Balancing the Potential Risks and Benefits of Out-of-Hospital Intubation in Traumatic Brain Injury: The Intubation/Hyperventilation Effect

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INTRODUCTION

The early management of patients with severe traumatic brain injury presents a challenge for both out-of-hospital and emergency department (ED) providers. Every year, more than 1.4 million patients are evaluated in US EDs for traumatic brain injury; 235,000 of these patients require hospitalization and 50,000 die.[1] The lifetime cost of traumatic brain injury sustained in 2000 alone was estimated to be more than $60 billion,[2,3] with more than 2% of the US population requiring long-term assistance with activities of daily living as a result of traumatic brain injury.[4] Although only a fraction of these patients require out-of-hospital intubation, the potential influence of this intervention remains high because the intubated subgroup is generally a severely injured cohort. However, controversy now surrounds this issue.[5]

Patient outcomes after traumatic brain injury may be affected by early care,[6,7] likely because outcomes are not determined solely by the severity of the initial insult, or primary brain injury. Additional secondary injury to the central nervous system may occur and increase disability or result in death. This potentially preventable or reversible damage may become indelible despite subsequent optimal management.[8-17]

In early traumatic brain injury care, intubation may be associated with worsened secondary injury. Some reports have implicated out-of-hospital intubation as a factor associated with negative outcomes.[5,15-20] Other investigations have demonstrated no difference or improved outcomes with field intubation.[13,14,17,21-23] These conflicting observations are the source of debate, complicated by growing evidence that postintubation hyperventilation is common and a cause of secondary brain injury. Even short periods of hyperventilation may result in increased morbidity and mortality.[8,13,22,24-33]

We review the potential risks and benefits of early intubation, with special emphasis on postintubation hyperventilation and secondary brain injury.

PHYSIOLOGY OF SECONDARY BRAIN INJURY

Secondary damage occurs after traumatic brain injury when perfusion of tissue susceptible to further damage is decreased or oxygen delivery to the brain is compromised. Secondary injury may be preventable or reversible and is a target for therapeutic interventions. Hypotension and hypoxemia are causes of secondary central nervous system damage.[5,9-15,17,30,34-49] Measures to ameliorate these factors can improve cerebral perfusion and oxygenation in the injured brain, enhancing outcomes in some settings.[50,51]

Although hypotension and hypoxemia are detrimental, they do not account for all of the observed differences in outcomes.[30,42] There is evidence that inadvertent hyperventilation has widespread detrimental cellular, local, cerebrovascular, cardiovascular, and pulmonary effects; it can cause secondary damage.[8,13,22,24-32] These hyperventilation-induced factors may overwhelm any benefit provided by placement of an advanced airway. Here we will give a brief description of the most salient local and systemic effects associated with hyperventilation and summarize them in the Figure.

The effects of hyperventilation occur at both the neuronal and cerebrovascular levels. Hyperventilation decreases the arterial $PaCO_2$, leading to central nervous system vasoconstriction, lower cerebral blood flow, and secondary neurologic tissue injury.[8,24,27-29,52-54] At the neuronal level, hypocarbia causes numerous detrimental effects. When $PaCO_2$ is decreased, an influx of calcium into cells occurs, resulting in neuronal depolarization, release of glutamate, and initiation of apoptosis.[8,24] Hypocarbia-induced pH changes cause increased cell membrane permeability and protein shifts that can lead to loss of membrane potential and mitochondrial rupture. This cascade of events can create free radicals and irreversible cellular damage.[24,55,56] Finally, increased pH leads to a left shift of the

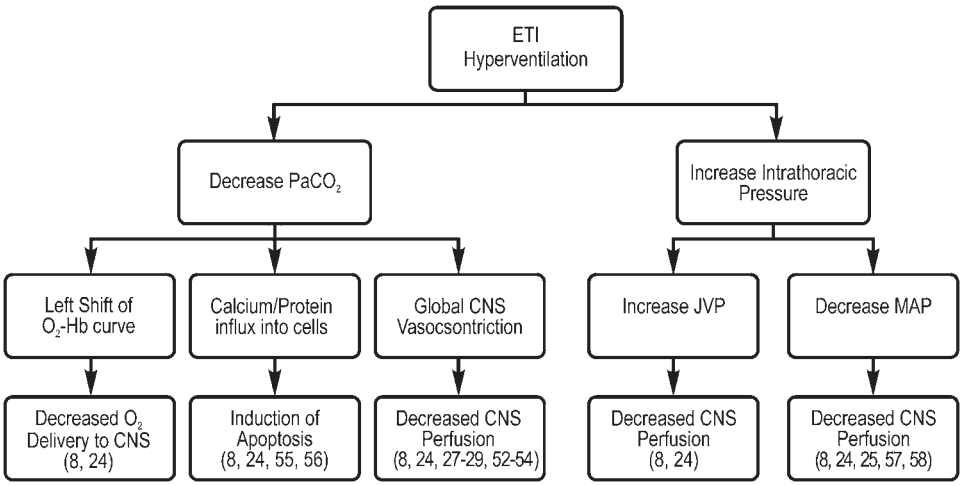

Figure. Mechanisms of secondary injury induced during hyperventilation. *ETI,* Intubation; O_2, oxygen; *Hb,* hemoglobin; *CNS,* central nervous system; *JVP,* jugular venous pressure.

oxygen-hemoglobin disassociation curve, resulting in further tissue hypoxia.[8,24]

The systemic effects of hyperventilation may also cause secondary damage. Controlled hyperventilation can decrease intracranial pressure in patients with elevations and improve cerebral perfusion pressure or dampen the risk of herniation. This intervention attempts to manipulate the relationship between cerebral perfusion pressure, mean arterial pressure (MAP), intracranial pressure, and jugular venous pressure illustrated in the equation cerebral perfusion pressure=MAP–intracranial pressure (or jugular venous pressure if jugular venous pressure is greater than intracranial pressure). Use of hyperventilation to improve cerebral perfusion pressure assumes that MAP will stay constant during hyperventilation. However, this is not universally true. When an advanced airway is placed and hyperventilation occurs, intrathoracic pressure increases. This decreases venous return to the heart, increases jugular venous pressure, and may decrease cerebral perfusion pressure.[8,24]

Decreased venous return can also reduce cardiac preload, cardiac output, and MAP.[8,24,25,57,58] In models, intracranial pressure decreases during periods of hyperventilation, along with MAP. Thus, there is no net improvement in cerebral perfusion pressure, and it may even decrease.[8,57] This effect is even more pronounced when MAP is altered because of hemorrhagic shock. In this case, hyperventilation results in even greater decreases in MAP and cerebral perfusion pressure.[8,25,58]

HISTORY OF HYPERVENTILATION AS PART OF TRAUMATIC BRAIN INJURY MANAGEMENT

Historically, hyperventilation has been used to treat increased intracranial pressure occurring after traumatic brain injury. The rationale was based on the initial observations by Johnston et al[59] in the early 1970s showing that patients with intracranial pressure less than 20 mm Hg had a neurologically intact survival rate of 56% compared with only 8% for those with intracranial pressure greater than 40 mm Hg. Because hyperventilation was known to be effective at reducing intracranial pressure, it was thought that this would lead to improved cerebral perfusion pressure.[59] Thus, hyperventilation became the preferred nonsurgical method to reduce intracranial pressure. Despite the absence of data linking this treatment to improved outcomes,[60] hyperventilation was used for years in both the out-of-hospital and inhospital settings to treat or to prevent increased intracranial pressure.

In the early 1990s, several studies led to a critical reevaluation of "therapeutic hyperventilation." Muizelaar et al[60] randomized patients with severe traumatic brain injury to normoventilation ($PaCO_2$=35 mm Hg) versus hyperventilation ($PaCO_2$=25 mm Hg) in the ICU, measuring outcomes at 3, 6, and 9 months after injury. Those patients with initial Glasgow Coma Scale motor score of 4 to 5 who underwent prophylactic hyperventilation were less likely to have good neurologic outcomes than those patients receiving normal ventilation (18% versus 48% and 24% versus 57%; $P<.05$) at 3 and 6 months after their initial injury, respectively. Subsequent research demonstrated that short periods of hypocarbia (intentional or inadvertent) led to decreased cerebral blood flow.[61,62]

In 1995, the first evidence-based guidelines for the management of severe traumatic brain injury recommended against prophylactic hyperventilation.[63] The guidelines emphasized the importance of secondary injury, stating that some areas of the brain are at risk of conversion from "borderline cerebral ischemia. . .into frank ischemia with ensuing neuronal death."[61] The guidelines recommended a shift from therapeutic hyperventilation as a means to reduce intracranial pressure to a focus on cerebral perfusion and maintaining tissue oxygenation at the cellular level.[6]

EFFECT OF EARLY INTUBATION ON OUTCOMES IN SEVERE TRAUMATIC BRAIN INJURY

Recently, the use of intubation in the out-of-hospital and early inhospital management of traumatic brain injury has generated debate. Proponents cite the early intubation potential benefits (treatment of hypoxemia, prevention of aspiration, facilitation of diagnostic evaluation, etc),[13,14,21-23,41] although opponents emphasized the potential risks (low success rates, increased out-of-hospital intervals, complications such as hypoxia, etc) associated with worse outcomes.[23,30,31,41-45,64]

In one prospective observational study, 209 patients underwent intubation in the out-of-hospital setting without any attempt to specifically regulate ventilation and were compared with historical controls. The cohort undergoing intubation had a 33% mortality rate compared with only 24% among patients managed without intubation. Although several factors were associated with increased mortality, hyperventilation and hypocarbia were among the most significant.[30] A follow-up analysis of the same population demonstrated an unadjusted odds ratio for death of 1.8 (95% confidence interval 1.1 to 3.0) if the $PaCO_2$ on arrival was less than or equal to 30 mm Hg.[31] When patients in the original study were stratified according to $PaCO_2$ at ED arrival, patients with $PaCO_2$ less than 33 mm Hg had a mortality of 39% compared with only 26% for those with a level of 33 mm Hg or greater.[30] The initial study and the series of published reanalyses all seemed to point to hyperventilation, rather than intubation per se, as a potential cause of the observed increase in mortality.[5,30-32,40]

EFFECT OF OUT-OF-HOSPITAL HYPERVENTILATION ON SEVERE TRAUMATIC BRAIN INJURY

Inadvertent hyperventilation occurs frequently in both the out-of-hospital and inhospital settings. One study reported that 59% of patients had at least 1 end-tidal CO_2 ($ETCO_2$) value of less than 25 mm Hg after intubation,[40] and others observed that some degree of hyperventilation is common after intubation.[8,22,30,36,38,40,65-68] Warner et al[22] reported that patients who were hypocarbic on ED arrival had increased mortality, from 16% to 35%. This effect is not isolated to out-of-hospital intubation. Denninghoff et al[42] reported that patients with severe traumatic brain injury who were hyperventilated during the out-of-hospital or early inhospital treatment period had a severity-adjusted mortality increase of nearly 6-fold.[42]

Two subsequent studies have evaluated the effects of strict control of ventilation after out-of-hospital intubation. Poste et al[32] compared 2 cohorts: (1) patients transported by air medical emergency medical services (EMS) who underwent intubation followed by strictly controlled ventilation with mechanical (as opposed to manual) ventilation and continuous ($ETCO_2$) measurement; and (2) patients undergoing intubation who were subsequently transported by ground EMS providers who did not have ventilators or the ability to monitor $ETCO_2$. The intubated air-transported group had a mortality of 28%, whereas the nonintubated air-transported cohort had a mortality rate of 31% ($P=.62$). However, the effect was opposite in ground-transported patients: intubation patients transported by ground had a mortality rate of 33% compared with 21% for ground patients without intubation ($P=.001$). In other words, intubation was associated with an increased severity-adjusted mortality among patients who did not have strictly controlled ventilation.[32] The hypothesis that out-of-hospital intubation with strictly controlled postintubation ventilation may improve outcomes was examined in prospective randomized trials by Bernard et al[13] and Bernard.[69] In these studies, $ETCO_2$ monitoring to carefully control postintubation ventilation with special emphasis on the prevention of hyperventilation showed an increase in favorable neurologic outcomes compared with nonintubation controls, with 51% versus 39% having favorable outcomes. Failure to intubate in the out-of-hospital setting led to an odds ratio for poor neurologic outcome of 1.28 (95% confidence interval 1.00 to 1.64). The intubation success rate in this study was 97%, high for this setting. In systems with lower intubation success rates, the survival advantage observed in the intubated group may be compromised by negative outcomes occurring in the unsuccessful intubation cohort.

There is a strong possibility that the negative effects of intubation that have been identified in several clinical trials may be due to a paradox: intubation may protect the airway and prevent hypoxia, but it also makes it easier to inadvertently hyperventilate. Consequently, although intubation is intended to reduce secondary brain injury, it may enhance it if specific, intentional measures are not taken to ensure proper postintubation ventilation.

THE INTERSECTION OF INTUBATION AND HYPERVENTILATION—CLINICAL IMPLICATIONS

Much of the literature about airway management of the patient with traumatic brain injury in the out-of-hospital and ED settings focused on the intubation procedure and has underestimated or ignored the negative effect of subsequent hyperventilation. We believe that the issue is much more complex than simply asking whether intubation is good or bad for severe traumatic brain injury.

Optimally, the care of patients after intubation should include continuous $ETCO_2$ monitoring.[66] This is highlighted in the current out-of-hospital traumatic brain injury guidelines, which recommend that $ETCO_2$ be maintained between 35 and 40 mm Hg and that hyperventilation be avoided.[9,70] This approach assumes that the EMS system provides appropriate intubation proficiency. The latter requires active medical direction that emphasizes intubation skills and has a quality improvement program that focuses on proper postintubation ventilation, with particular attention to preventing hyperventilation.

SUMMARY

When properly performed, intubation is effective for airway protection and ensures adequate oxygenation; it also makes hyperventilation (and associated negative outcomes) easier and more likely.[10,60,62,71,72] Optimal outcomes require choosing the right patients, achieving the highest success rates through training, and avoiding hyperventilation after intubation in patients with traumatic brain injury.

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