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Secondary Hematoma Expansion and Perihemorrhagic Edema after Intracerebral Hemorrhage: From Bench Work to Practical Aspects

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Intracerebral hemorrhages (ICH) represent about 10–15% of all strokes per year in the United States alone. Key variables influencing the long-term outcome after ICH are hematoma size and growth. Although death may occur at the time of the hemorrhage, delayed neurologic deterioration frequently occurs with hematoma growth and neuronal injury of the surrounding tissue. Perihematoma edema has also been implicated as a contributing factor for delayed neurologic deterioration after ICH. Cerebral edema results from both blood–brain barrier disruption and local generation of osmotically active substances. Inflammatory cellular mediators, activation of the complement, by-products of coagulation and hemolysis such as thrombin and fibrin, and hemoglobin enter the brain and induce a local and systemic inflammatory reaction. These complex cascades lead to apoptosis or neuronal injury. By identifying the major modulators of cerebral edema after ICH, a therapeutic target to counter degenerative events may be forthcoming.

Keywords: hypothermia, induced, neurosciences, brain edema, intracranial hypertension

INTRODUCTION

Intracerebral hemorrhage (ICH) comprises 10–15% of strokes annually in the United States and associated with the highest morbidity and mortality (1). There is approximately 40% mortality at 1-month postbleed, and only about 20% of those patients regain functional independence (2). A key factor affecting ICH outcome is hematoma size and hematoma expansion. Although death may occur acutely at the sentinel ICH event, delayed neurologic deterioration often occurs with the evolution of the hematoma and injury of the surrounding tissue. Key variables influencing the long-term outcome after ICH are hematoma size and location and are not modifiable at the onset of symptoms. Hematoma growth can also be a predictor of poor outcome, and recent clinical evidence suggests that it may be preventable. Additional risk factors for hematoma growth include antithrombotic therapy, hypertension, large initial hematoma size, and genetic predisposition such as with APOE genotype. Approximately 30% of patients demonstrate significant hematoma expansion during hospitalization (3). Therapies aimed at the prevention of hematoma growth generally target either blood pressure (BP) control or hemostasis. Recent large clinical trials tested therapies aimed at modifying these outcomes and included BP reduction and hemostatic therapy with recombinant factor VIIa (rFVIIa) assisted by computed tomography (CT) angiography (CT-A) findings (4).

Perihematoma edema (PHE) has also been implicated as a contributing factor for delayed neurologic deterioration after ICH (5). Cerebral edema forms within hours in the immediate vicinity of the clot (PHE) and can last for several weeks. PHE is the result of both blood–brain barrier (BBB) disruption and local generation of osmotically active substances that spread to adjacent structures (6). Inflammatory cellular mediators, activation of the complement, by-products of coagulation and hemolysis such as thrombin and fibrin, and hemoglobin spread into the brain tissue and induce a local and systemic inflammatory response. This process likely results from complex chemotactic signals including upregulation of adhesion molecules leading to leukocyte recruitment and migration into the brain tissue (7) (Table 1).

HEMATOMA GROWTH

Studies from ICH models that used histopathology, CT analysis, single-photon emission computed tomography (SPECT), and both conventional CT and CT-A techniques suggested that secondary multifocal bleeding into the perihematoma region is more likely to occur in individuals who experience early hematoma growth. Preliminary histopathological studies provide evidence that the presence of microscopic and macroscopic bleeds in the area surrounding hematoma may represent ruptured arterioles or venules (8). More recent studies that used CT and SPECT techniques have shown that in some patients, early hematoma growth is associated with secondary bleeding in the periphery of the existing hematoma and into congested areas of the perihematoma tissue (9).

Irregular clot morphology, which may represent ongoing or active bleeding after ICH, is another variable that has been associated with (10) early hematoma growth. In support, additional secondary studies from large randomized clinical trials on BP reduction after ICH have also demonstrated that irregular clot morphology is associated with worse long-term outcomes after ICH (11). One study using CT-A technology demonstrated that the presence of active contrast extravasation into the hematoma was associated with subsequent hematoma growth (12) and higher mortality (13) in 30–46% of patients (14, 15). Simultaneous bleeding from multiple lenticulostriate arteries has been demonstrated angiographically immediately after ICH (16, 17). This evidence suggests that early hematoma growth occurs because of bleeding into a congested layer of tissue that forms acutely at the periphery of the hematoma (18). Possible contributing factors include (a)

increased local tissue pressure leading to mechanical injury, (b) a local fibrinolytic effect, (c) plasma protease induction, and (d) secondary inflammation related to clotting proteins and end-blood products. However, the relative importance of these factors in the early hours after ICH is unclear (6, 19–21).

A proposed theory is that the increase in local tissue pressure occurs in the brain surrounding the hematoma at the expense of a form of “congestive” tissue ischemia. This phenomenon may be similar to what is seen after cerebral infarction from cortical vein or dural sinus thrombosis. All of these mechanisms coupled with regional mechanical and ischemic tissue damage and the possibility of a local coagulopathic environment may contribute to worsening secondary bleeding from venules and arterioles.

Clinical and Radiological Evidence in Support of Early Hematoma Growth

Early hematoma growth evidenced by consecutive CT scans can occur in 18–38% of patients scanned within 3 h of ICH onset. Multiple CT-based studies have provided further support for the occurrence of early hematoma growth after ICH (10, 22–26). The highest incidence of early hematoma growth (38%) was seen in the Brott and Broderick's study, but the investigators concluded that the true frequency of hematoma growth may have been higher because clinical deterioration and immediate surgical intervention precluded the performance of the follow-up CT scans in some of the studied patients (26). To summarize, the only consistently identified predictor of early hematoma growth is the time from the onset of ICH to CT scan, in other words, the earlier the first CT scan is done, the more likely subsequent bleeding will be detected on a follow-up CT scan (10, 25, 27).

To this end, hematoma expansion occurs in only 5% of patients who are initially scanned beyond 6 h of symptom onset (10, 25, 26, 28). Early hematoma expansion is consistently associated with poor clinical outcomes and higher mortality rates versus no expansion. Similarly, significantly greater reductions in the Glasgow Coma Scale and National Institute of Health Stroke Scales have been reported among patients with documented hematoma expansion on 1-h follow-up CT scans versus those without growth (26). These observations suggest that the reduction in hematoma growth may be an important strategy for improvement of survival and outcome after ICH.

TREATMENT STRATEGIES TO PREVENT HEMATOMA GROWTH

BP Control

Patients with ICH should have tightly managed BP, but it is frequently elevated acutely (29). In the majority of cases, extremely high admission BP is the primary therapeutic issue in ICH patients. In the Study of Treatment of Acute Hypertension (30), nearly 30% of patients who presented to an Emergency Department with acute hypertension had a demonstrable brain injury of which 30% were ICHs. Systolic blood pressure (SBP > 140 mmHg) is seen in >75% of patients with ICH (29, 31). Causes of this hypertensive response include upregulation of the sympathetic nervous system and the renin–angiotensin and

TABLE 1 | Phases of ICH and proposed pathophysiologic events [with permission from Rincon and Mayer (59)].

Phase	Event	Time	Implicated mechanism
I	Vascular rupture	1–10 s	Chronic vascular changes: lipohyalinosis, amyloid angiopathy, hypocholesterolemia
II	Hematoma formation	<1 h	Blood pressure, coagulation abnormalities
III	Hematoma expansion	1–6 h	Blood pressure, perihematomal vascular + tissue injury
IV	Edema formation	24–72 h	Cellular and humoral toxicity, blood degradation products

pituitary-adrenal axis (32). Single-center studies and a systematic review have independently demonstrated a higher risk of early clinical deterioration, mortality, and worst long-term outcome with either extreme high or low levels of BP after ICH (33–38).

Extreme levels of BP could theoretically contribute to acute hematoma growth and later aggravate PHE and intracranial pressure (ICP). This could potentially translate into worst short- and long-term outcomes after ICH (39, 40). Preliminary studies provided some evidence of early hematoma growth from bleeding into an ischemic penumbra zone surrounding the hematoma (41, 42). However, other studies did not confirm the existence of such ischemic and hypoperfused area in the periphery of the hematoma. In the landmark study by Brott et al. (26), acute hypertension after ICH was not associated with hematoma growth, but the authors suggested that the use of antihypertensive agents may have negatively confounded this association. Similarly, acute hypertension was not associated with hematoma growth in the Recombinant Activated Factor VII ICH Trial (43).

Despite this conflicting evidence, the overall consensus is that extreme levels of BP (either low or high) after ICH should be treated carefully. Controversy exists regarding the optimal threshold for treatment and target level [SBP versus mean arterial pressure (MAP)]. Aggressive BP reduction in the setting of impaired autoregulation may predispose to perihematomal or distant brain tissue ischemia, whereas intact autoregulation might result in reflex vasodilation and increase in cerebral edema resulting in higher ICP (44, 45). In a small pilot study of BP reduction after ICH, 14 patients with supratentorial ICH were randomized to receive either labetalol or nicardipine within 22 h of ictus with the aim to lower the MAP by 15%. Cerebral blood flow (CBF) studies were performed before and after treatment with positron emission tomography and [¹⁵O] water. No changes in global or perihematoma CBF were observed (46). Finally, earlier studies also demonstrated that a controlled pharmacologically based reduction in BP had no adverse effects on CBF in both humans and animals (47, 48). These preliminary evidence led to the development of clinical studies on aggressive BP control after ICH.

Seven clinical trials have evaluated the role of intensive BP reduction after ICH (49–55). The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT)-I phase II study was an open-label trial of 403 patients randomized to a target SBP of <180 (guideline recommendation) or <140 mmHg within 6 h of onset (56). The study showed a trend toward lower relative and absolute hematoma growth from baseline to 24 h in the intensive treatment group (SBP < 140 mmHg) compared with the control group. The phase III clinical trial INTERACT-II

concluded that aggressive BP control did not result in a significant reduction in the mortality rate or severe disability after ICH (54, 57). However, a trend was observed when the primary outcome was analyzed in an ordinal fashion, suggesting that in a selected cohort of ICH patients, intensive lowering of BP may improve long-term outcomes (57).

The Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH)-I trial (52, 58) confirmed the feasibility and safety of early rapid BP reduction in ICH. This phase II randomized prospective controlled study employed a dose escalation regimen of intravenous nicardipine for BP reduction in 80 patients with ICH. No effect was seen on outcome or neurological worsening. Both INTERACT-II and ATACH-I showed that although early and intensive BP lowering is clinically feasible and safe, this was not associated with meaningful clinical outcome differences (see **Table 2**).

The recently completed phase III ATACH-II clinical study was closed based on futility translating into no meaningful benefit from the intensive treatment group (SBP < 140 mmHg) compared to the guideline recommendation (SBP < 180 mmHg) (53). The ATACH-II trial was designed to evaluate the efficacy of aggressively lowering the SBP in ICH patients but in an earlier time-window (60). One aim of the ATACH-II trial was to show that a more rapid intensive reduction in the SBP level than that used in INTERACT-II would make it more likely to show a larger therapeutic benefit. However, the intensive and early treatment did not result in a lower rate of mortality or poor outcome.

In the Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH-ADAPT) I (55), the use of a strict triple-regimen BP lowering protocol permitted a significant BP difference between the groups at 2 h postrandomization. The target BP was achieved in 79% of patients in the <150 mmHg group at 2 h. The follow-up phase II ICH-ADAPT II is designed to test the hypothesis that aggressive antihypertensive therapy will alter the natural history of hematoma growth, improving outcomes after ICH using MRI and DWI as primary outcomes. The study will identify biomarkers that may be putative mediators of ischemic injury in ICH patients (49) (see **Table 3**).

Current recommendations for Guidelines for the Management of Spontaneous Intracerebral Hemorrhage from AHA/ASA state that for “ICH patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe (Class I; Level of Evidence A) and can be effective for improving functional outcome (Class IIA; Level of Evidence B)” (61). This recommendation is consistent with the results of the ATACH-II trial

TABLE 2 | Comparison of INTERACT-II versus ATACH-II trials.

	Randomization	Treatment group	Control group	Outcome
INTERACT-II	All within 6 h of symptom onset; 48% systolic blood pressure (SBP) > 180 mmHg	Target SBP < 180 mmHg within 1 h after randomization	Target SBP < 140 mmHg with agents of physician's choosing	No significant reduction in modified Rankin Scale (mRS) score at 3 months
ATACH-II	All within 4.5 h of symptom onset; SBP > 180 mmHg	Maintain SBP 140–179 mmHg during 24 h after randomization	Maintain SBP 110–139 mmHg during 24 h after randomization with first-line nicardipine and second-line labetalol	No significant reduction in mRS score at 3 months

TABLE 3 | Prospective clinical trials of blood pressure management in ICH.

Trial	Study design	SBP targets	Onset to randomization time	Medical intervention used	End point
INTERACT	<i>n</i> = 404, RCT, PROBE, phase II	Standard: <180 Intensive: <140	<6 h	Variable	24 h hematoma growth
INTERACT-II	<i>n</i> = 2,839, RCT, phase III	Standard: <180 Intensive: <140	<6 h	Variable	mRs at 90 days
ATACH	<i>n</i> = 60, RCT, phase II	Tier 1: <170–200 Tier 2: <140–170 Tier 3: <110–140	<6 h	Nicardipine	Treatment feasibility and safety
ATACH-II	<i>n</i> = 1,200, RCT, PROBE, phase III	Standard: <180 Intensive: <140	<4.5 h	Nicardipine	mRS at 90 days
ICH ADAPT	<i>n</i> = 75, RCT, PROBE, phase II	Standard: <180 Intensive: <150	<24 h	Labetalol Hydralazine Enalapril	Perihematoma CBF
ICH ADAPT II	RCT, PROBE, phase II	Standard: <180 Intensive: <140	<6 h	Labetalol Hydralazine Enalapril	DWI lesion frequency at 24 h

RCT, randomized control trial; PROBE, prospective randomized open blinded end point; CBF, cerebral blood flow; mRS, modified Rankin Scale; SBP, systolic blood pressure.

in which participants with intracerebral hemorrhage volume <60 cm³ and participants with intracerebral hemorrhage volume <60 cm³ and GCS > 5 were assigned to a SBP goal <140 mmHg or SBP < 180 mmHg. The ATACH-II trial did not result in a lower rate of death or disability with acute reduction of SBP to goal <140 mmHg than the standard goal SBP < 180 mmHg. The absolute difference between the two groups in the rate of death or disability was 1 percentage point (60). Although feasible and safe, the rate of renal adverse events within 7 days after randomization in ATACH-II was significantly higher in the intensive treatment group than in the standard-treatment group (9.0 versus 4.0%, *P* = 0.002) (60).

Hemostasis

As hematoma growth is a powerful predictor of outcome after spontaneous ICH, it makes biological sense to attempt to optimize hemostasis as early as possible. rFVIIa (Novoseven®, Novo Nordisk) has been approved for the management of bleeding patients with congenital forms of hemophilia and who are resistant to conventional factor VIII replacement therapy. There is substantial evidence that rFVIIa may optimize hemostasis in patients with normal coagulation function. Recently, a randomized controlled phase II study of 399 patients with spontaneous ICH demonstrated that the administration of rFVIIa at doses of 40, 80, or 160 µg/kg within 4 h of onset was associated with a 38% reduction in death and improved functional outcomes at 90 days, despite a 5% increase in the frequency of arterial thromboembolic adverse events (62). However, this effect was not replicated in the follow-up phase III FAST clinical trial of rFVIIa after ICH. In this study, doses of 80 and 20 µg/kg of rFVIIa were compared against placebo in 841 subjects with spontaneous ICH. The study found no significant difference in the proportion of patients with death or severe disability (mRS 5–6) at 90 days, but the hemostatic effect and adverse effect profiles were replicated (63). On the basis of these results, the

routine use of rFVIIa as a hemostatic therapy for patients with spontaneous ICH cannot be recommended. A *post hoc* study of the FAST clinical trial demonstrated that factor rFVIIa may be useful in younger patients who present within an earlier time-window, but further recommendations may need to be supported by future clinical trials (64).

A preliminary clinical study of the antifibrinolytic agent epsilon aminocaproic acid (ECA) was conducted with negative results (65). The management of ICH with Aminocaproic acid open-label pilot study (MANICHAN-PILOT) and the Antifibrinolytic Therapy in Acute Intracerebral Hemorrhage clinical trial are also designed to test the hypothesis that ECA administration within 3 h of ICH is associated with less hematoma growth and improved outcomes (66, 67). As antifibrinolytic therapies carry a higher risk of adverse thromboembolic events, additional studies have focused on determining the specific population of patients that might benefit from this therapy. Four ongoing clinical trials are studying if image-assisted antifibrinolytic therapy may offer further benefit by identifying ICH patients with ongoing bleeding and whom may benefit from acute hemostasis (68–71).

Although CT-A post-ICH is not routinely performed in all clinical centers, it may prove helpful in predicting hematoma growth and clinical outcomes (13, 72). In a prospective study of 39 patients with spontaneous ICH, focal enhancing foci (contrast extravasation, “spot sign”) seen in initial CT-A was associated with the presence and extent of hematoma progression with good sensitivity (91%) and negative predictive value (96%) (14). In the “Spot Sign” Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT), ICH patients with a “spot sign” (14) will be randomly assigned to a single injection of rFVII or placebo. The study aims at evaluating the rate of hematoma growth and the difference in proportion of clinical outcomes such as death and disability (69). In the Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT), investigators will

determine whether CT-A can predict which individuals with ICH will experience significant hematoma growth in the size of the hemorrhage and the effect of rFVIIa on hematoma growth (68). The end points of the Tranexamic Acid for Acute ICH Growth prEdicted by Spot Sign (TRAIGE) clinical trial and the Spot Sign and Tranexamic Acid On Preventing ICH Growth—AUStralasia Trial (STOP-AUST) are similar to STOP-IT, but in this study, the investigators will use tranexamic acid, a newer antifibrinolytic agent (70, 71).

Additional studies related to hemostasis involve the use of platelet transfusions and prothrombin complex concentrate (PCCs) for coagulopathic or antiplatelet-exposed ICH patients and optimization of coagulation before neurosurgical interventions (73–76). One study recently assessed the effect of platelet transfusion in an open-label inception cohort of ICH patients who underwent platelet function assays with Accumetrics (75). In those patients with abnormal platelet function results and risk of poorer outcome, early platelet transfusion improved platelet activity and was associated with smaller hematoma sizes and with a better functional outcome at 3 months (75). The recently finished Platelet Transfusion in Cerebral Hemorrhage (PATCH) clinical trial (73) aimed at determining whether platelet transfusion improves the risk of hematoma growth and functional outcome in ICH patients who were taking antiplatelet agents. The PATCH study demonstrated significant adverse events, higher mortality, and worst long-term functional outcome in ICH patients who received transfusion. On the basis of the results of this study, platelet transfusion cannot be recommended as a standard procedure in this specific patient population.

Other approaches to optimize antifibrinolytic therapy have been used in combination with surgical evacuation. In the “Intraoperative intravenous administration of rFVIIa and hematoma volume after early surgery for spontaneous intracerebral hemorrhage clinical trial,” the administration of intravenous rFVIIa did not change the hematoma volume or the functional outcome after ICH combined with early surgery. Interestingly, the study showed that there were no meaningful differences in the rates of deep venous thrombosis, myocardial infarction, or cerebral ischemia (77). In the “International Normalized Ratio (INR) Normalization in Coumadin Associated Intracerebral Hemorrhage phase III clinical study,” investigators will test the hypothesis that the treatment for coagulopathic ICH with PCC improves normalization of the INR, hematoma growth, and clinical outcomes compared to transfusions of fresh-frozen plasma (74).

PHE AFTER ICH

The secondary injury of ICH results is the formation of PHE, which may contribute to an increase in peri-hematoma volume by at least 75% (78). This progression of neuronal injury may lead to increased ICP, herniation, neurological deficits, and death. Enhanced models of hydrostatic and osmotic forces have been recently formulated to explain PHE based on the unique properties of the BBB. Early PHE is attributed to the transcapillary efflux of electrolytes and water from blood vessels (ionic

TABLE 4 | Mechanisms implicated in the genesis and worsening of perihematomal edema.

Early		Late
<24 h	24–72 h	>72 h
<ul style="list-style-type: none"> • Serum proteins • Glucose • Electrolytes (Na, K) 	<ul style="list-style-type: none"> • Cellular toxicity (white blood cells, platelets) • Humoral toxicity [interleukin (IL)-1, IL-6, intracellular adhesion molecule, tumor necrosis factor alpha, prostaglandins, leukotrienes, vascular endothelial growth factor, complement] • Coagulation cascade (thrombin, fibrinogen, t-PA) • Glutamate and amino acids • Epinephrine? 	<ul style="list-style-type: none"> • Blood degradation products (Hgb, Fe, biliverdin) • Nitric oxide • Free radicals • Apoptosis • Matrix metalloproteinases • Glutamate and amino acids

With permission from Ref. (59).

edema), osmotically active serum proteins, and cytotoxic edema from neuronal energy failure. Delayed PHE is produced by the BBB disruption (vasogenic edema) and neuronal death (cytotoxic edema) (20). Three intertwined neurotoxic cascades contribute to the development of delayed PHE: inflammation, erythrocyte lysis, and thrombin production (79). The combination of these processes results in BBB disruption and death of brain parenchyma cells (Table 4).

Edema formation after ICH progresses through several phases: a hyperacute phase involves transendothelial osmotic pressure, clot retraction, and cytotoxic edema in the first several hours; an acute phase in the first day involves the clotting cascade, thrombin production, and inflammatory activation; and a third phase, beginning approximately 72 h post-ICH, involves erythrocyte lysis and hemoglobin-induced neurotoxicity (80, 81). In general PHE progresses over 24 h, then remains relatively constant for about 4 days and resolves over a period of several weeks (6). Some studies suggest that a “penumbra” of progressive tissue damage and edema develop in the perihematomal region (82). A 75% median increase in relative edema and 100% median increase in absolute edema volume over the first 24 h after ICH has been observed (83). In one study using SPECT, perilesional CBF normalized from initially depressed levels as PHE formed during the first 72-h post-ICH. The eventual degree of PHE was associated with the volume of reperfused tissue implicating reperfusion injury in the pathogenesis of PHE formation (9). A significant heterogeneity in CBF can occur after ICH with lower CBF (hypoperfusion) near the hematoma and higher CBF (hyperperfusion) in healthy overlying subcortical and cortical regions. The vasodilatory response of pial arteries in the periphery of the injury zone may reflect a local inflammatory reaction.

Hyperacute Phase

In this phase, PHE starts with the extravasation of serum into the brain parenchyma and cellular dysfunction before BBB disruption. Several early pathophysiological events leading to early PHE are related to the blood itself, which acts as a “neurotoxic” substance (80, 81). During the first hours after ICH, clot retraction occurs

with decreasing clot volumes and increasing PHE volume. Plasma protein extravasation acts oncologically increasing the interstitial osmotic pressure to induce rapid PHE development, extravascular coagulation, and fibrin deposition (80, 81). Experimental evidence strongly supports the hypothesis that hyperacute PHE is largely composed of peripherally exuded serum proteins after clotting of the hematoma and consumption of plasma clotting factors (83–85). Cytotoxic edema secondary to transcellular shifts in Na^+ and Cl^- has also been shown to increase in the early phases after ICH (85). Within hours, the ensuing cytotoxic edema contributes to the transendothelial trans-BBB osmotic pressure gradient. The mechanisms implicated in early cytotoxic edema involve the extracellular accumulation of neurotoxins such as glutamate, which is associated with further mitochondrial and Na^+ -ATP pump failure (86).

Acute Phase

Delayed edema formation may result from neuroinflammation and erythrocyte lysis, mediated by the local and systemic upregulation of chemotaxins, the complement system activation, and the release of thrombin and hemoglobin by-products (87). Inflammatory mediators also enhance early PHE after ICH by activation of leukocytes and generation of chemokines and chemotaxins *via* activation of the transcription factor $\text{NF-}\kappa\text{B}$ (88). Both immunochemical and physical stress in the PHE area lead to $\text{NF-}\kappa\text{B}$ activation with subsequent pattern recognition by receptors such as toll-like receptors 2 and 4 and thrombin engagement *via* protease-activated receptors (PARs). After activation, the $\text{NF-}\kappa\text{B}$ leads to upregulation of target genes that encode for cytotoxic cytokines, chemokines, and matrix metalloproteinases (MMPs), which are implicated in further BBB disruption.

White blood cells (WBCs) and neutrophils infiltrate the hemorrhagic brain within 4–5 h and may cause neuronal damage by producing reactive oxygen species and pro-inflammatory proteases (89). Leukocytes die by apoptosis within 2 days after entering the hemorrhagic brain damaging brain tissue through microglia and macrophage activation (79). In this process, glutamate and other excitotoxic amino acids continue to accumulate transiently in the extracellular fluid of the perihematomal region. In one study, peak elevation in glutamate concentrations was observed as early as 30 min post-ICH (90, 91).

Two hypotheses may explain the release of the neurotoxic amino acids: ischemia and cellular trauma. In the setting of ischemic injury, release of amino acids has been recorded and cellular trauma to neurons has also been known to release intracellular stores of glutamate into the extravascular space. Damage to astrocytes normally involved in the removal of glutamate may also exacerbate the accumulation of extracellular glutamate and other excitotoxic amino acids. Extraneuronal glutamate-based neurotoxicity is the result of activation of the postsynaptic *N*-methyl-D-aspartate receptor. The activation of this receptor leads to cellular influx of Ca^{++} and Na^+ , leading to transcellular ionic shift, cellular edema by flow of free water, and subsequent neuronal death (92). Previous reports show that even a transient exposure to glutamate can result in enhanced neurotoxicity (93). One study for example showed that high concentrations

of glutamate in blood within the first 24 h of symptom onset were associated with an exaggerated subacute pro-inflammatory response and worst clinical outcome and increased volume of the residual cavity after ICH (94). This supports the hypothesis that excitotoxicity and inflammation have a role in PHE formation and secondary neuronal death after ICH.

In addition to glutamate, high concentrations of IL-6, tumor necrosis factor alpha (TNF- α), and intracellular adhesion molecule-1 (ICAM-1) have been detected in the hypodense area surrounding the hematoma. TNF- α was shown to increase BBB permeability and cause WBC activation after its administration in a piglet model of ICH (95). It may also have an effect on other intracellular pathways such as G-protein-coupled activation of phospholipases, which lead to the generation of free radicals and an unhealthy redox state (96). Complex mechanisms in the injured neuronal tissue activate both pro- and anti-inflammatory mediators for at least 7 days after ICH. In parallel, transcript expression of pro-inflammatory cytokines rise rapidly within 6 h after the onset of ICH (97). In addition to these mechanisms, local and systemic inflammatory mediators also enhance tissue damage by the activation of WBCs and generation of prostaglandins and leukotrienes (59).

Although CNS tissues are normally immunologically privileged, BBB disruption may be expected to facilitate immune cell entry into the peri-hemorrhagic tissue. Major inflammatory cells that are activated and accumulate within the brain after ICH are primarily brain trafficked monocytes and resident microglia (7, 98–105). Although pro-inflammatory cytokines IL-1/IL-6/TNF- α can be released by many cell types, including microglia, monocytes, and endothelial cells, their principal sources in the brain are from activated microglia and brain trafficked monocytes (105). The initial inflammatory response after ICH is primarily orchestrated by the cytokines, TNF- α , and IL-1 β , which are upregulated within hours and increase BBB permeability and allow entry of peripheral immune cells. The cellular sources of these cytokines change during the 7-day time course (106). When edema forms, activated microglia contributes to the pathologic process through inflammatory cells and mediators and cytokine release. TNF- α is present as early as 1 day after ICH suggesting that synthesis and secretion of cytokines may be an early response of microglia to ICH (7). It has been demonstrated that microglia can also be maximally activated at 7 and 10 days after ICH, which is the time frame when the hematoma is being reabsorbed. The ICAM-1 is inducible by tissue injury and other inflammatory cytokines (107). The induction of ICAM-1 in neurons could promote the attachment of WBCs to neurons inducing neuronal injury through direct cell-to-cell interaction and the release of cytotoxic substances (7).

Neutrophils are also implicated in the development of PHE *via* production of cytotoxic molecules such as pro-inflammatory cytokines, reactive oxygen radical species, and MMPs (108). This early inflammatory response has become an attractive therapeutic target. By inhibiting activation and migration of inflammatory cells, research has shown that minocycline, a tetracycline derivative, may reduce microvessel loss, plasma protein extravasation, and edema in addition to cytokine expression by reducing the

upregulation of some pro-inflammatory cytokines such as TNF- α and MMP-12 (109). This substance has been shown to reduce specific cytokines (TNF- α and IL-1 β) and MMPs implicated in BBB damage (110).

The complement system is classically excluded from the brain by the BBB, but it could enter in its activated form at the time of ICH or through BBB disruption (111). Complement-mediated brain injury is also assisted by the formation of the membrane attack complex (MAC) and the pro-inflammatory response that follows.

The MAC consists of the complement's C5b-9 particles assembled after its activation. Once activated, the MAC inserts into the cell membrane forming a pore. The formation of MAC in ICH models induces erythrocyte lysis, which has been implicated in the generation of PHE (87). Not only does MAC cause cell lysis but it also modulates other cellular pathways implicated in the generation and release of cytokine, eicosanoid, and oxygen radical species (112). Similarly, MAC insertion may also occur in neurons and endothelial cells, causing neuronal death, cytotoxic edema, and BBB leakage through damage of endothelial cells. In animal models of ICH, therapeutic blockade of receptors for C3a and C5a resulted in less neutrophilic infiltration and lower brain water content compared with no treatment.

The MMPs are a family of proteolytic enzymes involved in the reorganization of the extracellular matrix. Specifically, MMP-9 and MMP-2 degrade major components of the cellular wall's basal lamina and can disrupt the BBB (113). MMP-9 has been linked to the pathophysiology of different neurological conditions such as multiple sclerosis and cerebral ischemia (114, 115). One study showed that the levels of MMP-9 increased within the first 24 h in patients with supratentorial ICH and that the concentrations of MMP-9 positively correlated with PHE volumes in deep ICH (113).

Levels of MMPs and plasminogen activators are increased 16–24 h after in experimental collagenase-induced intracerebral hemorrhage models, suggesting that agents that block MMPs may reduce the swelling after ICH (21). In this model, treatment with an MMP inhibitor significantly reduced the brain edema in sites distant from the primary lesion, suggesting that the inhibitor blocked vasogenic edema. Excessive proteolysis is normally prevented by tissue inhibitors of MMPs, but during the inflammatory process, the balance is disturbed as their natural inhibitors (TIMPs) are destroyed, favoring proteolysis. Astrocytes, endothelial cells, and microglia secrete MMPs as inactive zymogens that must be activated by other enzymes such as plasmin and free radicals (21). One study investigated the temporal profile of MMPs and their natural inhibitors after ICH and showed increased MMP-9 with PHE and increased MMP-3 with mortality (5). MMP-3 is laminin whose degradation leads to neuronal death. The main form of cell death associated with ICH in the perihematoma region has been shown to be apoptosis during the first days and necrosis from inflammation after 5 days of symptom onset (90, 91). The apoptotic pathway in ICH may involve nuclear factor kappa beta, which is a transcription factor controlling MMPs (116). TIMPs are now recognized as exerting both MMP inhibition and antiapoptotic properties (5).

Early edema formation is associated with both the activation of the coagulation cascade and the generation of thrombin (80, 81). Thrombin is a serine protease produced in the brain immediately after ICH (117). It activates potentially harmful pathways such as apoptosis, microglia activation, and glutamate potentiation. Thrombin-induced brain edema results partly from the disruption in the BBB and may be mediated by the complement cascade. Thrombin is formed in the clot almost immediately after an ICH, but the influx of prothrombin into the brain tissue due to BBB disruption serves as a secondary source (6). Intracerebral infusion of thrombin showed an increase in complement C9 and deposition on neuronal membranes (118). Thrombin-cleaved C3a-like fragments are chemotactic for WBCs and can induce enzyme release for neutrophils (119). Higher levels of TNF- α were seen after the infusion of thrombin in one animal model of ICH (120).

The most direct effect of thrombin is its role in the coagulation cascade with cleavage of fibrinogen to fibrin and other effects are protease mediated. PARs regulate some of the pathological effects of thrombin and are involved in CNS pathophysiology in some animal studies (121). Thrombin is associated with permeability change in the BBB leading to edema through chemotaxin and MMP activation, as well as the release of vascular endothelial growth factor (VEGF) from neurons through receptor activation (122). VEGF increased vascular permeability and vasodilation *via* nitric oxide induction and may serve as a potential fuel for free radical generation (59). Thrombin at high concentrations also kills neurons and astrocytes *in vitro* (123). It can be detrimental at high concentration and protective at low concentrations (118). To this end, thrombin-mediated brain injury has been identified as a possible therapeutic target after ICH. Administration of a thrombin inhibitor may effectively limit PHE formation and secondary neuronal damage (124). In the GUSTO-1 trial, the onset of symptomatic ICH arising as a complication of thrombolysis for acute myocardial infarction was ascertained and the potential mechanisms studied. The *post hoc* analysis of GUSTO-1 study showed that there was minimal PHE when the patients received thrombolytic therapy, suggesting that thrombin levels may have been affected (125). Argatroban-mediated inhibition of thrombin proved effective in reducing the degree of PHE in a rodent model of ICH (126). The plasminogen activator inhibitor-1 (PAI-1) protein levels increase in the rat brain after ICH or thrombin infusion but brain levels of tPA remain unchanged (127). The upregulation of PAI-1 after ICH implies that endogenous inhibitors of thrombin may limit brain injury and could be potential future therapeutic agents. Although thrombin formation occurs rapidly after ICH, it may remain within the clot and linked to fibrin, which can in turn lead to delayed release of thrombin and therefore delayed PHE (126).

Hyperglycemia can induce inflammatory reactions in ICH leading to neuronal death (7, 128). Activated blood components triggered by high glucose levels may induce increased inflammatory cytokine activity such TNF- α and IL-1, which exacerbates BBB permeability causing vasogenic edema (129). Hyperglycemia increases the secretion of IL-1 β in cultured endothelial cells and TNF- α in epithelial cells (130, 131). Free radical formation is increased with hyperglycemia-induced brain injury

leading to increased BBB permeability and brain edema (132). Hyperglycemia also induces bradykinin-mediated vasodilation and inflammation. Bradykinin increases BBB permeability and facilitates extravasation by dilation of arterial blood vessels (133).

Subacute Phase

Thrombin and the coagulation cascade play a major role in acute edema formation following ICH as shown when thrombin inhibitors markedly reduce edema formation (84). In contrast, injection of whole red blood cells into brain fails to induce edema formation by 24 h (19). This delayed RBC lysis may be attributed to either activation of complement system and formation of MAC (134) or depletion of intracellular energy reserves (135). Hemoglobin has been shown to cause brain injury through inhibition of sodium/potassium ATPase activity, toxic radical generation, and lipid peroxidation (80, 81). In one study, upon injection of packed RBCs, there was no edema formation 24 h postinjection, but marked edema after 3 days. This delayed edema is explained by RBC lysis and hemoglobin release (80, 81). Hemoglobin release from erythrocyte lysis increases during the first few days after an ICH (136). Studies show that PHE formation after thrombin injection peaks at 1–2 days, whereas delayed edema formation from erythrocyte lysis peaks at 3 days (80, 81).

The adverse effects of hemoglobin in models of ICH may be due to the molecule itself or by its breakdown products. Hemoglobin rapidly activates lipid peroxidation directly in the first phase and then *via* iron, one of its breakdown by-products, in the following phase (137). Haptoglobin may inhibit phase I, whereas deferoxamine, an iron chelator, and transferrin, an iron-binding protein, can inhibit phase II. The heme from hemoglobin may be broken down by heme oxygenase (HO) into iron (a potent catalyst for lipid peroxidation), carbon monoxide, and biliverdin (138). In turn, the enzyme biliverdin reductase catalyzes the conversion of biliverdin to bilirubin. Both carbon monoxide and iron can stimulate free radical formation leading to PHE. HO is primarily increased in microglia cells around ICH, which are also the most ferritin- and iron-positive cells (139). The intracortical injection of iron, causes focal epileptiform discharges and more brain swelling (140). One study demonstrated that hemoglobin also upregulated HO levels in the brain and that HO inhibition by SnPP molecules reduced the classically observed hemoglobin-induced brain swelling (141). HO overexpression and reactive iron accumulation are also associated with oxygen and free-radical species-related cytotoxicity (142). Early expression of HO may result from induction of other plasma proteins and thrombin as well (143).

Intracerebral iron infusions have been shown to cause brain edema and free radical formation leading to neuronal damage (144). Erythrocyte lysis results in the accumulation of non-heme iron molecules in the brain tissue starting at day 3 and reaching its acme after about 7 days of ICH onset. The temporal relationship between HO and non-heme iron levels indicates that an increase in perihematomal HO levels may modulate home-based degradation and iron overload/toxicity in the brain with ICH (145). Previous studies have shown that hemoglobin is toxic to spinal neurons *via* an iron-dependent, oxidative mechanism involving

a hydrogen peroxide intermediate factor (146). Iron reacts with lipid hydroperoxides to produce free radicals. Deferoxamine, an iron chelator, is routinely used to treat hemochromatosis caused by iron toxicity. It also has been shown to reduce hemoglobin-induced cerebral edema, indicating that iron is a key factor in the pathway for delayed PHE formation after ICH. The degree of secondary neuronal damage may be limited by changes in iron-handling proteins. Specifically, an upregulation in the brain's iron-capturing protein ferritin may be neuroprotective.

Reactive oxygen species cause brain injury *via* many different pathways. Deoxyribonucleic acid is vulnerable to oxidative stress and markers have been observed at the perihematomal zone demonstrating that oxidative DNA damage is involved in hemorrhagic brain injury (144). Iron can induce lipid peroxidation and stimulate free radical formation, which in turn may cause DNA damage (140). Although apoptotic DNA damage may occur from erythrocyte-induced brain injury, non-apoptotic DNA damage may play an important role because iron levels in the brain are high after erythrocyte lysis (147). The degree of oxidative damage in tissues is limited by a number of free radical scavenging systems. Intracerebral infusion of lysed RBCs causes marked brain edema associated with increased protein carbonyl content and DNA damage and thus reflecting oxidative stress (147). The oxidative stress may be due to upregulation in HO with resultant iron release.

CONCLUSION

Spontaneous forms of ICH account for 10–20% of all strokes annually in the United States and is associated with the highest all-time morbidity and mortality (148). Among the factors related to poor prognosis after ICH are the hematoma size, growth, and PHE. To determine therapeutic targets, it is important to evaluate the mechanisms of each phase. Information of the pathophysiologic mechanisms of injury have been identified as primary and secondary.

Hematoma growth in the setting of ICH has a multifactorial etiology with contributing factors such as increased local tissue pressure, a fibrinolytic effect, plasma protease induction, and secondary inflammation. Reduction in hematoma size and growth will likely be important futuristic strategies to improve survival and outcome after ICH. This depends heavily on both BP management and hemostasis. Seven clinical trials have evaluated the role of intensive BP reduction after ICH and ultimately concluded that intensive lowering of BP (SBP < 140 mmHg) provides no significant improvement in outcome compared to the standard goal of SBP < 180 mmHg. Medical treatment for hemostasis varies if the patient was taking an anticoagulant or had an inherent coagulopathy. However, in spontaneous ICH, not related to anticoagulation, rFVIIa has been evaluated as a means to reduce hematoma growth and PHE formation. Although a phase II randomized clinical trial showed that treatment with rFVIIa reduced hematoma growth and improved clinical outcome after ICH, a conclusive phase III clinical trial failed to demonstrate any significant benefit.

The primary injury of hematoma formation and clot retraction occurs followed by secondary injury with BBB disruption

complicated by inflammation, coagulation, thrombin, and erythrocyte lysis. Edema formation after ICH progresses through several phases: a hyperacute phase, an acute phase, and a third phase, beginning approximately 72 h post-ICH. These complex cascades lead to worsening edema through BBB permeability and an end point of apoptosis or neuronal injury. By identifying the major modulators of cerebral edema after ICH, a therapeutic target to counter degenerative events may be forthcoming.

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KL-H and FR contributed equally to the development of this manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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