

Chronic cervical spinal cord injury and autonomic hyperreflexia in rats

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OSBORN, JOHN W., ROBERT F. TAYLOR, AND LAWRENCE P. SCHRAMM. *Chronic cervical spinal cord injury and autonomic hyperreflexia in rats*. *Am. J. Physiol.* 258 (Regulatory Integrative Comp. Physiol. 27): R169–R174, 1990.—Although it is well established that patients with cervical spinal cord injury are prone to acute, marked, hypertensive episodes, i.e., autonomic hyperreflexia, the specific mechanisms mediating this sometimes-fatal phenomenon are not completely understood. In this report, we describe the preparation and characterization of a rat model of chronic cervical spinal cord injury and autonomic hyperreflexia. Adult male Sprague-Dawley rats were chronically instrumented with arterial, venous, and gastric catheters. Beginning the first day after a complete cervical spinal transection (CST) and continuing for 1 wk, acute hypertensive responses to a modest increase of urinary bladder pressure (0–20 mmHg) were studied. Mean arterial pressure increased 25.9 ± 4.8 mmHg during bladder distension the first day after CST. This response was not significantly different 3, 5, and 7 days after CST (overall average = 18.0 ± 2.3 mmHg). The pressor response to bladder distension was completely abolished by intravesical lidocaine and autonomic ganglionic blockade (atropine + hexamethonium). Responses to bladder distension were not observed after the administration of chloralose anesthesia. We conclude that after cervical spinal transection the rat exhibits autonomic hyperreflexia similar to that seen in humans with spinal injury. Furthermore, autonomic hyperreflexia is completely established within 24 h after CST in the rat. Finally, some spinal autonomic reflexes are suppressed by chloralose anesthesia in the rat.

spinal autonomic reflexes; bladder afferents; sympathetic activity

IT IS CURRENTLY ESTIMATED that 12,000–15,000 Americans are rendered paraplegic or quadriplegic each year (2). Approximately 85% of these patients suffer from acute hypertensive episodes (8), which result from spinally mediated reflex increases in sympathetic nerve activity in response to cutaneous and visceral stimuli (see Ref. 11 for review). This condition, known as “autonomic hyperreflexia,” was first reported by Head and Riddoch (5) in 1917. Their work documented in great detail both the exaggerated autonomic (sweating) and somatic responses to bladder distension in patients with chronic spinal cord injury.

The consequences of autonomic hyperreflexia on arterial pressure were not documented until 1947 by Guttman and Whitteridge (4). The resulting increase in arterial pressure is often severe and may cause retinal,

cerebral, and subarachnoid hemorrhage and death (6). Although it is generally believed that these episodes are mediated by spinal reflexes, the specific mechanisms are not understood. For example, although it is well documented that distension of the urinary bladder and distal colon can elicit pressor responses in spinal patients, the extent to which activation of other visceral afferents contribute to autonomic hyperreflexia is not clear. In addition, the specific efferent mechanisms mediating these responses are not completely understood. It remains to be determined whether the autonomic hyperreflexia is generated by specific segmental or diffuse, multisegmental reflexes.

At the present time these issues remain unresolved, primarily because a conscious animal model of autonomic hyperreflexia has not been developed. Our current understanding of spinal regulation of cardiovascular function comes primarily from acute neurophysiological studies in anesthetized animals. Although these investigations provide essential information about the existence of spinal neuronal networks, the use of anesthesia compromises any interpretation of the physiology of these networks. Therefore, studies in conscious animals with chronic cervical spinal lesions are essential to our understanding of the functional role of these networks in the physiology and pathophysiology of cardiovascular regulation after spinal cord injury.

We have recently developed a chronic, cervical spinal rat model, developed for the purpose of investigating the mechanisms of autonomic hyperreflexia and spinal regulation of sympathetic activity in the unanesthetized animal. In this report we describe both the methods for producing the model as well as the initial characterization of autonomic hyperreflexia in the rat. Because most hypertensive episodes in humans with spinal injury occur in response to an increase of urinary bladder pressure (11), we have characterized the pressor responses to bladder distension in this model. More specifically we sought to determine the following. First, what is the time period in which autonomic hyperreflexia becomes fully established after cervical spinal transection in the rat? Second, are the pressor responses due to spinal autonomic reflexes? Finally, to what extent does anesthesia alter spinal autonomic reflexes in the rat?

METHODS

Experiments were performed on 17 male Sprague-Dawley rats (Harlan Sprague-Dawley; Frederick, MD)

ranging in weight from 290 to 350 g (mean = 320 ± 7 g). All surgical and experimental procedures were conducted in accordance with institutional and National Institutes of Health guidelines.

Surgical Procedures

Surgery was performed in two stages. First, chronic indwelling catheters were implanted as described below. Four days later, the cervical spinal cord was transected.

Chronic catheterization. Twelve to 24 h before surgery, rats were fasted and pretreated with antibiotic (gentamicin sulfate 5 mg/kg sc; Elkins-Sinn, Cherry Hill, NJ). Thereafter, antibiotics were administered daily (5 mg/kg iv) for the duration of the study. 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 2158, 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 intragastric infusion of a liquid diet as explained below. 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 fundal-antral 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. It was then tunneled subcutaneously to the scapular region.

The design of the gastric catheter was similar to that described by Tsukamoto et al. (16) with the exception that the intragastric segment was constructed from a 5-mm segment of PE-190, rather than PE-50 tubing. The tip was connected to a 30-cm length of Tygon tubing using a 18-gauge stainless steel connector. A 1-cm diameter circle of Dacron polyester was placed between the two pieces of tubing, which were then bonded with cyanoacrylate adhesive. The Dacron served as a temporary anchor point to the surface of the stomach. Within 24 h it was secured by fibrous adhesions.

The catheters were secured to the back of the neck with suture and dental acrylic. The arterial and venous cannulas were filled with 500 U/ml heparin, cut 1 cm above the skin, and plugged with 23-gauge stainless steel obturators. Thereafter, the vascular catheters were drained and filled daily with 1,000 U/ml heparin sodium. The distal end of the gastric catheter was passed through a lightweight flexible spring attached to an 18-gauge hydraulic swivel of our own design. Rats were then placed in a temperature-regulated caging system with the swivel mounted above. At least 4 full days were allowed for recovery from surgery before spinal transection.

Spinal-transection and bladder catheterization. Rats were premedicated with atropine (0.5 mg/kg iv) and

anesthetized with a short-acting barbiturate (Brevital; 35 mg/kg iv). The depth of anesthesia was considered to be appropriate if the corneal reflex and motor responses to noxious cutaneous stimuli were absent. Additional anesthetic was administered as required. Atropine proved essential for the prevention of acute respiratory complications after spinal transection. 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 co-workers (3). It is essential that the bladder be catheterized at the time of spinal transection. Initially, we attempted to manually express urine from the bladder three to four times a day. However, severe bladder hemorrhage and hypertensive episodes often resulted from this procedure. Furthermore, since we did not empty the bladder overnight, it is possible that acute hypertensive episodes occurred, which may have resulted in large increases of ventricular afterload and pulmonary edema. We suspect that this may have contributed to a large number of fatalities in our earlier studies. Indeed, every fatality occurred at night, and the bladder always contained at least 3 ml of urine at the postmortem examination. That is three times greater than the volume used in the present study to elicit acute hypertensive episodes (see below).

After bladder catheterization, the rat was placed in a stereotaxic apparatus for spinal transection. The seventh cervical (C₇) and first thoracic (T₁) vertebrae were exposed via a midline dorsal incision. At this time the depth of anesthesia was checked, and additional anesthetic was administered if needed.

The spinal cord was cut between C₇ and T₁ using a no. 11 scalpel blade followed by suction with a blunt hypodermic 22-gauge needle connected to a vacuum pump. Bleeding was minimal and usually stopped within 10–15 s. The completeness of the transection was then verified by careful inspection of the lesion with the aid of a high-intensity fiber optic lamp and a dissecting scope ($\times 40$ – 50 magnification). This procedure resulted in removing a 1- to 2-mm segment of the spinal cord. A complete transection was confirmed in all cases.

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 cage, in which the ambient temperature was increased from 21–23 to 33–35°C as described below.

Daily Care and Observation of Cervical Spinal Rats

Although cervical spinal rats retain use of their forelimbs and exhibit normal grooming behavior, they do not maintain their food and water intake after spinal transection. Initially we attempted to feed the rats via a chronically implanted stainless steel gastric fistula. Because commercially available liquid diets are commonly 1 kcal/ml, and a 300-g rat requires ~60 kcal/day, large amounts of liquid diet (15 ml) had to be administered four times a day. This proved to be both inconvenient and potentially stressful to the rat, since autonomic

reflexes may be triggered by gastric distension (9). Therefore, a continuous intragastric infusion was employed. At least 1 day before spinal transection, both food and water were removed from the cage. At that time, a continuous intragastric infusion of liquid diet (Bioserv, Frenchtown, NJ, product no. F1657) was administered via the implanted gastric catheter. The diet was infused at a constant rate of 2.5 ml/h using a syringe pump. This infusion provided a total of 60 kcal/24 h and 40 ml water/24 h as well as all other required nutrients. In addition to fixing water and nutrient intake at pretransection levels, we maintained body temperature within the normal range by raising the ambient temperature from 21–23 to 33–35°C after transection. The rats were housed within a Plexiglas box, and they were separated by stainless steel screens. The floor of the cage was also stainless steel screen with bedding below. The ambient temperature of the cage was controlled using a temperature servo-controller (Yellow Springs Instrument, model 74, Yellow Springs, OH), the output of which was connected to a heating coil in the water reservoir of a pediatric infant incubator (Air-Shields, Hatboro, PA). The humidified air was continuously circulated through the cages by the incubator fan unit.

Rats were removed from the cage and examined daily. At this time, rectal temperatures were measured, and the bladder catheter was checked for patency and cleaned by gentle aspiration. We have observed that healthy spinal rats exhibit normal grooming and exploratory behavior when removed from their home cage. Failure to exhibit these behaviors was considered a manifestation of distress. Rats that showed physical and behavioral indicators of stress were removed from the study and killed by intravenous administration of a lethal dose of pentobarbital sodium.

Experimental Protocols

Characterization of pressor responses to bladder distension: effect of time of recovery after cervical spinal transection. The responses of mean arterial pressure (MAP) and heart rate (HR) to a 20-mmHg increase of bladder pressure were determined in seven conscious rats after cervical spinal transection (CST) 1, 3, 5, and 7 days after CST. A Tygon catheter was filled with sterile 0.9% saline and connected to the stainless steel bladder catheter. The other end of the catheter was connected to a Statham P23 Db pressure transducer via a three-way stopcock. To control bladder pressure, the penis was clamped with a miniature hemostatic clip (Tiemann, Plainview, NY) to prevent fluid loss via the urethra during bladder distension. The arterial catheter was connected to a Century CP-02 pressure transducer via connecting tubing. The output of both transducers was amplified and displayed on a Grass polygraph (model 7). Bladder pressure and pulsatile and mean arterial pressures were monitored continuously. Heart rate was determined from the pulsatile-pressure tracing by periodically increasing the paper speed.

When both arterial pressure and HR were stable, control measurements were taken, and bladder pressure was increased in one step from 0 to 20 mmHg by injection

of warm saline (36–38°C) via the three-way stopcock. The stimulus was maintained until arterial pressure reached steady state. At that time, a HR measurement was made, and bladder pressure was allowed to return to 0 mmHg. In five of the seven rats, an estimate of bladder compliance was made by recording the volume required to increase bladder pressure to 20 mmHg.

Effect of intravesical lidocaine on pressor responses to bladder distension. Experiments were conducted to determine whether the pressor responses to bladder distension were elicited specifically by activation of bladder afferents. We hypothesized that intravesical lidocaine would abolish the response of bladder afferents to bladder distension. The method for bladder distension in these experiments was identical to that described above with the exception that the responses to three sequential distensions were measured rather than one. First, the bladder was distended with sterile saline. The bladder was then distended a second time with either a 2% lidocaine solution (lidocaine group; $n = 5$) or saline (control group; $n = 5$). Finally, the bladder was distended a third time with sterile saline. Distensions were separated by 10-min recovery periods.

Effect of autonomic-ganglionic blockade on the bladder-pressor reflex. Pressor responses to bladder distension were studied in six rats before (control) and 10 min after pharmacological blockade of autonomic ganglionic muscarinic and nicotinic receptors with a combination of atropine (0.5 mg/kg iv) and hexamethonium (20 mg/kg iv), respectively.

Comparison of the bladder-pressor reflex in conscious and anesthetized states. The pressor response to bladder distension was measured in three rats in the conscious state and 10 min after intravenous administration of α -chloralose (100 mg/kg).

Statistical Analysis

All values are reported as means \pm SE. The effects of bladder distension on measured variables over time were analyzed by a one-way analysis of variance (ANOVA) for repeated measures followed by Duncan's multiple range test when indicated. An identical analysis was used for the effects of lidocaine on the bladder-pressor reflex. The effects of ganglionic blockade and chloralose on pressor responses to bladder distension were tested using a paired Student's t test. Significance for all tests was set at the $P < 0.05$ level.

RESULTS

Characterization of Pressor Responses to Bladder Distension: Effect of Time of Recovery After CST

A sustained increase of arterial pressure was usually obtained within 30–60 s after the onset of bladder distension (Fig. 1). Although arterial pressure usually returned to control levels within 5 min after bladder distension, in some cases the pressor response lasted for 10–20 min.

The average responses of seven rats to bladder distension were determined 1, 3, 5, and 7 days after CST (Fig. 2). Basal levels of MAP before bladder distension averaged 76.8 ± 2.2 , 86.8 ± 1.7 , 86.0 ± 2.8 , and 87.3 ± 2.3

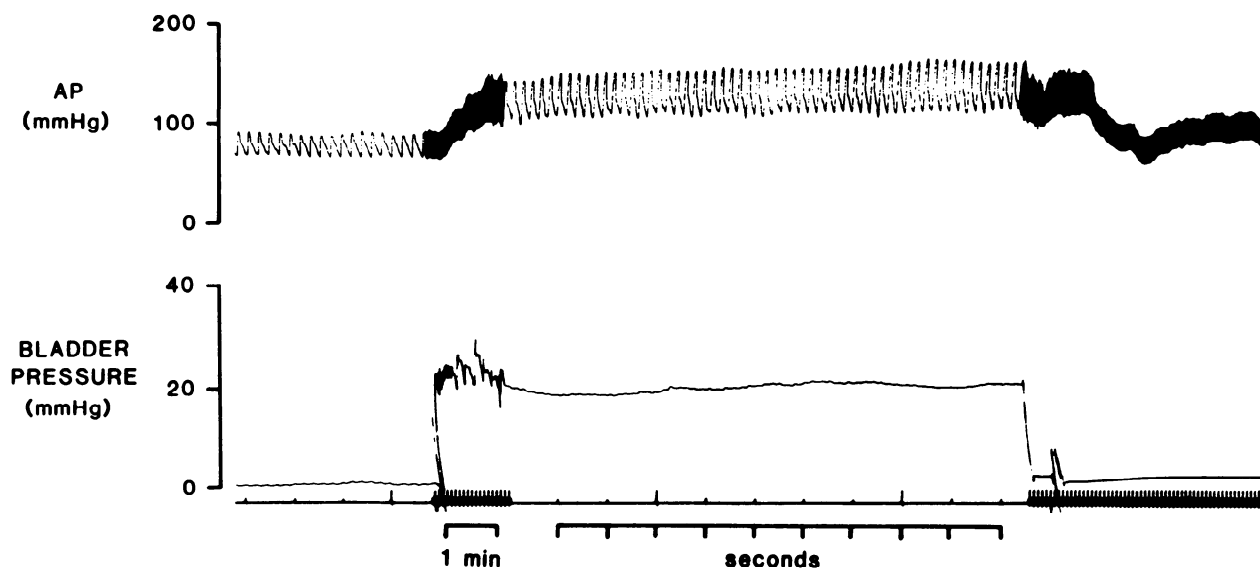


FIG. 1. Polygraph tracing of arterial pressure (AP) and bladder pressure in conscious rat during a typical experiment, 5 days after cervical spinal transection. Note changes in paper speed to obtain measurement of heart rate.

mmHg, respectively. Although there was a tendency for the pressor response to be greater the first day after CST, there were no statistically significant differences between responses. HR decreased significantly (-22.3 ± 8.5 beats/min) from a control level of 318.0 ± 2.6 beats/min on day 1, but it was not significantly decreased by bladder distension on days 3, 5, or 7.

Effect of Intravesical Lidocaine on Pressor Response to Bladder Distension

Three simultaneous distensions of the urinary bladder with saline, over a 20–30-min period, resulted in pressor responses that were not significantly different from each other (Fig. 3). However, when 2% lidocaine was used during the second distension, the response was attenuated by 60–70% (Fig. 3). When the bladder was distended a third time, 10 min after intravesical lidocaine, the response was abolished.

Effect of Autonomic-Ganglionic Blockade on Bladder-Pressor Reflex

Evidence that the pressor response to bladder distension was mediated by increased sympathetic activity is shown in Fig. 4. The pressor response was completely abolished by ganglionic blockade with atropine and hexamethonium.

Comparison of Bladder-Pressor Reflex in Conscious and Anesthetized State

Illustrated in Fig. 5 are the effects of intravenous chloralose on both resting arterial pressure and the pressor response to bladder distension. Chloralose significantly lowered resting levels of MAP from 96.7 ± 4.4 mmHg in the conscious state to 71.7 ± 3.3 mmHg 10 min after administration. Moreover, chloralose completely abolished the pressor response to bladder distension.

DISCUSSION

Chronic Cervical Spinal Rat as a Model of Autonomic Hyperreflexia

The model described in the present study seems ideally suited for investigating spinal autonomic reflexes in the unanesthetized animal and more specifically the mechanisms of autonomic hyperreflexia. Pressor responses to modest increases of bladder pressure were observed the first day after spinal transection. These responses were abolished by either intravesical lidocaine injection or ganglionic blockade. These observations suggest that the response was mediated by activation of urinary bladder afferents, which reflexly increased efferent sympathetic activity. Similar effects of lidocaine and ganglionic blockade on bladder-elicited pressor responses have been observed in spinal-injured humans (11).

The intensity of the afferent stimulus used in the present study is well within the physiological range of urinary bladder pressure. In normal humans, bladder pressure reaches 40 mmHg during micturition (12). The threshold pressure for activation of urinary bladder afferents in the cat ranges between 5 and 15 mmHg for the pelvic nerve afferents (1). Intravesical pressure is elevated to 40–50 mmHg during micturition in the rat (7). Although we used a distending pressure of 20 mmHg to characterize the model, we have observed marked pressor responses to distending pressures as low as 10 mmHg in CST rats.

In preliminary studies, we have observed pressor responses to other stimuli as well. In our initial experiments, the urinary bladder was not catheterized at the time of CST. The bladder was emptied either by manually expressing urine from the bladder or by aspirating urine via a 25-gauge needle inserted percutaneously into the bladder. However, as shown in Fig. 6, the latter procedure induced a hypertensive response. Note that the marked increase of arterial pressure was maintained for 20 min after removal of the stimulus. This response

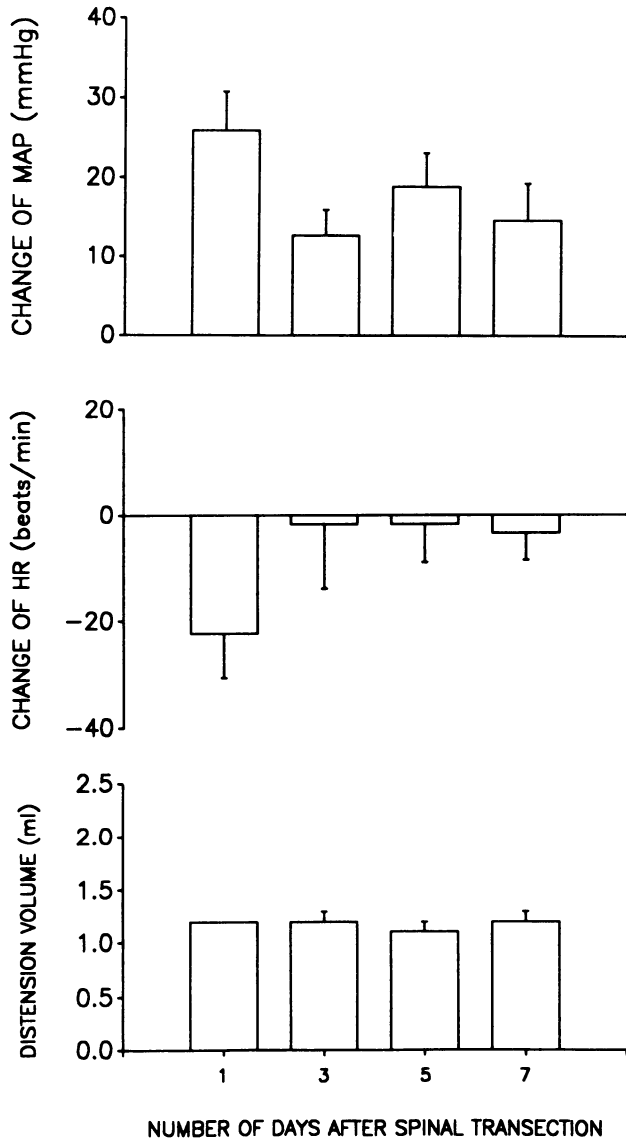


FIG. 2. Average changes (means \pm SE) of mean arterial pressure (MAP) and heart rate (HR) in response to a 20-mmHg increase in urinary bladder pressure 1, 3, 5, and 7 days after cervical spinal transection. Volume required to increase bladder pressure from 0 to 20 mmHg is shown in *bottom*. No significant changes were observed over time in any of these variables.

was obviously not the result of bladder distension. It was more likely due to the noxious cutaneous stimulation.

One objective of the present investigation was to characterize the pressor response to bladder distension over time to establish the "chronic" phase of recovery from spinal cord injury. In humans, autonomic hyperreflexia does not appear until weeks after spinal injury (11), presumably because of spinal shock. We reasoned that reflex responses to bladder distension may change as a result of other time-dependent alterations in the afferent and efferent limbs of the reflex as well. For example, after bladder catheterization, scarring may occur, which could decrease bladder compliance. This would result in a lower level of afferent discharge for a given intravesical pressure. However, the volume required to increase bladder pressure by 20 mmHg did not change during the first week after CST (Fig. 2, *bottom*). With regard to the

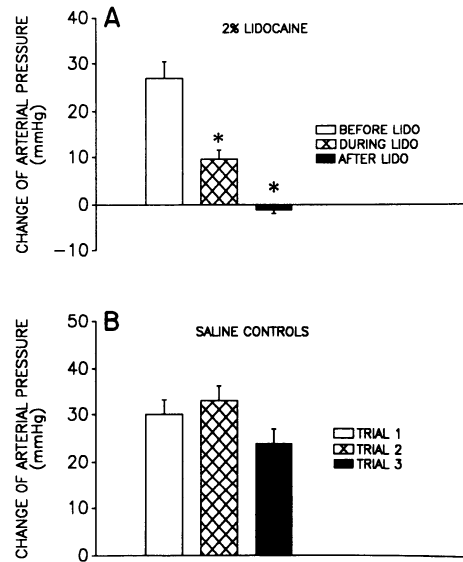


FIG. 3. A: changes of mean arterial pressure elicited by 3 sequential distensions of urinary bladder from 0 to 20 mmHg ($n = 5$). Responses were measured before, during, and after intravesical administration of lidocaine. Distensions were separated by 10-min recovery periods. B: saline controls. * $P < 0.05$ compared with before lidocaine (A) or trial 1 (B).

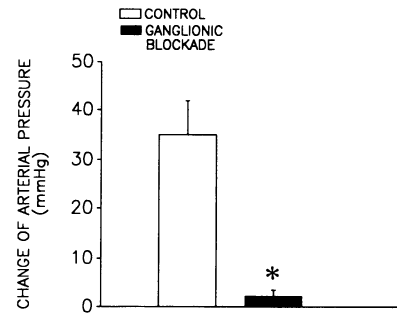


FIG. 4. Pressor response to bladder distension before and after ganglionic blockade (atropine + hexamethonium, $n = 6$). * $P < 0.05$ compared with control.

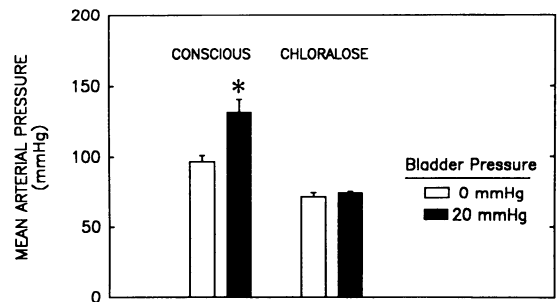


FIG. 5. Pressor responses to bladder distension were measured in conscious state and 10 min after chloralose (100 mg/kg iv, $n = 3$). Shown are values of mean arterial pressure before (open bars) and during steady-state response (closed bars) to a 20-mmHg increase of bladder pressure. * $P < 0.05$ compared with 0-mmHg bladder pressure.

efferent limb of the reflex, it might be expected that, after transection, a supersensitivity to catecholamines would develop as a result of a chronically low level of sympathetic nerve discharge. However, we have shown in a previous study, that there are no changes in pressor sensitivity to exogenous norepinephrine during the first week after CST (13). These observations, combined with

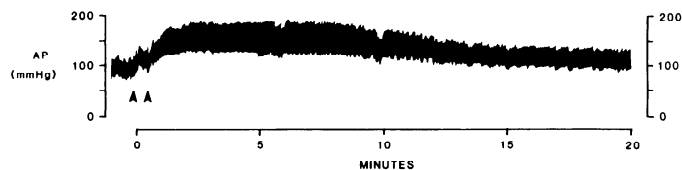


FIG. 6. Polygraph recording of arterial pressure in a conscious cervical spinal rat (5 days after CST) before, during, and after aspiration of urine from bladder. Arrows indicate period in which needle was inserted and withdrawn from the bladder.

the fact that pressor responses to bladder distension observed 24 h after CST were not different from that observed 7 days after CST, suggest that the rat is in the chronic recovery phase as soon as 24 h after spinal transection.

Effect of Anesthesia on Spinal Autonomic Reflexes

The pressor response to bladder distension was not observed in chloralose-anesthetized CST rats. This observation underscores the importance of studying the mechanisms of autonomic hyperreflexia in conscious animals. Anesthetics suppress autonomic hyperreflexia in spinal humans as well. Indeed, the depth of anesthesia has been used to control or prevent acute hypertensive episodes in spinal humans during general surgery (2, 14, 15).

We do not know whether chloralose suppressed pressor responses at a neural site or, by reducing excitability, at cardiac or vascular sites. Chloralose decreased resting arterial pressure in spinal rats by ~25 mmHg. In a previous study we have shown that arterial pressure in these rats is not being directly supported by sympathetic vasoconstrictor tone (13). Therefore, the depressor effects of chloralose are not due to a depression of ongoing sympathetic vasoconstrictor activity. This observation would imply that the chloralose-induced decrease of basal arterial pressure and abolition of autonomic hyperreflexia may not be due to a depression of neural activity but rather actions on the effector sites themselves. However, this hypothesis cannot be definitively tested without direct recordings of sympathetic activity in both conscious and anesthetized rats.

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