Selective Vulnerability of the Lumbosacral Spinal Cord After Cardiac Arrest and Hypotension

N. Duggal and B. Lach

*Stroke.* 2002;33:116-121
doi: 10.1161/hs0102.101923

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://stroke.ahajournals.org/content/33/1/116

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:

http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:

http://stroke.ahajournals.org//subscriptions/
Selective Vulnerability of the Lumbosacral Spinal Cord After Cardiac Arrest and Hypotension

N. Duggal, MD; B. Lach, MD, PhD

Background and Purpose—It is generally accepted that the gray matter in the watershed area of the midthoracic level of the spinal cord is the ischemic watershed zone of the spinal cord. We performed a retrospective study to reevaluate the frequency and distribution of spinal cord injury after a global ischemic event.

Methods—Clinical files and neuropathology specimens of all adult patients with either a well-documented cardiac arrest or a severe hypotensive episode, as well as pathologically confirmed ischemic encephalopathy and/or myelopathy, were reviewed by an independent reviewer.

Results—Among 145 cases satisfying selection criteria, ischemic myelopathy was found in 46% of patients dying after either a cardiac arrest or a severe hypotensive episode. Among the patients with myelopathy, predominant involvement of the lumbosacral level with relative sparing of thoracic levels was observed in >95% of cardiac arrest and hypotensive patients. None of the examined patients developed neuronal necrosis limited to the thoracic level only.

Conclusions—Our findings indicate a greater vulnerability of neurons in the lumbar or lumbosacral spinal cord to ischemia than other levels of the spinal cord. (Stroke. 2002;33:116-121.)

Key Words: heart arrest ▪ hypotension ▪ ischemia ▪ selective vulnerability ▪ spinal cord diseases

Although the pathological aspects and the topographic distribution of ischemic lesions after transient global ischemia have been extensively studied in the brain,1-4 very few studies have described the distribution of ischemic changes in the spinal cord after either cardiac arrest or severe hypotension. Historically, the literature has supported the notion of a spinal cord “watershed zone” of ischemic vulnerability centered at the mid-thoracic level (T4 to T6 level).3,5-10 This assumption was based largely on anatomic studies and case reports describing the relative hypovascularity of the midthoracic region from approximately T4 to T8.6,9,11,12 This pattern of vascularization of the spinal cord has been equated with increased sensitivity of this area to ischemic injury. There have been, however, individual case reports13-22 and clinical23 and clinicopathological studies20,24,25 suggesting that global ischemia may affect the low thoracic and lumbosacral cord to a greater extent than the other levels of the spinal cord. We performed a retrospective review of neuropathological changes in the brains and spinal cords of survivors of cardiac arrests or severe hypotensive episodes to reevaluate the frequency and distribution of neuronal injury in the spinal cord associated with ischemic encephalopathy in adults.

Materials and Methods

Neuropathology reports of 3497 consecutive autopsies performed between January 1, 1985, and December 31, 1995, were retrospectively reviewed in search of a microscopic diagnosis of either ischemic encephalopathy or ischemic myelopathy, as well as a premorbid well-documented history of either cardiac arrest or a severe sustained hypotensive episode. The patient population was derived from a university-affiliated teaching hospital. Informed consent for autopsy was obtained in all cases. Patients were excluded from the study if they had any clinical or pathological findings suggestive of spinal cord disease, including trauma, neoplasms, arachnoiditis, syringomyelia, infections, multiple sclerosis, collagen vascular disease, vasculitis, arteriovenous malformations, and spinal artery thromboembolism. The clinical, general autopsy and neuropathology records of 211 cases with the diagnosis of ischemic encephalopathy and/or myelopathy were subsequently reviewed in detail. Further cases were then excluded on the basis of the following criteria: (1) diagnosis of aortic disease except for atherosclerosis, including aneurysm, dissection, thrombus, or surgery (n=22); (2) incomplete clinical data (n=16); and (3) a survival interval between cardiac arrest or the hypotensive episode and death of <3 hours (n=28).

A total of 145 remaining cases had a well-documented history of either cardiac arrest or a paroxysmal, severe hypotensive episode with no confounding history of active spinal cord or aortic disease. Cardiac arrest was defined as cessation of cardiac mechanical activity documented by ECG and confirmed absence of detectable pulse.26 This was invariably accompanied by apnea, loss of consciousness, and unresponsiveness. Because the clinical records did

Received February 13, 2001; final revision received August 8, 2001; accepted September 18, 2001.

From the Department of Clinical Neurological Sciences (Neurosurgery), University of Western Ontario, London, Ontario (N.D.), and Department of Laboratory Medicine and Pathology, University of Ottawa and Ottawa Hospital, Ottawa (B.L.), Canada.


Correspondence to Neil Duggal, MD, London Health Sciences Centre, University Campus, 339 Windermere Rd, London, Ontario, Canada N6A 5A5.

E-mail neil.duggal@lhsc.on.ca

© 2002 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org

Downloaded from http://stroke.ahajournals.org/ by guest on February 27, 2014
occurrence and level of spinal cord injury was also studied. Both/H9273
In all cases of cardiac arrest, the association between duration of cord, the relationship between survival time and the development of terms of premorbid history of hypertension and coronary artery changes in the lumbosacral level. The 2 groups were compared in divided into 2 groups: 63 cases with and 82 cases without ischemic different stages of organization.

In cases with selective neuronal necrosis or gray matter infarction at changes were manifested by neuronal dropout with astrocytic gliosis./H11350

Clarke’s column of the low thoracic and lumbar levels and paramedian groups of nuclei of the anterior horns and ischemic changes involving the large neurons in the anterior group is summarized in Table 1. Ischemic changes in the brain and spinal cord were recorded. The minimum histological criteria for the diagnosis of ischemic neuronal necrosis were nuclear pyknosis and cytoplasmic eosinophilia.2,4 Longstanding ischemic changes were manifested by neuronal dropout with astrocytic gliosis in cases with selective neuronal necrosis or gray matter infarction at different stages of organization.

For statistical analysis of the data, the 145 cases were initially divided into 2 groups: 63 cases with and 82 cases without ischemic changes in the lumbosacral level. The 2 groups were compared in terms of premorbid history of hypertension and coronary artery disease, age, and degree of aortic atherosclerosis, graded as mild, moderate, or severe at the time of general autopsy.

For all 66 cases demonstrating ischemic changes in the spinal cord, the relationship between survival time and the development of ischemic changes at different levels of the spinal cord was evaluated. In all cases of cardiac arrest, the association between duration of cardiac arrest (1 to 10, 11 to 20, 21 to 30, and >30 minutes) and the occurrence and level of spinal cord injury was also studied. Both \( \chi^2 \) tests and Fisher’s exact tests were used for statistical analysis of the data. For all statistical tests, a value of \( P<0.05 \) was considered significant.

\section*{Results}

In the 145 cases with a documented postmortem diagnosis of anoxic-ischemic injury to the central nervous system, 83 patients had cardiopulmonary arrest, whereas 62 had an episode of sudden, severe hypotension that was not a component of the agonal episode. Patient information for each group is summarized in Table 1. Ischemic changes in the spinal cord were present in 66 cases (45.5\%). The distribution of ischemic changes to the spinal cord and brain is summarized in Table 2. Histologically, the cords demonstrated ischemic changes involving the large neurons in the anterior and paramedian groups of nuclei of the anterior horns and Clarke’s column of the low thoracic and lumbar levels (Figure 1). These ischemic changes were characterized by chromatolysis, prominent nuclear pyknosis, cytoplasmic eosinophilia, and disintegration of the neuronal perikarya to a variable degree (Figure 2). In the more advanced stages, the gray matter was infarcted and demonstrated various stages of organization. No cavitary necrosis was noted. In all 66 cases, spinal cord lesions were found in the gray matter. In the most severe cases with total infarction of the gray matter, there was a narrow rim of white matter necrosis and/or edema.

Four topographical patterns of spinal cord ischemia emerged (Figures 1 and 3). The most common was selective involvement of the lumbosacral levels of the spinal cord (46 cases, 69.7\%). The remaining 20 case (30.3\%) had additional involvement of other levels of the spinal cord in 1 of the following patterns (Figures 1 and 3): (1) ischemic changes extending over the entire length of the spinal gray matter, with the most severe involvement of the lumbosacral and cervical cords (11 cases, 16.7\%); (2) infarction at the lumbosacral level and patchy ischemic changes at the cervical level (6 cases, 9.5\%); and (3) ischemic changes at the cervical level only (3 cases, 4.5\%). Statistical analysis demonstrated that

\begin{table}
\centering
\caption{Patient Information}
\begin{tabular}{llll}
\hline
Variable & Cardiac Arrest (n=83, n) & Hypotension (n=62, n) \\
\hline
Age, y & & \\
<20 & 2 & 2 \\
20–29 & 6 & 5 \\
30–39 & 6 & 3 \\
40–49 & 8 & 4 \\
50–59 & 20 & 11 \\
60–69 & 23 & 15 \\
70–79 & 16 & 17 \\
>80 & 2 & 5 \\
Sex & & \\
M & 48 & 36 \\
F & 35 & 26 \\
Hypertension & & \\
Absent & 48 & 38 \\
Present & 35 & 24 \\
CAD & & \\
Absent & 51 & 37 \\
Present & 32 & 25 \\
Atherosclerosis & & \\
Mild & 11 & 8 \\
Moderate & 30 & 18 \\
Severe & 41 & 36 \\
ROSC, min & & \\
<10 & 16 & \\
11–20 & 38 & \\
21–30 & 20 & \\
>30 & 9 & \\
Survival time & & \\
12–24 h & 15 & 10 \\
1–3 d & 33 & 28 \\
4–7 d & 16 & 13 \\
8–21 d & 13 & 8 \\
>21 d & 6 & 3 \\
\hline
\end{tabular}
\end{table}

\textit{CAD} indicates coronary artery disease; \textit{ROSC}, restoration of spontaneous circulation.
the proportions between the various patterns of spinal cord ischemia were different from each another ($\chi^2=10.242$, $P=0.001$, $\chi^2$ test). The lumbosacral cord was statistically the most frequent site of ischemic change in the spinal cord. Of all 66 cases of ischemia involving the spinal cord, in only 3 instances was there no involvement of the lumbosacral cord. In each of these 3 cases, ischemic changes in the neurons were restricted to the cervical level. There was no single case with the pathological abnormalities limited to the midthoracic level of the spinal cord.

There was no significant morphological or topographical difference between the cardiac arrest and the hypotension group in the pattern of ischemic change involving the spinal cord. In the cardiac arrest group (n=83), ischemic changes involving the lumbosacral cord were present in 41 cases (49.4%). Additional involvement of the cervical cord was seen in 12 (18.2%) and of the thoracic cord in 7 (8.4%) cases (Table 2). Similar results were found in the hypotension group (n=62), in which ischemic changes in the lumbosacral cord were found in 22 cases (35.5%), with 8 (12.9%) showing cervical and only 4 (6.5%) demonstrating thoracic cord involvement (Table 2).

Among the patients sustaining a cardiac arrest for a period of 1 to 10 minutes (n=16), ischemic change in the lumbosacral cord was present in 33% of cases. The frequency of the spinal cord injury increased to 48% and 61% in cases of cardiac arrest with a duration of 11 to 20 minutes (n=38) and >20 minutes (n=29), respectively. There was, however, no statistically significant association between duration of ischemia and extent of spinal cord injury (ie, selective neuronal necrosis at the lumbosacral level only versus infarction of the gray matter at all the levels; $P=0.441$, Fisher’s exact test).

All patients remained comatose during the period between cardiopulmonary arrest or severe hypotension and death. Seventeen percent of patients survived >24 hours. Most patients (42%) survived 1 to 3 days. In the remaining patients, 20% survived 4 to 7 days, 15% survived 1 to 3 weeks, and 6% ultimately survived for >3 weeks before death. The length of survival time did not influence the development of ischemic changes in the lumbosacral spinal cord ($P=0.366$, Fisher’s exact test). In addition, there was no association between survival time and level of spinal cord involvement ($P=0.366$).

**TABLE 2. Distribution of Ischemic Changes to the Central Nervous System**

<table>
<thead>
<tr>
<th>Location</th>
<th>Cardiac Arrest (n=83)</th>
<th>Hypotension (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, n</td>
<td>Frequency, %</td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex (frontal lobe)</td>
<td>75</td>
<td>90.4</td>
</tr>
<tr>
<td>Hippocampus (CA1 sector)</td>
<td>78</td>
<td>94.0</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>66</td>
<td>78.6</td>
</tr>
<tr>
<td>Basal ganglia (globus pallidus)</td>
<td>57</td>
<td>68.7</td>
</tr>
<tr>
<td>Brainstem (midbrain)</td>
<td>46</td>
<td>55.4</td>
</tr>
<tr>
<td>Spinal cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>12</td>
<td>18.2</td>
</tr>
<tr>
<td>Thoracic</td>
<td>7</td>
<td>8.4</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>41</td>
<td>49.4</td>
</tr>
</tbody>
</table>

Figure 1. Topographical patterns of anoxic-ischemic injury to the spinal cord: infarction of the gray matter at all levels of the spinal cord (A), diffuse anoxic-ischemic changes at the cervical and lumbosacral cords with relative sparing of the thoracic level (B), and anoxic-ischemic changes limited to the lumbosacral level only (C).

Figure 2. Microphotograph of the spinal cord gray matter at the thoracic (left) and lumbar (right) levels from case A-101/87 shown in Figure 1C. Note the preservation of motor neurons at the thoracic level and selective neuronal necrosis of all neurons at the lumbar level. Magnification ×1050 and ×420, respectively.

Figure 3. Histological patterns of ischemic injury in the spinal cord. C indicates cervical; T, thoracic; L, lumbosacral level of spinal cord. *$P=0.001$, $\chi^2$ test.
Fisher’s exact test). Patients ranged from 16 to 88 years of age, with a mean age of 58±17 years at the time of death. Age did not influence the pattern of ischemic change in the spinal cord ($P=0.830$, Fisher’s exact test) or the occurrence of ischemic changes in the lumbosacral cord ($P=0.697$, Fisher’s exact test). A premorbid history of hypertension and coronary artery disease was present in 41% and 39% of cases, respectively. There was no association between hypertension or coronary artery disease and the occurrence of ischemic changes in the lumbosacral cord (chi-square test). Moderate or severe aortic atherosclerosis was noted in 86% of the patients. Again, no association was found between the degree of aortic atherosclerosis and the occurrence of ischemic changes in the lumbosacral cord ($P=0.376$, $\chi^2$ test).

### Discussion

Cardiac arrest and severe hypotension followed by restoration of normotension are the most common clinical examples of complete and incomplete transient global ischemia of the central nervous system in humans.2,3 In these conditions, development of ischemic necrosis in border zones between major arterial territories has been well documented in clinical and experimental animal studies.1,5,27,28 Because of the anatomic distribution of the spinal cord arteries with the relative paucity of radicular arteries in the thoracic region, the midthoracic level of the spinal cord (T4 to T8) has been recognized as the ischemic watershed zone of the spinal cord.5,5–10,16 Although most clinicopathological studies on spinal cord ischemia have focused on lesions associated with local vascular changes or aortic disease,22,29,35 or coronary artery disease and the occurrence of ischemic injury. The third pattern, that of concomitant cervical and lumbosacral levels involvement, likely corresponds to an intermediate degree of ischemia. In the 66 patients with documented spinal cord ischemia, statistical analysis demonstrated that the lumbosacral cord was most frequently involved compared with other regions (ie, cervical and thoracic) or the combination of these regions.

In our series of 145 cases of either cardiac arrest ($n=83$) or systemic hypotension ($n=62$), 66 patients (45%) had evidence of ischemic changes in the spinal cord. All of these cases were associated with ischemic changes in other parts of the central nervous system (Table 2). Among the 66 cases of ischemic myelopathy, 95.5% of specimens ($n=63$) demonstrated ischemic changes in the lumbosacral cord, with 69.7% ($n=46$) having changes restricted only to that level. Remarkably, the thoracic cord was affected in only 7.6% of cases and never in isolation. In contrast, the midthoracic spinal cord has been demonstrated to be the most poorly vascularized region of the spinal cord with an inconsistent arterial supply at T4 or T5.10,16 The lower thoracic and lumbar territory derives most of its blood supply from the artery of Adamkiewicz. Although the thoracic spinal cord may be the anatomic watershed zone with respect to regional blood supply, our findings indicate that the lumbosacral cord neurons appear to be more susceptible to ischemia.

The knowledge concerning global ischemia of the spinal cord is based on individual case reports13,14,18–22,29,35 or studies of small numbers of patients.6,7,15–17,23–25,34,36 Our results confirm select neuropathological studies reporting the predominance of ischemic changes in the lumbosacral cord after a global ischemic episode.15,17,24,25,34 Neuronal necrosis restricted to the lumbosacral level of the spinal cord was initially reported by Gilles and Nag24 in 6 neonates suffering transient cardiopulmonary arrest. These findings were later confirmed in a larger series of premature infants with clinically documented hypotensive episodes34 and 2 adult patients after cardiac arrest.15 Subsequently, Azzarelli and Roessmann25 in their material from 16 patients, including 11 adults with ischemic myelopathy, demonstrated lesions located throughout the spinal cord in 9 cases and restricted only to the lumbosacral cord in 4 patients.

After transient global ischemia, the development and extent of tissue damage is thought to be a function of the severity of blood flow reduction, the duration of ischemia, and the length of survival after the event.3 Statistical comparison did not demonstrate any difference between the cardiac arrest and hypotension groups in either the occurrence or distribution of ischemic changes in the spinal cord. In both groups, identical ischemic changes were found. Despite the obvious trend showing an almost doubling of the incidence of changes in the lumbosacral cord after 11 to 20 minutes compared with the 1 to 10 minutes group, duration of the ischemic episode was not statistically significant in predicting the occurrence of ischemic changes in the lumbosacral cord ($P=0.298$, Fisher’s exact test). This may also be related to the extent of the ischemic insult because both the duration and depth of ischemia (ie, the degree of reduction of blood flow) determine the extent and severity of the ischemic injury. Although delayed neuronal necrosis after global ischemia has been demonstrated in the human brain36,37 and in experimental spinal cord ischemia,38 the length of survival time did not appear to influence the development of ischemic changes in any segment of the spinal cord.

The histological and topographic patterns of pathologic changes in the spinal cord probably reflected the varying degrees of ischemia. In our limited number of patients, we were unable to demonstrate statistical significance between degree of ischemia and location of ischemic changes in the spinal cord. We suspect, however, that at one extreme of the spectrum, cases with pannecrosis of gray matter throughout the entire length of the spinal cord often represented examples of the most severe ischemic insult. In contrast, selective neuronal necrosis restricted solely to the lumbosacral cord resulted from the mildest ischemic injury. The third pattern, that of concomitant cervical and lumbosacral levels involvement, likely corresponds to an intermediate degree of ischemia. In the 66 patients with documented spinal cord ischemia, statistical analysis demonstrated that the lumbosacral cord was most frequently involved compared with other regions (ie, cervical and thoracic) or the combination of these regions.

High metabolic demands and the large number of neurons in the lumbosacral cord may be responsible for the preferential involvement of the motor neurons at the lumbosacral level after global ischemia. Vascular micro-injection studies indicate that lumbosacral and cervical levels contain a richer capillary network than the midthoracic level of the spinal cord.11,12 It has previously been demonstrated for other regions of the central nervous system that the number of capillaries is greatest in the areas of higher metabolic demand and regions directly associated with a higher neuronal density.39–42 The lumbosacral and cervical cord segments have the highest metabolic rate with the greatest oxygen demands. Further
studies are needed to confirm whether a differential vulnerability between neurons in various levels of the spinal cord is dependent on variations in the regional blood flow or their inherent metabolic properties. Alternatively, the tendency for aortic atherosclerosis to increase in severity from proximal to distal segments could explain in part the pattern of predominant lumbosacral cord involvement. Atherosclerosis involving the aorta typically is most severe at the aortic arch, proximal thoracic aorta, and abdominal aorta at the level of the renal arteries. Thus, differential blood flow resulting from vascular anatomy and/or vascular disease remains a possible explanation. The findings that cord damage did not appear to be age, hypertension, or coronary artery disease dependent may, however, mitigate against this possibility. Furthermore, statistical analysis did not demonstrate an association between the degree of aortic atherosclerosis and the occurrence of ischemic change in the lumbosacral cord.

With the increasing frequency of successful resuscitation of patients suffering cardiac arrest or profound hypotensive episodes, the understanding of the pattern of injury to the nervous system in these clinical setting is the first step to their prevention. In a clinical study by Cheshire et al., 23 44 patients were found to have spinal cord infarctions. Surprisingly, the mean sensory level of the deficits was found to occur at T8 and T9 in cases of global ischemia (cardiac arrest, n = 4). 23 A review of the clinical literature by Cheshire and colleagues suggests that the most commonly found sensory level after spinal cord infarction is centered at T12. There are many potential causes, including critical illness neuropathy, for generalized weakness in patients who have suffered a global ischemic event. We found the 46% of patients who died after either cardiac arrest or a severe hypotensive episode demonstrated histological changes consistent with ischemic myelopathy. Future studies correlating imaging studies (MRI) with clinical and pathological findings should provide further insight into the role of ischemic myelopathy in patients’ clinical presentation.

In conclusion, our findings indicate a greater vulnerability of lumbosacral neurons to ischemic insults from either cardiac arrest or a severe sustained episode of hypotension. This is most likely a consequence of greater metabolic demands of the gray matter at this level of the spinal cord. Furthermore, our results indicate a very high overall frequency of ischemic myelopathy in global ischemia after cardiac arrest and hypotension. Future preventive neuroprotective strategies in the setting of global ischemia should take into consideration the significant vulnerability of the lumbosacral level of the spinal cord.

Acknowledgments
We thank Drs Naven Duggal and Natalie Jette for their help in collecting the data, as well as Drs Anil Duggal, Balraj Jhawar, and Bart Demaerschalk for their assistance in the statistical analysis of the results. We appreciate Dr Volker K.H. Sonntag’s critical review of the manuscript. We also thank the staff of the Neuroscience Publications at Barrow Neurological Institute for their assistance with the typing of the manuscript.

References


