Pressor response resulting from experimental contusion injury to the spinal cord

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Experimental contusion paraplegic injury to the posterior spinal cord in cats results in a sudden increase of systemic blood pressure to between 200 and 250 mm Hg, and an increase in pulse pressure and a slowing of pulse rate. This initial hypertensive phase lasts approximately 3 to 4 minutes, and then is followed by a hypotensive phase. This pressor response is mediated by the alpha adrenergic receptor sites of the peripheral sympathetic nervous system and can be blocked by intravenous phenoxybenzamine, an alpha adrenergic blocking agent. The hypotensive phase is the result of an overall reduction in alpha adrenergic vascular tone and can be reversed by the infusion of metaraminol or intravenous fluids. The alterations in blood pressure that follow impact injury are most likely related to alterations of peripheral arteriolar resistance and venous return of blood to the heart.

KEY WORDS • experimental spinal cord injury • hypertension • hypotension • sympathetic nervous system

The alteration of systemic blood pressure resulting from increased intracranial pressure (ICP) has been well documented. The pressor response following experimental compression and contusion spinal cord injury has also been described. Clinically, hypotension occurs frequently following spinal cord injury. A study was undertaken to further investigate the acute changes in blood pressure resulting from transient, blunt contusion paraplegic injury to the posterior spinal cord in various segmental areas of the cat, and to investigate the contribution of the sympathetic nervous system to this response.

Methods and Materials

Adult cats weighing between 2.5 and 3.5 kg were anesthetized intraperitoneally with pentobarbital (35 mg/kg). A tracheostomy was performed, and respirations were controlled by a small-animal ventilator. A femoral artery and vein were cannulated for monitoring the systemic blood pressure by a Statham strain gauge transducer* and for the administration of intravenous fluids. The end-tidal tracheal pCO₂ was monitored and controlled between 2% and 4%. Body temperature was maintained at 36° to 38° C. After a laminectomy had been performed, trauma was administered by dropping a 25-gm weight 20 cm onto a contoured impounder resting on the exposed dura. This injury force has consistently produced permanent paraplegia in our chronic experimental animals. The blood-pressure response and pulse-rate changes were recorded before and for 1 hour after injury.

Six animals were used to study the pressor response at the T-5 segmental level. The pressor response was evaluated in six other animals at cervical, upper and lower thoracic, and lumbar segmental areas. Animals in this latter group each sustained multiple traumatic injuries in various segmental areas throughout the spinal cord.

Acute spinal cord transections were performed in six animals at T-1. After the animals had been allowed to stabilize for 1 hour, trauma was administered initially at C-5, and then at L-5 after a short period of observation. One hour later, three of the animals sustained trauma at T-3, while the other three were injured at T-9. Another six animals had a transection at T-6, followed by trauma 1 hour later at T-3 in three of the animals, or at T-9 in the other three animals. Three cats had bilateral adrenalectomies performed 24 hours before their traumatic injury at the T-5 segmental level.

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*Statham strain gauge transducer manufactured by Statham Laboratories, Inc., Hato Rey, Puerto Rico.
Pressor response in experimental spinal injury

The effects of intravenous sympatholytic agents were investigated in 12 cats. Alpha methyl tyrosine methyl ester HCl (AMT) (250 mg/kg), reserpine (2 mg/kg), or phenoxybenzamine (5 mg/kg) was given intravenously to groups of three animals each, according to a previously described protocol.\textsuperscript{29} The former two agents were given 24 hours before injury, and the latter was administered 2 hours before injury. Several control animals received metaraminol (Aramine), isoproterenol (Isuprel), or an increase of intravenous fluids during the posttraumatic hypotensive phase.

Results

Blunt contusion trauma to the posterior spinal cord at the T-5 segmental level in control animals consistently produced a pressor response after a latency of 2 to 5 seconds. This response was characterized by a sudden increase of the systolic blood pressure between 200 and 250 mm Hg, lasting from 3 to 4 minutes, and was accompanied by an increase in pulse pressure, slowing of the pulse rate, and occasionally irregularities in pulse rate (Fig. 1). The pulse-rate changes preceding the hypertensive component varied with either acceleration or slowing. Hypotension followed the hypertensive phase, reached a level of approximately 63% of the pretrauma systolic blood pressure, and usually returned to normal or slightly below normal pretrauma levels by 1 hour. Administration of intravenous fluids or metaraminol reversed this hypotensive phase, while intravenous isoproterenol accentuated hypotension (Fig. 2). The pressor response to trauma was observed in all segmental spinal areas of the cervical, thoracic, and upper lumbar spinal cord. Blood-pressure alterations observed in these areas did not appear to display any major differences from that observed at the T-5 segmental level. In lumbar segments below L-2, no change or, occasionally, hypotension was observed. Animals that were hypovolemic or had sustained repeated trauma demonstrated a diminution of the pressor response.

The mechanical trauma of an acute transection of T-1 or T-6 resulted in a brief pressor response. After a transection at T-1, trauma at cervical or lower lumbar segmental regions did not result in any pressor response, but normal responses were observed in the upper and lower thoracic segmental regions (Table 1). After a transection at T-6, however, trauma in the upper or lower thoracic segmental regions resulted in a hypertensive phase of less amplitude and of a shorter duration than that observed in control animals. Following this phase, hypotension was minimal with the systolic blood pressure remaining at ap-

![Fig. 1](image1.png)

**Fig. 1.** The pressor response resulting from contusion paraplegic injury to the T-5 spinal cord in the control group. Latency: 2 seconds; duration: 3 minutes. The initial hypertensive component is followed by a longer hypotensive phase.

![Fig. 2](image2.png)

**Fig. 2.** Infusion of isoproterenol during the hypotensive period results in an accentuation of hypotension. Infusion of metaraminol reverses the hypotensive phase.
TABLE 1
Blood pressure pre- and posttrauma in the hypertensive and hypotensive phases*

<table>
<thead>
<tr>
<th>Group</th>
<th>Pretrauma Phase (mm Hg)</th>
<th>Hypertensive Phase (mm Hg)</th>
<th>Hypotensive Phase (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control trauma T-5</td>
<td>132</td>
<td>229</td>
<td>83</td>
</tr>
<tr>
<td>(6 cats)</td>
<td>(100-160)</td>
<td>(200-250)</td>
<td>(60-100)</td>
</tr>
<tr>
<td>transection T-1</td>
<td>120</td>
<td>233</td>
<td>92</td>
</tr>
<tr>
<td>trauma T-3</td>
<td>(115-130)</td>
<td>(200-260)</td>
<td>(70-100)</td>
</tr>
<tr>
<td>(3 cats)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trauma T-9</td>
<td>126</td>
<td>200</td>
<td>88</td>
</tr>
<tr>
<td>(3 cats)</td>
<td>(100-150)</td>
<td>(180-220)</td>
<td>(70-100)</td>
</tr>
<tr>
<td>transection T-6</td>
<td>124</td>
<td>150</td>
<td>118</td>
</tr>
<tr>
<td>trauma T-3</td>
<td>(100-140)</td>
<td>(120-170)</td>
<td>(100-140)</td>
</tr>
<tr>
<td>(3 cats)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trauma T-9</td>
<td>114</td>
<td>160</td>
<td>104</td>
</tr>
<tr>
<td>(3 cats)</td>
<td>(100-140)</td>
<td>(120-180)</td>
<td>(90-120)</td>
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<tr>
<td>adrenalectomized</td>
<td>128</td>
<td>225</td>
<td>83</td>
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<tr>
<td>trauma T-5</td>
<td>(110-140)</td>
<td>(220-240)</td>
<td>(70-90)</td>
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<tr>
<td>(3 cats)</td>
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<tr>
<td>AMT</td>
<td>120</td>
<td>220</td>
<td>93</td>
</tr>
<tr>
<td>trauma T-5</td>
<td>(100-140)</td>
<td>(160-250)</td>
<td>(80-110)</td>
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<tr>
<td>(3 cats)</td>
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<tr>
<td>reserpine trauma T-5</td>
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<td>233</td>
<td>97</td>
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<tr>
<td>(3 cats)</td>
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<td>(180-250)</td>
<td>(70-100)</td>
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<tr>
<td>phenoxybenzamine</td>
<td>83</td>
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<td>60</td>
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<tr>
<td>trauma T-5</td>
<td>(75-100)</td>
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<td>(50-70)</td>
</tr>
<tr>
<td>(3 cats)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Blood pressure represents a mean value of systolic pressure (mm Hg). Numbers in parentheses represent the range of systolic blood pressure. AMT = alpha methyl tyrosine.

proximately 93% of the pretrauma levels. Adrenalectomized animals displayed no significant changes in the blood-pressure responses to injury when compared to controls.

Pretreatment with AMT or reserpine 24 hours before trauma did not affect the degree of systemic blood pressure elevation (Table 1). However, the latency of the response was prolonged, ranging from 8 to 13 seconds. Pretreatment with phenoxybenzamine did result in complete absence of the hypertensive response to injury, and a transient hypotensive phase initially following injury was observed instead (Fig. 3). This agent also accentuated posttraumatic hypotension and resulted in a reduction of the pretrauma systemic blood pressure (Table 1).

Discussion

The cardiovascular alterations resulting from experimentally increased ICP have been well known since the 19th century. The clinical importance of an elevation of systemic blood pressure, increased pulse pressure, and bradycardia resulting from increased ICP was emphasized initially by Cushing. A similar pressor response has been demonstrated when direct mechanical pressure or compression is applied to the intact spinal cord. Recently, the pressor response to posterior contusion paraplegic injury has been described and characterized. The hypertensive component is similar to that observed with increased ICP and from spinal cord compression. However, there is a hypotensive phase which has not been previously described experimentally.

The demonstration of the pressor response to trauma in all areas of the thoracic and upper lumbar spinal segments confirms that the sympathetic nervous system is involved in the mediation of this response. Although no preganglionic sympathetic neurons are present in the cervical spinal cord, trauma in the high cervical region without high thoracic transection results in a pressor response by activation of descending central sympathetic efferents in the cervical cord. Studies have demonstrated that the descending pathways that mediate vasomotor responses are mainly localized in the lateral and ventrolateral funiculi of the spinal cord. The absence of the response to trauma in lower lumbar areas indicates that traumatic activation of preganglionic neurons of the parasympathetic nervous system does not result in an elevation of blood pressure. An intact thoracic spinal cord is necessary for the full production of the pressor response as demonstrated by the results of the acute mid-thoracic transection studies. The degree of systolic-pressure elevation in these animals was less than that observed in control traumatized animals. The brief latency of the pressor response and the finding of no major alterations of this response in adrenalectomized animals confirms previous reports that circulating catecholamines are not involved in its mediation.

The blood-pressure alterations that were observed following posterior paraplegic contusion injury to the thoracic spinal cord are most likely related to alterations of caliber in the peripheral arteriolar resistance and venous capacitance vessels. The sympathetic nervous system exerts predominant control of active constriction of these vessels. Trauma results in sympathetic discharge with activation of both alpha and beta receptors in various vascular beds. The constric-
tion of arterioles in the skin, mucosa, and abdominal viscera results in a marked increase in systolic and diastolic pressure and an increase in pulse pressure. The increase in venous return resulting from venoconstriction also contributes to the elevation of blood pressure by increasing cardiac output.

The initial slowing of the pulse rate before the blood-pressure elevation may indicate that parasympathetic vagal responses are activated primarily from trauma as well. Preliminary studies have demonstrated that these pulse-rate changes can be abolished with atropine.11 The relative slowing of the heart rate during the initial hypertensive phase results from compensatory reflexes to increased blood pressure mediated by the carotico-aortic baroreceptor system.8,10 Vagotomy and carotid-sinus denervation have been reported to abolish the pulse-rate changes in the pressor response from increased ICP.7,8,12

Although catecholamines and the autonomic nervous system have little importance in the maintenance of resting, non-stressful arterial blood pressure, they do play a major role in the reflex control of blood pressure through the arterial baroreceptor reflexes.4 Epinephrine and norepinephrine occur naturally, while isoproterenol is a synthetic catecholamine. Norepinephrine is the neurochemical transmitter at postganglionic sympathetic nerve terminals. Drugs that mimic the effects of sympathetic nervous system stimulation or adrenal medullary discharge are termed sympathomimetic agents.22 The response of these agents is determined by the predominant effect of the alpha or beta receptors of the effector cells. On the basis of the effector system response to various sympathomimetic agents, sympathetic nervous system stimulation may activate hypothetical alpha and/or beta receptor sites in the effector cells.1,10,11 Generally, sympathetic activity on vasculature can be classified as either excitatory to skin, mucous membranes, and abdominal viscera with alpha receptor activity predominant, or peripherally inhibitory to skeletal muscle with beta receptor activity predominant.14 The important major effect of alpha receptor activation in vasculature is vasoconstriction.24 When both classes of receptors are activated, the alpha receptor predominates. However, as demonstrated by this study, if the initial pressor response is blocked with phenoxybenzamine, an alpha adrenergic blocking agent, a slight depressor effect may be observed. Activation of beta receptors in skeletal muscle, skin, and abdominal viscera may have resulted in vasodilatation with a transient drop in systemic blood pressure. This slight diminution in blood pressure lends support to previous reports that the contribution of beta receptor sites for neural control of peripheral blood pressure is negligible.17,20 Trauma most likely also induces beta receptor activation which is masked by the more predominant alpha activation. Cholinergic responses have been observed to produce vasodilatation in vascular beds, particularly skeletal muscle, but their physiological significance is thought to be minor.17

The predominant control of the sympathetic nervous system mediated through alpha receptor activity of vasomotor tone in peripheral capacitance vessels indicates that an overall reduction of sympathetic vascular tone is probably responsible for the hypotensive phase that follows the initial hypertensive component. This likely accounts for the hypotension that is observed clinically after spinal cord injury. In cats, recovery from this phase occurs usually by 1 hour after injury. The minimal hypotensive phase observed in those animals following high or low thoracic spinal cord trauma after a mid-thoracic transection may indicate that alpha adrenergic vascular tone is partially preserved by the non-traumatized thoracic spinal cord. The infusion of metaraminol, a sympathomimetic agent that acts predominantly on alpha receptors and is similar in its effects to norepinephrine,24 reverses the hypotensive phase. Experimentally, this phase can be potentiated by isoproterenol, a beta sympathomimetic. This indicates that although the contribution of beta receptor sites for neural control of peripheral blood pressure is thought to be negligible,17,20 circulating beta sympathomimetics can result in a significant vasodilatation of skeletal muscle and abdominal viscera.

The presence of high concentrations of biogenic amines in the lateral horn of the thoracic spinal cord may indicate that they serve a neurotransmitter function similar to the peripheral sympathetic nervous system.25 Inhibition of synthesis or depletion of norepinephrine in the thoracic spinal cord should represent an optimal mechanism of sympathetic neuron blockade centrally. Alpha methyl tyrosine (AMT) is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in the initial pathway of the conversion of tyrosine to norepinephrine in the central nervous system.20,21 Reserpine, a Rauwolfia alkaloid, depletes stores of norepinephrine, dopamine, and serotonin.26 Infusion of AMT or reserpine 24 hours before trauma resulted in no appreciable reduction of the pressor response, although a prolonged latency was observed. A separate study has demonstrated that 24-hour pretreatment with either of these two agents results in almost undetectable levels of norepinephrine at the T-5 spinal cord segment.28 Since the pressor response is mediated by the peripheral sympathetic nervous system after traumatic activation of preganglionic sympathetic neurons in the spinal cord, the role of norepinephrine as the neurotransmitter of descending central sympathetic neurons at spinal cord levels does not appear to be substantiated by this study. Phenoxybenzamine, a haloalkylamine, acts as an alpha adrenergic blocking agent. The mechanism of this blockade occurs at the receptor site in the peripheral sympathetic nervous system by blocking re-uptake of norepinephrine, and it is independent of any effects on noradrenergic

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metaraminol, an alpha sympathomimetic agent. In this study, phenoxybenzamine pretreatment 2 hours before trauma resulted not only in blocking of the hypertensive component of the pressor response but also in a marked hypotension after injury. The mechanism of abolition of the hypertensive component is then related to peripheral alpha adrenergic blockade of vasoconstrictor activity.

Clinically, the hemodynamic alterations of acute quadriplegia are well known and are characterized by hypotension, bradycardia, and an increase in venous capacitance. The lack of early blood-pressure measurements in acute quadriplegia resulting from accidental injury precludes the documentation of the early hypertensive phase observed after experimental impact injury. However, an abrupt elevation in systemic blood pressure occurring during spinal surgery, particularly in the cervical or thoracic region, that is not related to anesthesia levels may indicate inadvertent operative trauma to the spinal cord. The reduction in sympathetic vascular tone is responsible for the hypotension. Greene notes that venodilatation with pooling has greater importance than the reduction of peripheral arteriolar resistance in determining the response to acute sympathetic denervation. Bradycardia resulting from spinal anesthesia, which is the purest form of acute sympathetic denervation, is related to a decrease in right auricular pressure and is a direct function of decreased venous return.

The maintenance of an adequate venous return is the sine qua non for the safe management of a patient with impaired activity of the sympathetic nervous system. Experimentally and clinically, the hypertensive phase can be reversed with the use of alpha sympathomimetic vasopressor agents or increased administration of intravenous fluids. Clinically, respiratory insufficiency and pulmonary edema have been documented when large volumes of fluids are administered. This may occur without significant elevation of the central venous pressure. Monitoring of pulmonary pressure and of pulmonary arterial wedge pressure by the use of the Swan-Ganz catheter has been advocated as a more sensitive indicator for impending pulmonary edema in spinal cord injury. Meyer, et al., believe that the capacitance vessels retain their ability to constrict. This has been confirmed by our observations that in the hypertensive phase, metaraminol, an alpha sympathomimetic agent that acts predominantly by vasoconstriction, can result in a reversal of the hypotension. However, isoproterenol, a pure beta agonist produces accentuation of the hypotension, probably by a decrease in peripheral arteriolar resistance and/or a reduction in venous constriction. The results of this experiment suggest that early treatment with an alpha sympathomimetic agent rather than isoproterenol, a beta sympathomimetic, should be used in those cases with acute quadriplegia or paraplegia that result with significant hypotension. The use of alpha sympathomimetic agents after large volumes of intravenous fluids have been administered could result in a sudden overload in the vascular system resulting in pulmonary edema. Blood pressure should be corrected only to a normotensive range, as experimental studies have indicated that induced hypertension following a posterior impact injury will result in increased hemorrhages and edema.

References
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†Swan-Ganz catheter manufactured by Edwards Laboratories, 17221 Red Hill Avenue, Santa Ana, California.
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