Effect of experimental cervical spinal cord injury on respiratory function

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The effect on respiratory function of crushing the C-4 level of the cervical spinal cord was evaluated in monkeys. Spontaneous respiration ceased immediately after the crush due to direct mechanical trauma, but could be recovered provided a respirator was used and certain areas of the anterolateral columns remained intact. This acute respiratory paralysis occurred even in minimally damaged cords in which most of the anterolateral columns were spared, and led to death due to hypoxia if a respirator was not used. The delayed spinal cord swelling due to edema and centrifugal pressure from an expanding central cord lesion gradually caused delayed respiratory paralysis; durotomy relieved the pressure effects and markedly facilitated recovery.

KEY WORDS • spinal cord injury • respiratory paralysis • quadriplegia • durotomy

Among the most serious traumatic injuries are those that involve the spinal cord at the cervical level. Aside from devastating motor and sensory paralysis occurring from lesions at this level, additional complex physiological changes occur that principally involve the respiratory system and quite often lead to death.

This primate study was designed to examine the mechanisms of cervical cord injury that result in respiratory arrest, and to evaluate therapeutic procedures that might reverse this process.

Methods

Sixteen rhesus monkeys (Macaca mulatta) ranging in weight from 3 to 4 kg were used. All animals were anesthetized with 25 mg/kg of intravenous sodium pentobarbital and intubated with a No. 3.0 to 3.5 Air-Ion endotracheal tube.* The monkey was then placed in a modified Kopf stereotaxic instrument† adapted for mounting the cord-impounding apparatus and to allow a laminectomy from C2-5. The head was mounted in the standard position in the head holder and, just prior to the time of impounding, the head was rotated ventrally by gentle traction on a screw inserted close to the external occipital protuberance; excessive hyperflexion was carefully avoided. The body was placed on an elevated rack so that the thoracic lumbar, and cervical portions of the

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†Kopf stereotaxic instrument made by David Kopf Instrument, 7324 Elmo Street, Tujunga, California 91042.
cord were on the same level plane. This also placed the cervical spinal cord in a horizontal position at right angles to the impounding apparatus. A calibrated weight was then dropped from a measured height through a lucite plastic tube onto an impounder contoured to cover the dorsal surface of the spinal cord area at the C-4 level. Three crushing devices were designed to deliver a range of crushing forces: 1) a 20-gm weight was dropped a distance of 30 cm to deliver a maximum 600 grams centimeter force (gcf); 2) a 50-gm weight was dropped 30 cm to deliver up to 1500 gcf; 3) a 200-gm weight dropped 25 cm delivered up to 5000 gcf. All weights were dropped through plastic tubes of the appropriate diameter and struck an impounder designed to fit the contour of the spinal cord at the C-4 level. Immediately after impounding, the flexed head position was released, thus relieving any pressure that might interfere with chest and diaphragmatic movements. The C-4 cord was chosen as the impounding site because the descending respiratory tracts extend at least as far caudalward as the fourth cervical segment where the phrenic nerves originate in the rhesus monkey.

Respiratory function was analyzed by recording the flow rate of both inspiration and expiration phases by way of a Grass pneumotachometer. The tidal and minute respiratory volumes, as well as respiratory rate and pattern, were evaluated from the recorded pneumotachogram. A Bird Mark IV respirator* driven by either 40% oxygen or room air was used when respiratory support was indicated. Blood pressure and ECG were monitored by a Grass polygraph, and arterial blood samples were taken periodically and analyzed; pO₂, pCO₂, pH, and hematocrits were parameters evaluated on each sample.

The determination of the respiratory function (by pneumotachograph) as well as the blood samples taken frequently during periods of nonrespiratory assistance were used to evaluate the cardiovascular status; if severe hypoxia developed, the respirator was again applied. All respiratory support was terminated 5 hours following durotomy.

Since all monkeys that received a crushing blow at the C-4 level were quadriplegic, early postoperative intensive care was necessary. Hand feeding and watering, periodic rotation of the monkey, manipulation of extremities, daily grooming, and maintenance of normal body temperature were meticulously attended to during the intensive care period. The recovery of motor function was carefully observed and, in general, after maximum recovery was attained, the monkey was sacrificed. The spinal cord was serially sectioned at 20 μ and stained with either hematoxylin and eosin or the Weigert methods.

Results

Table 1 summarizes respiratory changes following C-4 cord lesioning in terms of apneic period, duration of mechanical respiratory support, and recovery of both minute respiratory volume and respiratory rate with or without durotomy. The cardiovascular changes included a temporary fluctuation of blood pressure and bradycardia accompanied with arrhythmia immediately after impounding (Figs. 1 and 2). These parameters returned to the precrush level when the respiration became normal either spontaneously or with respiratory assistance. No deaths occurred.

Acute Respiratory Paralysis

When the cervical cord was experimentally traumatized at C-4, spontaneous respiration stopped immediately in all monkeys and apnea lasted 10 sec to 12 min. Apneic periods correlated well with various types of pathological changes found on autopsy. In the animals that showed minimal damage to the central cord areas and little involvement of surrounding white matter, the acute respiratory paralysis returned to normal spontaneously even though the respiratory pattern was temporarily spastic (Monkeys 12, 15, and 16). However, in Monkey 25, which was subjected to the same 1000-gcf crush as Monkey 16, recovery from apnea resulting from the impounding tended to be somewhat shorter (top record of Fig. 1) but was so shallow and ineffective that gradual deterioration developed and death occurred 17 min later (bottom record of Fig. 1).

*Pneumotachometer and polygraphs made by Grass Instrument Company, Quincy, Massachusetts 02169.
†Mark IV respirator made by Bird Corporation, Palm Springs, California.
Respiratory function in cervical cord injury

TABLE 1
Results of C-4 crush on respiratory function

<table>
<thead>
<tr>
<th>Monkey No.</th>
<th>Force (gm/cm)</th>
<th>Apneic Period*</th>
<th>Respirator† (min)</th>
<th>Time to Durotomy† (min)</th>
<th>% Respiratory Recovery§</th>
<th>Time Observed**</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>600</td>
<td>10 sec</td>
<td>(-)</td>
<td>ND</td>
<td>81 (91)</td>
<td>ND 60 days</td>
</tr>
<tr>
<td>15</td>
<td>900</td>
<td>20 sec</td>
<td>(-)</td>
<td>ND</td>
<td>75 (103)</td>
<td>ND 46 days</td>
</tr>
<tr>
<td>16</td>
<td>1000</td>
<td>15 sec</td>
<td>(-)</td>
<td>ND</td>
<td>92 (96)</td>
<td>ND 43 days</td>
</tr>
<tr>
<td>25</td>
<td>1000</td>
<td>10 sec</td>
<td>ND</td>
<td>0 (0)</td>
<td>ND</td>
<td>17 min</td>
</tr>
<tr>
<td>17</td>
<td>1500</td>
<td>20 sec</td>
<td>ND</td>
<td>96 (108)</td>
<td>ND</td>
<td>103 days</td>
</tr>
<tr>
<td>18</td>
<td>2000</td>
<td>60 sec</td>
<td>ND</td>
<td>89 (104)</td>
<td>ND</td>
<td>29 days</td>
</tr>
<tr>
<td>19</td>
<td>2000</td>
<td>30 sec</td>
<td>ND</td>
<td>81 (88)</td>
<td>ND</td>
<td>16 days</td>
</tr>
<tr>
<td>21</td>
<td>3000</td>
<td>90 sec</td>
<td>ND</td>
<td>17 (67)</td>
<td>48 (72)</td>
<td>ND 84 days</td>
</tr>
<tr>
<td>32</td>
<td>3000</td>
<td>4 min</td>
<td>300</td>
<td>120</td>
<td>7 (46)</td>
<td>37 (51) NR</td>
</tr>
<tr>
<td>33</td>
<td>3000</td>
<td>10 sec</td>
<td>70</td>
<td>60</td>
<td>15 (57)</td>
<td>47 (68) 12 hrs</td>
</tr>
<tr>
<td>28</td>
<td>4000</td>
<td>6 min</td>
<td>150</td>
<td>120</td>
<td>29 (39)</td>
<td>46 (69) 56 days</td>
</tr>
<tr>
<td>29</td>
<td>4000</td>
<td>12 min</td>
<td>300</td>
<td>60</td>
<td>7 (43)</td>
<td>23 (52) NR</td>
</tr>
<tr>
<td>30</td>
<td>4000</td>
<td>5 min</td>
<td>300</td>
<td>240</td>
<td>13 (35)</td>
<td>21 (37) NR</td>
</tr>
<tr>
<td>31</td>
<td>4000</td>
<td>10 min</td>
<td>300</td>
<td>45</td>
<td>9 (50)</td>
<td>37 (54) NR</td>
</tr>
<tr>
<td>24</td>
<td>5000</td>
<td>5 min</td>
<td>300</td>
<td>30</td>
<td>20 (63)</td>
<td>15 (26) NR</td>
</tr>
<tr>
<td>20</td>
<td>5000</td>
<td>7 min</td>
<td>300</td>
<td>ND</td>
<td>7 (37)</td>
<td>ND NR</td>
</tr>
</tbody>
</table>

*Apneic period = the interval between the time of crush and that of the initial appearance of spontaneous respiratory movement.
†(-) = without respiratory assistance.
‡ND = no durotomy.
§Values compared with those of the precrush period, which were determined right before the durotomy and at the end of the experiment, usually 4 or 5 hrs later.
**NR = subjects failed to survive after 5 hrs of respiratory assistance because spontaneous respiration never reached optimal levels.

Figure 3 shows a microscopic section from the maximally damaged C-4 cord of Monkey 25. Scattered hemorrhages of a radiating nature centered in the gray matter were apparent. It is noteworthy that there was relatively little damage to the anterolateral columns but, in spite of this, the monkey died in a relatively short time after impounding.

Extensive damage characterized by severe demyelination and central cavitation that extended well into the surrounding white matter was observed in monkeys crushed by more than 1500 gcf. However, application of a respirator during apneic or shallow respiration periods resulted in gradual recovery of tidal respiratory volume and respiratory rate, so that these animals regained spontaneous respiration without durotomy and survived.

Delayed Respiratory Paralysis

There was a gradually appearing respiratory deterioration, usually within 30 to 60 min, in severely damaged monkeys subjected to more than 3000-gcf impounding; this correlated with the increased swelling observed under an operating microscope in the damaged segments of the cervical cord. Durotomy was performed when respiratory function became critical, and swelling had reached maximum. Respiratory function immediately improved in three out of seven animals, which subsequently survived (Table 1).

Delayed respiratory paralysis in Monkey 33 was typical (Figs. 2 and 4). Immediate apnea occurred within 10 sec of impounding. This was followed by gradual recovery of a typical depressed and irregular spontaneous respiration (top record of Fig. 2). However, respiratory deterioration appeared in 2½ min, and a respirator was required. With respiratory support the monkey recovered from acute respiratory paralysis, and 30 min later the minute respiratory volume reached 34% of the precrush level, together with 60% recovery of the respiratory rate. The monkey maintained its own respiration without assistance for another 20 min, although arterial pCO₂, pO₂, and pH indicated a state of hypoxia (Fig. 5). Forty minutes later respiration began to deteriorate, and the concomitant cardiovascular changes such as a temporary hypertension progressing to.
hypotension with arrhythmia became apparent. It was necessary to apply the respirator again (middle record of Fig. 2). At this time, marked cord swelling and sluggish blood flow were observed on the dorsal cord surface within the impounded area. This late-appearing respiratory deterioration was typical of the animals categorized by delayed respiratory paralysis. Durotomy was performed over the three involved segments 60 min later. Marked improvement in respiratory function occurred almost immediately (lower record of Fig. 2). The minute respiratory volume returned to 47% of the precrush level and was accompanied by a 68% recovery in the rate of respiration. This animal showed a good immediate recovery pattern but died during the first night 12 hrs postoperatively.

A similar respiratory pattern was observed in Monkey 21, in which durotomy was also performed at 60 min after impounding. However, this animal required respiratory support for 80 min, when respiratory function approached normal, and it survived for 84 days (Fig. 4). A second animal (Monkey 32) had a prolonged poor recovery with a long apneic period (4 min). Although following durotomy minute respiratory volume and rate improved markedly, the animal failed to survive after the 5-hr respiratory assistance period prescribed in the methodology. This was the course of events that followed durotomy in all subjects impounded with forces of 4000 gcf or above, except for Monkey 28, which will be described later.

Figure 5 shows sequential changes of arterial pCO$_2$, pO$_2$, and pH following 3000-gcf and 5000-gcf crushes. Respiratory distress mentioned previously was reflected by the hypoxic state with resulting acidosis; improvement followed durotomy as in the animals damaged with 3000 gcf or less. Even though improvement of respiratory volumes and rates was noted in some animals impounded with 4000 gcf or more, the pCO$_2$, pO$_2$, and pH failed to improve as illustrated in Monkeys 20 and 24, which died.
Respiratory function in cervical cord injury

Figure 2. Monkey 33. Pneumotachogram, blood pressure, and ECG traces showing acute and delayed respiratory failure following a 3000-gcf impact lesion on C-4 (double arrows). Top trace shows immediate respiratory arrest with characteristic cardiovascular changes; middle trace shows delayed respiratory deterioration requiring a respirator at 45 min post crush; bottom trace shows improved respiration after durotomy 180 min post crush.

Figure 6 is a photomicrograph presenting the most severely damaged spinal cord segment at the C-4 level (Monkey 28). This monkey survived, with meticulous post-damage care. There was extensive destruction and atrophy involving almost the entire segment but sparing of small portions of the white matter including parts of the anterolateral columns. This monkey showed apnea lasting 6 min following a 4000-gcf crush. Immediate respiratory assistance and durotomy performed at 120 min post-impounding improved respiratory function; spontaneous respiration returned 3 hrs following durotomy, and thereafter approached precrush levels. After 56 days of survival, the respiration remained paradoxical and there were spastic signs; this state was accompanied by severe quadriplegia.

Discussion

The efferent respiratory pathway descends ipsilaterally in the anterolateral quadrant of the spinal cord to the C-4 level, innervating the motor neurons of the principal respiratory muscles in the dog, cat, and the human.

Figure 3. Monkey 25. Photomicrograph of a section of the C-4 segment. Note scattered hemorrhages of the central gray matter and adjacent white matter. Weigert staining, X 11.
Bilateral transection of this tract causes cessation of respiration. It is of interest that Monkeys 21 and 33 both reflected the same pattern of early recovery, but Monkey 33 died during the first night, approximately 12 hrs following trauma to the spinal cord. Respiratory death during sleep following high cervical cordotomy has been reported, and depressed activity of the reticular formation following anterolateral cordotomy has also been postulated as a possible cause of respiratory failure leading to death.

When the cervical cord of the rhesus monkey was damaged by the direct impact at the C-4 segment, two types of respiratory paralysis, acute and delayed, resulted. Apnea occurred immediately after cervical cord crush in all the animals regardless of weight applied. This acute respiratory paralysis was transitory in minimal injuries even when hemorrhage-induced necrosis of the central gray matter and adjacent white matter was observed. Respiration recovered spontaneously but was spastic for some time. On the other hand, in more extensively damaged cords there was either a prolonged apneic period or ineffective shallow respiration. Mechanical respiratory support was necessary until spontaneous respiration recovered to the optimal level. If this procedure was neglected a respiratory crisis occurred and was followed by death. Destructive changes found in the bilateral anterolateral columns as well as the cells of origin contributing to the phrenic nerve were postulated as possible causes of respiratory paralysis. Actually lesions of this sort were documented in the most heavily damaged cords that showed almost complete transection, but not in animals surviving more than 12 hours. It is interesting to note that respiratory support was required even in monkeys with severe damage but of a sort that spared the structures essential for maintaining respiration. Therefore, we suggest that acute respiratory paralysis occurring soon after injury does not necessarily result in serious damage to the respiratory pathway.
Respiratory function in cervical cord injury

FIG. 5. Graph showing sequential changes of arterial pCO₂, pO₂, and pH following 3000-gcf (solid line) and 5000-gcf (dotted line) impounding (double arrows) and durotomy (single arrow) in five monkeys. Note improvement in hypoxic state following durotomy after 3000 gcf but not after 5000 gcf.

and that recovery can be expected if a respirator is applied immediately. This observation emphasizes the importance of mechanical respiratory support in acute respiratory paralysis since, in the minimally damaged cervical cord, death can ensue due to acute hypoxia, as typically seen in Monkey

25. Furthermore, early respiratory support may prevent the development of cord swelling due to acute hypoxia as well as prevent the cord injury from becoming irreversible.

As our animals recovered from the acute apneic period, delayed respiratory paralysis gradually developed. It appeared that either secondary respiratory deterioration or delayed recovery from the acute respiratory paralysis was concomitant with extensive cord swelling to such a degree as to obliterate the subarachnoid space. The depressed tidal volume together with a spastic and sometimes paradoxical respiratory pattern was usually seen in delayed respiratory deterioration, which was also reflected in poor minute respiratory volume and blood gas values, hypoxia, and respiratory acidosis. The developing edema in the white matter and centrifugal pressure from an expanding central lesion may be responsible for this delayed appearance of respiratory deterioration. When cord swelling increased enough to obliterate the subarachnoid space, secondary ischemia added to the extent of damage. Durotomy was beneficial in relieving the delayed effects on respiratory function and, in fact, lessened respiratory difficulties as long as the changes affecting the respiratory pathway remained reversible. It has been reported that part of the anterolateral columns at the level of phrenic nerve outflow must remain intact to insure survival.

FIG. 6. Monkey 28. Photomicrograph of a cord section at the C-4 segment 56 days after 4000-gcf impounding. This animal survived on his own respiration for 3 hrs post crush but suffered severe quadriplegia. Almost the entire C-4 segment is atrophied except for small areas of white matter including one anterolateral column (black-stained areas). Weigert staining, × 8.5.
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