Invited Review

The Simple Model Versus the Super Model: Translating Experimental Traumatic Brain Injury Research to the Bedside

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ABSTRACT

Despite considerable investigation in rodent models of traumatic brain injury (TBI), no novel therapy has been successfully translated from bench to bedside. Although well-described limitations of clinical trials may account for these failures, several modeling factors may also contribute to the lack of therapeutic translation from the laboratory to the clinic. Specifically, models of TBI may omit one or more critical, clinically relevant pathophysiologic features. In this invited review article, the impact of the limited incorporation of several important clinical pathophysiologic factors in TBI, namely secondary insults (i.e., hypotension and/or hypoxemia), coma, and aspects of standard neurointensive care monitoring and management strategies (i.e., intracranial pressure [ICP] monitoring and ICP-directed therapies, sedation, mechanical ventilation, and cardiovascular support) are discussed. Comparative studies in rodent and large animal models of TBI (which may, in some cases, represent super models) are also presented. We conclude that therapeutic breakthroughs will likely require a multidisciplinary approach, involving investigation in a range of models, including clinically relevant modifications of established animal models, along with development and application of new innovations in clinical trial design.

Key words: brainstem; coma; controlled cortical impact; dog; fluid percussion; head injury; ICP; impact acceleration; pig; primate

INTRODUCTION

Despite years of promising, carefully conducted research in experimental traumatic brain injury (TBI), no specific therapy has been proven efficacious in the treatment of patients. Current standard of care for severe TBI consists solely of supportive measures. Laboratory studies have yet to produce a clinical therapeutic breakthrough. In fact, current standard of care in severe TBI (i.e., mechanical ventilation, sedation, hemodynamic support, and control of intracranial hypertension) is based largely on clinical experiences, not on extensive testing in experimental models.

There are several possible explanations for the failed translation of laboratory investigation to clinical TBI, including some well-described limitations of clinical trials...
(Bullock et al., 1999; Doppenberg and Bullock, 1997; Maas et al., 1999). One important cause may be differences between experimental models and clinical TBI scenarios. Incorporation of additional clinically relevant TBI pathophysiology into animal models may be necessary to successfully transfer therapeutic modalities from bench to bedside. Several key questions can be raised. Are we modeling TBI accurately? Which clinically relevant factors are we failing to model? Should our current experimental models be changed, embellished, or developed into supermodels of experimental TBI? (These questions were addressed at the 18th Annual National Neurotrauma Society Symposium in November of 2000 in a lecture given by Dr. Kochanek. This review represents a synopsis of that lecture and is not intended to be a comprehensive review of all experimental models of TBI.)

Rodent models of focal injuries, such as controlled cortical impact (CCI) and fluid percussion injury (FPI), are the most commonly used experimental models in TBI. Experimental investigation in these well-established models has elucidated many mechanistic features of TBI. Although they were not intended to model clinical TBI exactly, results of the investigations in these focal contusion models are commonly generalized to diverse clinical situations. While both models reliably reproduce many individual features of TBI, neither adequately represents the complex pathophysiologic heterogeneity of clinical TBI (Povlishock et al., 1994). For example, CCI, as it is most commonly applied in male adult rats, with impact centered on the lateral aspect of the parietal cortex (Dixon et al., 1991), may realistically model the 31-year-old male construction worker struck in the head by a brick, but it fails to recreate many common clinical scenarios. Some of the clinical scenarios of TBI that are not modeled include the following: (1) a 21-year-old female pedestrian struck by a motor vehicle with multiple trauma including frontal contusion, apnea, and hemorrhagic shock from a lacerated liver; (2) a 68-year-old male unrestrained passenger in a high-speed collision with diffuse axonal injury (DAI) and sustained coma, but no intracranial hypertension; (3) a 19-year-old female in a cycling accident with a rapidly expanding epidural hematoma who presents with signs and symptoms of impending uncinate herniation; (4) an 8-year-old male kicked in the occiput by a horse who presents with a brainstem contusion and rapid development of neurogenic pulmonary edema requiring high-dose dopamine and nor epinephrine; and (5) a 2-month-old male victim of shaken baby syndrome.

These scenarios highlight several important, clinically relevant factors that are generally not incorporated into experimental models of TBI: multiple trauma, secondary insults, age, gender, genetic predisposition, frontal lobe injury, alcohol consumption, intracranial hemorrhage, and surgical intervention. Many additional factors are considered in patients with TBI as well, including fever, seizures, fluid resuscitation strategies, electrolyte disturbances, and blood transfusion thresholds. This review will focus on three of the most clinically relevant, but often neglected factors: secondary insults, coma, and application of neurointensive care monitoring and management strategies (Fig. 1).

Secondary Insults

Hypotension and/or hypoxemia occur in approximately one-third of patients with severe TBI (Chestnut et al., 1993). Hypotension is one of the principal predictors of poor outcome after TBI (Chestnut et al., 2000; Pigula et al., 1993). A single episode of hypotension (systolic blood pressure of < 90 mm Hg) has been associated with a 150% increase in mortality rate (Chestnut et al., 1993). Similarly, isolated hypoxemia has also been associated with poor outcome after clinical TBI, but appears to be a much less powerful predictor than either isolated hypotension or combined hypotension plus hypoxia (Chestnut et al., 1993).

Despite the frequency of secondary insults in patients with TBI, they are rarely incorporated into rodent models of TBI. A review of the in vivo animal model studies of TBI published in the Journal of Neurotrauma over the past 5 years (1996–2000) reveals 168 reports, only 7% of which have included a secondary insult (Fig. 2). Most likely related to technical ease, secondary hypoxemia, rather than hypotension, has most commonly been incorporated into rodent models of TBI. Nevertheless, in rats, posttraumatic hypoxemia has been reported to worsen motor and cognitive deficits, prolong glutamate efflux, and augment neuronal death (Bauman et al., 2000; Bramlett et al., 1999; Clark et al., 1997; Ishige et al., 1987a,b,c; Matsushita et al., 2000).

Posttraumatic hypotension has been incorporated into a few rodent models, but usually in combination with or as a result of hypoxemia. Ishige et al. (1988) showed that hypotension after TBI causes both pronounced depletion of high-energy phosphates and more intracellular acidosis than TBI alone, suggesting that neuronal injury is potentiated by posttraumatic hypotension. This may be related, in part, to impaired posttraumatic vasodilatory capacity (Lewelt et al., 1982). Similarly, Ito et al. (1996) demonstrated that intracranial hypertension, cerebral edema, and neuronal death were exacerbated by hypotension and hypoxemia after TBI (produced by impact-acceleration in rats; Fig. 3). Indeed, in the impact-acceleration model that was used, intracranial hypertension and neuronal death were largely absent without the sec-
ondary insult. Yamamoto et al. (1999) also used the impact-acceleration model in rats and found that combined hypotension and hypoxemia after TBI markedly increased neuronal injury versus TBI alone.

The effects of isolated hypotension after TBI have been addressed more commonly in large animal models (pigs and cats) than in rodents. However, the majority of these studies have evaluated the effects of various fluid resuscitation strategies on systemic and intracranial physiology and mortality rate (Bourguignon et al., 1998; Dewitt et al., 1996; Glass et al., 1999; Remming et al., 1994; Shackford 1997; Stern et al., 2000; Zhuang et al., 1995). These studies have included intracranial pressure (ICP) monitoring, assessment of cerebral blood flow (CBF) and oxygen delivery, and/or evaluation of cerebral contusion volume; however, TBI with and without the secondary insult are generally not compared. Thus, these models have neither specifically addressed the mechanisms of neuronal damage exacerbated by secondary insults nor tested the effects of novel therapies. Still, defining the optimal approach to fluid resuscitation in the TBI victim with hypotension does have merit. In a model of hemorrhagic shock after cryogenic cerebral injury in pigs, Alspaugh et al. (1999) compared restoration of mean arterial pressure (MAP) by either fluid resuscitation or treatment with the vasopressor phenylephrine. Although both treatments produced similar increases in MAP and cerebral perfusion pressure (CPP—defined as MAP minus ICP), fluid resuscitation, rather than phenylephrine, trended toward earlier restoration of CBF and smaller cerebral contusion size.

Further studies of TBI with secondary insults are needed in both rodent and large animal models. Additional investigation will certainly reveal that restoration of MAP alone will neither reverse the cascade of secondary neuronal injury invoked by hypotension nor result in complete salvage of vulnerable neurons. Even with optimal restoration of hemodynamic disturbances and/or hypoxemia, important mechanisms involved in the evolution of secondary damage in the injured brain must be untangled and therapeutically addressed (Kochanek et al., 2000). Encouragingly, the incorporation of secondary insults into experimental models of TBI is increasing, as reflected by an analysis of studies published in the Journal of Neurotrauma (Fig. 2). However, further incorporation of isolated hypotension after TBI is needed, particularly in the rodent models where considerable inroads into defining key cellular and molecular mechanisms of neuronal injury have already been made, and genetic modification (i.e., transgenic, knockout strains) is readily available.

**Posttraumatic Coma**

In patients with severe TBI, coma is a virtually universal finding, often sustained, and an important prognosticator for morbidity and mortality (Chestnut et al., 2000; Gennarelli, 1983). For example, an initial Glasgow Coma Scale (GCS) score of 3 predicts only a 20% chance of survival and a 10% chance of a good functional outcome (Chestnut et al., 2000). Posttraumatic coma in the

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**FIG. 1.** Factors that contribute to both the evolution of secondary damage and outcome after clinical TBI, but are generally not incorporated into contemporary rodent models of TBI. Secondary insults, coma, and neurointensive care (highlighted by the shaded circles) are the focus of this review.

**FIG. 2.** Graph depicting the percent of studies of experimental TBI incorporating use of a secondary insult that were published in the Journal of Neurotrauma between 1996 and 2000. Although secondary insults such as hypotension and/or hypoxemia occur in over one-third of patients with severe TBI, they were incorporated into less than 5% of laboratory studies up until 1999. The trend toward increasing use of secondary insults in experimental TBI is reflected in the data from 1999 and 2000.
FIG. 3. Graph demonstrating marked exacerbation of intracranial pressure (ICP) by secondary hypotension and hypoxemia after experimental TBI in rats produced by impact acceleration. HH, hypotension and hypoxia; THH, trauma coupled with hypotension and hypoxia. (From Ito et al., 1996, with permission.)

Clinical setting may result from a variety of causes, including brainstem compression, DAI, cerebral ischemia, metabolic disturbances, and/or a constellation of lesions.

A common clinical etiology of coma is mass effect from acute hemorrhage with brainstem compression and impending herniation (Gennarelli, 1983). Approximately 50% of patients presenting with coma after severe TBI, however, do not have any evidence of hemorrhage or mass effect (Gennarelli et al., 1982a). In these patients, coma is frequently attributed to DAI in the cerebral hemispheres and/or brainstem (Gennarelli, 1983). DAI is caused by angular acceleration injury, such as occurs in motor vehicle accidents. Severe DAI, although poorly understood, carries a 65% mortality rate (Gennarelli, 1983).

Modeling coma in experimental TBI has proven extremely difficult. Gennarelli et al. (1982b) were the first to successfully model posttraumatic coma, using a nonimpact angular acceleration model in primates. Concussive injury (coma of less than 15 min) was produced by acceleration in the sagittal plane; however, none of the animals had either sustained coma or DAI. In contrast, coma lasting longer than 6 h was produced in 50% of animals subjected to lateral acceleration (in the coronal plane). DAI was produced in all of these animals, and the severity of DAI was directly proportional to the duration of coma. The degree of DAI, and thus the length of coma, could be altered by adjusting the rate and duration of lateral acceleration (Fig. 4). The average duration of coma was 2.5 days, and 84% of the surviving animals experienced severe functional disability. A similar angular acceleration model of TBI in pigs was initially shown to produce considerable DAI without coma (Smith et al., 1997). However, in a subsequent report (Smith et al., 2000), modification of the model to produce angular rotation in the axial plane produced both brainstem DAI and coma. The duration of coma ranged from 3.5 to 8 h, and correlated with the severity of DAI in the brainstem. These findings suggest that, although DAI has been strongly associated with coma, DAI alone is insufficient to produce coma. The location of the axonal injury (brainstem and midline structures) appears critical.

Several valiant but unsuccessful efforts have been made to model sustained traumatic coma in rats. Although experimental modeling of coma in larger animals has been achieved in association with DAI, the rodent impact acceleration model of TBI reliably produces DAI, but not coma (Foda et al., 1994; Marmarou et al., 1994). Similarly, combined CCI and bilateral craniotomy produces DAI without coma (Meaney et al., 1994). Xiaosheg et al. (2000) recently described an angular acceleration injury model for the rat that produces subarachnoid hemorrhage, intracerebral hemorrhages, and histologi-
cally confirmed brainstem DAI. Once again, however, coma was not produced, and rats exhibited only modest deficits, characterized by posttraumatic behavior suppression for 11–15 min, and disoriented and slow appearance for 2–3 days after injury. The difficulty producing severe DAI with coma in rats may be related to differences in brain structure between rodents and larger animals. Rats are lissencephalic, have smaller brain mass, and lack the cortical gyri seen in larger gyrencephalic animals (Gennarelli, 1982b). These structural features may provide protection from acceleration and sheering injury due to rotational insults, limiting both the severity of DAI and the mechanical induction of coma in rodent models of TBI.

Successful production of prolonged stupor/coma, lasting 12–24 h, has been achieved in the rat using an asphyxial model of cardiac arrest (Katz et al., 1995). Incorporation of asphyxia (hypoxemia with hypercarbia) into the current rodent models of TBI may be necessary to successfully produce sustained coma. Although this approach may not accurately model DAI-induced coma in the rat, impact apnea with hypoxia and hypercarbia is common after TBI in humans and may contribute to the development of coma in some patients. Remarkably, despite the common occurrence of impact apnea with hypoxia and hypercarbia in humans, to our knowledge controlled asphyxial insults have rarely been superimposed as a secondary insult in experimental TBI. Although not a true asphyxial insult, Glass et al. (2001) recently incorporated acute hypercarbia in a porcine model of FPI. Surprisingly, acute hypercarbia reduced the incidence of focal parenchymal hemorrhage, albeit in a small number of animals.

Coma has also been produced in large animal models by mass effect with brainstem compression. Pomeranz et al. (1993) developed a model of epidural cerebral compression that produced marked intracranial hypertension with brainstem compression, systemic hypotension, and coma in dogs. Mass lesions, however, have not been found to produce coma in rodent models. This may be due to many factors, including, in part, functional decompression via an open craniotomy site or from skull fracture after TBI. Alternatively, neuronal injury from mass effect in rodents may be so severe that it is lethal without the mechanical ventilatory support, ICP monitoring, hemodynamic support, and ICP-directed therapies that are commonly applied in large animal models.

Although mechanical insults, such as brain stem compression and DAI are common after TBI, the etiology of posttraumatic coma may be multifactorial. Transient unconsciousness has been modeled in large animals even without mechanical injury. Hayes et al. (1984) induced unconsciousness in the absence of mechanical damage by isolated activation of cholinergic pontine sites in cats. Structural injury alone may thus not fully explain posttraumatic coma.

Coma is an important, clinically relevant, poorly understood, and difficult to model sequela of TBI. It is an aspect of clinical TBI that has not yet been produced in rodent models; thus, large animal models may be required. The heterogeneous results produced in the different animal models of posttraumatic coma suggest fundamental differences between species. Large animal models, such as those developed by Gennarelli et al. (1982a,b), and more recently Smith et al. (2000) and Pomeranz et al. (1993), may prove necessary to most accurately reproduce this aspect of the clinical TBI scenario. Further investigation into the pathogenesis, modeling and treatment of post-traumatic coma is clearly needed; however, it remains to be proven that modeling coma in TBI is essential to successfully bringing a therapy from bench to bedside.

Neurointensive Care Monitoring and Management Strategies

Two main objectives of clinical neurointensive care after severe TBI are the prevention and treatment of both secondary ischemia and the devastating consequences of cerebral herniation. Outcome after severe TBI has been improved by using a CPP-directed strategy to avert ischemia (Rosner et al., 1995). Knowledge of ICP is thus essential for both titration of CPP-directed care and management of intracranial hypertension. The degree of in-
tracranial hypertension has been shown to be a consistent predictor of poor outcome in a majority of clinical studies. Recently, this was confirmed by Juul et al. (2000), who reported that the occurrence of an ICP of >20 mm Hg was the most powerful predictor of neurological deterioration in patients after severe TBI.

Despite its clinical importance, ICP is rarely monitored in rodent models of TBI. Often craniotomy sites are not closed or, in models with an intact cranium, skull fractures variably occur limiting the value of monitoring ICP. ICP and CPP have, however, been assessed after experimental TBI in a limited number of studies in rats. Cherian et al. (1994) evaluated ICP in the acute phase after CCI with varying severity and found that peak ICP correlated with impact velocity. Despite limited assessment of CPP in rodent models of TBI, Kroppenstedt et al. (1999) recently evaluated the effects of CPP on lesion volume after TBI in rats. Lesion volume was smallest with CPP values between 70 and 105 mm Hg. Low CPP, as expected, exacerbated neuronal damage, but surprisingly, modest increases in CPP were associated with considerable increases in lesion size (Fig. 5).

Despite the apparent importance of ICP/CPP in rodent studies of TBI, assessment of the efficacy of specific ICP or CPP directed therapies in these models has been limited. Recently, Mirski et al. (2000) compared the use of mannitol vs hypertonic saline to reduce ICP in rats subjected to cryogenic lesion. They reported that although both agents reduced ICP, hypertonic saline was more effective at controlling ICP within the first 8 h. A number of other studies targeting posttraumatic edema/brain water, rather than ICP, have been conducted in the rodent models of TBI (Bareyre et al., 1997; Feldman et al., 1995; Talmor et al., 1998; Whalen et al., 2000). However, further assessments of intracranial dynamics and therapeutic strategies to control ICP after TBI are needed—particularly during the subacute period (1–4 days post-trauma).

To date, one of the great strengths of the investigations in rodent models has been extensive assessment of both functional deficits after TBI and the effects of treatments on functional outcome. Both motor and cognitive outcomes have been well characterized. Treatments targeting neurotransmitter systems and neuronal death have been the subject of extensive investigation in these functional outcome paradigms. Unfortunately, the effects of treatments targeting posttraumatic cerebral edema and/or intracranial hypertension on functional outcome have been subjected to only limited study in these models. Indeed, the majority of these studies have assessed regional

![Graph demonstrating the relationship between contusion volume (as percent of control) and cerebral perfusion pressure (CPP) after controlled cortical impact in rats. CPP was maintained at the desired level using an intravenous infusion of dopamine. Surprisingly, lesion volume was importantly increased with both reduced and mildly increased CPP; *p < 0.05 versus control animals. (From Kroppenstedt et al., 1999, with permission.)](image)
molecular mechanisms of injury, not the effects of intracranial dynamics on either the overall injury process or functional outcome. Additionally, since rodents are not generally maintained on aggressive support with mechanical ventilation and strict control of ICP, it is possible that the overall severity of injury is less in rodent models. Testing of pharmacologic therapies may thus be conducted in insults of lesser severity than in the clinical setting. Moreover, in rodent models in which larger lesions are produced (i.e., severe CCI), open craniotomy sites may compensate for ICP increases. The rodent models may thus behave very differently than an equally severe insult in the clinical setting where no decompressive craniotomy is done. Finally, herniation due to refractory intracranial hypertension is an important complication in clinical TBI that has not been effectively modeled in rodents. As discussed later, this has been modeled in large animals (Pomeranz et al., 1993) and may represent an important paradigm for testing novel therapies.

The effect of anesthetics and sedatives on patients with TBI is an aspect of neurointensive care that is largely unappreciated in both clinical and experimental TBI. Historically, anesthetic choice in experimental TBI has been based either on convenience or to limit potential side effects, such as the need for prolonged intubation and mechanical ventilation. Compounding the problem, anesthetics have been used in experimental TBI with little attention to their influence on histopathologic or functional outcome. Recently, in the rat CCI model, we directly compared 4 h of anesthesia with either isoflurane (1% by inhalation), one of the most commonly used anesthetics in experimental models, or fentanyl (10 mcg/kg bolus iv then 50 mcg/kg/h infusion), which is routinely given to patients early after TBI (Statler et al., 2000c). Importantly, isoflurane produced markedly better long-term functional outcome and greatly reduced CA1 hippocampal cell death after TBI vs fentanyl anesthesia (Fig. 6).

Further study by our group revealed that the benefits of isoflurane (versus fentanyl) are conferred at or near the time of injury (Statler et al., 2000a). Specifically, rats were anesthetized with either fentanyl or isoflurane (using the doses above) for 30 min before CCI, allowed to recover tail pinch response, and then immediately subjected to CCI. Rats pretreated with isoflurane performed markedly better on both motor and cognitive testing during the initial 21 days after TBI. Posttraumatic administration of isoflurane to rats pretreated with fentanyl, even when initiated immediately after CCI, failed to improve functional outcome.

Putative neuroprotective actions of isoflurane include CBF promotion (Hendrich et al., 2001) and considerable antiexcitotoxic properties (Bickler et al., 1994; Harada et al., 1999; Kimbro et al., 2000; Patel et al., 1995, 1998), among other mechanisms. Recently, isoflurane anesthesia was shown to augment CBF and reduce posttraumatic hyperglycolysis vs fentanyl in rats (Hendrich et al., 2001; Statler et al., 2000b). Finally, in a comparison of a series of agents commonly used in clinical and/or experimental TBI, rats treated with either narcotics or propofol exhibited the greatest posttraumatic functional deficits (Statler et al., 2000a). A major concern raised by this recent work is the fact that the most clinically relevant anesthetics/sedatives (i.e., narcotics, propofol) are associated with the poorest outcomes in the CCI model in rats.

These studies suggest that anesthetic choice strongly influences outcome after TBI. The common use of isoflurane anesthesia may be critically masking the benefits of novel therapeutic agents tested in experimental TBI. Greater use of more clinically relevant and/or less potentially confounding anesthetics, such as fentanyl, appears to be prudent in future studies using experimental models of TBI. Additionally, in clinical practice, sedatives are most commonly used in combination, such as a narcotic plus a benzodiazepine. To our knowledge, such combination treatment has not yet been evaluated in experimental TBI and deserves further study. Finally, it may be difficult or impossible to translate a novel therapy from bench to bedside—particularly one targeting excitotoxic mechanisms—without better understanding how the therapy is affected by clinically relevant anesthetics/sedatives.

Many other important, routine aspects of neurointensive care are rarely addressed in animal models of TBI,
including (but not limited to) the effects of inspired oxygen concentration, hemodynamic support with catecholamines, and surgical decompression. Menzel et al. (1999) reported that increasing inspired oxygen concentration to produce PaO2 values greater than those needed to fully saturate hemoglobin attenuated the increase in brain interstitial lactate concentrations in patients with severe TBI. Providing 100% inspired oxygen after TBI in experimental models may have similar effects, potentially minimizing relative ischemia and secondary damage. Since 100% inspired oxygen is routinely administered to patients in the resuscitation phase after severe TBI, this could raise the bar for any novel therapeutic modality that is being tested in the clinical setting, particularly in the early phase after injury.

Similarly, exogenous catecholamines are commonly administered to patients with severe TBI to titrate MAP and CPP. However, the effects of intravenously administered catecholamines on the injured brain are poorly understood. McIntosh et al. (1994) reported reductions in cerebral levels of endogenous catecholamines in injured brain regions after FPI. Similarly, dopamine D2 receptor protein is chronically downregulated in frontal cortex after CCI (Yan et al., 1999). Supporting this finding, no-radenergic augmentation, in the classic work of Feeney (1993), facilitated motor recovery in rats after TBI. In contrast, intravenous administration of dopamine, in a clinically relevant paradigm, worsened cerebral edema after TBI in rats, possibly by exacerbating oxidative stress (Beaumont et al., 2000). As more experimental models incorporate hemodynamic support to study CPP-directed therapies, understanding the local effects of catecholamines in injured brain regions may be very important to interpreting experimental results. Studies are needed to delineate the actions of exogenously administered catecholamines on the injured brain, using clinically relevant paradigms.

Finally, patients with mass lesions or refractory intracranial hypertension may benefit from surgical resection and decompressive craniotomy. Although surgical decompression has not yet been rigorously applied in contemporary models of experimental TBI, early decompressive craniotomy was recently found to significantly reduce infarct size after hemispheric stroke in rats (Engelhorn et al., 1999). Application of surgical intervention in experimental models of refractory intracranial hypertension is warranted. This may become particularly important if clinical trials document benefit of this approach in human head injury. Additionally, although some large animal models use a balloon catheter to mimic mass lesions from hemorrhage, models of mass lesions are lacking in rodent models of TBI.

Pomeranz et al. (1993) incorporated several of these important neurointensive care issues into an experimental canine model of cerebral compression ischemia. An epidural balloon model that produce marked intracranial hypertension with brainstem compression, systemic hypotension, and coma was used to compare outcome with posttraumatic hypothermia vs normothermia (Fig. 7). Similar to the neurointensive care techniques applied in patients with severe TBI, the dogs received 90 h of ICU care with controlled mechanical ventilation and monitoring of MAP and ICP. Therapeutic strategies included analgesia with fentanyl, volume resuscitation titrated to central venous pressure monitoring, hemodynamic support with norepinephrine, administration of mannitol for ICP control, and empiric antibiotic treatment with ceftriaxone. Outcome was assessed by a canine coma scale score (based on the GCS score) and by an overall performance category ranging from normal behavior to brain death. Although hypothermia reduced intracranial hypertension and histologic damage, it failed to consistently prevent late cerebral herniation. Dogs had a 50% mortality rate in both experimental groups. Although a model of cerebral compression ischemia and not TBI was used, this report demonstrates the feasibility of incorporating neurointensive care techniques into large animal models.

**FIG. 7.** Coronal brain sections at 90 h after brain injury produced by epidural balloon inflation (90 min) followed by comprehensive neurointensive care including controlled mechanical ventilation, fentanyl analgesia, norepinephrine infusion to control blood pressure, and mannitol treatment. Dogs were also treated with either normothermia or induced hypothermia for the initial 24 h. The normothermic example illustrated here showed marked hemispheric swelling with cerebral herniation and brainstem compression (arrow). Cerebral herniation was prevented by hypothermia in this study (data not shown). (From Pomeranz et al., 1993, with permission.)
of TBI. Similar application of these techniques in models of TBI with the incorporation of long-term functional outcome assessment and/or investigation of cellular and molecular mechanisms of secondary injury would certainly advance our understanding of TBI. It is possible that such a comprehensive approach, either in rodent or large animals, may be the only way to successfully model the clinical scenario and delineate clinically relevant treatment strategies.

CONCLUSION

Despite well-established rodent models and years of carefully conducted research, a clinical therapeutic breakthrough in severe TBI remains elusive. This may be due, in part, to discrepancies between commonly used animal models and clinical scenarios. Although the established models have helped us begin to elucidate a number of biochemical, cellular, and molecular factors important to the evolution of secondary damage and repair after TBI, none has recreated common, albeit complex, clinical scenarios that represent the ultimate setting for trials of therapeutic efficacy. The interplay of numerous factors likely determines outcome in patients with severe TBI. Our current modeling strategies, coupled with contemporary cellular and molecular techniques, have focused on simple models and individual mechanistic aspects of TBI, generally studied in isolation. This approach has provided us with considerable new insight into the pathobiology of important mechanisms, such as neuronal death and axonal damage. Unfortunately, this insight has not yet been successfully translated to an efficacious clinical therapy.

Investigation of specific aspects of TBI should continue in established rodent models. However, embellishment of these models to more closely recreate clinical scenarios represents another potentially fruitful avenue that may increase the likelihood of developing effective therapies. Incorporation of secondary insults, along with combined assessment of cerebral dynamics, biochemical, molecular and cellular alterations, functional outcome, and histology are needed. Additionally, species differences, particularly in the ability to produce traumatic coma or cerebral herniation and to define the clinically relevant therapeutic window for individual treatments, may prove vitally important to more effectively understanding TBI and identifying potential therapeutic modalities. Large animal models may be necessary to address these issues and truly recreate clinical scenarios. A review of the in vivo animal model studies of TBI published in the Journal of Neurotrauma over the past 5 years (1996–2000) reveals that fewer than 10% of studies have been carried out in large animal models in each of these years (Fig. 8). Alternatively, as our invasive monitoring and microimaging capabilities continue to advance, similar comprehensive studies may be feasible in established rodent models as well. In either case, these models would facilitate extended monitoring in a simulated neurointensive care environment with application of ICP and CPP directed therapies.

While large animal models of TBI may help to define the complex interplay between individual factors in the pathogenesis and treatment of severe TBI, large animal studies present several unique limitations. For example, our current rodent models of TBI provide a gold standard approach to assessing functional outcome after TBI; however, good cognitive outcome testing and data are lacking in large animals. Additionally, the wealth of investigation in small animal models has provided a background for testing novel therapeutic agents that has yet

**FIG. 8.** Graph depicting the percent of studies of experimental TBI that have been carried out in large animal (open bars) versus rat and mouse (solid bars) models that were published in the Journal of Neurotrauma between 1996 and 2000. Less than 10% of laboratory studies have used large animals.
to be matched in large animal models. Similarly, molecular tools such as specific receptor localization techniques, transgensics, and knockout animal development are not yet available for large animal models. Also, new techniques such as genomics and proteomics will allow the simultaneous assessment of the effect of treatments on multiple mechanisms. These tools should be able to be rapidly applied to the established rodent models. Finally, the cost of large animal models can quickly become prohibitive. Experimental investigations in a combination of rodent and large animal models will thus likely be necessary to further our understanding of the effects of treatment techniques on both TBI pathophysiology and functional outcome.

As clinician-scientists, we have focused much of this review on the development of more clinically realistic models of TBI. However, as mentioned in the introduction, the failure to achieve a therapeutic breakthrough in TBI may not be the result of limitations of the animal models. Clinical TBI trials are fraught with difficulties that may limit proof of clinical efficacy, such as heterogeneous patient populations, delayed randomization, and insensitive outcome measures (Bullock et al., 1999; Doppenberg and Bullock, 1997; Maas et al., 1999). In conclusion, achievement of a therapeutic breakthrough in TBI will likely require a multifaceted approach, combining innovations in clinical trial design with clinically relevant modifications in established animal models and/or the development and use of “super models.”

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