Hemorrhagic Progression of a Contusion after Traumatic Brain Injury: A Review

David Kurland¹, Caron Hong,² Bizhan Aarabi,¹ Volodymyr Gerzanich,¹ and J. Marc Simard^{1,3,4}

Abstract

The magnitude of damage to cerebral tissues following head trauma is determined by the primary injury, caused by the kinetic energy delivered at the time of impact, plus numerous secondary injury responses that almost inevitably worsen the primary injury. When head trauma results in a cerebral contusion, the hemorrhagic lesion often progresses during the first several hours after impact, either expanding or developing new, non-contiguous hemorrhagic lesions, a phenomenon termed hemorrhagic progression of a contusion (HPC). Because a hemorrhagic contusion marks tissues with essentially total unrecoverable loss of function, and because blood is one of the most toxic substances to which the brain can be exposed, HPC is one of the most severe types of secondary injury encountered following traumatic brain injury (TBI). Historically, HPC has been attributed to continued bleeding of microvessels fractured at the time of primary injury. This concept has given rise to the notion that continued bleeding might be due to overt or latent coagulopathy, prompting attempts to normalize coagulation with agents such as recombinant factor VIIa. Recently, a novel mechanism was postulated to account for HPC that involves delayed, progressive microvascular failure initiated by the impact. Here we review the topic of HPC, we examine data relevant to the concept of a coagulopathy, and we detail emerging data elucidating the mechanism of progressive microvascular failure that predisposes to HPC after head trauma.

Key words: coagulopathy; contusion; hemorrhage; traumatic brain injury

Introduction

TRAUMATIC BRAIN INJURY (TBI) is the most disabling of traumatic injuries, often leading to lifelong physical, cognitive, behavioral, and emotional impairments (Langlois et al., 2006; Selassie et al., 2008; Thurman et al., 1999). Nearly half of hospitalized survivors of TBI experience long-term disabilities (Selassie et al., 2008; Thurman et al., 1999; Zalosnjaja et al., 2008). The lifetime costs of TBI in the United States, including medical costs and costs due to lost productivity, total an estimated \$60 billion annually, constituting one of the largest expenditures in the health care system (Langlois et al., 2006; Selassie et al., 2008; Thurman et al., 1999). TBI encompasses numerous types of insults to the brain, with one of the most severe being a hemorrhagic cerebral contusion. TBI associated with cerebral contusion is a frequent cause of death and disability in trauma victims who reach the hospital alive (Alahmadi et al., 2010).

Excellent reviews on the natural history of cerebral contusions have been published (Alahmadi et al., 2010), but our purpose is different. Here we focus specifically on the phe-

nomenon of hemorrhagic progression of a contusion (HPC), a secondary injury process that designates the enlargement or new appearance of a parenchymal hemorrhagic contusion due to delayed bleeding. Not only does HPC greatly exacerbate an already grave situation, but most frustrating to healthcare providers and patients, it does so during the several hours or early days after trauma when patients are already hospitalized. Ample opportunity would be available to intervene if proper intervention could be devised.

In this review, we begin by documenting the characteristic features of HPC. Then we examine two mechanisms that have been implicated in its development. First, we consider the conventional explanation, that an explicit or latent coagulopathy leads to continued or delayed bleeding of microvessels fractured at the time of primary injury. Next we consider a novel, recently discovered mechanism postulating that microvessels in the region of injury (penumbra) receive kinetic energy from the impact that is not sufficient to fracture them, but is sufficient to induce a series of maladaptive molecular events that eventually results in their structural failure, leading to delayed formation of petechial hemorrhages which

Departments of ¹Neurosurgery, ²Anesthesiology, ³Pathology, and ⁴Physiology, University of Maryland School of Medicine, Baltimore, Maryland.

then coalesce to produce hemorrhagic progression. Distinguishing between these two mechanisms is important, because the implications for treatment are quite different. For the first mechanism, treatment must be aimed at normalizing coagulation, whereas for the second, treatment must block the maladaptive molecular events in microvascular endothelial cells.

Primary versus secondary injury

Tissue damage after head trauma is due to primary injury plus secondary injury. Primary injury refers to the physical destruction of tissues that occurs within moments of impact. Kinetic energy deposited by the impact causes shearing of the tissues. The primary injury ruptures neurons, astrocytes, and oligodendrocytes, causing their immediate necrotic death. Necrotic cell death releases intracellular substances (e.g., excitatory amino acids and heat-shock proteins) that incite secondary injury responses. The primary injury also ruptures microvessels, causing extravasation of blood and the loss of function of those vessels, which leads to ischemia. Breakdown products of extravasated blood are extremely toxic to central nervous system (CNS) cells and also incite secondary injury responses.

Secondary injury responses are numerous (Table 1). All lead, more or less, to further tissue injury that worsens the primary injury. Many secondary injury responses are simply the natural consequence of primary tissue damage, such as the release of excitotoxic substances, free radical damage from blood breakdown products, and ischemia due to loss of microvessels. Other secondary injury responses are evolutionarily favored to accomplish useful functions, such as clearing tissue debris. Secondary injury due to the latter is said to be a “bystander” injury, or the unintended consequences of a process that is supposed to be beneficial but that mistakenly goes too far. The classic example is the inflammatory response, involving both endogenous (microglia) and exogenous (neutrophils and macrophages) cells. Neutrophils phagocytize cellular debris, serving to clear it, but in the process they release free radicals that harm otherwise normal cells nearby, inadvertently propagating tissue injury (Blight, 1992; Hampton et al., 1998; Ryter et al., 2007; Smith, 1994; Whitney et al., 2009).

Contusive injury to the brain invariably is complicated by secondary injury due to microvascular dysfunction (Yokota, 2007), which worsens with time and leads to growth or expansion of the primary lesion. Microvascular dysfunction has numerous causes and correlates, including endothelial

swelling, vasoconstriction, vasospasm, and occlusion due to platelet and leukocyte aggregation and adhesion. Microvascular dysfunction leads to: (1) tissue ischemia due to impairment of blood flow; (2) the formation of vasogenic edema, which causes tissue swelling that further exacerbates ischemia; and (3) in the worst cases, loss of the structural integrity of surrounding microvessels, which results in expansion or progression of the hemorrhagic lesion, known as HPC. The extravasated blood from the primary contusion, the edema, and the additional extravasated blood resulting from HPC together produce mass effect, which compresses adjacent healthy tissues, and if unchecked, leads to further ischemia. Together, these processes raise intracranial pressure (ICP), may cause herniation syndromes, and may necessitate surgical decompression to prevent death.

Hemorrhagic progression of a contusion

On a computed tomography (CT) scan, a contusion generally appears as a hemorrhagic lesion, although sometimes injured tissues or part of a contusive lesion can appear normal (isodense) or as a hypodensity. A contusion is distinguished from a laceration by the fact that with a contusion, the pia mater remains intact. A contusion is distinguished from a hematoma by the fact that with a contusion, blood is intermixed with brain tissue.

When head trauma results in a contusion, the hemorrhagic lesion often expands or a new hemorrhagic lesion may develop remotely (non-contiguously) from the original contusion during the first several hours after impact (Fig. 1; Alahmadi et al., 2010). HPC is a phenomenon that was first appreciated at the dawn of the CT era (Gudeman et al., 1979), and continues to be diagnosed best by CT.

HPC may be referred to by various terms, including delayed traumatic intracerebral hematoma (DTICH) (Gudeman et al., 1979), progressive hemorrhagic injury (Oertel et al., 2002; Smith et al., 2007), traumatic intracerebral hemorrhage (Narayan et al., 2008b), or colloquially, as a contusion that has “blossomed.” Unfortunately, there is ambiguity in the literature. “Delayed intracerebral hematoma” or DTICH may refer to cases that present many weeks after injury, when delayed hemorrhage may be due to a traumatic intracranial aneurysm (Horiuchi et al., 2007; Hossain et al., 2002; Kaplan et al., 2003; McFeeley et al., 1988; Yang et al., 2007). The term “progressive hemorrhagic injury” has been used to refer to progression of an epidural hematoma, subdural hematoma, intraparenchymal contusion or hematoma, or subarachnoid hemorrhage (Oertel et al., 2002). Such broad usages are

TABLE 1. ADDITIONAL MECHANISMS OF SECONDARY INJURY IN TRAUMATIC BRAIN INJURY (TBI) NOT COVERED IN THIS REVIEW

Molecular cascades and inflammation	Lenzlinger et al., 2002; Morganti-Kossmann et al., 2002; Otto et al., 2002; Yatsiv et al., 2002; Lu et al., 2011; Hong et al., 2010
Excitotoxicity	Yi and Hazell, 2006; Yi et al., 2006
Metabolic derangements	De et al., 2011; Lakshmanan et al., 2010; Scafidi et al., 2009; Marcoux et al., 2008; Vespa et al., 2005
Apoptosis/necrosis/autophagy	Shojo et al., 2010; Nakajima et al., 2010; Hoh et al., 2010; Yamashima and Oikawa, 2009; Itoh et al., 2010; Robertson et al., 2009; Luo et al., 2010; Luo et al., 2011; Liao et al., 2009
Ischemia	Aoyama et al., 2008; Stiefel et al., 2005; Engel et al., 2005; Mendez et al., 2004; Buczek et al., 2002; Oertel et al., 2005

FIG. 1. Hemorrhagic progression of a contusion (HPC). (A and B) A 21-year-old female pedestrian struck by a motor vehicle had a computed tomography (CT) examination performed within 2 h of trauma, and a repeat CT examination 6 h later. Note the expansion of the right frontal contusion. (C and D) A 44-year-old male motorcyclist involved in a collision had a CT examination performed within 2 h of trauma, and a repeat CT examination 5 h later, immediately following decompressive craniectomy and evacuation of a left temporal lobe hematoma. Note the appearance of a new hemorrhagic lesion at a remote location marked by a hypodensity on the initial scan (arrows).

imprecise, and the molecular mechanisms responsible for progression in each case is likely to be different. To avoid ambiguity, here we adopt the term "hemorrhagic progression of a contusion" (HPC). By using this term, we convey two things: (1) our focus is on the traumatic cerebral contusion and its hemorrhagic progression; and (2) our goal is not simply to characterize the phenomenology of more blood on the CT scan, but to illuminate the process, the molecular mechanisms responsible for hemorrhagic progression. In our subsequent analysis, we use the term HPC where appropriate, and we add clarification in instances when the authors being reviewed did not make such a distinction.

In the earliest description, Gudeman and associates (Gudeman et al., 1979) reported on 12 cases of HPC in patients who were comatose. The interval from injury to diagnosis was within 48 h in 11 of the 12 cases; 6 patients had no decompressive surgery before the development of HPC; 4 patients had undergone decompressive surgery and then developed HPC on the contralateral side; 2 patients developed lesions in

the vicinity of the operative site that were thought not to be the result of the operation.

In another early paper, Fukamachi and colleagues (Fukamachi et al., 1985) described two patterns of hemorrhagic progression (small or medium hemorrhages initially that later increased in size; a "salt and pepper" or "flecked" abnormality initially seen on CT that later changed to a high-density appearance), and pointed out that in cases with extra- and intracerebral hemorrhages, surgical treatment of an extracerebral hematoma may play a role in progression of the intraparenchymal component.

Servadei and co-workers (Servadei et al., 1995) identified a group of 22 patients admitted in coma who harbored hematomas that evolved into lesions requiring surgical removal. Fifteen of these patients had initial diagnoses of diffuse injury that evolved, whereas the remaining seven patients had already undergone surgery and developed new, non-contiguous, hemorrhagic lesions. This study reinforced the early observations of Gudeman and associates (Gudeman

et al., 1979), and of Fukamachi and colleagues (Fukamachi et al., 1985), that HPC frequently continues after craniotomy. That HPC frequently continues after craniotomy also is noted in more recent literature (Aarabi et al., 2009).

Oertel and co-workers (Oertel et al., 2002) performed a retrospective study of patients who underwent two CT scans within 24 h of head injury. Their study examined progression of all hemorrhagic lesions, including epidural, subdural, subarachnoid, and intraparenchymal (contusion) hemorrhages. Overall, they found that early progression of hemorrhage occurs most frequently in contusions, with a likelihood of 51%. They also observed that about half of the patients who underwent craniotomy after the first CT scan later showed evidence of hemorrhagic progression, in accord with the aforementioned study by Servadei and associates (Servadei et al., 1995).

In a prospective study, Narayan and colleagues (Narayan et al., 2008b) demonstrated that hemorrhage expansion between the baseline and 24-h CT scans occurred in over 50% of subjects who presented with traumatic hemorrhagic lesions 2 mL or larger. They also found that while small hemorrhagic lesions may expand, lesions that were larger at baseline tended to have substantially greater increases, with an associated greater likelihood of clinical impact.

Alahmadi and associates (Alahmadi et al., 2010) performed a retrospective review of patients with brain contusions who initially underwent non-operative treatment, defining patients with significant progression as those with a 30% or more increase in contusion size on CT scan (progression on CT scans could result from expansion of the hematoma, the appearance of perihematoma hypodensity, or development of new lesions that were not present on initial scans). Of 98 patients, 44 (45%) had significant progression on CT, and 19 (19%) required decompressive surgery. They also determined that patients with large contusions and low initial Glasgow Coma Scale (GCS) scores were at greater risk for delayed deterioration.

HPC may be detected on CT scan even in cases of mild head injury. In two studies (Sifri et al., 2004, 2006), Sifri and colleagues found that progression was evident on follow-up CT in almost half of patients with an intracranial hemorrhage and a worsening neurologic status (contusive injuries comprised the majority of their intracranial hemorrhages). Moreover, even in cases in which patients did not show neurological deterioration, up to 15% still showed evidence of progression of an intracerebral hemorrhage.

From the foregoing, it is evident that a contusion on the admission CT scan should be a cause for vigilance regarding possible HPC. A traumatic subarachnoid hemorrhage (tSAH) may be similarly predictive (Chieragato et al., 2005; Fainardi et al., 2004). In their prospective study of tSAH, Chieragato and associates (Chieragato et al., 2005) found that 60% of patients with tSAH exhibited HPC on follow-up CT. Of patients who had any CT progression, 20% presented with entirely new contusions, and 80% had a doubling of contusion volumes on follow-up CT. Independent factors associated with significant CT progression were the amount of tSAH and the presence or volume of brain contusions at admission. HPC was associated with poor clinical outcomes.

The aforementioned reports represent a sampling of the available articles on HPC. Other studies have contributed to our understanding of this phenomenon (Allard et al., 2009;

Chang et al., 2006; Compagnone et al., 2009; Diaz et al., 1979; Patel et al., 2000; Servadei et al., 2000a; Smith et al., 2007; Stein et al., 1992, 1993; Tian et al., 2010; Tseng, 1992; Wang et al., 2006; Young et al., 1984). Together, these studies permit some important generalizations about HPC:

- Approximately half of patients with contusions demonstrate HPC on serial CT scans.
- HPC may involve not only the expansion of existing contusions, but the delayed appearance of non-contiguous hemorrhagic lesions.
- HPC is equally common without surgery and after decompressive craniectomy.
- HPC is equally common in cases with tSAH.
- The earlier after injury that the initial CT scan is obtained, the greater the likelihood that HPC will be found on a subsequent scan.
- HPC generally occurs within the first 12 h, but may occur as late as 3–4 days after head trauma.
- Small contusions that progress are usually clinically silent and are unlikely to require surgical decompression (Smith et al., 2007).
- Large contusions in patients with low initial GCS scores are likelier to progress and often require surgical decompression.

Why is HPC bad?

Edema formation and HPC are both manifestations of microvascular dysfunction, but there is a critically important distinction: one is associated with potentially reversible injury, whereas the other is associated with almost certain irreversible harm. Disregarding the underlying cause that induces formation of edema (e.g., ischemia or hemorrhage), the effects of edema *per se* are reversible, at least in principle, if treatment is early and sufficient (e.g., by osmotherapy or decompression; Engel et al., 2008; Zweckberger et al., 2006).

This is not the case with HPC. Contused tissues consist of blood intermixed with brain tissue. For over a century, neuropathologists have recognized that extravasated blood is exquisitely toxic to brain cells, and that the presence of blood generally is associated with necrosis of intermixed CNS tissues (hemorrhagic necrosis; Ramon y Cajal, 1991). In addition, a hemorrhagic contusion inevitably results in the formation of edema, further contributing to the mass of extravasated blood (Engel et al., 2008; Zweckberger et al., 2006).

A hemorrhagic contusion on CT scan demarcates tissues with essentially total, unrecoverable loss of function. The volume and location of a hemorrhagic contusion observed during the acute phase after head trauma predicts the volume and location of dysfunctional tissue that will exist after recovery. The predictive power of the CT scan in contusive head trauma resembles the predictive power of diffusion weighted imaging (DWI) on magnetic resonance imaging (MRI) in stroke; although the two are not equivalent, both identify tissues that are essentially irretrievably lost.

This pessimistic assessment of pathology is corroborated by clinical experience. Although not universal (Gudeman et al., 1979), a large number of studies suggest that the development of HPC is associated with a worse clinical course and higher rates of mortality (Allard et al., 2009; Chieragato et al., 2005; Nelson et al., 2010; Oertel et al., 2002; Servadei et al., 2000b; Stein et al., 1992, 1993; Tian et al., 2010). In the

study by Stein and associates (Stein et al., 1993), delayed injury was associated with higher mortality, slowed recovery, and poorer outcome at 6 months; the authors concluded that HPC is associated with dramatically worse outcomes for each category of initial injury severity. Servadei and colleagues (Servadei et al., 2000a) found that when the initial CT scan demonstrated a diffuse injury without swelling or shift, evolution to a mass lesion was associated with a statistically significant increase in the risk of an unfavorable outcome (62% versus 38%). In the study by Chieregato and co-workers (Chieregato et al., 2005), patients who experienced significant progression of their lesion had a significantly higher risk of an unfavorable outcome (32% versus 10%). Allard and associates (Allard et al., 2009) found that progression was associated with a fivefold higher risk of death (32% versus 8.6%).

Thus, HPC is detrimental because it results in irrevocable loss of brain tissue that was ostensibly intact immediately following the primary injury. Even in patients in whom HPC is not fatal, there is significant likelihood of increased morbidity. HPC is a progressive, secondary injury that occurs relatively late after trauma, and almost invariably occurs while under medical care. As such, it may be preventable if underlying molecular mechanisms can be identified so that appropriate treatments can be applied.

Coagulopathy in TBI

Historically, HPC has been attributed to continued bleeding of microvessels fractured at the time of primary injury. This concept has given rise to the notion that continued bleeding might be due to an overt or latent coagulopathy (Van Beek et al., 2007). In the TBI literature, coagulopathy is often broadly defined as any perturbation in a patient's coagulation parameters, and may include a prolongation of the prothrombin time (PT), an elevation of the International Normalized Ratio (INR), an elevation of the activated partial thromboplastin time (aPTT), or a decrease in the platelet (PLT) count (Engstrom et al., 2005).

Depending on the severity of injury, time of testing, sensitivity of clotting tests, and the specific parameter being measured, the incidence of clotting abnormalities in TBI patients is reported to vary from 15–100% (refer to Stein and Smith, 2004 for an excellent review). More recent studies of isolated severe TBI by Lustenberger and colleagues (Lustenberger et al., 2010a, 2010b) found that up to 45% of these patients become coagulopathic, a finding that is in accord with a meta-analysis of 34 studies done by Harhangi and associates (Harhangi et al., 2008; weighted average of 32.7%). Coagulopathy can develop up to 5 days after injury, and the incidence appears to be linearly correlated with increasing severity of injury (Lustenberger et al., 2010a, 2010b; Sun et al., 2011).

The exact mechanisms that account for coagulopathy in TBI have not been fully elucidated, and disagreements persist as to the cause (Cohen et al., 2007; Halpern et al., 2008). Tissue factor (tissue thromboplastin) is abundant in the brain (Astrup, 1965), and may be released in large quantities following trauma. Diffuse activation of the extrinsic coagulation pathway may lead to disseminated intravascular coagulation (DIC). Subsequent consumption of clotting factors may underlie a bleeding diathesis. Other explanations have been offered, noting that coagulopathy is more likely to occur when both tissue injury and hypoperfusion are present, with the

protein C pathway perhaps playing an important role (Cohen et al., 2007).

Mechanisms aside, surgeons fear coagulopathy because of the perceived risk of hemorrhage. Although coagulopathy after TBI has long been recognized to be a non-specific indicator of poor prognosis (Greuters et al., 2011; Harhangi et al., 2008; Stein et al., 1992; Wafaisade et al., 2010), review of the literature does not support a simple causative relationship between coagulopathy and progressive delayed hemorrhage. A comparison of the incidence of HPC and related outcomes in patients with or without coagulopathy is instructive.

Abnormal coagulation

Elevated PT/INR. The reported incidence of an elevated PT or INR in the context of TBI varies widely. A recent study of moderate and severe TBI by Carrick and colleagues (Carrick et al., 2005) reported an incidence of 5%, but a meta-analysis (Van Beek et al., 2007) of data from the large IMPACT study found an overall incidence of 26%. Several studies have reported on PT measurements and the incidence of HPC. Tian and co-workers (Tian et al., 2010) observed that only 7.4% of the patients who showed progressive injury on CT had an elevated PT. An earlier study by Stein and associates (Stein et al., 1992) observed that of the patients who exhibited progression on CT, only 31% had an abnormal PT (65% of the patients who exhibited progressive injury had either an intracerebral hematoma or contusion). A widely cited report by Oertel and colleagues (Oertel et al., 2002), in which serial coagulation tests were obtained, found that 57% of patients who had elevated PT on a first coagulation panel exhibited progression on CT, and 60% who had elevated PT on a second coagulation panel did not exhibit progression (66% of patients presented with an intraparenchymal lesion). Engstrom and co-workers (Engstrom et al., 2005) found no difference in PT values at any time between groups that would or would not later develop HPC (HPC represented 18/19 cases in this report). Additionally, Allard and associates (Allard et al., 2009) observed that 42% of patients with normal INR values showed evidence of HPC (HPC accounted for 89% of all instances of lesion progression). Thus while the statistical association of elevated prothrombin times with HPC cannot be refuted, it is evidently not reliably causative.

Elevated aPTT. Abnormalities in aPTT occur with an overall frequency of 1–30% in TBI patients (Allard et al., 2009; Carrick et al., 2005; Oertel et al., 2002; Stein et al., 1992; Tian et al., 2010). Some of the variability is due to differences in injury severity, time of testing, and definitions of elevated laboratory values (Oertel et al., 2002). Several studies reported data relating HPC and elevated aPTT values. Allard and colleagues (Allard et al., 2009) observed that while all their patients with abnormal aPTT (7% of patients studied) experienced progression of hemorrhagic injury on CT, 48% of patients with normal aPTT values also showed evidence of HPC. Of the 194 patients studied by Tian and co-workers (Tian et al., 2010), only 4.9% of those who had lesion progression also had abnormal aPTT. Oertel and associates (Oertel et al., 2002) observed that 3.4% of the patients who progressed on follow-up CT had an elevated aPTT (2 out of 58), and furthermore, out of all of the patients who had elevated aPTT, either on the first or second coagulation panel

(203 patients), only 5.4% would later exhibit lesion progression. Engstrom and colleagues (Engstrom et al., 2005) found no difference in aPTT values at any time between groups that would or would not later develop HPC. And in the study by Stein and co-workers (Stein et al., 1992), of all the patients who exhibited lesion progression on CT, only 12% had an elevated aPTT. Although statistically associated, elevated aPTT in TBI patients accounts for a very small proportion of patients who will exhibit HPC.

Thrombocytopenia. The comprehensive meta-analysis of the IMPACT study data by Van Beek and associates (Van Beek et al., 2007) calculated that thrombocytopenia occurs in 7% of TBI patients upon admission, but this value appears to be variable and highly dependent on when the test is performed (Carrick et al., 2005; Oertel et al., 2002). Engstrom and colleagues (Engstrom et al., 2005) found no statistical difference in initial PLT count between groups of patients that would or would not exhibit HPC (in fact, less than half of the cohort that would later show progressive hemorrhage had low PLT count upon admission). Allard and associates (Allard et al., 2009) observed that while 91% of patients with a low PLT count progressed, 44% of patients with a normal PLT count also progressed. In the study by Tian and co-workers (Tian et al., 2010), the authors found that only 13.6% of patients with lesion progression had an abnormal PLT count. Oertel and associates (Oertel et al., 2002) observed that 50% of patients who had an abnormal PLT count on either coagulation panel did not exhibit progressive injury. In the report by Stein and colleagues (Stein et al., 1992), only 11% of the patients with evidence of hemorrhagic progression had an abnormal PLT count. Some of these studies documented correlations and associations between low PLT count and outcome, but this is not always the case; it may be that platelet dysfunction is more important than overall platelet count when determining risk factors for TBI patients (see Nekludov et al., 2007). Nonetheless, it appears that up to 90% of patients who will develop progression of a hemorrhagic injury may not present with abnormalities in PLT count.

Any coagulopathic parameter. As noted above, coagulopathy (by any measure) is reported to occur with some variability upon admission (Lustenberger et al., 2010a; Wafaisade et al., 2010; Zehtabchi et al., 2008), and may increase in the days following injury (Carrick et al., 2005; Greuters et al., 2011). The aforementioned meta-analysis of 34 studies by Harhangi and associates (Harhangi et al., 2008) reported an overall prevalence of 32.7%. Smith and colleagues (Smith et al., 2007) found that coagulopathy at admission was not associated with HPC in their study (HPC accounted for 92% of the incidences of progressive lesions), and out of the 38 patients with HPC in the report by Patel and colleagues (Patel et al., 2000), only 2 (5.2%) were coagulopathic. Servadei and co-workers (Servadei et al., 1995) found that while only 16% of their patients were coagulopathic, over 35% were observed to deteriorate clinically. Kaups and associates (Kaups et al., 2004) observed that 73% of patients who had a progression on follow-up CT were not coagulopathic, and furthermore, 65% of coagulopathic patients had unchanged or even improved follow-up CT scans. An influential study by Stein and colleagues (Stein et al., 1993) noted that over 40% of patients that exhibited radiological evidence of delayed cerebral injury did

not have an abnormality in any coagulation measurement. Allard and co-workers (Allard et al., 2009) observed that evidence of a progressive lesion was present in 80% of patients who had any abnormal coagulation parameter; however, they also noted that 36% of non-coagulopathic patients developed HPC.

Thus, a large percentage of patients who develop HPC may not have clotting abnormalities, and conversely, many patients with coagulopathy will not develop HPC. We can reasonably conclude that the relationship between HPC and measurable coagulopathy, while clinically useful, is not one of simple cause and effect.

Recombinant factor VIIa (rFVIIa)

The potential involvement of coagulopathy, latent or otherwise, has prompted attempts to reverse such coagulopathy with agents such as recombinant factor VIIa.

Zaaroor and associates (Zaaroor et al., 2008) studied the safety of rFVIIa in 12 patients with severe TBI who had no underlying coagulopathy, but were considered to be at increased risk for lesion progression. There was limited success with respect to halting lesion progression, but since this study was small and not controlled, few conclusions could be drawn.

Narayan and associates (Narayan et al., 2008a) conducted a prospective dose-escalation trial of rFVIIa in traumatic intracerebral hemorrhage (ICH). They found that 15-day mortality rates were identical for the placebo and rFVIIa-treatment groups. The most frequent cause of death was the TBI (e.g., hematoma expansion and brain herniation) in all treatment groups. Critically, they found that there was no significant difference in rates of lesion progression between the placebo group and the rFVIIa group, at any dose. Also of note, in the placebo group, HPC occurred in 25% of coagulopathic patients versus 33% of non-coagulopathic patients.

A comprehensive review of randomized clinical trials for hemostatic therapy was carried out by Al-Shahi and associates (Al-Shahi, 2009). This review focused on non-traumatic ICH, not TBI, but it is most informative. The authors found that rFVIIa did not significantly reduce 90-day morbidity or mortality rates. Also, there was a trend toward increased serious thromboembolic events in patients who received rFVIIa. Radiological progression could not be meta-analyzed due to differences in outcome measurement between trials, but all of the studies analyzed suggested potential adverse effects of hemostatic therapy.

Reviewing the available randomized clinical trials of rFVIIa in TBI specifically, Perel and colleagues (Perel et al., 2010) concluded that "there is no reliable evidence from randomized controlled trials to support the effectiveness of hemostatic drugs in reducing mortality or disability in patients with TBI." The weak association between coagulopathy and HPC or other progressive hemorrhagic lesions is apparently well recognized, as reflected by the fact that only a small number of studies have examined hemostatic therapy in patients with TBI. While there remains a desire by some for additional large-scale, controlled trials on the efficacy of rFVIIa in TBI, such trials may be difficult to justify. It may be that a specific subpopulation of patients would benefit from hemostatic therapy following TBI (see Zaaroor et al., 2008), but this remains speculative.

Progressive microvascular failure leading to HPC

Although evident, it is useful to recall that coagulopathy *per se* does not cause hemorrhage into the brain; microvessels first must be fractured or otherwise opened to allow extravasation of blood. Patients without head trauma are routinely anticoagulated for a variety of reasons and generally do not bleed into their brains (annual risk, 0.3–1.0%; Flaherty, 2010). Head-injured patients often develop new hemorrhagic lesions hours after trauma in regions where there was no blood on the initial CT scan (Fig. 1D). As reviewed above, delayed hemorrhage can occur in a context of either normal coagulation or a coagulopathy, each occurring about half of the time. What is the source of the new hemorrhage? For delayed hemorrhage to occur, either microvessels must have been fractured at the time of impact, even though they showed no evidence of bleeding initially, or microvessels not fractured at the time of impact must finally be opened, hours after the impact, to allow extravasation of blood. Recent findings indicate that the latter scenario prevails (Patel et al., 2010; Simard et al., 2009b). Importantly, these new findings are based on the study of early cellular and molecular events that occur in microvessels after impact injury to the cortex in animal models of contusive injury that accurately replicate HPC (Fig. 2).

When kinetic energy from a focal impact is delivered to the surface of the brain, the energy is distributed within the viscoelastic tissues in a three-dimensional gaussian-like distribution, with the epicenter receiving the peak energy, and surrounding regions receiving progressively less energy with distance, both laterally and deep. For heuristic purposes, we divide the three-dimensional continuum from the epicenter outward into three distinct regions: (1) a volume of initial contusion; (2) a “shell” of penumbra surrounding the contusion; and (3) a “shell” of para-penumbra surrounding the penumbra (Fig. 3A). In all three regions, enough kinetic energy is deposited to have important biological consequences. Outside of the para-penumbra, the energetic disturbance is minimal and of little biological consequence. (Note that this idealized description of energy distribution applies best to a lissencephalic cortex subjected to a laboratory-controlled focal impact; the gyrencephalic human brain subjected to typical

head injury is expected to exhibit complex distortions in the three-dimensional shapes of our idealized volume and shells.)

In the case of a typical contusion, sufficient energy is deposited near the epicenter of the impact to shear tissues and fracture microvessels, resulting in an immediate hemorrhagic lesion—the initial contusion (Fig. 3A). In the penumbra—the shell of tissue surrounding the contusion—the amount of energy deposited is not enough to shear tissues and fracture microvessels, but it is enough to activate mechanosensitive molecular processes, most importantly in microvessels, thereby initiating a series of events that later will lead to the delayed catastrophic structural failure of microvessels, or HPC (Simard et al., 2009b). In the para-penumbra—the shell of tissue surrounding the penumbra—the amount of energy deposited is not enough to lead to HPC, but it is enough to initiate other, more subtle mechanosensitive events that will lead eventually to neuronal apoptosis (but not hemorrhage) (Patel et al., 2010). Alternatively, in cases in which a hemorrhagic contusion is not apparent initially, the contused epicenter may be thought of as being vanishingly small. However, as in the scenario above, the region surrounding the epicenter still receives enough kinetic energy to activate mechanosensitive molecular processes in microvessels that later will lead to the delayed catastrophic structural failure of microvessels, resulting in the delayed appearance of a new hemorrhagic contusion.

The vascular system of the brain, including both vascular smooth muscle cells and endothelial cells in larger vessels and in microvessels, is exquisitely mechanosensitive. Numerous signaling pathways involving integrins, ion channels, and transcription factors contribute to this mechanosensitivity. Here we focus on two transcription factors, specificity protein 1 (Sp1) and nuclear factor- κ B (NF- κ B), both of which are mechanosensitive (Abumiya et al., 2002; Davis et al., 2004; Korenaga et al., 2001; Verstraeten et al., 2010; Yun et al., 2002), and both of which play key roles in transcriptional regulation of sulfonylurea receptor 1 (Sur1) (Simard et al., 2006, 2009a). Sur1 forms the regulatory subunit of the NC_{Ca}-ATP channel, which has been implicated in microvascular dysfunction, including edema formation and HPC (called “progressive secondary hemorrhage” in the original articles) following CNS

FIG. 2. Hemorrhagic progression of a contusion (HPC) in a rat model of impact injury to the brain. (A–C) Surface views (top) and coronal views of the same brains taken at the epicenter of injury (bottom), from rats euthanized immediately after, 3 h after, or 8 h after impact injury, as indicated. All rats were perfused with saline to remove intravascular blood. From Simard et al., 2009b.

FIG. 3. Distribution of kinetic energy and nuclear translocation of transcription factors after focal impact. (A) Hematoxylin and eosin-stained coronal section of a rat brain 24h after impact injury, showing three idealized regions: (1) the initial contusion (the size was estimated from animals sacrificed 15 min after impact); (2) the surrounding penumbra, where delayed capillary fragmentation occurs due to molecular events initiated at the time of impact in mechanosensitive microvessels; and (3) the para-penumbra, where hemorrhage is not observed, but where delayed cell death occurs due to molecular events initiated at the time of impact in mechanosensitive neurons. Immunolabeling of penumbra (B and D), and para-penumbra (C and E), for the transcription factors p65, a subunit of nuclear factor- κ B (NF- κ B; B and C), and specificity protein 1 (Sp1; D and E). In each section, the nuclei are stained with 4,6-diamino-2-phenylindole (DAPI) (blue), and the secondary antibody used to detect the transcription factor is labeled with Cy3 (red), so that nuclear localization is indicated by pink nuclei. Note that Sp1 nuclear localization is found in both the penumbra and the para-penumbra, whereas p65 nuclear localization is found only in the penumbra. The impact used for this experiment was of less magnitude than the one used for the experiment in Figure 2, accounting for the absence of hemorrhage in the hippocampus. From Patel et al. 2010.

ischemia and trauma (Simard et al., 2006, 2007, 2008, 2009a). Notably, transcriptional events initiated by transcription factors require a long time, typically hours, to play out, providing a rational molecular explanation for the seemingly long interval between impact and the delayed development of new hemorrhages that characterize HPC.

The essential features of the molecular events initiated at the time of impact, which set the stage for later structural failure of microvessels, were described only recently (Patel et al., 2010; Simard et al., 2009b). The sequence begins with activation of the two mechanosensitive transcription factors, Sp1 and NF- κ B, by the kinetic energy deposited in the

FIG. 4. Delayed capillary fragmentation accounts for hemorrhagic progression of a contusion (HPC). (A and B) Brain sections 24 h after impact injury from rats treated with vehicle (CTR) or with glibenclamide (GLIB), immunolabeled for vimentin to identify microvessels. The regions shown are of the penumbra outside the initial contusion. Note the foreshortened fragmented capillaries in the vehicle-treated rat (A) compared to the elongated capillaries seen in the glibenclamide-treated rat (B). (C) Histogram of capillary length in vehicle- versus glibenclamide-treated rats (3 rats per group; $**p < 0.01$). From Simard et al., 2009b.

penumbra by the impact (Fig. 3B and D). Sp1 and NF- κ B (p65), which are directly linked to Sur1 transcription, are activated and undergo nuclear translocation within moments of the impact. A few hours later, microvessels in the same region begin exhibiting newly-expressed Sur1 (the pore-forming subunit of the channel has not yet been studied). Transcriptional upregulation followed by opening of the Sur1-regulated channel has been linked to oncotic cell swelling and oncotic (necrotic) cell death of neurons, astrocytes, and endothelial cells (Chen and Simard, 2001; Chen et al., 2003; Simard et al., 2006). Oncotic (necrotic) death of endothelial cells results in physical disruption of the capillary, termed capillary fragmentation. Immunolabeling of penumbral tissues shows foreshortened, broken segments of capillaries in penumbral regions where hemorrhages develop (Fig. 4; Simard et al., 2009b). Capillary fragmentation leads to the extravasation of blood—the formation of a petechial hemorrhage. Over the

12 h after injury, petechial hemorrhages continue to form, grow in number, and coalesce, resulting in progressive accumulation of extravasated blood, or HPC. An overview of some of the molecular events thought to transpire in penumbral capillaries, from impact to capillary fragmentation leading to HPC, is depicted in Figure 5.

In animal models of contusive TBI, HPC (or progressive secondary hemorrhage) is blocked by administering antisense oligodeoxynucleotide directed against *Abcc8*, the gene that encodes Sur1 (Simard et al., 2009b). Also, this process is eliminated by administering the potent Sur1 inhibitor glibenclamide. As a result, the volume of hemorrhage shows only a minimal increase beyond that associated with the primary hemorrhage, and the volume of the lesion with hemorrhagic necrosis is limited to that due to the primary injury; there is no HPC.

In the para-penumbra that surrounds the penumbra, only Sp1 is activated, NF- κ B is not (Fig. 3C and E; Patel et al., 2010).

FIG. 5. Schematic representation of the essential molecular events in the penumbra that are believed to account for hemorrhagic progression of a contusion (HPC). Kinetic energy from the impact is deposited in penumbral microvessels, resulting in activation and nuclear translocation of the mechanosensitive transcription factors specificity protein 1 (Sp1) and nuclear factor- κ B (NF- κ B). As a result, transcription of sulfonylurea receptor 1 (Sur1)-regulated NC_{Ca}-ATP channels ensues in endothelial cells. Hours later, after the newly-expressed channels have been inserted into the plasmalemmal membranes of endothelial cells and have become activated, the endothelial cells undergo oncotic (necrotic) cell death, resulting in capillary fragmentation and formation of petechial hemorrhages, thereby accounting for HPC (RBC, red blood cell).

In the para-penumbra, delayed hemorrhage is not observed. However, mechanosensitive Sp1 upregulates transcription of Sur1 and of another cell death protein, caspase-3, in neurons but not in microvessels. In the para-penumbra, neurons with Sp1 nuclear localization later exhibit cleaved caspase-3, consistent with apoptosis, and they undergo degeneration marked by Fluoro-Jade staining.

Following TBI, ischemia due to microvascular failure (endothelial swelling, vasoconstriction, and vasospasm), or microvascular occlusion (platelet/leukocyte aggregation/adhesion) contributes significantly to the overall injury. Notably, the ischemic environment surrounding a contusion may amplify HPC. Upregulation of Sur1 with expression of the Sur1-regulated NC_{Ca-ATP} channel also occurs following ischemia, but in this case, the transcriptional mechanism involves hypoxia inducible factor-1 (Hif-1) working via Sp1 (Simard et al., 2006). Hypoxia-sensitive transcription of Sur1 thus reinforces mechanosensitive transcription of Sur1. Hypoxia/ischemia is a common occurrence in brain regions surrounding a contusion (Dietrich et al., 1998; Engel et al., 2008; Longhi et al., 2007), further emphasizing the important role of Sur1 in contusive brain injury.

Conclusion

Functional outcome after TBI is determined largely by the location of the cerebral injury and by the final volume of irreversible tissue damage sustained. Tissue damage is determined by the magnitude of the primary injury that is sustained at the time of impact plus multiple secondary injury responses that inevitably worsen the primary injury. Arguably, one of the most important secondary injury mechanisms is HPC. Once blood is extravasated, involved tissues are doomed to hemorrhagic necrosis. Most frustrating, HPC occurs in a delayed fashion, hours after patients come under medical care, suggesting that there should be time to act to prevent this dreadful phenomenon from occurring. There is an urgent need to develop better treatment strategies to minimize HPC, something that will be feasible only with a better understanding of the underlying molecular mechanisms responsible. The identification of the molecular events detailed above that occur in the penumbra constitutes just the beginning of a long journey to unravel the mysteries of progressive microvascular failure initiated by impact injury. Such discoveries hold promise that future efforts will reveal the long-sought solution to the enormous problem of HPC.

Acknowledgments

J.M.S. is supported in part by grants from the Department of Veterans Affairs (Baltimore, MD), the National Heart, Lung and Blood Institute (HL082517), and the National Institute of Neurological Disorders and Stroke (NINDS) (NS061808 and NS060801). V.G. is supported in part by a grant from NINDS (NS061934).

Author Disclosure Statement

No competing financial interests exist.

References

Aarabi, B., Hesdorffer, D.C., Simard, J.M., Ahn, E.S., Aresco, C., Eisenberg, H.M., McCunn, M., and Scalea, T. (2009). Com-

- parative study of decompressive craniectomy after mass lesion evacuation in severe head injury. *Neurosurgery* 64, 927–939.
- Abumiya, T., Sasaguri, T., Taba, Y., Miwa, Y., and Miyagi, M. (2002). Shear stress induces expression of vascular endothelial growth factor receptor Flk-1/KDR through the CT-rich Sp1 binding site. *Arterioscler. Thromb. Vasc. Biol.* 22, 907–913.
- Al-Shahi, S.R. (2009). Haemostatic drug therapies for acute spontaneous intracerebral haemorrhage. *Cochrane Database Syst. Rev.* CD005951.
- Alahmadi, H., Vachhrajani, S., and Cusimano, M.D. (2010). The natural history of brain contusion: an analysis of radiological and clinical progression. *J. Neurosurg.* 112, 1139–1145.
- Allard, C.B., Scarpellini, S., Rhind, S.G., Baker, A.J., Shek, P.N., Tien, H., Fernando, M., Tremblay, L., Morrison, L.J., Pinto, R., and Rizoli, S.B. (2009). Abnormal coagulation tests are associated with progression of traumatic intracranial hemorrhage. *J. Trauma* 67, 959–967.
- Aoyama, N., Lee, S.M., Moro, N., Hovda, D.A., and Sutton, R.L. (2008). Duration of ATP reduction affects extent of CA1 cell death in rat models of fluid percussion injury combined with secondary ischemia. *Brain Res.* 1230, 310–319.
- Astrup, T. (1965). Assay and content of tissue thromboplastin in different organs. *Thromb. Diath. Haemorrh.* 14, 401–416.
- Blight, A.R. (1992). Macrophages and inflammatory damage in spinal cord injury. *J. Neurotrauma* 9 Suppl. 1, S83–S91.
- Buczek, M., Alvarez, J., Azhar, J., Zhou, Y., Lust, W.D., Selman, W.R., and Ratcheson, R.A. (2002). Delayed changes in regional brain energy metabolism following cerebral concussion in rats. *Metab. Brain Dis.* 17, 153–167.
- Carrick, M.M., Tyroch, A.H., Youens, C.A., and Handley, T. (2005). Subsequent development of thrombocytopenia and coagulopathy in moderate and severe head injury: support for serial laboratory examination. *J. Trauma* 58, 725–729.
- Chang, E.F., Meeker, M., and Holland, M.C. (2006). Acute traumatic intraparenchymal hemorrhage: risk factors for progression in the early post-injury period. *Neurosurgery* 58, 647–656.
- Chen, M., and Simard, J.M. (2001). Cell swelling and a nonselective cation channel regulated by internal Ca^{2+} and ATP in native reactive astrocytes from adult rat brain. *J. Neurosci.* 21, 6512–6521.
- Chen, M., Dong, Y., and Simard, J.M. (2003). Functional coupling between sulfonylurea receptor type 1 and a nonselective cation channel in reactive astrocytes from adult rat brain. *J. Neurosci.* 23, 8568–8577.
- Chierigato, A., Fainardi, E., Morselli-Labate, A.M., Antonelli, V., Compagnone, C., Targa, L., Kraus, J., and Servadei, F. (2005). Factors associated with neurological outcome and lesion progression in traumatic subarachnoid hemorrhage patients. *Neurosurgery* 56, 671–680.
- Cohen, M.J., Brohi, K., Ganter, M.T., Manley, G.T., Mackersie, R.C., and Pittet, J.F. (2007). Early coagulopathy after traumatic brain injury: the role of hypoperfusion and the protein C pathway. *J. Trauma* 63, 1254–1261.
- Compagnone, C., d'Avella, D., Servadei, F., Angileri, F.F., Brambilla, G., Conti, C., Cristofori, L., Delfini, R., Denaro, L., Ducati, A., Gaini, S.M., Stefani, R., Tomei, G., Tagliaferri, F., Trincia, G., and Tomasello, F. (2009). Patients with moderate head injury: a prospective multicenter study of 315 patients. *Neurosurgery* 64, 690–696.
- Davis, M.E., Grumbach, I.M., Fukui, T., Cutchins, A., and Harrison, D.G. (2004). Shear stress regulates endothelial nitric-oxide synthase promoter activity through nuclear factor kappaB binding. *J. Biol. Chem.* 279, 163–168.

- De, F.M., Rammo, R., O'Phelan, K., and Bullock, M.R. (2011). Alterations in cerebral oxidative metabolism following traumatic brain injury. *Neurocrit. Care* 14, 91–96.
- Diaz, F.G., Yock, D.H. Jr., Larson, D., and Rockswold, G.L. (1979). Early diagnosis of delayed posttraumatic intracerebral hematomas. *J. Neurosurg.* 50, 217–223.
- Dietrich, W.D., Alonso, O., Busto, R., Prado, R., Zhao, W., Dewanjee, M.K., and Ginsberg, M.D. (1998). Posttraumatic cerebral ischemia after fluid percussion brain injury: an autoradiographic and histopathological study in rats. *Neurosurgery* 43, 585–593.
- Engel, D.C., Mies, G., Terpolilli, N.A., Trabold, R., Loch, A., De Zeeuw, C.I., Weber, J.T., Maas, A.I., and Plesnila, N. (2008). Changes of cerebral blood flow during the secondary expansion of a cortical contusion assessed by ¹⁴C-iodoantipyrine autoradiography in mice using a non-invasive protocol. *J. Neurotrauma* 25, 739–753.
- Engel, D.C., Slemmer, J.E., Vlug, A.S., Maas, A.I., and Weber, J.T. (2005). Combined effects of mechanical and ischemic injury to cortical cells: secondary ischemia increases damage and decreases effects of neuroprotective agents. *Neuropharmacology* 49, 985–995.
- Engstrom, M., Romner, B., Schalen, W., and Reinstrup, P. (2005). Thrombocytopenia predicts progressive hemorrhage after head trauma. *J. Neurotrauma* 22, 291–296.
- Fainardi, E., Chierigato, A., Antonelli, V., Fagioli, L., and Servadei, F. (2004). Time course of CT evolution in traumatic subarachnoid haemorrhage: a study of 141 patients. *Acta Neurochir. (Wien.)* 146, 257–263.
- Flaherty, M.L. (2010). Anticoagulant-associated intracerebral hemorrhage. *Semin. Neurol.* 30, 565–572.
- Fukamachi, A., Nagaseki, Y., Kohno, K., and Wakao, T. (1985). The incidence and developmental process of delayed traumatic intracerebral haematomas. *Acta Neurochir. (Wien.)* 74, 35–39.
- Greuters, S., van den Berg, A., Franschman, G., Viersen, V.A., Beishuizen, A., Peerdeman, S.M., and Boer, C. (2011). Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury. *Crit. Care* 15, R2.
- Gudeman, S.K., Kishore, P.R., Miller, J.D., Girevendulis, A.K., Lipper, M.H., and Becker, D.P. (1979). The genesis and significance of delayed traumatic intracerebral hematoma. *Neurosurgery* 5, 309–313.
- Halpern, C.H., Reilly, P.M., Turtz, A.R., and Stein, S.C. (2008). Traumatic coagulopathy: the effect of brain injury. *J. Neurotrauma* 25, 997–1001.
- Hampton, M.B., Kettle, A.J., and Winterbourn, C.C. (1998). Inside the neutrophil phagosome: oxidants, myeloperoxidase, and bacterial killing. *Blood* 92, 3007–3017.
- Harhangi, B.S., Kompanje, E.J., Leebeek, F.W., and Maas, A.I. (2008). Coagulation disorders after traumatic brain injury. *Acta Neurochir. (Wien.)* 150, 165–175.
- Hoh, N.Z., Wagner, A.K., Alexander, S.A., Clark, R.B., Beers, S.R., Okonkwo, D.O., Ren, D., and Conley, Y.P. (2010). BCL2 genotypes: functional and neurobehavioral outcomes after severe traumatic brain injury. *J. Neurotrauma* 27, 1413–1427.
- Hong, Y., Yan, W., Chen, S., Sun, C.R., and Zhang, J.M. (2010). The role of Nrf2 signaling in the regulation of antioxidants and detoxifying enzymes after traumatic brain injury in rats and mice. *Acta Pharmacol. Sin.* 31, 1421–1430.
- Horiuchi, T., Nakagawa, F., Miyatake, M., Iwashita, T., Tanaka, Y., and Hongo, K. (2007). Traumatic middle cerebral artery aneurysm: case report and review of the literature. *Neurosurg. Rev.* 30, 263–267.
- Hossain, M., Brown, J., McLean, A.N., and Fraser, M.H. (2002). Delayed presentation of post-traumatic aneurysm of the posterior inferior cerebellar artery in a patient with spinal cord injury. *Spinal Cord* 40, 307–309.
- Itoh, T., Satou, T., Nishida, S., Tsubaki, M., Imano, M., Hashimoto, S., and Ito, H. (2010). Edaravone protects against apoptotic neuronal cell death and improves cerebral function after traumatic brain injury in rats. *Neurochem. Res.* 35, 348–355.
- Kaplan, M., Ozveren, M.F., Topsakal, C., Erol, F.S., and Akdemir, I. (2003). Asymptomatic interval in delayed traumatic intracerebral hemorrhage: report of two cases. *Clin. Neurol. Neurosurg.* 105, 153–155.
- Kaups, K.L., Davis, J.W., and Parks, S.N. (2004). Routinely repeated computed tomography after blunt head trauma: does it benefit patients? *J. Trauma* 56, 475–480.
- Korenaga, R., Yamamoto, K., Ohura, N., Sokabe, T., Kamiya, A., and Ando, J. (2001). Sp1-mediated downregulation of P2X4 receptor gene transcription in endothelial cells exposed to shear stress. *Am. J. Physiol. Heart Circ. Physiol.* 280, H2214–H2221.
- Lakshmanan, R., Loo, J.A., Drake, T., Leblanc, J., Ytterberg, A.J., McArthur, D.L., Etchepare, M., and Vespa, P.M. (2010). Metabolic crisis after traumatic brain injury is associated with a novel microdialysis proteome. *Neurocrit. Care* 12, 324–336.
- Langlois, J. A., Rutland-Brown, W., and Wald, M.M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *J. Head Trauma Rehabil.* 21, 375–378.
- Lenzlinger, P.M., Marx, A., Trentz, O., Kossmann, T., and Morganti-Kossmann, M.C. (2002). Prolonged intrathecal release of soluble Fas following severe traumatic brain injury in humans. *J. Neuroimmunol.* 122, 167–174.
- Liao, Z.B., Jiang, G.Y., Tang, Z.H., Zhi, X.G., Sun, X.C., Tang, W.Y., and Wu, M.J. (2009). Erythropoietin can promote survival of cerebral cells by downregulating Bax gene after traumatic brain injury in rats. *Neurol. India* 57, 722–728.
- Longhi, L., Pagan, F., Valeriani, V., Magnoni, S., Zanier, E.R., Conte, V., Branca, V., and Stocchetti, N. (2007). Monitoring brain tissue oxygen tension in brain-injured patients reveals hypoxic episodes in normal-appearing and in peri-focal tissue. *Intensive Care Med.* 33, 2136–2142.
- Lu, K.T., Sun, C.L., Wo, P.Y., Yen, H.H., Tang, T.H., Ng, M.C., Huang, M.L., and Yang, Y.L. (2011). Hippocampal neurogenesis after traumatic brain injury is mediated by vascular endothelial growth factor receptor-2 and the Raf/MEK/ERK cascade. *J. Neurotrauma* 28, 441–450.
- Luo, C.L., Chen, X.P., Yang, R., Sun, Y.X., Li, Q.Q., Bao, H.J., Cao, Q.Q., Ni, H., Qin, Z.H., and Tao, L.Y. (2010). Cathepsin B contributes to traumatic brain injury-induced cell death through a mitochondria-mediated apoptotic pathway. *J. Neurosci. Res.* 88, 2847–2858.
- Luo, C.L., Li, B.X., Li, Q.Q., Chen, X.P., Sun, Y.X., Bao, H.J., Dai, D.K., Shen, Y.W., Xu, H.F., Ni, H., Wan, L., Qin, Z.H., Tao, L.Y., and Zhao, Z.Q. (2011). Autophagy is involved in traumatic brain injury-induced cell death and contributes to functional outcome deficits in mice. *Neuroscience* 184, 45–63.
- Lustenberger, T., Talving, P., Kobayashi, L., Barmparas, G., Inaba, K., Lam, L., Branco, B.C., and Demetriades, D. (2010a). Early coagulopathy after isolated severe traumatic brain injury: relationship with hypoperfusion challenged. *J. Trauma* 69, 1410–1414.
- Lustenberger, T., Talving, P., Kobayashi, L., Inaba, K., Lam, L., Plurad, D., and Demetriades, D. (2010b). Time course of

- coagulopathy in isolated severe traumatic brain injury. *Injury* 41, 924–928.
- Marcoux, J., McArthur, D.A., Miller, C., Glenn, T.C., Villablanca, P., Martin, N.A., Hovda, D.A., Alger, J.R., and Vespa, P.M. (2008). Persistent metabolic crisis as measured by elevated cerebral microdialysis lactate-pyruvate ratio predicts chronic frontal lobe brain atrophy after traumatic brain injury. *Crit. Care Med.* 36, 2871–2877.
- McFeeley, P.J., and Blisard, K.S. (1988). Delayed traumatic intracerebral hematoma (DTICH) and the determination of the manner of death. A case report and review of the literature. *J. Forensic Sci.* 33, 801–805.
- Mendez, D.R., Cherian, L., and Robertson, C.S. (2004). Laser Doppler flow and brain tissue PO₂ after cortical impact injury complicated by secondary ischemia in rats treated with arginine. *J. Trauma* 57, 244–250.
- Morganti-Kossmann, M.C., Rancan, M., Stahel, P.F., and Kossmann, T. (2002). Inflammatory response in acute traumatic brain injury: a double-edged sword. *Curr. Opin. Crit. Care* 8, 101–105.
- Nakajima, Y., Horiuchi, Y., Kamata, H., Yukawa, M., Kuwabara, M., and Tsubokawa, T. (2010). Distinct time courses of secondary brain damage in the hippocampus following brain concussion and contusion in rats. *Tohoku J. Exp. Med.* 221, 229–235.
- Narayan, R.K., Maas, A.I., Marshall, L.F., Servadei, F., Skolnick, B.E., and Tillinger, M.N. (2008a). Recombinant factor VIIA in traumatic intracerebral hemorrhage: results of a dose-escalation clinical trial. *Neurosurgery* 62, 776–786.
- Narayan, R.K., Maas, A.I., Servadei, F., Skolnick, B.E., Tillinger, M.N., and Marshall, L.F. (2008b). Progression of traumatic intracerebral hemorrhage: a prospective observational study. *J. Neurotrauma* 25, 629–639.
- Nekludov, M., Bellander, B.M., Blomback, M., and Wallen, H.N. (2007). Platelet dysfunction in patients with severe traumatic brain injury. *J. Neurotrauma* 24, 1699–1706.
- Nelson, D.W., Nystrom, H., MacCallum, R.M., Thornquist, B., Lilja, A., Bellander, B.M., Rudehill, A., Wanecek, M., and Weitzberg, E. (2010). Extended analysis of early computed tomography scans of traumatic brain injured patients and relations to outcome. *J. Neurotrauma* 27, 51–64.
- Oertel, M., Boscardin, W.J., Obrist, W.D., Glenn, T.C., McArthur, D.L., Gravori, T., Lee, J.H., and Martin, N.A. (2005). Post-traumatic vasospasm: the epidemiology, severity, and time course of an underestimated phenomenon: a prospective study performed in 299 patients. *J. Neurosurg.* 103, 812–824.
- Oertel, M., Kelly, D.F., McArthur, D., Boscardin, W.J., Glenn, T.C., Lee, J.H., Gravori, T., Obukhov, D., McBride, D.Q., and Martin, N.A. (2002). Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. *J. Neurosurg.* 96, 109–116.
- Otto, V.I., Gloor, S.M., Frentzel, S., Gilli, U., Ammann, E., Hein, A.E., Folkers, G., Trentz, O., Kossmann, T., and Morganti-Kossmann, M.C. (2002). The production of macrophage inflammatory protein-2 induced by soluble intercellular adhesion molecule-1 in mouse astrocytes is mediated by src tyrosine kinases and p42/44 mitogen-activated protein kinase. *J. Neurochem.* 80, 824–834.
- Patel, A.D., Gerzanich, V., Geng, Z., and Simard, J.M. (2010). Glibenclamide reduces hippocampal injury and preserves rapid spatial learning in a model of traumatic brain injury. *J. Neuropathol. Exp. Neurol.* 69, 1177–1190.
- Patel, N.Y., Hoyt, D.B., Nakaji, P., Marshall, L., Holbrook, T., Coimbra, R., Winchell, R.J., and Mikulaschek, A.W. (2000). Traumatic brain injury: patterns of failure of nonoperative management. *J. Trauma* 48, 367–374.
- Perel, P., Roberts, I., Shakur, H., Thinkhamrop, B., Phuentsathom, N., and Yutthakasemsunt, S. (2010). Haemostatic drugs for traumatic brain injury. *Cochrane Database Syst. Rev.* CD007877.
- Ramon y Cajal, S. (1991). Atrophic phenomena consequent on cerebral wounds, in: *Cajal's Degeneration and Regeneration of the Nervous System*. J. DeFelipe and E.G. Jones (eds). Oxford University Press: London, pps. 704–713.
- Robertson, C.L., Scafidi, S., McKenna, M.C., and Fiskum, G. (2009). Mitochondrial mechanisms of cell death and neuroprotection in pediatric ischemic and traumatic brain injury. *Exp. Neurol.* 218, 371–380.
- Ryter, S.W., Kim, H.P., Hoetzel, A., Park, J.W., Nakahira, K., Wang, X., and Choi, A.M. (2007). Mechanisms of cell death in oxidative stress. *Antioxid. Redox. Signal.* 9, 49–89.
- Scafidi, S., O'Brien, J., Hopkins, I., Robertson, C., Fiskum, G., and McKenna, M. (2009). Delayed cerebral oxidative glucose metabolism after traumatic brain injury in young rats. *J. Neurochem.* 109 Suppl. 1, 189–197.
- Selassie, A.W., Zaloshnja, E., Langlois, J.A., Miller, T., Jones, P., and Steiner, C. (2008). Incidence of long-term disability following traumatic brain injury hospitalization, United States, 2003. *J. Head Trauma Rehabil.* 23, 123–131.
- Servadei, F., Murray, G.D., Penny, K., Teasdale, G.M., Dear-den, M., Iannotti, F., Lapierre, F., Maas, A.J., Karimi, A., Ohman, J., Persson, L., Stocchetti, N., Trojanowski, T., and Unterberg, A. (2000a). The value of the “worst” computed tomographic scan in clinical studies of moderate and severe head injury. *European Brain Injury Consortium. Neurosurgery* 46, 70–75.
- Servadei, F., Nanni, A., Nasi, M.T., Zappi, D., Vergoni, G., Giuliani, G., and Arista, A. (1995). Evolving brain lesions in the first 12 hours after head injury: analysis of 37 comatose patients. *Neurosurgery* 37, 899–906.
- Servadei, F., Nasi, M.T., Giuliani, G., Cremonini, A.M., Cenni, P., Zappi, D., and Taylor, G.S. (2000b). CT prognostic factors in acute subdural haematomas: the value of the “worst” CT scan. *Br. J. Neurosurg.* 14, 110–116.
- Shoji, H., Kaneko, Y., Mabuchi, T., Kibayashi, K., Adachi, N., and Borlongan, C.V. (2010). Genetic and histologic evidence implicates role of inflammation in traumatic brain injury-induced apoptosis in the rat cerebral cortex following moderate fluid percussion injury. *Neuroscience* 171, 1273–1282.
- Sifri, Z.C., Homnick, A.T., Vaynman, A., Lavery, R., Liao, W., Mohr, A., Hauser, C.J., Manniker, A., and Livingston, D. (2006). A prospective evaluation of the value of repeat cranial computed tomography in patients with minimal head injury and an intracranial bleed. *J. Trauma* 61, 862–867.
- Sifri, Z.C., Livingston, D.H., Lavery, R.F., Homnick, A.T., Mosenthal, A.C., Mohr, A.M., and Hauser, C.J. (2004). Value of repeat cranial computed axial tomography scanning in patients with minimal head injury. *Am. J. Surg.* 187, 338–342.
- Simard, J.M., Chen, M., Tarasov, K.V., Bhatta, S., Ivanova, S., Melnitchenko, L., Tsybalyuk, N., West, G.A., and Gerzanich, V. (2006). Newly expressed SUR1-regulated NC(Ca-ATP) channel mediates cerebral edema after ischemic stroke. *Nat. Med.* 12, 433–440.
- Simard, J.M., Geng, Z., Woo, S.K., Ivanova, S., Tosun, C., Melnichenko, L., and Gerzanich, V. (2009a). Glibenclamide reduces inflammation, vasogenic edema, and caspase-3 activation after subarachnoid hemorrhage. *J. Cereb. Blood Flow Metab* 29, 317–330.

- Simard, J.M., Kilbourne, M., Tsybalyuk, O., Tosun, C., Caridi, J., Ivanova, S., Keledjian, K., Bochicchio, G., and Gerzanich, V. (2009b). Key role of sulfonylurea receptor 1 in progressive secondary hemorrhage after brain contusion. *J. Neurotrauma* 26, 2257–2267.
- Simard, J.M., Tsybalyuk, O., Ivanov, A., Ivanova, S., Bhatta, S., Geng, Z., Woo, S.K., and Gerzanich, V. (2007). Endothelial sulfonylurea receptor 1-regulated NC Ca-ATP channels mediate progressive hemorrhagic necrosis following spinal cord injury. *J. Clin. Invest.* 117, 2105–2113.
- Simard, J.M., Woo, S.K., Bhatta, S., and Gerzanich, V. (2008). Drugs acting on SUR1 to treat CNS ischemia and trauma. *Curr. Opin. Pharmacol.* 8, 42–49.
- Smith, J.A. (1994). Neutrophils, host defense, and inflammation: a double-edged sword. *J. Leukoc. Biol.* 56, 672–686.
- Smith, J.S., Chang, E.F., Rosenthal, G., Meeker, M., von Koch, K.C., Manley, G.T., and Holland, M.C. (2007). The role of early follow-up computed tomography imaging in the management of traumatic brain injury patients with intracranial hemorrhage. *J. Trauma* 63, 75–82.
- Stein, S.C., and Smith, D.H. (2004). Coagulopathy in traumatic brain injury. *Neurocrit. Care* 1, 479–488.
- Stein, S.C., Spettell, C., Young, G., and Ross, S.E. (1993). Delayed and progressive brain injury in closed-head trauma: radiological demonstration. *Neurosurgery* 32, 25–30.
- Stein, S.C., Young, G.S., Talucci, R.C., Greenbaum, B.H., and Ross, S.E. (1992). Delayed brain injury after head trauma: significance of coagulopathy. *Neurosurgery* 30, 160–165.
- Stiefel, M.F., Tomita, Y., and Marmarou, A. (2005). Secondary ischemia impairing the restoration of ion homeostasis following traumatic brain injury. *J. Neurosurg.* 103, 707–714.
- Sun, Y., Wang, J., Wu, X., Xi, C., Gai, Y., Liu, H., Yuan, Q., Wang, E., Gao, L., Hu, J., and Zhou, L. (2011). Validating the incidence of coagulopathy and disseminated intravascular coagulation in patients with traumatic brain injury: analysis of 242 cases. *Br. J. Neurosurg.* 25, 363–368.
- Thurman, D.J., Alverson, C., Dunn, K.A., Guerrero, J., and Snieszek, J.E. (1999). Traumatic brain injury in the United States: A public health perspective. *J. Head Trauma Rehabil.* 14, 602–615.
- Tian, H.L., Chen, H., Wu, B.S., Cao, H.L., Xu, T., Hu, J., Wang, G., Gao, W.W., Lin, Z.K., and Chen, S.W. (2010). D-dimer as a predictor of progressive hemorrhagic injury in patients with traumatic brain injury: analysis of 194 cases. *Neurosurg. Rev.* 33, 359–365.
- Tseng, S.H. (1992). Delayed traumatic intracerebral hemorrhage: a study of prognostic factors. *J. Formos. Med. Assoc.* 91, 585–589.
- Van Beek, J.G., Mushkudiani, N.A., Steyerberg, E.W., Butcher, I., McHugh, G.S., Lu, J., Marmarou, A., Murray, G.D., and Maas, A.I. (2007). Prognostic value of admission laboratory parameters in traumatic brain injury: results from the IMPACT study. *J. Neurotrauma* 24, 315–328.
- Verstraeten, S.V., Mackenzie, G.G., and Oteiza, P.I. (2010). The plasma membrane plays a central role in cells response to mechanical stress. *Biochim. Biophys. Acta.* 1798, 1739–1749.
- Vespa, P., Bergsneider, M., Hattori, N., Wu, H.M., Huang, S.C., Martin, N.A., Glenn, T.C., McArthur, D.L., and Hovda, D.A. (2005). Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. *J. Cereb. Blood Flow Metab* 25, 763–774.
- Wafaisade, A., Lefering, R., Tjardes, T., Wutzler, S., Simanski, C., Paffrath, T., Fischer, P., Bouillon, B., and Maegele, M. (2010). Acute coagulopathy in isolated blunt traumatic brain injury. *Neurocrit. Care* 12, 211–219.
- Wang, M.C., Linnau, K.F., Tirschwell, D.L., and Hollingworth, W. (2006). Utility of repeat head computed tomography after blunt head trauma: a systematic review. *J. Trauma* 61, 226–233.
- Whitney, N.P., Eidem, T.M., Peng, H., Huang, Y., and Zheng, J.C. (2009). Inflammation mediates varying effects in neurogenesis: relevance to the pathogenesis of brain injury and neurodegenerative disorders. *J. Neurochem.* 108, 1343–1359.
- Yamashima, T., and Oikawa, S. (2009). The role of lysosomal rupture in neuronal death. *Prog. Neurobiol.* 89, 343–358.
- Yang, T.C., Lo, Y.L., Huang, Y.C., and Yang, S.T. (2007). Traumatic anterior cerebral artery aneurysm following blunt craniofacial trauma. *Eur. Neurol.* 58, 239–245.
- Yatsiv, I., Morganti-Kossmann, M.C., Perez, D., Dinarello, C.A., Novick, D., Rubinstein, M., Otto, V.I., Rancan, M., Kossmann, T., Redaelli, C.A., Trentz, O., Shohami, E., and Stahel, P.F. (2002). Elevated intracranial IL-18 in humans and mice after traumatic brain injury and evidence of neuroprotective effects of IL-18-binding protein after experimental closed head injury. *J. Cereb. Blood Flow Metab* 22, 971–978.
- Yi, J.H., and Hazell, A.S. (2006). Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. *Neurochem. Int.* 48, 394–403.
- Yi, J.H., Hoover, R., McIntosh, T.K., and Hazell, A.S. (2006). Early, transient increase in complexin I and complexin II in the cerebral cortex following traumatic brain injury is attenuated by N-acetylcysteine. *J. Neurotrauma* 23, 86–96.
- Yokota, H. (2007). Cerebral endothelial damage after severe head injury. *J. Nippon Med. Sch.* 74, 332–337.
- Young, H.A., Gleave, J.R., Schmidek, H.H., and Gregory, S. (1984). Delayed traumatic intracerebral hematoma: report of 15 cases operatively treated. *Neurosurgery* 14, 22–25.
- Yun, S., Dardik, A., Haga, M., Yamashita, A., Yamaguchi, S., Koh, Y., Madri, J.A., and Sumpio, B.E. (2002). Transcription factor Sp1 phosphorylation induced by shear stress inhibits membrane type 1-matrix metalloproteinase expression in endothelium. *J. Biol. Chem.* 277, 34808–34814.
- Zaaroor, M., Soustiel, J.F., Brenner, B., Bar-Lavie, Y., Martinowitz, U., and Levi, L. (2008). Administration off label of recombinant factor-VIIa (rFVIIa) to patients with blunt or penetrating brain injury without coagulopathy. *Acta Neurochir. (Wien.)* 150, 663–668.
- Zaloshnja, E., Miller, T., Langlois, J.A., and Selassie, A.W. (2008). Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. *J. Head Trauma Rehabil.* 23, 394–400.
- Zehtabchi, S., Soghoian, S., Liu, Y., Carmody, K., Shah, L., Whittaker, B., and Sinert, R. (2008). The association of coagulopathy and traumatic brain injury in patients with isolated head injury. *Resuscitation* 76, 52–56.
- Zweckberger, K., Eros, C., Zimmermann, R., Kim, S.W., Engel, D., and Plesnila, N. (2006). Effect of early and delayed decompressive craniectomy on secondary brain damage after controlled cortical impact in mice. *J. Neurotrauma* 23, 1083–1093.

Address correspondence to:

J. Marc Simard, M.D.

Department of Neurosurgery

University of Maryland School of Medicine

22 South Greene Street, Suite S12D

Baltimore, MD 21201-1595

E-mail: msimard@smail.umaryland.edu