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Determinants of arterial pressure after chronic spinal transection in rats

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OSBORN, JOHN W., ROBERT F. TAYLOR, AND LAWRENCE P. SCHRAMM. *Determinants of arterial pressure after chronic spinal transection in rats.* Am. J. Physiol. 256 (Regulatory Integrative Comp. Physiol. 25): R666–R673, 1989.—The present study was conducted to determine whether sympathetic vasoconstrictor activity is a determinant of mean arterial pressure (MAP) hours and days after cervical spinal transection (CST) in unanesthetized rats. MAP on the 2 days before CST was 107.2 ± 3.6 and 103.3 ± 3.0 mmHg, respectively, and fell to 77.7 ± 1.1 mmHg on *day 1* after CST. MAP returned to control levels over the course of the study and, by *day 9* after CST, was not statistically different from control (98.6 ± 3.4 mmHg). Neither autonomic ganglionic blockade nor α-adrenergic blockade affected MAP the 1st day after CST. Similarly, α-adrenergic blockade was without effect on *days 3, 5,* and *7* after CST. Administration of a vasopressin V_1-antagonist had no effect on MAP on *day 1* or *day 8* after CST. However, blockade of angiotensin-converting enzyme with captopril decreased arterial pressure both on *day 1* (−22.1 ± 2.6 mmHg) and *day 8* (−23.3 ± 2.9 mmHg) after CST. We conclude that neither sympathetic nor vasopressin vasoconstrictor activity affected MAP within the 1st wk after CST. Although the vasoconstrictor actions of angiotensin II were important, these effects were not responsible for the normalization of MAP observed after CST.

sympathetic activity; vasopressin; angiotensin II; vasoconstrictor; renal nerves; splenic nerves

IT IS GENERALLY BELIEVED that the level of ongoing sympathetic nerve activity is entirely dependent on descending excitatory input from supraspinal regions to the sympathetic preganglionic neurons of the thoracolumbar spinal cord. This concept was originally based on the observation that complete transection of the cervical spinal cord in anesthetized animals resulted in a profound decrease of arterial pressure (1). However, several recent studies from our laboratory, using direct recordings of sympathetic nerve activity in chloralose-anesthetized rats, have shown that although cervical spinal transection dramatically decreases lumbar sympathetic activity (22), sympathetic nerve discharge to the kidney (18, 20, 22), stomach, and spleen (22) actually increases twofold. Although autoregulatory vasodilation prevented renal vasoconstrictions during transection-induced elevations in renal sympathetic activity (18), ganglionic blockade lowered arterial pressure (22), suggesting that there was significant sympathetic vasomotor activity to other vascular beds. These studies clearly demonstrate that in the anesthetized acute spinal-transected rat, a significant amount of sympathetic nerve activity can be generated at spinal levels.

Is sympathetic activity a determinant of arterial pressure in unanesthetized chronic spinal-transected animals? Few studies have been conducted to answer this question. Although arterial pressure is generally low in conscious spinal animals (2, 12, 16), this is not a good indicator of sympathetic activity because factors influencing sodium and water balance have not been precisely controlled or measured in previous studies. Based on the effect of ganglionic blockade on arterial pressure, there is sympathetic vasoconstrictor activity in chronic spinal-transected cats (2) but not spinal dogs (12, 16) within 2 wk after spinal transection. It is not clear whether the discrepancy between these animal studies was due to species or methodological differences.

Because we have observed that spinal transection in anesthetized rats actually increases sympathetic activity to some vascular beds, we sought to determine whether sympathetic hyperactivity persisted chronically in the absence of anesthesia in this species. More specifically, this study was designed to answer the following questions. First, what is the effect of cervical spinal transection on chronic levels of arterial pressure in the unanesthetized rat? Second, is spinally generated sympathetic vasoconstrictor activity a determinant of arterial pressure in the conscious spinal rat? Third, what is the contribution of hormonal vasoconstrictors to the maintenance of arterial pressure after spinal transection?

METHODS

Experiments were performed on 30 male Sprague-Dawley rats (Harlan Sprague-Dawley, Frederick, MD) ranging in weight from 290 to 350 g [320 ± 7 (SE)]. All surgical and experimental procedures were conducted in accordance with institutional and National Institutes of Health guidelines.

Surgical Procedures

Chronic catheterization. Twelve to 24 h before surgery, all rats were fasted and pretreated with antibiotic (gentamicin sulfate 5 mg/kg sc, Elkins-Sinn, Cherry Hill, NJ). Thereafter, gentamicin was administered daily (5 mg/kg iv) for the duration of the study. On the day of

surgery, rats were atropinized (0.5 mg/kg ip), anesthetized with pentobarbital sodium (50 mg/kg ip), and placed on a heated surgical table for catheter implantation. Polyvinyl chloride cannulas (Dural Plastics, Dural, NSW, Australia) were placed in the abdominal aorta and vena cava via the left femoral vessels for measurement of arterial pressure and intravenous administration of drugs, respectively. The distal ends of these catheters were then tunneled subcutaneously to the scapular region.

After placement of the vascular catheters, a gastric cannula was implanted to permit infusion of a liquid diet. A 5-cm midline abdominal incision was made, and the stomach was exposed and retracted. A 5-0 silk purse-string suture was placed in the wall of the fundus immediately above the fundalantral line. A small incision was made within the circle of sutures, the tip of the gastric catheter was inserted, and the sutures were tightened securely. The stomach was then returned to its original position. The distal end of the catheter was passed through a small stab wound in the abdominal wall, 2 cm lateral to the midline, and tunneled subcutaneously to the scapular region. The abdominal incision was closed in two layers.

The design of the gastric catheter was similar to that described by Tsukamoto et al. (24) with the exception that the intragastric segment was constructed from a 5-mm segment of PE-190 rather than PE-50 tubing. The superficial end of the catheter was connected to a 30-cm length of Tygon tubing with the use of a 18-gauge stainless steel connector. A 1-cm-diam circle of Dacron polyester was placed between the two pieces of tubing that were then bonded with cyanoacrylate adhesive.

All catheters were secured to the back of the neck with suture and dental acrylic. The arterial and venous cannulas were filled with heparin (500 U/ml), cut 1 cm above the skin, and plugged with 23-gauge stainless steel obturators. Thereafter, the vascular catheters were drained and filled daily with heparin (1,000 U/ml). The distal end of the gastric catheter was passed through a lightweight flexible spring attached to an 18-gauge hydraulic swivel. Rats were then placed in a temperature-regulated caging system with the swivel mounted above. At least 2 full days were allowed for recovery from surgery and acclimatization to the environment. All studies were conducted while the animals rested quietly in their home cages.

Spinal transection and bladder catheterization. Rats were premedicated with atropine (0.5 mg/kg iv) and anesthetized with a short-acting barbiturate, methohexital sodium (Brevital, 35 mg/kg iv). Additional anesthetic was administered as required. Because spinal transection impairs micturition reflexes, a bladder catheter was implanted before spinal transection. The cannula was implanted via a midline incision according to the method of Gellai and Valtin (9).

Subsequent to bladder catheterization, the rat was placed in a stereotaxic apparatus for spinal transection. A midline dorsal incision was made through skin and neck muscles, and the seventh cervical (C_7) and first thoracic (T_1) vertebrae were exposed. The spinal cord was cut between the C_7 and T_1 vertebrae using a no. 11 scalpel blade followed by suction with a blunt 22-gauge needle. Bleeding was minimal and usually stopped within 10–15 s. The incision was closed in two layers with the use of 3-0 silk.

Immediately after spinal cord transection, the rats were allowed to recover on a heated pad and were closely monitored for signs of respiratory or circulatory distress. Typically, the animals were awake and mobile (using forelimbs) 30–45 min after surgery. The rats were then returned to their cages in which the ambient temperature was increased from 21–23 to 33–35°C. Sham-operated control rats were subjected to the same procedure with the exception that the spinal cord was not sectioned and the bladder was not cannulated.

Daily Care and Observation of Cervical Spinal Rats

As described below, food and water intake as well as body temperature were maintained at pretransection levels. In addition, we have observed that healthy spinally transected rats exhibit normal grooming and exploratory behavior when removed from their home cage for daily examination. Failure to exhibit these behaviors were considered manifestations of distress. Rats that showed physical and behavioral indicators of stress were removed from the study.

Experimental Protocols

Long-term effects of cervical spinal transection on arterial pressure. Twenty-four hours before the experiment, all food and water was removed from the cage, and a continuous intragastric infusion of liquid diet (Bioserv, Frenchtown, NJ, no. F1657) was started. This diet provided all required nutrients including the following (per 24 h); 60 kcal, 0.7 meq sodium, and 40 ml water. The diet was infused via an hydraulic swivel at a constant rate (total volume = 60 ml/24 h) with the use of either a Razel A99-H or Harvard 2681 syringe pump.

On each of the 11 subsequent days, rectal temperatures were measured, and the rats were removed from the cage and weighed. Bladder cannulas were checked for patency and cleaned. After flushing the arterial and venous catheters, rats were returned to their cages, and, sequentially, their arterial cannulas were connected to a Century CP-02 pressure transducer. Arterial pressures and heart rates were recorded on a Grass model 7 polygraph over a 30- to 60-min period. Mean arterial pressure was obtained by electrical damping of the pulsatile signal, and heart rate was measured from the pulsatile tracing taken at fast paper speed.

Control measurements of mean arterial pressure, heart rate, body weight, and body temperature were obtained for 2 days. After the second day, rats were anesthetized and underwent either cervical spinal transection (CST; $n = 9$) or sham-CST ($n = 7$) as described above. Measurements were continued for 9 days after CST or sham-CST.

Contribution of sympathetic vasoconstrictor mechanisms to maintenance of arterial pressure after CST. The role of sympathetic vasoconstrictor mechanisms in the

maintenance of arterial pressure was investigated by measuring the effects of sympathetic blockade on arterial pressure. Two approaches were employed.

EFFECT OF AUTONOMIC GANGLIONIC BLOCKADE ON ARTERIAL PRESSURE 1 DAY AFTER SPINAL TRANSECTION. The effect of ganglionic blockade on arterial pressure was determined in seven rats on the day before and the day after spinal transection. After base-line arterial pressure was measured, a combination of atropine (0.5 mg/kg) and either hexamethonium (20 mg/kg, $n = 3$) or chlorasondamine (2.5 mg/kg, $n = 4$) was administered over a 1-min period in 0.3 ml of sterile 0.9% saline. Measurements of arterial pressure were made at 1–5, 10, 15, and 20 min after drug administration. Twenty minutes after blockade, one-half of the initial dose was administered to verify that blockade was still effective at that time.

EFFECT OF α-ADRENERGIC BLOCKADE ON ARTERIAL PRESSURE 1–7 DAYS AFTER CST. In seven CST rats, the effect of α-adrenergic blockade on arterial pressure was measured on *days 1, 3, 5,* and *7* after spinal transection. This additional approach was chosen over use of a ganglionic blocker because completeness of blockade could be tested with exogenous α-agonists. First, atropine was administered (0.5 mg/kg iv) to block vagal baroreflexes, which would obscure sympathetic responses. Ten minutes later, peak pressure responses to increasing doses (0.25, 0.5, 0.75, and 1.0 μg/kg iv) of the α-adrenergic agonist phenylephrine (Neo-synephrine, Winthrop-Breon Laboratories, New York, NY) were measured. The volume of each injection was 150 μl. Five minutes after arterial pressure had returned to normal, the α-adrenergic antagonist phentolamine (Regitine mesylate, Ciba-Geigy, Summit, NJ; 2 mg/kg iv) was administered, and MAP was measured 5 min later. Finally, phenylephrine (PE) injections were repeated to test the efficacy of α-adrenergic blockade.

In addition to testing the completeness of adrenergic blockade, the dose-response curves relating the four doses of PE to changes in MAP were evaluated on *days 1, 3, 5,* and *7* to investigate the possibility that time-related changes in pressor sensitivity to catecholamines may occur after CST (i.e., denervation supersensitivity). To control for possible changes in pressor sensitivity to catecholamines independent of spinal transection, the same PE dose-response experiments were conducted in sham-CST rats in which autonomic reflexes were blocked with atropine (0.5 mg/kg iv) and hexamethonium (20 mg/kg iv).

Contribution of hormonal vasoconstrictors to the maintenance of arterial pressure after spinal transection. Because plasma levels of both arginine vasopressin (AVP) and angiotensin II (ANG II) may be elevated during hypotensive states, we conducted experiments to determine the contribution of AVP and ANG II to maintenance of arterial pressure in chronic spinal rats. The effect of sequential administration of an AVP V_1-antagonist (Manning Compound, Bachem, Torrance, CA; 10 μg/kg iv) and the converting enzyme inhibitor, captopril (E.R. Squibb & Sons, Princeton, NJ; 10 mg/kg iv), on arterial pressure was measured on the 1st (*group 1; n* = 7) and 8th (*group 2; n* = 7) day after spinal transection.

Efficacy of vasopressin blockade was established in three rats by showing that administration of a dose of vasopressin (5 ng/kg iv) that increased arterial pressure ~30 mmHg before the antagonist, had no effect after blockade. Similarly, efficacy of converting enzyme blockade with captopril was verified by the administration of a dose of ANG I (Sigma Chemical, St. Louis, MO; 40 ng/kg) that increased arterial pressure 25–50 mmHg before blockade.

Preparation of drugs. All drugs were dissolved in sterile 0.9% saline the day of the experiment with the following exceptions. The vasopressin antagonist was dissolved in sterile saline at a concentration of 10 μg/ml and frozen in 1-ml aliquots. On the day of the experiment the aliquot was allowed to reach room temperature before administration. Potency of the frozen AVP antagonist was periodically tested in separate rats over the time course of these studies. Phenylephrine was purchased in solution (1 mg/ml) and diluted to the appropriate concentrations with sterile saline.

Statistical analysis. The effect of CST and sham-CST on variables measured daily was analyzed by a two-way analysis of variance (ANOVA) for repeated measures in one dimension. A significant F ratio was followed by the Dunnett's test (within-group comparison) for multiple comparisons with a control or Duncan's multiple-range test (between-groups comparison). A similar analysis was employed to test the effect of ganglionic blockade on arterial pressure before and after CST as well as the pressor sensitivity to phenylephrine. The effect of hormonal blockade on arterial pressure was tested by a one-way ANOVA followed by Duncan's multiple-range test. All other comparisons were made with the use of a paired t test. Statistical significance was set at the $P < 0.05$ level. All values are reported as the means ± SE.

RESULTS

Long-Term Effects of CST on Arterial Pressure, Heart Rate, and Body Weight

The effects of CST and sham-CST on MAP, heart rate (HR), and body weight are shown in Fig. 1. MAP on the 2 days before CST was 107.2 ± 3.6 and 103.3 ± 3.0 mmHg, respectively. The first day after CST, MAP had fallen by ~30 mmHg (77.7 ± 1.1 mmHg), but by *day 9* it had risen to levels (98.6 ± 3.4 mmHg) not significantly different from *day 0.* In contrast, HR fell significantly after CST and remained low for the duration of the study. The fall of HR was not secondary to hypothermia in spinal-transected rats because body temperature was maintained at normal levels by increasing the ambient temperature of the cage. Although not shown, there was no significant difference in body temperature before and after transection or between CST and sham-CST rats. Although CST and sham-CST rats received an identical intake of nutrients and water, CST rats began to lose weight within 3 days after spinal transection. Compared with their body weight on *day 0* (317.0 ± 5.5 g), CST rats had lost ~30 g by *day 9* (286.3 ± 6.9 g).

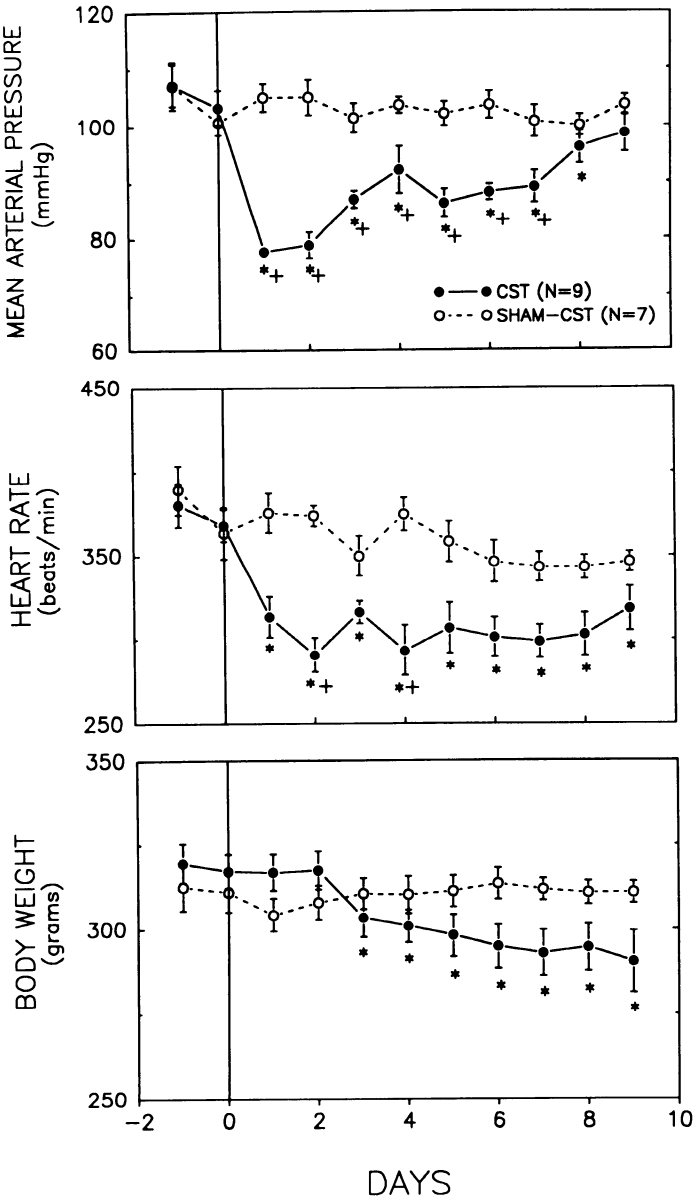

FIG. 1. Mean arterial pressure, heart rate, and body weight in 9 cervical spinal-transected (CST) rats and 7 sham-CST rats. Vertical line at *day 0* indicates day of CST or sham-CST. *$P < 0.05$ compared with *day 0* (within-group comparison); †$P < 0.05$ CST rats compared with sham-CST.

Effect of Autonomic Ganglionic Blockade on Arterial Pressure 1 Day after Transection

Autonomic ganglionic blockade had no effect on arterial pressure in CST rats the 1st day after spinal transection (Fig. 2). Before transection, ganglionic blockade in these same rats had resulted in a profound fall of arterial pressure within the first minute after drug administration. Pressure partially recovered over the next 5 min, and, within 10 min, it had stabilized at a level not different from that seen 24 h after spinal transection.

Effect of α-Adrenergic Blockade on Arterial Pressure in CST Rats

Atropine was administered before α-adrenergic blockade to eliminate vagally mediated alterations of arterial pressure that could potentially obscure the effects of phentolamine. The effects of atropine on MAP and HR are summarized in Table 1. Atropine had negligible effects on MAP and only minimal effects on HR. Significant increases of heart rate were observed on *days 3* and *5* after spinal transection, with increases averaging between 20 and 30 beats/min.

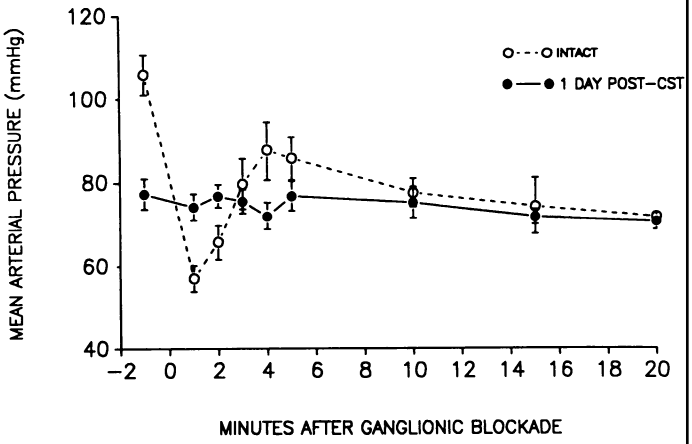

FIG. 2. Effect of autonomic ganglionic blockade on arterial pressure in 7 rats day before (intact) and day after spinal transection (1 day post-CST). For definition of abbreviation, see Fig. 1 legend.

TABLE 1. *Effect of atropine on mean arterial pressure and heart rate in CST rats*

	MAP, mmHg	HR, beats/min
	1 Day after CST	
Control	79.1±1.9	322.3±14.0
Atropine	76.1±1.3	335.7±12.8
	3 Days after CST	
Control	91.0±1.6	306.9±4.4
Atropine	86.0±2.1	334.3±9.6*
	5 Days after CST	
Control	89.3±3.8	300.0±12.3
Atropine	82.1±3.2*	322.3±12.4*
	7 Days after CST	
Control	84.7±3.3	318.9±11.7
Atropine	85.1±3.4	325.7±8.9

MAP, mean arterial pressure; HR, heart rate. $n = 7$ rats. * $P < 0.05$ compared with control.

α-Adrenergic blockade had no effect on base-line MAP up to 7 days after CST (Fig. 3). In all cases, phentolamine completely blocked the pressor responses to exogenous phenylephrine. The average pressor responses over the 4 days (*1, 3, 5,* and *7*) to increasing doses of phenylephrine before blockade were 19.3 ± 1.3, 30.5 ± 2.0, 37.9 ± 2.0, and 44.0 ± 1.7 mmHg. Pressor responses after blockade were 0.5 ± 0.3, −1.0 ± 0.6, −0.9 ± 0.6, and −0.8 ± 0.6 mmHg.

Studies were conducted to determine whether the pressor sensitivity to exogenous catecholamines increased over time due to the development of a "denervation supersensitivity" in CST rats. Pressor responses of atropinized-CST rats were measured and compared with those of sham-CST rats after ganglionic blockade. Resting arterial pressures before PE injections in these two

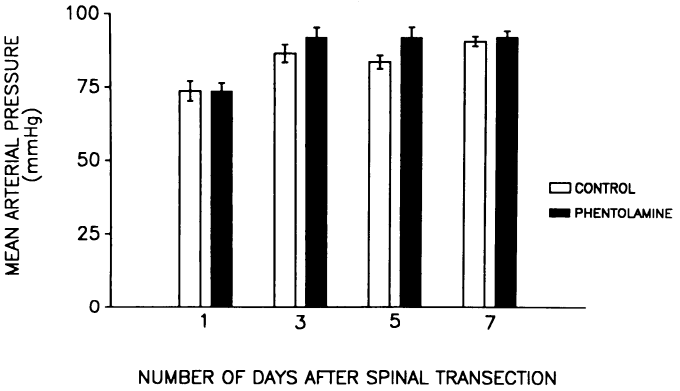

FIG. 3. Mean arterial pressure in 7 atropinized cervical spinal transected rats before (□) and after (■) administration of phentolamine (2 mg/kg). Measurements were made on *days 1, 3, 5,* and *7* after spinal transection. There were no statistically significant effects of phentolamine on any of days tested.

TABLE 2. *MAP before phenylephrine injections in atropinized-CST and ganglionic-blocked sham-CST rat*

	Number of Days after CST or Sham-CST			
	1	3	5	7
CST	75.8±1.3	86.0±2.1	82.1±3.2	85.1±3.4
Sham-CST	70.7±2.5	72.9±4.2	75.0±4.6	74.3±2.8

MAP, mean arterial pressure; CST, cervical spinal transection. n = 7 rats.

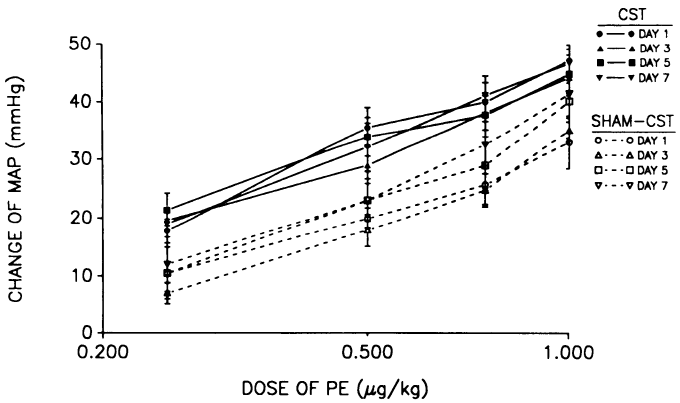

FIG. 4. Change of mean arterial pressure (MAP) in response to bolus injections of phenylephrine (PE) in atropinized cervical spinal transected (CST) rats and sham-CST rats after ganglionic blockade (atropine plus hexamethonium). Pressor sensitivity was measured on *days 1, 3, 5,* and *7* after either CST (n = 7) or sham-CST (n = 7).

groups are shown in Table 2. There were no significant differences between atropinized-CST rats and ganglionic blocked sham-CST rats at any time after transection. Moreover, no changes in pressor sensitivity to PE over time were observed in either group (Fig. 4).

Contribution of Hormonal Vasoconstrictor Mechanisms to the Maintenance of Arterial Pressure after Spinal Transection

The contribution of vasopressin and ANG II to the maintenance of arterial pressure was investigated on the 1st and 8th days after spinal transection. The effect of sequential administration of the vasopressin and ANG II antagonists was nearly identical on *days 1* and *8* after spinal transection (Fig. 5). Whereas AVP blockade had no significant effect on arterial pressure on either day, a marked fall of arterial pressure was observed after the administration of captopril. Moveover, the absolute change in arterial pressure after captopril administration was not significantly different on *day 1* (−22.1 ± 2.6 mmHg) compared with *day 8* (−23.3 ± 2.9 mmHg).

DISCUSSION

The present study was designed to establish whether spinally generated sympathetic vasoconstrictor activity was a determinant of arterial pressure in unanesthetized rats hours and days after CST. The major findings of these investigations can be summarized as follows. First, although rats were hypotensive the 1st day after CST, arterial pressure returned to control levels 8–9 days later. Second, sympathetic vasoconstrictor activity was not a determinant of arterial pressure at any time tested after CST. Finally, spinal rats were, in part, dependent on ANG II vasoconstrictor activity for the maintenance of arterial pressure. The importance of each of these findings, in relation to previous studies, is discussed below.

Effect of CST on Long-Term Regulation of Arterial Pressure

To our knowledge, this is the first study to characterize the chronic effects of cervical spinal cord transection on arterial pressure in the rat. In addition, this is the first investigation, in any species, suggesting that interruption of supraspinal control of sympathetic preganglionic neurons does not result in chronic hypotension. Indeed, to our knowledge, there is only one other report in which a systematic investigation of the effects of cervical spinal transection on chronic regulation of arterial pressure in conscious animals has been carried out. Kaneko et al. (12) demonstrated in the dog that during the first 24 h after CST, arterial pressure fell by ~25–30 mmHg. Within 6–10 days, arterial pressure returned to within 10–15 mmHg of pretransection levels. This recovery was mediated almost entirely by an increase of peripheral vascular resistance (12). Others have observed hypotension in chronic cervical spinal-transected dogs (16) and cats (2). However, it is difficult to interpret these latter

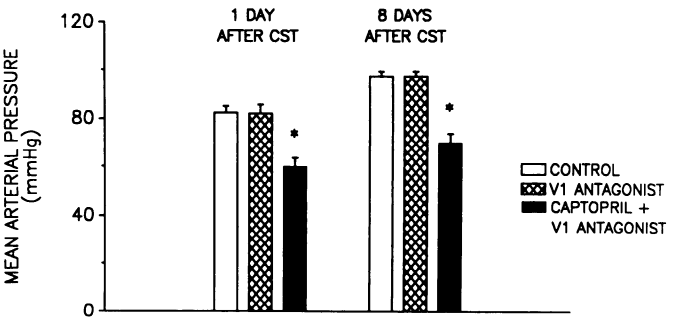

FIG. 5. Effect of sequential administration of a vasopressin V_1-antagonist and converting enzyme inhibitor captopril on mean arterial pressure in 2 separate groups of cervical spinal transected (CST) rats. Drugs were administered on *day 1* (n = 7) and *day 8* (n = 7) after spinal transection. *$P < 0.05$ compared with previous measurement.

studies because either MAP before spinal transection was not measured (16) or the experiments were conducted in anesthetized animals (2).

Although there are few animal studies of the effects of CST on chronic regulation of arterial pressure, there is an abundance of clinical data from spinal cord-injured patients. However, investigations in patients with cervical transections are difficult to interpret because the exact location and completeness of the lesion is not usually known. In addition, their arterial pressures may vary with uncontrolled sodium intake or the effects of medications. The majority of studies indicate that these patients are chronically hypotensive (see Ref. 15 for review). However, there are reports of normotensive (11, 17) and hypertensive (23) spinal humans.

Why was the normalization of arterial pressure after CST observed in the present investigation not seen in previous animal studies (2, 12, 16)? At least three possibilities exist. First, ours is the first study in the rat, and species differences may exist. Indeed, our previous observation of an increase in sympathetic nerve activity after spinal transection in the anesthetized rat (18, 20, 22) has not been reported in other species. Second, it is important to consider not only neurohumoral regulation of vascular tone but also factors that influence sodium and water homeostasis. Mikami and co-workers (16) have shown in chronic CST dogs that, over a period as short as 12–36 h, base-line arterial pressure is directly related to the level of salt and water intake. Therefore it is conceivable that small deficits in sodium and water intake may have resulted in chronic hypotension after spinal transection in previous studies. A key difference between our study and previous investigations is that the intake of both sodium and water, as well as all other nutrients, was fixed at pretransection levels by a continuous intragastric infusion. A third difference between our study and others is that, at the time of spinal transection, we implanted a chronic bladder catheter to permit continuous emptying of the bladder after CST. We have observed that if the catheter was not kept open, bladder pressure would eventually increase to levels high enough to force urine through the urethra. The chronic increase of bladder pressure resulted in hydronephrosis, evident by gross dilation of the ureters and renal pelvis. This condition, which impairs renal concentrating mechanisms, may potentially lead to uremia and excessive fluid loss that would exacerbate the hypotension. In the present study, if either the gastric or bladder catheter became blocked the animal was eliminated from the experiment. As a result, our study includes only those animals in which sodium and water intake was precisely maintained at pretransection levels and in which bladder emptying was not impaired after CST. This careful attention to maintenance of normal nutrient intake and renal function may explain why the normalization of arterial pressure was observed in the present study and not in others.

Does Spinally Generated Sympathetic Activity Contribute to the Normalization of Arterial Pressure in Chronic Spinal Rats?

We hypothesized that the normalization of arterial pressure after CST could result from either an increased vascular sensitivity to a constantly low level of sympathetic activity, a steadily increasing level of sympathetic nerve discharge, or both. However, our results suggest that neither sympathetic vasoconstrictor activity nor elevated sensitivity to catecholamines played a role in the recovery of arterial pressure during the 1st wk after spinal transection.

Ardell and colleagues (2) reported that there is substantial sympathetic nerve discharge in chronic CST cats within 9–14 days after spinal transection, although this was demonstrated only in anesthetized cats. Our results corroborate those reported in chronic CST dogs in which ganglionic blockade had no effect on arterial pressure (12, 16). However, it should be noted that, unlike the rat, sympathetic blockade has no effect on either peripheral resistance (13) or arterial pressure (13, 21) in the conscious intact dog.

The lack of an increase of pressor sensitivity, resulting from a denervation supersensitivity, is in agreement with investigations of adrenergic receptor density in spinal patients (8, 19). Failure to observe an increase in pressor sensitivity may be explained by periodic acute increases of sympathetic activity (19) as well as by the fact that α_2-receptor-mediated reuptake mechanisms are still intact (8).

We have previously shown that sympathetic vasoconstrictor activity is a determinant of arterial pressure in chloralose-anesthetized, acute-CST rats (22). What is the explanation for the absence of sympathetic vasoconstrictor effects in the unanesthetized, chronic-CST rat? There are several possibilities. First, it is conceivable that spinally generated activity is maintained for only a few hours after CST. This would not be expected, and, in fact, the opposite should be seen. That is to say, as spinal shock subsides, neural activity should increase over time. Indeed, Ardell and colleagues (2) have shown in spinal-transected cats that spinally generated sympathetic nerve activity increases over a period of days after spinal transection. Assuming that the period of spinal shock is shorter in rat than in cat, we should have seen spinally generated sympathetic activity within the time period we investigated.

A second explanation is that the increase in sympathetic nerve activity observed after acute-CST in our previous studies (18, 20, 22) is unique to the chloralose-anesthetized, surgically stressed rat. However, similar effects of cervical spinal transection on arterial pressure have been observed in rats in which the surgery was performed under ether anesthesia (10). In that study, administration of hexamethonium 2 h after CST, when the rats were fully awake, decreased arterial pressure to the same extent as that observed in chloralose-anesthetized CST rats (22). Therefore, although there were differences between studies in both the anesthetic used and the extent of surgical preparation, similar results were obtained. This would argue against the concept that sympathetic vasoconstrictor activity after CST was dependent on either the degree of surgical stress or on anesthesia.

A third explanation is that the competition between sympathetic vasoconstrictor effects and local control

mechanisms is shifted toward an autoregulatory vasodilation within 24 h after CST. Indeed, in our previous study of the renal vascular bed, a twofold increase of renal nerve activity after spinal transection failed to elicit renal vasoconstrictions (18). We concluded that the fall in lumbar sympathetic activity after CST (22) produced a fall in MAP, resulting in a secondary renal autoregulatory vasodilation that completely antagonized sympathetic vasoconstrictor input to the kidney. Based on that observation and the results of the present study, we hypothesize that although sympathetic vasoconstriction may be able to compete with local control mechanisms during the first few hours after spinal transection, within 24 h, autoregulatory controllers are completely dominant such that any remaining sympathetic vasoconstrictor activity is without effect.

Do Humoral Vasoconstrictor Mechanisms Contribute to the Normalization of Arterial Pressure in Chronic Spinal-Transected Rats?

Based on the effects of acute blockade of the sympathetic nervous system, the renin-angiotensin system, and vasopressin, we conclude that the normalization of arterial pressure in spinal rats was not due to increased vasoconstrictor activity of any of these systems.

Although administration of captopril decreased arterial pressure ~25 mmHg, this response was equal on the first and eighth days after transection. Although the vasoconstrictor activity of these systems does not appear to contribute to the normalization of arterial pressure in CST rats, it is possible that these systems act through regulation of sodium and water balance to influence arterial pressure. That is to say that renal sympathetic nerve activity, the renin angiotensin system, and vasopressin all may enhance renal retention of sodium and water that chronically would influence arterial pressure. Indeed, we have shown in a previous study, that the increase of renal sympathetic nerve activity seen in chloralose-anesthetized, acute CST rats did not influence renal vascular resistance but did enhance sodium and water reabsorption (18). The hypothesis that spinally generated renal sympathetic nerve activity is a determinant of arterial pressure in the unanesthetized chronic CST rat remains to be tested.

Clinical studies do not lend support to this hypothesis. Although patients with functionally complete cervical spinal cord transections have elevated renin activity compared with intact controls (11, 14), estimates of body fluid volumes have shown that both total body water (4) and blood volume (5) are decreased in quadriplegics. Moreover, Clause-Walker and co-workers (6) have shown that, in the acute phase of spinal cord injury, there is a profound increase in the urinary excretion of salt and water that is maintained to a lesser degree in the chronic phase. Similarly, we found that body weight began to fall significantly within 3 days after CST, and it continued to decline for the duration of the study. This occurred despite the fact that water and nutrient intake was maintained at pretransection levels. Although it was evident on examination of the rats that some of the loss of body weight was due to a decrease of lean body mass, secondary to hindlimb paralysis, the above studies suggest that loss of body fluids may also be involved. The mechanisms of body fluid loss after CST are unknown.

Finally, another mechanism, unrelated to classical blood pressure-regulating systems, must be considered for the rise of arterial pressure observed over the course of this study. It is well-known that, after spinal cord injury, patients go through a period of flaccid paralysis, characterized by complete absence of spinal somatic reflexes. Return of somatic motor tone may not occur for months after the injury. Eventually, somatic motor spasms develop that acutely increase arterial pressure (7), presumably due to increased central venous volume (decreased compliance of skeletal muscle beds), as well as physical compression of the skeletal muscle beds (increased vascular resistance). Indeed, spinal anesthesia in awake quadriplegic patients results in a fall of peripheral vascular resistance (3). Because there is little evidence of sympathetic vasoconstrictor activity in these patients (15), this observation can only be explained by effects on the somatic nervous system.

We have observed the same course of events in this study on an accelerated time scale. Hindlimb somatic reflexes are easily obtained within minutes after spinal transection. Spontaneous somatic motor spasms have been noted as soon as 3 days after CST, and, by 10 days after CST, all rats exhibit periods of spontaneous somatic motor spasms. It is possible that such spasms, increasing in their strength and frequency, exert a tonic influence on the hindlimb circulation such that a substantial level of arterial resistance and a reduced venous compliance are maintained in the absence of autonomic tone.

The purpose of these studies was to establish whether spinally generated sympathetic vasoconstrictor activity was a determinant of arterial pressure in chronic unanesthetized cervical spinal-transected rats. Although arterial pressure was normalized within 8–9 days after CST, we found no evidence of sympathetic vasoconstriction at any time tested. In addition, vasopressin-mediated vasoconstrictions were not a determinant of arterial pressure after CST. Although the vasoconstrictor actions of the renin-angiotensin system contributed to basal levels of arterial pressure in chronic-CST rats, it was not responsible for the normalization of arterial pressure. We conclude that sympathetic vasoconstriction is not a determinant of arterial pressure in chronic unanesthetized CST rats and that normalization of arterial pressure after CST cannot be explained by increased vasoconstrictor activity of the sympathetic nervous system, vasopressin, or ANG II.

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