Hypotension, Hypoxia, and Head Injury

Frequency, Duration, and Consequences

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Background: Retrospective studies have suggested an association between systemic hypotension and hypoxia and worsened outcome from traumatic brain injury. Little is known, however, about the frequency and duration of these potentially preventable causes of secondary brain injury.

Hypothesis: Early episodes of hypoxia and hypotension occurring during initial resuscitation will have a significant impact on outcome following traumatic brain injury.

Design: Prospective cohort study.

Setting: Urban level I trauma center.

Patients: Patients with a traumatic brain injury who had a Glasgow Coma Score of 12 or less within the first 24 hours of admission to the hospital and computed tomographic scan results demonstrating intracranial pathologic features. Patients who died in the emergency department were excluded from the study.

Main Outcome Measures: Automated blood pressure and pulse oximetry readings were collected prospectively from the time of arrival through initial resuscitation. The number and duration of hypotensive (systolic blood pressure, ≤90 mm Hg) and hypoxic (oxygen saturation, ≤92%) events were analyzed for their association with mortality and neurological outcome.

Results: One hundred seven patients met the enrollment criteria (median Glasgow Coma Score, 7). Overall mortality was 43%. Twenty-six patients (24%) had hypotension while in the emergency department, with an average of 1.5 episodes per patient (mean duration, 9.1 minutes). Of these 26 patients with hypotension, 17 (65%) died (P = .01). When the number of hypotensive episodes increased from 1 to 2 or more, the odds ratio for death increased from 2.1 to 8.1. Forty-one patients (38%) had hypoxia, with an average of 2.1 episodes per patient (mean duration, 8.7 minutes). Of these 41 patients with hypoxia, 18 (44%) died (P = .68).

Conclusions: Hypotension, but not hypoxia, occurring in the initial phase of resuscitation is significantly (P = .009) associated with increased mortality following brain injury, even when episodes are relatively short. These prospective data reinforce the need for early continuous monitoring and improved treatment of hypotension in brain-injured patients.

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Brain injury is a major cause of death following trauma. The traumatized brain is highly vulnerable to secondary brain injuries, which can be caused by seizures, an elevated temperature, hypoxia, and hypotension. These latter 2 insults may occur immediately after injury, when the brain is most susceptible to ischemia. Retrospective studies from large databases (the Traumatic Coma Data Bank and the National Pediatric Trauma Registry) have suggested that early hypotension following brain injury doubles the mortality. The influence of hypoxia alone on mortality is less dramatic, but has not been intensively studied in a prospective fashion. In addition, little is known about the outcome of patients who have sustained early secondary brain injuries but survived. We undertook this investigation to prospectively study the frequency and duration of secondary brain insults occurring during the early resuscitative phase following severe to moderate head injury. We hypothesized that early episodes of hypoxia and hypotension would have a significant impact on the outcome following traumatic brain injury.
PATIENTS AND METHODS

All adult patients (defined as those aged ≥15 years in this study) who arrived at San Francisco General Hospital, San Francisco, Calif, with moderate to severe head injuries (Glasgow Coma Score [GCS] of ≤12 within the first 24 hours) and computed tomographic scan results demonstrating intracranial pathologic features were considered candidates for enrollment into this prospective study. Immediately on arrival in the emergency department (ED), automated blood pressure and pulse oximetry measurements were collected with bedside monitors (Hewlett-Packard, Palo Alto, Calif) set to cycle at 2-minute intervals. Data were stored automatically for later retrieval. For this study, hypotension was defined as any systolic blood pressure (SBP) of 90 mm Hg or lower and hypoxia as an oxygen saturation of 92% or less. These data were collected throughout resuscitation in the ED. Other data collected included demographic characteristics, mechanism of injury, associated injuries, and operative procedures. Patients who died in the ED were excluded from the study. Patients were treated in accordance with advanced trauma life support guidelines for airway and fluid management. Initial computed tomographic scans were reviewed within 24 hours of admission to the hospital, and patients with evidence of head injury by computed tomographic scan (skull fractures, diffuse axonal injury, or intradural or extradural hemorrhage) were retained in the study. The results of a neurological examination (GCS) were documented daily for 7 days. The Injury Severity Score (ISS) was calculated using the Abbreviated Injury Scale (AIS). At 1 and 3 months postinjury, the Glasgow Outcome Scale (GOS) was obtained through patient and family interviews (Table 1).

Data were analyzed using the Spearman rank correlation for ordered outcomes. A univariate analysis of survival was conducted using the Fisher exact test for categorical data and the Mann-Whitney test for ordered variables. Individual logistic regressions were performed for each predictor and confounding variable.

Sixty-four patients (60%) were admitted to the intensive care unit (ICU) following resuscitation in the ED. The remaining 43 patients (40%) were taken directly to the operating room for surgical management. There was no significant (P = .16) difference in ED length of stay between the 2 groups.

Of the 107 patients, 51 (48%) had 1 or more episodes of either hypoxia or hypotension during resuscitation. Fifteen patients (14%) had both hypotension and hypoxia. Twenty-six patients (24%) had at least 1 episode of hypotension while in the ED. The frequency of hypotensive episodes is shown in Figure 1A. The number of hypotensive episodes ranged from 1 to 3, with a mean ± SD of 1.5 ± 0.7 episodes per patient. The duration of these episodes ranged from 2 to 35 minutes, with a mean ± SD of 9.1 ± 8.4 minutes (Figure 1B). Forty-one patients (38%) had at least 1 episode of hypoxia. The number of episodes of hypoxia ranged from 1 to 10, with a mean ± SD of 2.1 ± 1.7 episodes per patient (Figure 2A). The duration of hypoxic episodes ranged from 1 to 45 minutes, with a mean ± SD duration of 8.7 ± 10.5 minutes (Figure 2B).

Of the 26 patients with hypotension, 17 (65%) died (P = .009). The impact of repeated episodes of hypotension is shown in Figure 3A. Patients with only 1 episode of hypotension had a 53% mortality rate, whereas all patients with 3 episodes of hypotension died. In contrast to hypotension, only 18 (44%) of the 41 patients with hypoxia died (P = .68). Repeated episodes of hypoxia did not increase mortality (P = .86). In this study, patients with 2 episodes of hypoxia had a higher mortality rate than did patients with 3 or more episodes (Figure 3B). The duration of hypoxia had no significant influence on outcome. The mean ± SD duration of hypoxia for those who lived was 3.8 ± 9.3 minutes vs 3.0 ± 5.2 minutes for those who died (P = .36). Of the 72 patients with isolated head injuries, 30 (42%) died. Of the 35 patients who had additional injuries in other body regions, 16 (46%) died. There was no significant difference in mortality between the 2 groups (P = .84). Of the 12 patients with hypotension and an isolated head injury, 8 (67%) died, and of the 14 with hypotension and multiple systems injury, 9 (64%) died. Again, there was no significant difference in mortality between the groups (P = .99). Findings were similar for patients with hypoxia. Of the 31 patients with hypoxia and an isolated head injury, 13

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>(Good outcome)</td>
</tr>
<tr>
<td>4</td>
<td>(Moderately disabled)</td>
</tr>
<tr>
<td>3</td>
<td>(Severely disabled)</td>
</tr>
<tr>
<td>2</td>
<td>(Persistent vegetative state)</td>
</tr>
<tr>
<td>1</td>
<td>(Death)</td>
</tr>
</tbody>
</table>

Table 1. Glasgow Outcome Scale

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died, and of the 10 with hypoxia and multiple systems injury, 5 (50%) died ($P=0.73$).

The overall mortality in this series of patients was 43%. Of the patients who died, 59% did so within 24 hours of admission. A careful analysis of these deaths demonstrated that all were attributable to severe head injury; no patient died from uncontrolled hemorrhage. A univariate analysis of factors predictive of overall mortality is listed in Table 2. Patients with hypotension during resuscitation were 3 times more likely to die compared with those without hypotension. Repeated episodes of hypotension have an additive effect, ie, when the number of episodes increases from 1 to 2 or more, the odds ratio for death increases from 2 to 8. The same effect was not seen with hypoxia. A high ISS, a low initial GCS, and older age were all significantly associated with death after head injury. A multivariate analysis of these factors confirmed the significant ($P<0.05$) independent risk of hypotension, age, ISS, and GCS in severely brain-injured patients (GCS of $\leq 8$). When patients with a moderate head injury (GCS of 9-12) are included, hypotension is no longer an independent risk factor.
Prospective data for the impact of hypotension and hypoxia on neurological outcome at 3 months (modified GOS) are shown in Table 3. These data are presented as mutually exclusive categories using the format used by Chesnut et al1 for the Traumatic Coma Data Bank. Separation of the data into mutually exclusive categories highlights the substantial effect of hypotension on neurological outcome, with 80% of the patients dead at 3 months. The neurological outcome of patients with hypoxia alone was not significantly different (P = .31) different from that of patients with neither hypotension nor hypoxia. In this study, the combination of hypotension and hypoxia did not appear to be additive.

**COMMENT**

A prospective observation of patients with moderate to severe brain injury revealed a significant relationship between the frequency and duration of hypotensive episodes and poor outcome. Although the association between systemic hypotension and worsened outcome from severe brain injury has been reported in retrospective studies,1,3 we have extended these observations to define the frequency and duration of this potentially preventable secondary brain injury.

Injury to the central nervous system is responsible for more deaths and more permanent disabilities, and is more costly than any other type of trauma. Traumatic brain injury may be significantly worsened by secondary events surrounding the injury. It appears that the injured brain is sensitive to secondary ischemic insults, which may be compounded by the relative inability to increase cerebral blood flow in response to hypotension, hypoxemia, and acute anemia.4 Cerebral blood flow is significantly reduced following injury, and ischemic brain damage has been found to be present in up to 90% of head-injured patients at autopsy.5 Although the pathogenesis of ischemic brain damage post-injury is not fully understood, it is found more commonly in patients who have sustained a known clinical episode of hypoxia or hypotension or who have an elevated intracranial pressure. Avoiding ischemia, therefore, may be one of the most powerful means of improving outcome from severe brain injury.

The idea that early insults to the injured brain are associated with a worse outcome is not a new concept. More than 20 years ago, Miller and others5 retrospectively studied 100 patients with serious head injury and found that 44 had arterial hypotension, anemia, hypercapnia, or hypoxia at the time of admission to the ED. Although anemia and hypotension were most common in patients with multisystem injuries, the presence of 1 or both of these insults at the time of admission significantly worsened outcome from brain injury. Hypoxia was found in patients with isolated head injuries and in patients with multiple injuries and was associated with a worse outcome in both groups compared with patients without hypoxia. These researchers postulated that the high prevalence of systemic insults at the time of arrival to the hospital would greatly diminish the effectiveness of aggressive neurosurgical care received after admission.

Chesnut et al3 examined the data from the Traumatic Coma Data Bank to further investigate the role of secondary insults on outcome following severe head injury. Using an SBP of lower than 90 mm Hg to define hypotension and a PaO2 of 60 mm Hg or lower to define hypoxia, data from injury through resuscitation were analyzed for 717 patients with a GCS of 8 or less on admission or within 48 hours of injury. One hundred sixty-one (22%) of these patients were hypoxic at some point between the time of insult through resuscitation, 82 (11%) were hypotensive, and 166 (23%) had evidence of both hypotension and hypoxia. Among the 308 patients with no secondary insult, 54% had a good to moderate recovery and 27% died. Of the 161 patients with hypoxia alone, 33% had a good to moderate recovery and 50% died. The presence of both insults increased the mortality to 57%. Overall, hypotensive events, with or without hypoxia, doubled the mortality and significantly increased the morbidity of severe head injury.

Three additional studies6-8 have confirmed that the presence of shock on admission is associated with increased mortality in patients with head injury. In earlier studies from our own institution, Newfield et al6 found that the presence of shock (SBP of <90 mm Hg) during the first 24 hours increased the mortality from 45% to 83%, when compared with patients with head injury and no shock. Shock was found to correlate better with mortality than coma score or the degree of injury. In an-

<table>
<thead>
<tr>
<th>Insult</th>
<th>No. of Patients</th>
<th>Good or Moderately Disabled</th>
<th>Severely Disabled or in a Persistent Vegetative State</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>51</td>
<td>10 (20)</td>
<td>18 (35)</td>
<td>23 (45)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>24</td>
<td>8 (33)</td>
<td>7 (29)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>10</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Hypoxia and hypotension</td>
<td>14</td>
<td>1 (7)</td>
<td>3 (21)</td>
<td>10 (71)</td>
</tr>
</tbody>
</table>

*Of the 107 patients, 18 were lost to follow-up.
†Data are given as number (percentage) of patients.

Table 2. Univariate Analysis of Factors Associated With Mortality

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio of Death</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>3.39</td>
<td>1.34-8.56</td>
</tr>
<tr>
<td>1 Episode</td>
<td>2.05</td>
<td>0.67-6.23</td>
</tr>
<tr>
<td>≥2 Episodes</td>
<td>8.07</td>
<td>1.63-39.9</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>1.26</td>
<td>0.56-2.83</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.01-1.05</td>
</tr>
<tr>
<td>GCS (ED)</td>
<td>0.77</td>
<td>0.69-0.88</td>
</tr>
<tr>
<td>ISS</td>
<td>1.06</td>
<td>1.02-1.10</td>
</tr>
</tbody>
</table>

*GCS indicates Glasgow Coma Score; ED, emergency department; and ISS, Injury Severity Score.

Table 3. Modified Glasgow Outcome Scale at 3 Months Postdischarge by Secondary Insult (Mutually Exclusive Categories)

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other early study, Jeffreys and Jones\(^7\) also concluded that potentially avoidable factors (ie, hypotension) contribute to death from head injury. In a more recent report, Hill and others\(^8\) carefully examined factors affecting outcome in the resuscitation of 40 severely injured patients in Australia. Eleven of these patients died during the resuscitative phase, and 9 died during the definitive care phase. Hypotension at the scene of injury was found to be significantly correlated with a fatal outcome in both groups of patients. The medianprehospital time was 33 minutes in patients who were hypotensive in the field, and the median ED time was 70 minutes for hypotensive patients. These researchers concluded that survival following severe trauma might be increased by shortening the time from injury to definitive care and by preventing secondary insults in patients with head injury.

The effects of hypotension and hypoxia on outcome following severe head injuries have also been examined in children. In 1981, Mayer and others\(^9\) reported that there were clear differences in outcome between children with an isolated head injury and those with a head injury plus multiple trauma (13% vs 28% mortality and 0% vs 2% in a vegetative state). Children in the multitrauma group had a significantly higher incidence of shock and hypoxia compared with children with isolated head injuries. In a related study, Luerssen et al\(^10\) examined the outcome from head injury in 8814 patients, including 1906 pediatric patients. Although overall children had a dramatically lower mortality rate than adults with a similar injury severity, an SBP of 30 mm Hg less than the expected norm produced a mortality of 33% in children, compared with only 11.8% for adults with this degree of hypotension. Pigula and coauthors,\(^2\) using data from the National Pediatric Trauma Registry, examined the effect of hypoxia (PaO\(_2\) of <60 mm Hg) and/or hypotension (SBP of <90 mm Hg) on the outcome of 509 pediatric patients with a GCS of less than 8. Twenty percent of these children were hypotensive on arrival and had an overall mortality of 61%, compared with 21% among those without hypotension. While hypoxia alone did not significantly increase mortality, children who were both hypotensive and hypoxic on arrival had a mortality of 85%. These researchers suggested that the presence of hypotension following head injury negates the survival advantage normally seen in children compared with adults with similar GCSs. These reports underscore the concept that adequate resuscitation is the single most critical factor for survival following traumatic brain injury in children and in adults.

The previously mentioned studies have concentrated on secondary brain insults occurring during the early resuscitative phase following trauma. Additional research has demonstrated that hypotension and hypoxia are also common in the ICU setting and that these events may also affect outcome. Jones and others\(^11\) described the incidence of secondary insults occurring during the ICU setting in 124 adult patients with head injury. In addition to hypotension and hypoxia, these researchers examined episodes of elevated intracranial pressure, fever, hypertension, bradycardia, and tachycardia. Insults were found in 91% of the patients, although most were of short duration. The most significant predictors of mortality were the duration of hypotension, fever, and hypoxic events. Hypotensive insults were also significantly associated with a poor outcome at 12 months postinjury.

Winchell et al\(^12\) also examined transient hypotensive events occurring in the ICU setting in patients with head injury. Among 157 patients with severe head injury (AIS of >4), a total of 831 episodes of systolic hypotension were observed (55% of the patients). Most of these events were short (<1 hour). The mortality increased from 9% in patients with no ICU hypotensive events to 25% in patients with 1 to 10 events, and up to 37% in those with more than 10 such events. Functional recovery sufficient for discharge to home decreased from 61% in patients without hypotension to 25% in patients with more than 10 events.

Marmarou and others\(^13\) examined data from the Traumatic Coma Data Bank for the impact of intracranial pressure instability in the ICU and hypotension on outcome in patients with severe head trauma. From the total database of 1030 patients, 428 with intracranial pressure monitors and outcome data were selected for inclusion in the study. Using a stepwise logistic regression model, age, admission motor score, and abnormal pupils were each highly significant in explaining outcome. Beyond these factors, however, the proportion of hourly intracranial pressure readings greater than 20 mm Hg and the proportion of hourly SBP readings lower than 80 mm Hg were highly significant in explaining outcome. Chesnut\(^14\) also suggested that episodes of hypotension in the ICU phase of care were common (>25%) and that such episodes appear to be significant predictors of poor outcome independent of their causes and of preresuscitation secondary insults.

On the other end of the spectrum, little is known about the episodes of hypotension and hypoxia that occur before admission to the hospital in patients with cerebral trauma. In the only study of its kind, Carrel and others\(^15\) described the incidence of secondary insults occurring during helicopter transport with an anesthesiologist in attendance. In a group of 51 patients with severe head injury (GCS of ≤8) who were rescued by the medical helicopter, advanced life support protocols were used, including intubation, hyperventilation with a fraction of inspired oxygen of 1, and restoration of the SBP to higher than 95 mm Hg. Nineteen patients were admitted without secondary systemic insults to the brain, and 42% of them had a poor GOS at 3 months. Thirty-two patients had 1 or more recognized secondary insults, and 72% of them had a low GOS at 3 months. From this study, it is apparent that some, but not all, secondary systemic insults to the already injured brain can be avoided by advanced trauma life support at the scene and during transport. However, when they do occur, prehospital secondary systemic insults have a major impact on outcome in patients with severe head injury.

Our study is unique in that it is the only truly prospective study, to our knowledge, specifically designed to describe the frequency and the duration of hypotensive and hypoxic events in the early resuscitative phase following moderate to severe head injury. As has been concluded from previously cited studies,\(^1,3\) we have confirmed that early hypotension has a direct impact on neu-
rological outcome and mortality. Furthermore, similar to the ICU study by Winchell et al,\textsuperscript{12} we have shown that repeated episodes of hypotension in the early phases of resuscitation dramatically worsen outcome from head injury. While it is intuitive that hypotension and hypoxia would be more likely to occur in patients with associated injuries, we found that there was no difference in the frequency of these events and outcome between those with an isolated head injury and those with multiple injuries. One possible explanation is that episodes of hypotension and hypoxia in patients with an isolated head injury may be neurogenic in nature, as suggested by Chesnut et al.\textsuperscript{16}

The association of hypoxia with mortality in our study was not significant. This is similar to the finding from Pigula et al,\textsuperscript{3} but different from the retrospective analysis by Chesnut et al.\textsuperscript{1} There are several reasons that may account for these differences. First, in our study, hypoxia was measured with pulse oximetry and was not validated with arterial blood gas analysis. Thus, it is possible that episodes of hypoxia were not detected or were artifactual. Our data showing increased frequency of hypoxia in patients with good outcomes would support the latter hypothesis. Second, the study populations were different. Our patients, whose median age was 42 years, were older than those from the Traumatic Coma Data Bank (median age, 25 years) and our average admission GCS was higher (7 vs 3). The effects of the inclusion of patients with a moderate head injury are seen in the results of the multivariate analysis, in which hypotension was an independent predictor of outcome only in patients with a GCS of 8 or less. Further investigation into the effects of hypotension and hypoxia on patients with a moderate head injury is warranted since the physiological effects of these secondary insults may be different in this population. While we were able to demonstrate a significant association between hypotension and GOS, the outcome at 3 months was admittedly influenced by deaths that occurred in the early stages of trauma management. It is likely that improved measures of neurological outcome will be required to fully assess the impact of these secondary brain injuries, particularly in patients with mild and moderate head injuries.

We have prospectively documented the frequency and duration of hypotensive and hypoxic events during the early phase of trauma care after brain injury. The association between hypotension and death is strong, and repeated insults are additive in their negative impact on mortality. Our data demonstrate that, even in a level I trauma center, the influence of hypotension on outcome from head injury is not fully appreciated. While only injury prevention measures can decrease the absolute number of brain injuries, measures to improve the detection and prevention of hypotension have the potential to decrease the number of deaths resulting from secondary brain injury.

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**REFERENCES**