end-diastolic pressure increased by 45 and 68%, respectively ($P < 0.03$). Our data demonstrate that peripheral sympathetic nervous system responses to blood loss are transmitted by the greater splanchnic

nerve. These responses are important compensatory mechanisms during periods of hemorrhage and hypotension and help maintain intravascular homeostasis. (Key words: Anesthetic techniques, spinal: splanchnic nerve activity. Blood flow: adrenal medulla; abdominal organ. Blood pressure: hypotension. Sympathetic nervous system, catecholamines: epinephrine.)

THE SPLANCHNIC NEURONAL SYSTEM transmits a wide variety of sympathetic responses to the periphery.¹⁻⁵ Although it is generally accepted that splanchnic responses act to compensate for hypotension, it has not been clearly shown that splanchnic sympathectomy causes the cardiovascular instability and decreased tolerance to blood loss observed during the induction and maintenance of spinal anesthesia.^{6,7}

In response to hemorrhagic hypotension, hormones and polypeptides are released by the adrenal medulla into the systemic circulation and act to mediate a variety of peripheral effects.⁸ Recent studies demonstrate that increases in adrenal secretion are mediated neuronally during hypotension.⁹⁻¹¹ These studies also show that hormones released by adrenal chromaffin cells act locally to stimulate medullary vascular β receptors, resulting in vasodilation, increased medullary blood flow, and enhanced delivery of adrenal catecholamines to the systemic circulation.⁹ These data suggest that medullary secretion and blood flow are important components of the adrenal response to hemorrhagic hypotension.

In response to hypotension, the blood supply to splanchnic organs decreases.^{4,12,13} Greenway¹⁴ and Lundgren¹⁵ found that this vasoconstriction shunts blood away from the splanchnic bed and leads to the expulsion of "reservoir" blood into the systemic circulation. Although multiple factors may modify this response, alterations in abdominal organ blood flow induced by acute blood loss are, for the most part, neuronally mediated.¹⁵

To confirm that adrenal medullary and splanchnic vascular responses to hypotension are neuronally mediated, we subjected adult mongrel dogs to hemorrhagic hypotension in the presence and absence of bilateral splanchnic nerve section or spinal anesthesia. To further document neuronal transmission of these responses, we attempted to elicit the adrenal and abdominal organ changes by subjecting normotensive animals to electrical stimulation of the splanchnic nerve.

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Materials and Methods

This study was approved by the Animal Care and Use Committee of Columbia University. In mongrel dogs (35–45 kg), anesthesia was induced with pentobarbital (20–30 mg · kg⁻¹) and maintained by a constant infusion at 0.1 mg · kg⁻¹ · min⁻¹. After tracheal intubation, the animals' lungs were mechanically ventilated by a Harvard volume cycle ventilator (tidal volume of 15 ml · kg⁻¹) to maintain end-tidal carbon dioxide concentration at ~ 4%. Supplemental oxygen was given to maintain arterial oxygen tension constant (between 100 and 150 mmHg). Temperature and pH were held constant throughout the experiment. Arterial blood gases were measured by a Radiometer-ABL 3 (electrode) analyzer and hematocrit (in triplicate) by a Damon microhematocrit centrifuge, and vascular pressures were recorded by a Hewlett Packard four-channel polygraph (model 7820) using Trantec (model 60–800) transducers referenced to the level of the animal's right atrium. Temperature was maintained at 38 ± 1° C with a heating pad.

The right and left axillary arteries were cannulated for the purpose of obtaining microsphere withdrawal samples, arterial blood chemistry data, and arterial pressure measurements. For the purpose of microsphere injection, a 7-Fr pigtail catheter was placed in the left ventricle *via* a right femoral arteriotomy. Position was verified by pressure waveform. To impose controlled blood loss, the tip of a wide-bore catheter was placed in the left femoral artery and connected to an aspiration bottle pressurized to the animal's mean arterial pressure. For the purpose of measuring central venous and pulmonary artery pressures, a pulmonary artery catheter was positioned through a right internal jugular vein.

After this initial preparation, each animal was subjected to a midline laparotomy. Bilaterally, the greater splanchnic nerve was identified and isolated just below the diaphragm. Animals were then allowed to rest undisturbed for 1 h before experimentation.

RADIOLABELED MICROSPHERE TECHNIQUE

Regional adrenal and abdominal organ blood flows were measured with radiolabeled microspheres (15 ± 1.5 μm in diameter, NEN-Du Pont) using the reference sample method.^{9,16} In brief, the vials containing spheres were shaken vigorously by hand and then agitated. Approximately 4 × 10⁶ spheres, labeled with ¹⁵³Gd, ¹¹⁴In, ¹¹³Sn, ¹⁰³Ru, ⁹⁵Nb, or ⁴⁶Sc, were injected into the left ventricle for each measurement of blood flow, and reference blood samples were withdrawn with a Harvard withdrawal pump at a rate of 4.94 ml · min⁻¹. Reference blood samples were collected beginning 15 s before the injection and continuing for at least 2 min after injection.

At the conclusion of the experiment, the animal was killed with an intravenous bolus of potassium chloride, and the kidneys, small bowel, large bowel, spleen, pancreas, and adrenal glands were removed, weighed, and placed in glass test tubes for counting. The adrenal glands were removed and placed in 10% buffered formalin for 48 h. The adrenal medulla was then manually separated from the cortex after tissue fixation and was weighed and placed in test tubes for counting. Tissue samples were counted in a Minaxi Multichannel Analyzer with a sodium iodide crystal. Reference blood samples were divided into aliquots so that counting geometry was similar to that of the tissue samples. The energy windows used for ¹⁵³Gd, ¹¹⁴In, ¹¹³Sn, ¹⁰³Ru, ⁹⁵Nb, or ⁴⁶Sc isotopes were 70–140, 174–280, 370–440, 460–550, 710–820, and 840–1200 KeV, respectively. Backscatter from higher isotopes into windows of lower energy emission were subtracted for a corrected count value using differential spectroscopy by the method of Rudolph and Heymann.¹⁶

CATECHOLAMINE ASSAY

The blood plasma assay for epinephrine consisted of a two-part process that entailed aluminum oxide purification followed by a final separation and quantification with high-pressure liquid chromatography.¹⁷

Two milliliters of plasma were placed in a known amount of 3,4-dihydroxybenzylamine, which served as an internal standard. One milliliter of a 1.5 M Trizma buffer solution (pH 8.6) was added and shaken for 5 min, adsorbing the desired amines onto the alumina stationary phase. The mixture was then allowed to settle, aspirated to near dryness, and washed three times with water. One milliliter of 0.1 M perchloric acid was added. The mixture was then vortexed, centrifuged, and filtered through a 0.25-μm high-pressure liquid chromatography syringe filter.

After the initial batch aluminum oxide purification, 100 μl of the final acidic eluate was injected onto a Bio-phase ODS column (Bioanalytical Systems 250 × 4.66 mm column, 5-μm particle). All components were eluted within 20 min using the mobile phase (0.1 M monoacetoacetate, 1 mM EDTA, 2.8 mM sodium octyl sulfate, and 7.5% acetonitrile, pH 3.0) at a flow rate of 2 ml · min⁻¹. Detection was accomplished by monitoring column eluate oxidation by LC-4A amperometric detector (potential +0.700 V, sensitivity 1 nA/V, and offset 1–10 nA). An on-line digital integrator operating according to the method of internal standard directly calculated quantities of epinephrine. Interassay variability was 5%, with a range of 1.5 to 6.5%. Average percent recovery was 83.9 ± 3% for epinephrine.

PROTOCOL

After surgical preparation and the 60-min equilibration period, adrenal medullary blood flow, arterial epinephrine concentration, abdominal organ blood flow, and pulmonary artery pressures were measured and recorded for each animal. Subjects were then given a hemorrhagic hypotensive stimulus (mean arterial pressure 60 mmHg) for 15 min by withdrawal of appropriate amounts of blood into the pressurized bottle system. The initial withdrawal of blood was rapid and accomplished within 2 min. Ten minutes after this hypotensive stimulus was begun, the above measurements were repeated. Once these determinations were made, the volume of blood withdrawn was recorded and reinfused. Animals were then randomly allocated to one of four test groups.

Group 1: Control (n = 4)

In the absence of additional drugs or surgical interventions, animals were allowed to rest for 30 min. They were then subjected to a second, identical hemorrhagic hypotensive stimulus (mean arterial pressure of 60 mmHg) for 15 min.

Before this stimulus and 10 min after it was begun, the parameters of adrenal medullary blood flow, arterial epinephrine concentration, abdominal organ blood flow, and the volume of blood removed from the animal were measured and recorded.

Group 2: Denervation (n = 4)

In these animals the right and left greater splanchnic nerves were cut and ligated as they exited from below the diaphragm.¹¹ The animals were allowed to rest for 30 min and then subjected to a repeat hemorrhagic hypotensive stimulus (mean arterial pressure 60 mmHg) for 15 min by withdrawal of the appropriate amount of blood.

Before this stimulus and 10 min after it was begun, the parameters of adrenal medullary blood flow, arterial epinephrine concentration, abdominal organ blood flow, and the volume of blood removed were measured and recorded.

Group 3: Spinal Anesthesia (n = 4)

These animals were given a subarachnoid bolus of 35 mg of isobaric lidocaine hydrochloride (3 ml at the L3–L4 level). The lumbar area was prepared with the animal in the right lateral position. An 18-G spinal needle was inserted to the subarachnoid space. Lidocaine 2% (1.75 ml) was mixed with the cerebrospinal fluid (1.25 ml) and then slowly injected through the spinal needle. Animals were then allowed to rest, undisturbed, for 20 min. They

were then subjected to a second hemorrhagic hypotensive stimulus (mean arterial pressure of 60 mmHg) for 10 min.

Before this hypotensive stimulus and 10 minutes after it was begun, the parameters of adrenal medullary blood flow, arterial epinephrine concentration, abdominal organ blood flow, and the blood volume withdrawn were measured and recorded.

Group 4: Nerve Stimulation (n = 4)

In these animals, the left lumboadrenal vein was cannulated, using the technique of Hume and Nelson,¹⁸ and the adrenal effluent collected. The left greater splanchnic nerve was ligated and the distal end placed across two copper electrodes connected to a Grass stimulator set at 10 Hz, 0.5-ms duration, and 5 V, with a 0.8-s pause per second. After a 30-min rest period, animals were subjected to electrical stimulation of the greater splanchnic nerve for 15 min.

Before and after 10 min of stimulation, adrenal medullary blood flow, abdominal organ blood flow, and adrenal venous norepinephrine and epinephrine concentrations were measured and recorded.

STATISTICAL ANALYSIS

The effect of bilateral splanchnic nerve section and spinal anesthesia on adrenal medullary blood flow, arterial epinephrine concentration, and abdominal organ blood flow was assessed by using one-way analysis of variance for repeated measures. One-way analysis of variance was also used to evaluate changes induced by hemorrhagic hypotension or electrical stimulation of the splanchnic nerve in adrenal medullary blood flow, abdominal organ blood flow, and plasma catecholamines.

To assess the effect of bilateral splanchnic nerve section and spinal anesthesia of hemorrhagic hypotension-induced changes in adrenal medullary blood flow, arterial epinephrine concentration, and abdominal organ blood flow, two-way analysis of variance for repeated measures (between-within format) was used.

Statistical significance was defined by $P < 0.05$ and all data are presented as means \pm standard error.

Results

Hemorrhagic hypotension, to a mean arterial blood pressure of 60 mmHg, characteristically resulted in a 3-fold increase in adrenal medullary blood flow (430 ± 24 to 1181 ± 137 ml \cdot min⁻¹ \cdot 100 g⁻¹), $P = 0.0001$, a 40-fold increase in arterial epinephrine concentration (91 ± 24 to 3750 ± 512 pg \cdot ml⁻¹), $P = 0.0003$, and a 61% decrease in abdominal organ blood flow (55 ± 4 to 21 ± 4 ml \cdot min⁻¹ \cdot 100 g⁻¹), $P = 0.0018$. Whereas the blood flow to each splanchnic organ was measured directly by

TABLE 1. Hemorrhage-Induced Changes in Tissue Blood Flow and Vascular Resistance

	Weight (g)	Blood Flow (ml · min ⁻¹ · 100 g ⁻¹)	Abdominal Organ Blood Flow (% blood flow)	Vascular Resistance (mmHg · ml ⁻¹ · min ⁻¹ · 100 g ⁻¹)
Abdominal organs				
Kidney	105	385 ± 43 to 141 ± 4	67 to 67	0.40 ± 0.03 to 0.55 ± 0.09
Small bowel	950	36 ± 2 to 14 ± 1	6 to 7	4.1 ± 0.1 to 4.8 ± 0.4
Large bowel	795	34 ± 3 to 16 ± 4	6 to 8	4.4 ± 0.3 to 5.4 ± 0.9
Spleen	175	95 ± 6 to 34 ± 2	17 to 16	1.6 ± 0.1 to 2.0 ± 0.1
Pancreas	200	23 ± 2 to 5 ± 1	4 to 2	6.3 ± 0.4 to 15.9 ± 2.4
Other organs				
Adrenal medulla	0.09	430 ± 24 to 1181 ± 137		
Adrenal cortex	1.10	265 ± 24 to 178 ± 16		

Data obtained from all control animals (n = 4) during hypotensive hemorrhage.

Weighted average for abdominal organ blood flow is reported as milliliters per minute per 100 g. Weighted average abdominal organ blood flow was 55 ± 5 ml · min⁻¹ · 100 g⁻¹ before hypotension and 21 ± 4 ml · min⁻¹ · 100 g⁻¹ during hypotension.

the radiolabeled microsphere technique, abdominal organ blood flow was calculated as the weighted average of kidney, large bowel, small bowel, spleen, and pancreas blood flows (table 1). Because the portal circulation supplies two thirds of the blood flow to the liver, total liver blood flow could not be measured using this radiolabeled microsphere technique.

In group 1 animals (control animals), similar adrenal medullary blood flow, arterial epinephrine, and abdominal organ blood flow responses were elicited by our first and second hemorrhagic hypotensive stimuli (fig. 1). Also, the amount of blood that had to be removed from these animals to produce each hypotensive stimulus was not significantly different.

Bilateral splanchnic nerve section (group 2) attenuated the adrenal medullary blood flow, arterial epinephrine, and abdominal organ blood flow responses to hypotension (fig. 2). In these animals, the adrenal medullary blood

flow response was decreased by 86% (310 ± 21 to 1035 ± 91 and 230 ± 15 to 322 ± 22 ml · min⁻¹ · 100 g⁻¹ for control and bilateral splanchnic nerve section response, respectively), P = 0.008; the arterial epinephrine response was decreased by 64% (190 ± 70 to 5700 ± 800 and 70 ± 30 to 770 ± 250 pg · ml⁻¹ for control and bilateral splanchnic nerve section response, respectively), P = 0.0007; and there was a 66% attenuation of the abdominal organ blood flow response (65 ± 5 to 14 ± 2 and 61 ± 4 to 45 ± 3 ml · min⁻¹ · 100 g⁻¹ for control and bilateral splanchnic nerve section response, respectively), P = 0.0003. The blood volume withdrawn from the animals to produce the hypotensive stimulus of 60 mmHg was also reduced by 42% (750 ± 30 ml before nerve section and 430 ± 50 ml after nerve section, a change of 22 ± 0.9 to 12 ± 1.4 ml · kg⁻¹).

Subarachnoid blockade (group 3) altered the adrenal medullary blood flow, arterial epinephrine, and abdom-

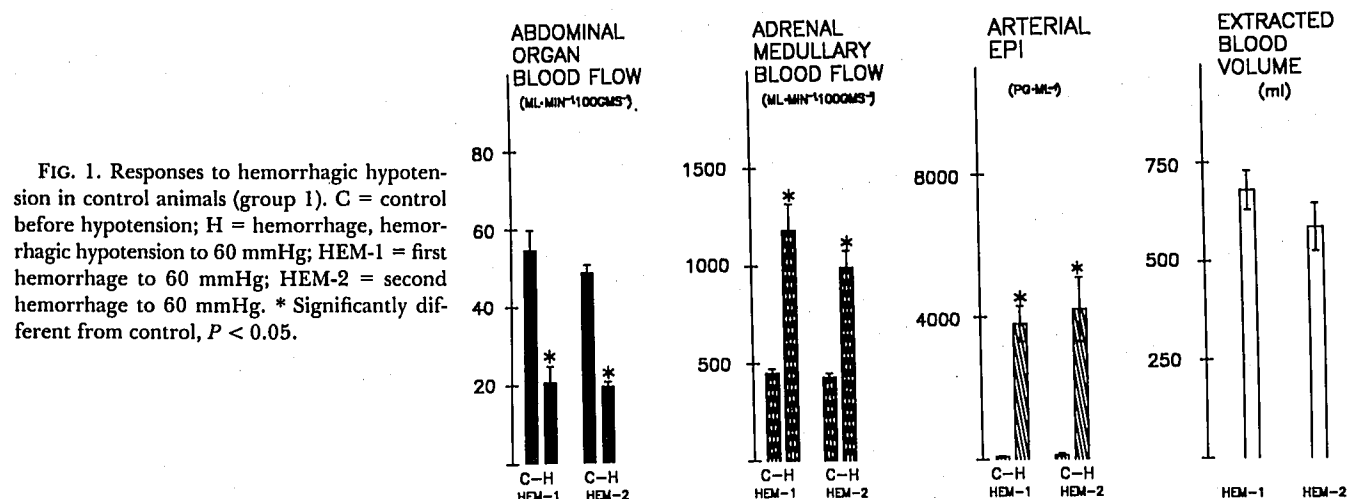


FIG. 1. Responses to hemorrhagic hypotension in control animals (group 1). C = control before hypotension; H = hemorrhage, hemorrhagic hypotension to 60 mmHg; HEM-1 = first hemorrhage to 60 mmHg; HEM-2 = second hemorrhage to 60 mmHg. * Significantly different from control, P < 0.05.

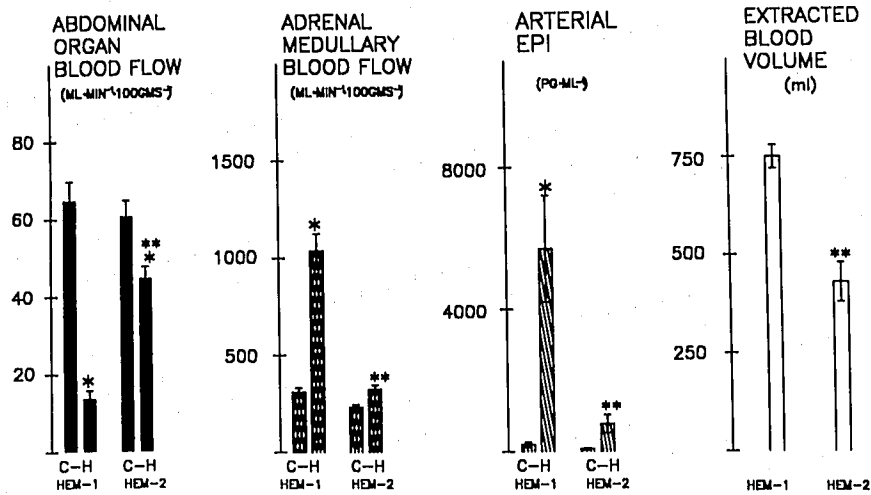


FIG. 2. Responses to hemorrhagic hypotension in animals subjected to bilateral splanchnic nerve section (group 2). C = control, before hypotension; H = hemorrhage, hemorrhagic hypotension to 60 mmHg; HEM-1 = first hemorrhage to 60 mmHg; HEM-2 = second hemorrhage to 60 mmHg. * Significantly different from control, $P < 0.05$; ** HEM-2 different from HEM-1, $P < 0.05$.

inal organ blood flow responses to hemorrhagic hypotension (fig. 3). The adrenal medullary blood flow response was completely eliminated (435 ± 19 to $1,085 \pm 47$ and 219 ± 14 to $157 \pm 12 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ for control and spinal anesthesia response, respectively); the arterial epinephrine response was decreased by 79% (140 ± 40 to $3,500 \pm 600$ and 70 ± 40 to $350 \pm 120 \text{ pg} \cdot \text{ml}^{-1}$ for control and spinal anesthesia response, respectively), $P = 0.002$; and the abdominal organ blood flow response was attenuated by 57% (58 ± 7 to 21 ± 4 and 37 ± 2 to $29 \pm 3 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ for control and spinal anesthesia response, respectively), $P = 0.013$. The blood volume withdrawn to achieve a mean arterial blood pressure of 60 mmHg was also reduced by 55% (650 ± 35 to $290 \pm 22 \text{ ml}$, a change of 19 ± 1 to $8 \pm 0.7 \text{ ml} \cdot \text{kg}^{-1}$, for control and spinal anesthesia, respectively). Control parameters of abdominal organ and adrenal medullary blood flow obtained before and after spinal anesthesia were significantly different (58 ± 7 to $37 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$

for abdominal organ blood flow and 435 ± 19 to $219 \pm 14 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ for adrenal medullary blood flow).

Changes caused by electrical stimulation (group 4) mimicked the adrenal medullary blood flow, arterial epinephrine, and abdominal organ blood flow alterations seen during hemorrhagic hypotension (fig. 4). Mean arterial blood pressure and pulmonary artery end diastolic pressure increased significantly. Adrenal medullary blood flow increased 4-fold (243 ± 16 to $1,318 \pm 44 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ for control and nerve stimulation, respectively); adrenal venous epinephrine concentration increased 200-fold (4.4 ± 4 to $2,300 \pm 155 \text{ ng} \cdot \text{ml}^{-1}$ for control and nerve stimulation, respectively); and abdominal organ blood flow decreased by 54% (55 ± 4 to $25 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$, for control and nerve stimulation, respectively).

Calculated vascular resistance data (table 2) reveal that nerve section and spinal anesthesia markedly attenuated

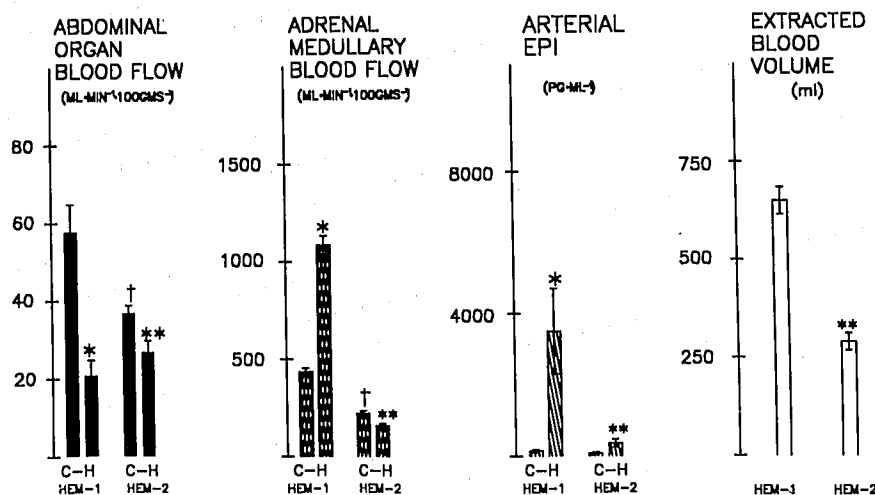


FIG. 3. Response to hemorrhagic hypotension in animals subjected to spinal anesthesia (group 3). C = control, before hypotension; H = hemorrhage, hemorrhagic hypotension to 60 mmHg; HEM-1 = first hemorrhage to 60 mmHg; HEM-2 = second hemorrhage to 60 mmHg. * Significantly different from control, $P < 0.05$; ** HEM-2 significantly different from HEM-1, $P < 0.05$; † Control values for HEM-1 and HEM-2 significantly different, $P < 0.05$.

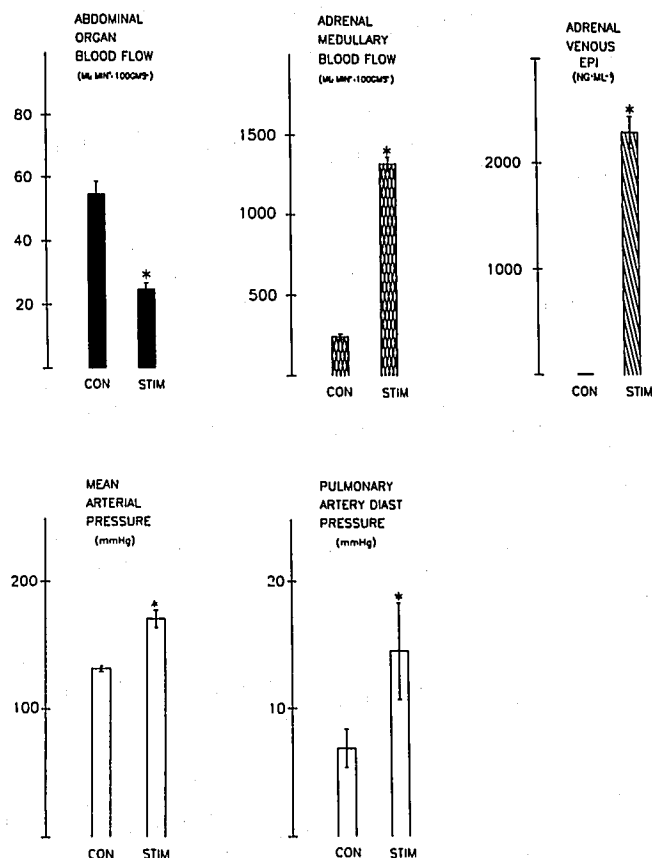


FIG. 4. Response to electrical stimulation of the splanchnic nerve (group 4). CON = control, before stimulation; STIM = during stimulation. * STIM significantly different from CON, $P < 0.05$.

the abdominal organ and adrenal medullary responses to hemorrhagic hypotension. These data also show that splanchnic nerve stimulation increased abdominal organ vascular resistance and reduced adrenal medullary vascular resistance dramatically.

For all groups, arterial oxygen and carbon dioxide tensions, pH, temperature, and hematocrit were constant throughout the protocol.

Discussion

Data acquired from the present study demonstrates that hemorrhagic hypotension elicits a 3-fold increase in adrenal medullary blood flow, a 40-fold increase in arterial epinephrine concentration, and a 61% decrease in abdominal organ blood flow. We observed that these responses to hemorrhagic hypotension could be mimicked by electrical stimulation of the splanchnic nerve and attenuated by bilateral splanchnic nerve section or spinal anesthesia. We also observed that bilateral splanchnic nerve section and spinal anesthesia markedly reduced the volume of blood that had to be removed from the animal in order to produce a given level of hypotension. These data suggest that specific peripheral sympathetic effector responses to hemorrhagic hypotension are transmitted to the periphery by the splanchnic sympathetic neuronal system and show that these splanchnic responses play an important role in regulating systemic blood volume and distributing regional blood flow.

In our study, we monitored three specific splanchnic nerve-transmitted responses. First, we assessed adrenal secretion by measuring arterial epinephrine concentration. Engeland *et al.*¹⁹ and others^{9,10} showed that hemorrhagic hypotension-induced increases in adrenal secretion are neuronally mediated. Although circulating levels of dopamine, norepinephrine, and other polypeptides increase during hemorrhagic hypotension, epinephrine release is confined to the adrenal medulla and abdominal paraganglia and should accurately reflect splanchnic nerve mediated glandular release during hemorrhagic hypotension.^{20,21} Second, we measured adrenal medullary

TABLE 2. Calculated Adrenal Medullary and Abdominal Organ Vascular Resistance

		First Hypotension (mmHg · ml ⁻¹ · min ⁻¹ · 100 g ⁻¹)	Second Hypotension (mmHg · ml ⁻¹ · min ⁻¹ · 100 g ⁻¹)	Difference Between First and Second Hypotension
Group 1 (control)	AOVR	4.0 ± 0.2 to 5.5 ± 0.7	4.1 ± 0.2 to 5.8 ± 4	Not significant
	AMVR	0.33 ± 0.06 to 0.053 ± 0.005	0.32 ± 0.06 to 0.064 ± 0.007	
Group 2 (nerve section)	AOVR	3.6 ± 0.3 to 6.9 ± 0.8	3.1 ± 0.3 to 2.2 ± 0.2	Ablated
	AMVR	0.49 ± 0.08 to 0.06 ± 0.006	0.59 ± 0.09 to 0.20 ± 0.03	
Group 3 (spinal)	AOVR	3.8 ± 0.2 to 5.4 ± 0.9	4.9 ± 0.5 to 3.9 ± 0.6	Ablated
	AMVR	0.32 ± 0.07 to 0.05 ± 0.009	0.56 ± 0.08 to 0.39 ± 0.05	
Unilateral splanchnic nerve stimulation (mmHg · ml ⁻¹ · min ⁻¹ · 100 g ⁻¹)			Response	
Group 4	AOVR	3.8 ± 0.3 to 9.9 ± 0.8	Increased ≈ 300%	Decreased 77%
	AMVR	0.539 ± 0.08 to 0.129 ± 0.038	Decreased 77%	

AOVR = weighted average of abdominal organ vascular resistance; AMVR = adrenal medullary vascular resistance.

blood flow. Current studies clearly demonstrate that this β adrenergic peripheral sympathetic response to hemorrhagic hypotension is neuronally mediated and can modify adrenal secretion.^{9,11} Finally, abdominal organ blood flow was the third parameter used to assess splanchnic nerve function. Caldini *et al.*²² and others^{14,15,23} have shown that this splanchnic organ vasoconstrictive response to hemorrhagic hypotension is mediated neuronally by α -receptor stimulation and is the major component of the "reservoir blood" response. During this response, systemic blood flow is diverted away from splanchnic organs, and reservoir-blood volume is expelled into the systemic circulation. The systemic vascular "two-compartment" model is well documented^{22,23} and has been studied intensively with a variety of techniques.²⁴⁻²⁶

In the present study, we assessed the splanchnic vascular "capacitance" system by using the radiolabeled-microsphere technique to measure the blood flow to specific splanchnic organs. Although we observed a uniform percent decrease in small bowel, large bowel, kidney, spleen, and pancreas blood flows during the first 15 min of blood loss, pilot studies showed that the uniformity of this response was not maintained during longer periods of hypotension. Therefore, we limited our hypotensive stimulus to 15 min in an attempt to minimize mechanisms that locally regulate splanchnic organ blood flow and limit the effects of neuronal autoregulatory escape. Thus, we believed that a clear assessment of splanchnic neuronal activity could be obtained by monitoring the parameters of adrenal medullary blood flow, arterial epinephrine concentration, and abdominal organ blood flow.

The attenuation of sympathetic function by spinal anesthesia has been studied for many years,^{6,7} and it has already been established by Engeland *et al.*,¹⁹ Bonica *et al.*,⁷ and others⁶ that sensory spinal blockade to T5 alters splanchnic nerve function. Our findings are consistent with these previous reports. We did not measure the level of sensory blockade established in our animals. However, because the response to hypotensive hemorrhage was similar in animals subjected to spinal anesthesia or surgical denervation, we are convinced that the level of spinal anesthesia was at least T5.

Whereas nerve section and spinal anesthesia attenuated splanchnic responses, electrical nerve stimulation mimicked the splanchnic responses generated by hemorrhagic hypotension. Adrenal secretion dramatically increased, and abdominal organ blood flow was reduced. In addition, we observed that mean arterial blood pressure and left ventricular filling pressures increased. Marley and Paton²⁷ have shown that adrenal secretion is an important component of the sympathetic stress response, which can be elicited by artificial electrical stimulation of the splanchnic nerve. Although adrenally secreted products are able to

increase blood pressure and compensate for hypotension,⁸ during electrical stimulation in the current study the adrenal effluent was exteriorized from the animal and collected. Despite this loss of adrenal products, mean arterial blood pressure and pulmonary artery diastolic pressure increased. These data suggest that the adrenal gland is not solely responsible for the compensatory mechanisms called into play during hemorrhagic hypotension. The data indicate that neuronal and humoral components of the splanchnic sympathetic system can play a major role in increasing blood pressure and volume during hypotension.

In our study, tolerance to hemorrhagic hypotension was judged by measuring the blood volume that had to be removed from the animal to produce a hypotensive stimulus of 60 mmHg. Using this physiologic approach, we found that, in comparison to the appropriate controls, significantly less blood volume had to be removed from animals subjected to bilateral splanchnic nerve section and subarachnoid blockade in order to induce hypotension. The work of Bonica *et al.*⁷ and Engeland *et al.*¹⁹ supports these data. In our study, the similarity between the ability of bilateral splanchnic nerve section and spinal anesthesia to decrease tolerance to acute blood loss was quite striking. Our data suggests, therefore, that bilateral nerve section or spinal anesthesia attenuates compensatory splanchnic responses to hemorrhagic hypotension and results in decreased tolerance to blood loss.

While it could be argued that the contractile spleen of the dog may contribute disproportionately to the amount of blood expelled from the splanchnic bed to the systemic circulation, Shoukas *et al.*²⁸ have determined that the spleen is not the major contributor to the total blood volume shift caused by the baroreceptor reflex. These data imply that other organs or venous beds play an important role in blood volume mobilization. In addition, these authors also report that acute laparotomy and manipulation of the intestinal vascular bed alter vascular responses after splenectomy. Thus, we believe that surgical splenectomy before instituting the present protocol would neither alter our findings significantly nor substantially diminish the relevancy of our results with respect to humans.

Although we could not distinguish a significant difference between the ability of spinal anesthesia and bilateral splanchnic nerve section to attenuate compensatory responses to hypotension, spinal anesthesia decreased adrenal medullary and abdominal organ blood flow values before the induction of hypotension. Bilateral splanchnic nerve section, in contrast, did not significantly alter adrenal medullary blood flow, arterial epinephrine concentration, or abdominal organ blood flow in the absence of hypotension. Although we cannot rule out incomplete denervation, we speculate that this difference may be due

to venous pooling in the lower extremities, blockade of the cardiac sympathetic nerves, or increased blood flow to other than splanchnic regions during spinal anesthesia. Studies by Breslow¹⁰ and others¹⁹ demonstrated that complete adrenal denervation decreases adrenal venous epinephrine concentrations and significantly reduces adrenal medullary blood flow. Although the numbers of animals used to establish these statistical differences in those studies were larger than that of the present study, we did not deviate from their denervation protocol. Our data, therefore, imply that spinal anesthesia decreases intravascular stability in the absence of volume loss and suggest that cardiovascular collapse during high spinal anesthesia is quite possible when minimal blood loss occurs.

In conclusion, the present study demonstrates that hemorrhagic hypotension elicits dramatic increases in adrenal medullary blood flow, arterial epinephrine concentration, and abdominal organ vasoconstriction. Our data show that 1) these responses are attenuated by splanchnic nerve section and spinal anesthesia; 2) these responses can be mimicked by electrical stimulation of the splanchnic nerve; and 3) these responses increase the tolerance to hemorrhage. Thus, changes in splanchnic neuronal transmission by subarachnoid blockade alter homeostasis by modifying compensatory splanchnic responses to hemorrhagic hypotension.

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