

Priorities for Clinical Research in Intracerebral Hemorrhage

Report From a National Institute of Neurological Disorders and Stroke Workshop

NINDS ICH Workshop Participants*

Background and Purpose—Spontaneous intracerebral hemorrhage (ICH) is one of the most lethal stroke types. In December 2003, a National Institute of Neurological Disorders and Stroke (NINDS) workshop was convened to develop a consensus for ICH research priorities. The focus was clinical research aimed at acute ICH in patients.

Methods—Workshop participants were divided into 6 groups: (1) current state of ICH research; (2) basic science; and (3) imaging, (4) medical, (5) surgical, and (6) clinical methodology. Each group formulated research priorities before the workshop. At the workshop, these were discussed and refined.

Results—Recent progress in management of hemorrhage growth, intraventricular hemorrhage, and limitations in the benefit of open craniotomy were noted. The workshop identified the importance of developing animal models to reflect human ICH, as well as the phenomena of rebleeding. More human ICH pathology is needed. Real-time, high-field magnets and 3-dimensional imaging, as well as high-resolution tissue probes, are ICH imaging priorities. Trials of acute blood pressure-lowering in ICH and coagulopathy reversal are medical priorities. The exact role of edema in human ICH pathology and its treatment requires intensive study. Trials of minimally invasive surgical techniques including mechanical and chemical surgical adjuncts are critically important. The methodologic challenges include establishing research networks and a multi-specialty approach. Waiver of consent issues and standardizing care in trials are important issues. Encouragement of young investigators from varied backgrounds to enter the ICH research field is critical.

Conclusions—Increasing ICH research is crucial. A collaborative approach is likely to yield therapies for this devastating form of brain injury. (*Stroke*. 2005;36:e23-e41.)

Key Words: acute care ■ brain edema ■ cerebral amyloid angiopathy ■ hematology
■ intracerebral hemorrhage ■ stroke, acute

Intracerebral hemorrhage (ICH) is a particularly lethal stroke type. Mortality approaches 50%¹ and disability in survivors is common. ICH has a predilection for minority populations in North America, including blacks and Hispanics.²

Effective treatments can only be developed when the sequence of pathologic events initiated by hemorrhage is known. In November 2003, a National Institutes of Neurological Disorders and Stroke (NINDS) workshop was convened in Washington DC to discuss research priorities in the ICH field. Nontraumatic ICH was the focus. Invited participants were asked to look into the future and suggest approaches to further the field toward therapy for patients with acute ICH. The theme of the workshop was the approach to the acute ICH patient in the emergency department. The scope was limited to clinical research priorities, with only a modest examination of basic science, epidemiology, and rehabilitation priorities, which are all critically important

topics worthy of separate workshops. Table 1 provides a summary of the top research priorities identified at the workshop.

The participants (see Appendix) were divided into 6 subgroups: (1) current state of ICH research; (2) basic science priorities; (3) medical priorities; (4) surgical priorities; (5) imaging priorities; and (6) clinical research methodology challenges in ICH. Each group prepared a document before the workshop and then the document was edited based on feedback at the workshop. The groups' documents contained research priorities and suggested approaches to the problem and areas for involvement of new investigators in the stroke field. The documents are combined here as a report from the NINDS ICH workshop.

Current State of ICH Research

The deleterious effects of ICH may be divided into primary and secondary injury. Primary injury refers to the immediate

Received July 7, 2004; final revision received November 22, 2004; accepted November 29, 2004.

*For a listing of all NINDS ICH Workshop Participants please see Appendix.

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DOI: 10.1161/01.STR.0000155685.77775.4c

TABLE 1. Research Priorities in Intracerebral Hemorrhage

Fundamental Questions
What is the natural history of primary and secondary injury in ICH?
What is the time course and clinical impact of edema?
Basic Science Priorities
Develop and validation of appropriate models of ICH and hemorrhagic transformation that reflect the human condition
Develop molecular and cellular targets which may lead to clinically relevant protection of injured tissues (eg, vascular, neuronal, glial, and other)
Description of the course and exploration of reparative processes using gene-based model constructs and stem cell biology (eg, inhibitors and promoters of cell survival in the injured field and mechanisms thereof, including genomic and proteomic approaches)
Imaging Research Priorities
Development of real-time techniques for identifying ICH cause and expansion
Development of real-time techniques for identifying perihematoma and global perfusion/hypoperfusion
Development of high-resolution molecular probes for identifying ICH-related tissue injury, response, and recovery
Medical Research Priorities
A trial of acute reduction in blood pressure to assess safety and efficacy in decreasing the risk of hematoma enlargement
A trial studying antithrombotic/finbrinolytic coagulopathy reversal in patients with ICH
Studies identifying the best strategy for limiting the development of cerebral edema
Surgical Research Priorities
A trial of minimally invasive surgical techniques to assess their ability to improve the outcome of spontaneous supratentorial ICH
Investigate local (topical and or endovascular) delivery of protective/restorative agents' ability to improve outcome and restore biology
Determine if there is a role for delayed restorative surgical procedures
Clinical Research Priorities
Improve methods to maximize recruitment and process of informed consent in randomized trials of ICH including involvement of neurosurgical and emergency medicine communities and development of multidisciplinary ICH treatment networks
Standardization of management interventions as well as organization and experience of trial team
Stratification of disease severity and choice of the most relevant outcome parameters

effects such as hemorrhage growth and increased intracranial pressure, whereas secondary injury is related to downstream effects that may occur soon after ICH, as well as effects that occur up to 2 weeks later, such as edema.

Primary Injury

Until recently, ICH was thought to be a discrete event. There is now evidence that early hematoma growth is common in patients with normal coagulation profiles.³⁻⁶ Ongoing bleeding can be demonstrated with contrast-enhanced computed tomography (CT)⁷ and magnetic resonance imaging (MRI).⁸ Hematoma enlargement is associated with worse outcome.⁷ Based on the only prospective study of this question, hematoma growth primarily occurs within the first few hours of the onset of bleeding (up to 40% in the first 3 hours) and is rare after 24 hours.³ Predictors of hemorrhage expansion include initial hematoma volume, early presentation, irregular shape, liver disease, hypertension, hyperglycemia, alcohol use, and hypofibrinogenemia.^{4,9,10}

Potential interventions to prevent hematoma growth focus on administration of agents to reduce bleeding. Appeal for the

antifibrinolytics (eg, aminocaproic and tranexamic acid) is reduced because they limit breakdown of an existing thrombus but do not promote clot formation, and unpublished data indicate a lack of efficacy in small series. A smaller pilot study of epsilon-aminocaproic acid for this indication was stopped because of lack of efficacy, with the investigators concluding that either earlier treatment or higher doses were needed.⁹

Synthetic activated factor VII is a natural initiator of hemostasis acting locally in regions where there has been endothelial disruption and vascular injury.¹¹ Because it promotes coagulation, this agent carries a risk of causing deep venous thrombosis (DVT), pulmonary embolism, or myocardial infarction; however, this has not been apparent in those with hemophilia.¹² Two phase IIA dose-escalation feasibility and safety studies have been completed successfully administering factor VII within 4 hours of acute ICH to patients with normal coagulation status. These studies demonstrated safety and feasibility but a low rate of hematoma extension in the placebo arm. A larger phase IIB dose-ranging (placebo, 40, 80, 160 $\mu\text{g}/\text{kg}$) "proof-of-concept" study with 100 pa-

tients/group has just been completed. In a presentation at the 2004 World Stroke Congress (<http://www.prouss.com/web-caster/wsc2004/>), the authors reported that treatment of ICH with rVIIa within 4 hours of onset decreases hematoma growth and improves clinical outcome despite a small increase in thromboembolic events. Design of future studies will need to incorporate knowledge gained from this trial.

Surgical Evacuation/Decompression

Surgical therapy of acute ICH must take into account advanced hypertensive vasculopathy in the surrounding brain, tissue destruction from the hemorrhage itself, and a variety of toxic secondary effects on the surrounding brain. Nevertheless, a variety of surgical techniques offer a seductive opportunity to remove the hematoma and thus reduce intracranial pressure (ICP) problems, correct tissue distortion, and decrease the time in which toxic compounds actually contact surrounding tissue. These potential benefits must be weighed against the disruption of normal brain tissue required to gain access to the hematoma.

Despite careful study over the past half-century, a clear benefit of surgery has not been identified. Most neurosurgeons and neurologists agree that surgical evacuation of life-threatening lobar and cerebellar hematomas is beneficial. Treatment of patients presenting with ganglionic hematomas, however, remains controversial. Within this category of ganglionic hematomas, it is generally accepted that small clots with mild deficits should be treated medically and that those with deep coma from massive dominant hematomas are not benefited by any form of therapy.

At least 4 prospectively randomized trials of medical management versus surgical therapy are available.^{13–16} Although each of these trials varied somewhat in inclusion criteria as well as surgical methods, no clear benefit of surgical hematoma evacuation has emerged. Whereas it is intuitive that a significant component of ultimate disability relates to the dissection of tissue, only sporadic nonrandomized reports have suggested a benefit of minimally invasive surgical interventions.¹⁷ A complicating factor in evaluating past trials concerns design limitation of older trials, the continued evolution of medical therapy (prevention of early rebleeding, critical care management), and the development of new medical and surgical technologies. In addition to microsurgery, contemporary neurosurgeons also have access to minimally invasive techniques, including stereotactic access,^{18–20} endoscopic techniques, and adjunctive thrombolytic infusions.^{16,21} In recognition of these advances, Mendelow et al have allowed physician choice in terms of specific procedures in the STICH trial.²² There were 1033 patients with spontaneous supratentorial intracerebral hemorrhage randomized from 27 countries. There were 23.8% favorable outcomes in the “Initial Conservative Treatment” group compared with 26.1% in the “Early Surgery” group. These differences were not significant (odds ratio, 0.89; 95% confidence interval, 0.66 and 1.19). There was no difference in mortality (36.3% compared with 37.4%).²³ The trial randomized patients only when the treating physician was uncertain if surgical or medical treatment was best; this may have prevented randomization in two-thirds of eligible sub-

jects. In 12% of subjects randomized to surgery, either surgery did not occur or happened >24 hours after randomization. Of those randomized to medical treatment, 26% crossed-over to surgery.

Decompressive craniectomy is a surgical procedure that has been used for the treatment of intracerebral hemorrhage producing mass effect on the brain. Some neurosurgeons use the procedure in selected cases, after internal decompression to allow for more effective reversal of mass effect and to mitigate the effect of delayed brain swelling after a hemorrhage is removed. This procedure can also be used alone, without clot evacuation, most commonly in cases in which the blood clot is located in eloquent cortex.^{24,25} Improvement in measures of intracranial pressure, hemodynamics, and metabolic parameters after decompressive craniectomy have been documented.²⁶

A number of case control series have described the use of the procedure and recorded outcome in small cohorts.^{24,25} Dierssen et al²⁴ reported outcome in 73 patients with spontaneous intracerebral hematomas treated by surgical evacuation of the clot and decompressive craniectomy. A statistically significant improvement in the mortality rate after craniectomy could be observed compared with another series of patients (54 cases) treated only with surgical removal of the clot without decompressive craniectomy.²⁴ Prospective trials are needed to determine the effect on outcome of ICH evacuation alone versus decompressive craniectomy with or without ICH evacuation.

Posterior fossa decompressive craniectomy is commonly performed in combination with internal decompression (clot evacuation) to treat cerebellar hemorrhages. This procedure can be life-saving when performed expeditiously in patients with primary intracerebellar hemorrhage who have impaired brain stem function. Controversies regarding treatment include timing, use of ventriculostomy, and surgical indications based on size of the hemorrhage and neurological condition.^{27–32}

Secondary Injury

Chronic hypertension is a potent risk factor for ICH and predicts acute hypertension on presentation.³³ There remains a subjectively logical, but, as of yet, unproved, concern that hypertension promotes rebleeding. Yet simultaneously there is fear that treating acute hypertension in this setting will exacerbate or induce ischemia. One retrospective study suggested that outcome was better if blood pressure (BP) was lowered below a mean arterial pressure of 125 mm Hg;³⁴ however, another indicated that rapid dramatic reductions of BP (up to 60 torr in 24 hours) were associated with worse outcome.³⁵ The only prospective studies of this question have been physiological. One positron emission tomography (PET) study found stable perihematomal cerebral blood flow (CBF) with PET during a 15% to 20% reduction in mean arterial pressure of hypertensive patients (mean arterial pressure >120 mm Hg) with small to moderate-sized hemorrhages.³⁶ Another single-photon emission computed tomography (SPECT) study³⁷ found that CBF decreased if BP was lowered >20%. Whereas these data suggest that modest reduction in BP does not adversely affect the cerebral

circulation, the clinical safety and efficacy of this intervention remain to be established.

Perihematomal Ischemia

The presence of an “ischemic penumbra” surrounding an ICH has long been assumed, based on the belief that the hematoma compresses surrounding tissue and that CBF was reduced in experimental models of ICH.³⁸ Several recent PET and MRI studies have questioned the existence of such a penumbra. Although reduced CBF was evident using PET³⁹ and SPECT,⁴⁰ it was not associated with increased oxygen extraction fraction in patients studied 6 to 22 hours after ICH with small and moderate-sized hematomas.³⁹ Hypoperfusion surrounding the hematoma was not evident on 2 MRI studies,^{41,42} thus the regions of increased diffusion-weighted imaging that were present^{41–43} were not attributed to ischemia but rather speculated to be “metabolic suppression.” The nature and cause of this metabolic suppression remain unknown. This calls into question the therapeutic goal of optimizing perfusion by not treating hypertension. These data suggest that ischemia is unlikely to be an important issue after 6 hours and in small and moderate-sized hemorrhages. Questions remain about its existence earlier and in larger hemorrhages.

Edema

Perihematomal edema may also lead to neurological deterioration; however, the association is less clear than with hemorrhage growth. One study reported neurological deterioration within 24 hours caused by edema in 9 of 46 patients.¹⁰ Conversely, another study of 97 patients found worsening edema in 61%, but none had clinical deterioration.⁴⁴ Ironically, one study found early edema volume to be the strongest independent predictor of *improved* 12-week functional outcome.⁴⁵ The effect of late perihematomal edema formation is also not clear. One study of 76 patients found edema growth occurred late (between 9 and 21 days) and was associated with neurological deterioration in only 3 patients.⁴⁶ The bulk of perihematomal edema develops in the first 24 to 48 hours,^{47,48} but its relationship to clinical deterioration remains unclear. Studies do not support the use of steroids in ameliorating edema in this setting.

Intraventricular Extension and Hydrocephalus

Intraventricular extension of hemorrhage is associated with a worse outcome.^{49–53} Recently, hydrocephalus has emerged as an independent prognostic indicator^{54,55} and an important cause of neurological deterioration.⁵⁶ Questions remain about the importance of hemorrhage location (medial versus lateral) and whether ventriculostomy, although supported anecdotally, improves outcome.

Intraventricular hemorrhage can occur as a primary event without associated intraparenchymal hemorrhage, or as a complication of parenchymal hemorrhage with extension into the ventricular system. Treatment options of intraventricular hemorrhage have included observation, ventricular drainage, surgical evacuation of the hemorrhage, or ventricular drainage with infusion of thrombolytic agents. Naff et al initially conducted a pilot trial of urokinase and ventricular drainage

in patients with primary intraventricular hemorrhage that showed promising results.⁵⁷ This study led to a subsequent double-blinded, placebo-controlled, multicenter trial of tissue plasminogen activator (tPA) versus placebo. The trial included 48 ICH patients (8 mL) with severe IVH (53 mL), all treated with external ventricular drainage to 3-mg intraventricular recombinant tPA (rtPA) or vehicle injected every 12 hours for as long as the drain was in place. The average number of doses administered was 10.2 ± 8.0 , with a range of 1 to 28. The prespecified safety thresholds of 75% mortality, 35% rebleeding, and 30% ventriculitis were not exceeded in either treatment arm. Mortality was substantially lower than the severity-adjusted, predicted mortality:⁵⁸ rtPA (19% versus 76%) and placebo (23% versus 75%). A similar decline in severity-adjusted mortality did not occur in patients screened for the study but not enrolled (predicted mortality 42%, actual 46%). The primary efficacy variable was the rate of clot resolution. The active treatment group demonstrated 18% per day clot reduction versus 8% per day in the placebo group.⁵⁹

Other

Seizures occur at the onset of ICH,^{60,61} and electrographic seizures have been reported in 28% of patients during the first 72 hours after admission.⁶² In that study, seizures were more common in lobar hemorrhages but occurred in 21% of subcortical hemorrhages. Posthemorrhagic seizures were associated with neurologic worsening and an increase in midline shift. There was a trend toward increased poor outcome. In another recent study, the incidence of seizures was considerably lower at 7.5%. Early seizures were associated with lobar location and neurologic complications, mainly rebleeding. In an observational-only study of patients with lobar ICH, the data suggest that the risk of early seizures was reduced by prophylactic anti-epileptic drug therapy.⁶³ The incidence, impact, and role of anticonvulsants is poorly understood. Fever may account for transient decreases in responsiveness; its impact on outcome is less clear. Some studies have found a worse outcome with fever,⁶⁴ whereas others have not.⁵⁴

Basic Science Research in ICH

Three important areas of research of current and future interest are: (1) the development of appropriate models of hemorrhage-associated brain tissue injury; (2) intense study of the molecular and cellular consequences of hemorrhage in the brain in focal ischemia (hemorrhagic transformation) and primary ICH; and (3) translational research.

Animal Models of Hemorrhage-Associated Brain Injury

Research achievements with models of hemorrhage-associated brain injury have been modest, caused in part by limitations of model systems to reproduce the clinical situation. Cerebral hemorrhage has been modeled in the rat, rabbit, cat, dog, swine, and primate.^{65–67} Significant technical and species differences in hemostasis question whether outcomes of model studies can be related to the human condition.

These model systems have been used to examine the impact of hemorrhage on brain tissues: (1) models mimicking

primary hemorrhage involve induced cerebral artery rupture, stereotactic injection of blood into selected brain regions (eg, basal ganglia), or stereotactic injection of matrix proteases (eg, collagenase);^{67–87} and (2) models of focal cerebral ischemia in which hemorrhagic transformation naturally occur (eg, primates and select rodent strains).⁶⁵

These systems have intrinsic limitations. Hemorrhagic transformation has been modeled in the dog, cat, primate, rabbit, and rat in which single arterial occlusion generates focal ischemia.^{88,89} Canine models subject to hypertension^{90,91} and hematomas induced in the maturing infarction in rhesus monkeys by arterial BP elevation⁹² consistently produce hemorrhages encapsulated within structural boundaries (eg, putamen, globus pallidus, claustrum). Current thromboembolic models do not resemble these types of lesions. Hemorrhagic infarction accompanies focal cerebral ischemia in the nonhuman primate in a manner similar to ischemic stroke.^{90,91} Few studies have been reported using rodent species. Primate and rodent studies have demonstrated the importance of platelet function for protection from hemorrhagic transformation. They also indicate that observations of hemorrhage in ischemic stroke are not uniformly mimicked in focal ischemia models.

For modeling of ICH, intraparenchymal injection of autologous blood in rodent is the most commonly used method for pathophysiologic, biochemical, and behavioral studies.⁹² However, it does not reproduce the bleeding event of spontaneous ICH in humans. Those have established that perihematoma edema accompanies activation of hemostasis with thrombin generation, complement activation, and products of erythrocyte breakdown. Rabbit models have been developed for descriptive studies. Primates have been used to examine pressure relationships set up by basal ganglia or thalamic hemorrhage.^{92,93} The impact of evacuation of lobar hematomas after instillation of plasminogen activators (eg, rtPA) has been studied in this model.^{94,95} Importantly, a porcine model of lobar ICH has been used for a growing number of studies of white matter injury, surgical evacuation techniques, perihematoma edema formation, pathophysiology, and treatment.^{64,68,82,96,97}

In model systems using extracellular matrix proteolysis by stereotactic injection of bacterial collagenase to induce local intracerebral hemorrhage, the exaggerated inflammatory and chemical injury and the limited clinical relevance outweigh the reproducibility of hemorrhage formation.^{98,99}

Because many current models have limitations inappropriate for the study of the impact of hemorrhage on brain tissue,^{65,100} new models are needed that reflect the biology of ICH in humans and do not cause perturbations of brain function that interfere with the potential impact of the hemorrhage. These may be summarized as follows.

Primates mimic human hemorrhagic transformation and are appropriate for experimental study.^{100–103} Swine are challenging in this setting because their rete mirabile prevents embolic ischemic stroke production and their very small middle cerebral artery limits the surgical approach.

The porcine lobar ICH model enables the study of white matter injury from ICH and also permits hematoma volumes comparable to moderately large hematomas in humans (30 to

50 mL). This model has also been used for neurosurgical clot removal studies. Although dogs and cats have been used as ICH models, their companion animal status and cost make them less attractive. Rat models involve blood infusions in the striatum and have focused solely on gray matter injury. Blood infusion models can induce ventricular rupture during the infusion, thereby potentially producing only ventricular hemorrhages. The rabbit ICH model^{104,105} and other models suffer from imprecise outcomes.

From these observations, the development of appropriate animal model systems for ICH and hemorrhagic transformation must be a priority. Models are needed that mimic human brain injury from hemorrhage. The requirement for models that involve both gray and white matter injury necessitates the use of species with larger quantities of white matter (eg, swine, primates). Models are needed that allow the study of hemorrhagic transformation from ischemic stroke. Model systems that closely recapitulate the neuroanatomy and physiology of human stroke are required. Models that allow study of ICH are needed. Characteristics of spontaneous intracerebral hemorrhage that include the elements of ventricular extension, lobar localization, vascular rupture, and/or the ability to examine the impact of hemorrhage on the surrounding tissue are needed. Models that allow study of the impact of second hemorrhage are needed. Rebleeding or continued hemorrhage is observed in $\approx 30\%$ of ICH patients. This phenomenon has not been studied in any animal model. Models that examine the ability of hemorrhage to generate local cerebral edema and hemispheric swelling are needed, as are models that allow study of the local effects of petechial hemorrhage or spontaneous microvascular rupture.

In addition to large animal models, knockout and transgenic murine systems are appropriate to explore the roles of cellular inflammation, cytokine effects, and alterations in hemostasis in ongoing brain injury processes that may lead to hemorrhagic transformation or ICH.^{106,107}

Molecular and Cellular Consequences of Hemorrhage

In addition to the pressure-related effects of an expanding hemorrhage, there is good evidence that molecular mechanisms of cellular injury are initiated. These include thrombin^{108–111} and other breakdown products of hemoglobin.^{68,96} Those observations suggest potential therapeutic approaches for hemorrhage after ischemia. Because changes in brain issue are time-dependent, the biology of ischemia demands very early study of pathology with longitudinal investigation of behavioral outcomes.

Axonal Integrity and Hemorrhage Into White Matter

Theoretically, hemorrhage into white matter can dissect along fiber tracts and push axons aside; morbidity could result from the stretching of white matter tracks as the hematoma enlarges. Tissue factor, the principal procoagulant in the central nervous system, is 10-fold more abundant in the gray matter, allowing the possibility that hemorrhage can extend through white matter tracts.¹¹² It is also possible that nondisruptive axonal injury,¹¹³ with disrupted myelinated nerve

fibers,¹¹³ and marked edema with loss of myelin^{66,67} can contribute to the injury caused by the ICH, as observed in several models. However, edema development and myelin injury leading to axonal injury is plausible but unproven. Thus, experimental studies to detail these pathophysiological processes are needed.

Inflammation

The degree to which inflammation contributes to brain injury after intracerebral hemorrhage or hemorrhagic transformation is undefined. Some aspects of the immune response are beneficial for the injury repair processes, whereas others are detrimental.^{114–117} Injection of autologous blood and blood-related products initiates NF- κ B activation and recruitment of leukocyte subsets to the site of injection.^{72,118,119} These inflammatory cells mediate damage, in part, by the substances they secrete, including neurotoxic cytokines, IL-1 β , tumor necrosis factor- α , and select proteases.^{120–122} Therefore, a systematic study of these inflammatory agonists and their actions in the setting of ICH must be undertaken.

Liquefaction of experimental ICH with plasminogen activators can increase the inflammatory response and edema.^{21,95} The degree and timing of the inflammatory responses to ICH and in infarction-related hemorrhage are unclear. Also uncertain are the potential effects of anti-inflammatory strategies in these settings. Although benefit has been attributed to thrombin inhibitors, corticosteroids, and hypothermia,^{123–125} both the scope of the contribution of inflammation to the evolving injury and the impact of approaches with purported benefit must be studied.

Metalloproteinases

An association between the inactive pro-MMP-9 in injured brain tissue and hemorrhagic transformation has been shown in the primate, which has been corroborated in human stroke.^{126,127} However, vascular matrix dissolution accompanies hemorrhagic transformation and is felt to play a causal role in evolution of the injury during focal ischemia. Hence, causality and mechanisms must be explored. The possibility that matrix protease inhibitors could reduce the contribution of hemorrhage to outcome is testable.

Translational Research Opportunities

Proinflammatory cytokines might be blocked by targeted pharmacological approaches to the proteasome, upstream inflammation-related transcription factors, inflammatory cells, immune mechanisms, and free radical therapy.^{123,128–132} Microglia may be an initiating factor in amplifying the inflammatory process.¹³³ Heme oxygenase-1, induced in response to ICH, mediates release of iron from heme deposited during hemorrhage.^{68,96,134} Studies evaluating inhibition of heme degradation may prove useful.

Thrombin, and other hemostatic proteins activated in brain tissue after hemorrhage, may alter neuron and microglial function.^{66,110,111,135,136} Agents such as select thrombin inhibitors might be useful in early hemorrhage to block the cytotoxic effects of thrombin.

The identity of apoptotic cells in areas surrounding ICH is unknown, but their appearance provides logic for treatment approaches that inhibit this form of cell death.¹³⁷

Vascular integrity can be jeopardized by matrix dissolution, caused by increased matrix protease activity (eg, MMPs). Inhibitors of these enzymes may prevent hemorrhagic transformation and edema formation in animal models.

The potential benefit of stem cells from several sources and their mechanisms are undergoing study in ischemic model systems. Studies of this type should be extended to experimental hemorrhage, for which early data are supportive.^{138,139}

Genomics and Proteomics

These are early days in the application of gene-based and proteomics methods. How they can be applied to experimental ICH is unknown. One recent report described unique genomic responses at 24 hours after ICH in a rat model.¹⁴⁰ Rodent knockout and transgenic preparations also may allow the study of nonenvironmental genetic contributions to post-hemorrhagic brain injury.

Imaging Priorities

A unifying principle in the approaches described is their potential to suggest molecular and cellular targets for treatment, to stratify potential treatment subjects, and to assess whether candidate therapies act as predicted.

Neuroimaging of Hematoma Properties: Cause and Expansion

Although acute treatment strategies have generally not differed according to ICH cause, the various pathophysiologies of nontraumatic ICH (including hypertensive vasculopathy, cerebral amyloid angiopathy [CAA], and arteriovenous malformation) may well follow different clinical courses and require different treatments. The vascular lesions underlying ICH often go unrecognized, however, particularly the microvasculopathies associated with hypertensive vasculopathy and CAA. As the resolution of imaging modalities such as MRI, magnetic resonance angiography, and computed tomographic angiography improves, it may prove possible to detect other small vasculopathic changes such as Charcot-Bouchard aneurysms in hypertensive vasculopathy or microaneurysms and vessel splitting associated with CAA.¹⁴¹ Another very promising approach to diagnosis of CAA is the labeling and imaging of components of vascular amyloid, including the β -amyloid peptide itself.¹⁴²

For the immediate future, the primary clue to ICH mechanism is likely to be the distribution of old microhemorrhages detected by gradient-echo MRI.^{143–145} A potentially important advance in this regard is the development of very-high-field MRI devices,^{146,147} recently ruled by the Food and Drug Administration as a nonsignificant risk up to 8 T in adults. Whereas the clinical use of these new systems is in its early stages, the additional signal-to-noise ratios provided by high-field (Figure 1) promises to improve neuroimaging in general and the depiction of microhemorrhage in particular. Our understanding of the time course, cause, and pathophysiology of microhemorrhages would be further enhanced by improve-

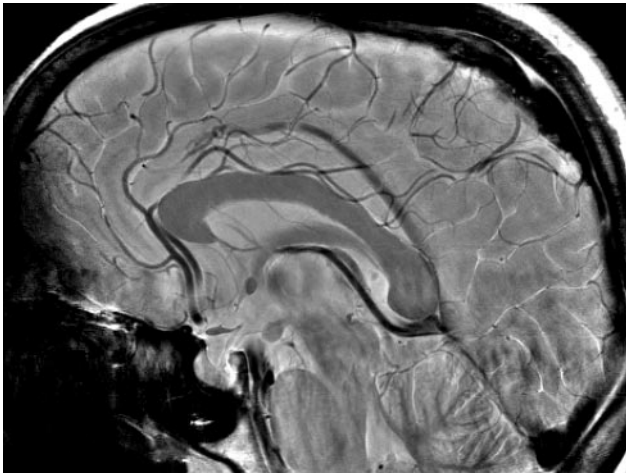


Figure 1. Magnetic susceptibility effects at 7T magnetic field strength. Sagittal T2-weighted image of the brain at 7T showing highly visible vessels because of magnetic susceptibility effects that highlight the presence of hemoglobin. High-resolution and high-field-strength MRI may be particularly well suited for evaluating both acute and chronic hemorrhage because of the presence of iron. (Image courtesy of Lawrence Wald, PhD, Massachusetts General Hospital, HST AA Martinos Center.)

ments in MRI allowing more precise dating of hemorrhages and individual blood products.

A key property of ICH in need of improved neuroimaging is hematoma expansion.^{3,6} An ideal imaging modality would be one that continuously tracks the size of a hematoma rather than defining its size at specific time intervals. Is growth slow and steady or abrupt? Are there different patterns of growth with different causes of hemorrhage? Three-dimensional imaging would allow a better understanding of the vectors of hematoma growth. Future imaging approaches to hematoma expansion should also allow fine differentiation of the age of clot that might be separated by minutes or hours rather than the current MRI classification of acute, subacute, and chronic. Finally, the ability to image the distribution of specific blood and cellular components such as thrombin, plasmin, plasminogen activators, inflammatory cells, platelet aggregation, and clot dissolution would be a major step toward elucidating the balance of thrombosis and thrombolysis in the process of clot expansion.

Neuroimaging of Vascular Properties: Perihematoma Perfusion and Hypoperfusion

Compromised cerebral perfusion, either as a direct consequence of ICH or as an unintended effect of candidate treatments such as BP reduction for preventing expansion or rebleeding,¹⁴⁸ is a potential source of tissue injury in ICH and an important target for neuroimaging. There are 2 questions to be addressed in these measurements: what is the perfusion immediately around the clot, and what is the perfusion remote from the clot?

At some relatively large clot volume (depending on the extent of atrophy), there should be an elevation of intracranial pressure and a decrease of global cerebral perfusion, particularly in subjects treated with BP reduction. This effect would be global, perhaps with a gradient from the immediate perihematoma region to adjacent intracranial compartments.

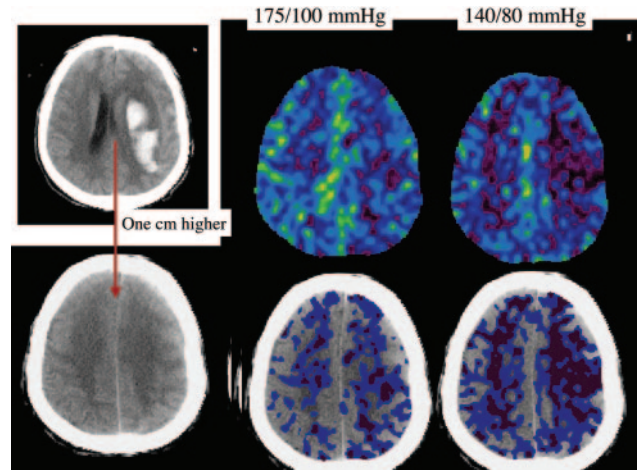


Figure 2. Perihematoma hypoperfusion demonstrated by xenon-enhanced CT scan. Imaging was performed 4 hours after the onset of right hemiparesis and aphasia in a 54-year old woman with history of hypertension. The xenon/CT cerebral blood flow images were obtained 1 cm above the level of the hematoma, initially at a blood pressure of 175/ 100 mm Hg and again 20 minutes later at a pressure of 140/80 mm Hg after intravenous treatment with labetalol. The lower blood pressure appears to result in more extensive tissue hypoperfusion. The lower images are windowed to show pixels with flow values below 20 cc/100gms/min in blue and pixels with values below 8 cc/100gms/min in lavender.

An ideal modality for monitoring this effect would be a rapidly accessible, quantitative blood flow study. This information might be acquired by measure of a blood flow-related variable such as tissue oxygen availability. A matrix of tissue oxygen monitors using near-infrared spectroscopy¹⁴⁹ placed over both hemispheres (technology currently available) could provide access to continuous flow-related information that could help guide the question of global harm caused by hypoperfusion.

The safety of aggressive BP reduction for a smaller hemorrhage demands monitoring of local flow changes. Flow information would be needed for this application, because it would not be desirable to reduce the pressure to the point of causing an elevation of lactate or glutamate or the depletion of ATP, steps that mark permanent damage to the surrounding tissues. Measurement of cerebral blood flow by xenon-enhanced CT scan (Figure 2) is an example of an emerging real-time, high-resolution technique also potentially available for bedside use with increasing availability of portable CT scanners. Magnetic resonance spectroscopy and PET are also potentially useful.

A specific mechanism of compromised perfusion to be investigated by tomographic high-resolution flow imaging is the remote effects of ICH caused by compression of the anterior or posterior cerebral arteries. A similar set of questions pertains to the possible effects on perfusion of delayed perihematoma edema, which may cause compression of local perforating vessels as well as remote major cerebral vessels. Studies of perfusion at baseline or after manipulation of BP or CO₂, ideally coupled with measurements of metabolism and oxygen extraction, could provide insight as to whether such alterations in perfusion are a cause (rather than an effect) of perihematoma tissue injury.

Some caution will be required in determining whether post-ICH levels of perfusion decrease below ischemic thresholds, which are undoubtedly reduced by decreases in metabolic activity in the region of the hematoma.^{39,149} Interpretation of the information will also be complicated by the fact that the greatest effect of subcortical ICH is on the white matter, for which we do not have a defined ischemic threshold.

Diffusion-weighted imaging including apparent diffusion coefficient mapping offers an alternative approach for identifying perihematoma regions with bioenergetic compromise potentially caused by ischemia. Several small-scale studies suggest there may be a subgroup of patients with decreased perihematoma apparent diffusion coefficient values in the hyperacute phase.^{41,150} Additional large-scale, prospective studies are needed to confirm this. Magnetic resonance spectroscopic studies acquired at the same scanning session can provide complementary information regarding the time course and frequency of changes in lactate and *N*-acetyl aspartate.¹⁵¹

Neuroimaging of Tissue Properties: Perihematoma Injury, Edema, Response, and Recovery

An important target for noninvasive imaging is the location and mechanism of neuronal cell death in ICH. Studies primarily in the cardiology field have demonstrated that the mechanism of cell death can be noninvasively detected and that the presence, location, and pathophysiology of cell death can be used in evaluating the nature, timing, and efficacy of treatments. Necrosis and apoptosis, 2 related mechanisms of cell death, are candidates for imaging after ICH. The disruption of cell membrane integrity characteristic of cell necrosis has been imaged in infarcted myocardium by antibody tracers such as antimyosin Fab antibody fragments and by chemical approaches such as glucaric acid binding to histones and broken-down organelles.¹⁵² Conversely, the redistribution of phospholipids from inner to outer plasma membranes that distinguishes noninflammatory programmed cell death in apoptosis can be detected by tracers specific for these anionic phospholipids such as the binding proteins annexin V^{153,154} and synaptotagmin I.¹⁵⁵ Similar approaches adapted to brain cell death would be a major step toward understanding toxic mechanisms in ICH.

A second set of targets for molecular probes are the inflammatory pathways induced by ICH. Metabolic markers such as deoxyglucose uptake¹⁵² can image the high-energy requirements of various types of inflammatory cells. More specific identification of inflammatory cells has been approached through use of radiolabeled cytokines, lymphokines, and growth factors, which avidly bind to receptors on cells of specific classes and states of activation.¹⁵⁶ Further molecular probes for the intracellular and intercellular signaling pathways activated in response to ICH are likely to emerge with our growing understanding of these signal transduction pathways.

Another major goal in studying the tissue response to ICH is to understand the formation of perihematoma edema. Serial studies using MRI fluid-attenuated inversion recovery (FLAIR) sequences should be undertaken to document the

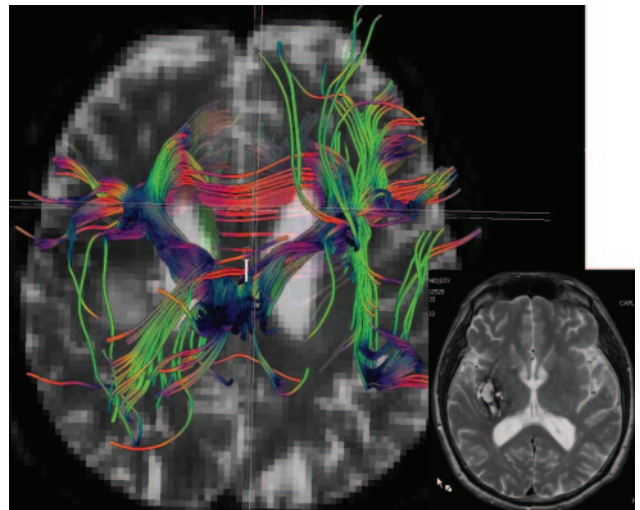


Figure 3. Diffusion tensor tractography demonstrating severe asymmetry after hemorrhagic stroke. Inset shows a T2-weighted image five months after ictus demonstrating residual hemorrhage in the posterior right basal ganglia. Tractography using symmetrical seed-points in the brainstem demonstrates marked reduction of fiber tracts in the affected (right) hemisphere compared to the left. Directional color scheme: red indicates right-left; green, anterior-posterior; blue, superior-inferior. Diffusion tractography may be able to identify white matter tracts and changes in them related to ICH and recovery. (Image courtesy of A. Gregory Sorensen, MD, Massachusetts General Hospital, HST AA Martinos Center.)

evolution of edema and correlate it with hemorrhage size and location. Neuroimaging can also serve as a bridge between human ICH and experimental models, which have implicated thrombin and other blood breakdown products as contributors to perihematoma edema through effects on the blood-brain barrier and direct tissue injury.^{110,156} Post-gadolinium FLAIR studies of the HARM (hyperintense acute reperfusion marker) phenomenon observed in ischemic stroke, for example, may provide insight into the nature and time course of blood-brain barrier disruption.¹⁵⁷ A potentially powerful method for defining molecular mechanisms active in the perihematoma tissue is analysis of the association between neuroimaging and gene expression data. Specimens for human studies could be derived from tissue obtained at surgical evacuation or biopsy. This would allow correlation of events occurring in the perihematoma molecular cascade of injury with radiological progression of ICH, edema, and clinical outcome.

These molecular approaches to tissue injury and inflammation can be supplemented by functional assessments of neuronal and neural circuit integrity. Functional neuroimaging provides the possibility of mapping not only deficits expected from the initial hemorrhage but also those functions potentially altered by further clot expansion or edema. Performing functional studies in acutely ill ICH patients will require new functional paradigms that can be applied to aphasic or patients with alteration in consciousness. Another emerging approach for detecting the integrity of neural circuits is through imaging of water diffusion along white matter tracts, including the sensitive techniques of diffusion-tensor (Figure 3) and diffusion-spectrum imaging.^{158,159} Both

techniques allow characterization of the direction as well as the diffusibility of water in the brain; diffusion-tensor imaging assumes water mobility can be described by a Gaussian function or tensor, whereas diffusion-spectrum imaging does not make such simplifying (and time-saving) assumptions.

Novel Imaging Agents

There are several important challenges in applying molecular imaging approaches to ICH. Probes will need to be modified to cross the blood–brain barrier. Studies aimed at delivery of drugs to the central nervous system have developed several promising approaches to this problem, such as use of drug-carrying nanoparticles coated with nonionic substances to reduce uptake by reticuloendothelial cells.¹⁶⁰ To minimize nonspecific backgrounds, the molecular probes will ideally exit the central nervous system rapidly as well. Finally, it will be important to develop agents detectable by MRI (for example, by conjugation to superparamagnetic iron oxide nanoparticles¹⁵⁵) to take advantage of the high spatial resolution and widespread availability of this imaging modality.

Animal Models

One approach to this goal would be to develop animal models of the same vascular pathologies that underlie spontaneous ICH; an example are mice transgenic for mutant β -amyloid precursor protein that demonstrate advanced cerebral amyloid angiopathy and ICH.^{161,162} An ideal animal model for neuroimaging purposes would be one in which ICH could be reliably triggered to establish the timing of any identified neuroimaging features.

Neuroimaging and Clinical Studies

The wide diversity of imaging protocols and software/hardware configurations has complicated attempts to pool data across collaborating sites. Creation of standardized parameters for imaging and a multicenter repository for clinical and radiographic data would be an important step toward assessing the clinical significance of novel radiographic markers and allowing them to be used in large-scale studies of ICH.

Further neuroimaging studies are needed to characterize radiographic markers of response to putative therapies such as hematoma drainage and neuroprotection, and of neurologic outcome. In the case of ICH evacuation, serial imaging will likely provide a means to assess the effect of evacuation techniques and monitor for early hemorrhage recurrence. Additional studies are needed to identify baseline characteristics of patients likely to have good or bad outcome without intervention, as well as characteristics of patients most likely to experience ongoing injury or to respond to acute therapies.^{41,163,164}

Medical Priorities

We propose 3 imperatives for research to generate clinically useful data for the medical care of patients with ICH. These include evaluation of BP management in acute ICH, determination of the best approach to reversing antithrombotic induced coagulopathy, and assessment of therapies to limit cerebral edema. Although such medical interventions may constitute the sole treatment for patients with ICH, it is also

likely that these interventions will be used in conjunction with surgical approaches to the treatment of ICH.

BP Management

Observational studies show that hematoma enlargement occurs more commonly in patients who are hypertensive at presentation, suggesting that acute elevations in BP contribute to ongoing hemorrhage.^{6,7} Based on these observations, BP is routinely lowered in patients with ICH who present with marked hypertension. The current recommendations for BP management are based on theoretical constructs only and suggest that the mean arterial BP be maintained at <130 mm Hg in patients with a premonitory history of hypertension to prevent hematoma enlargement and >90 mm Hg to ensure adequate cerebral perfusion.¹⁶⁵ A prospective randomized control trial needs to be performed to determine appropriate BP goals and the best strategies to achieve those goals. This study, by necessity, will need to incorporate measurement of ICP and cerebral perfusion pressure, as well as serial imaging studies to assess hematoma growth. In addition to providing a definitive answer about the usefulness of acute BP management in ICH, this study should provide abundant data regarding the natural history of ICH.

There are several medical therapies that have not been adequately evaluated in the treatment of ICH; however, based on experimental and clinical data in traumatic and ischemic brain injury, they may be of benefit. Given the pathophysiology of ICH-induced cerebral injury, however, the absolute benefit of these therapies is likely to be limited. The therapeutic utility of these medical interventions could therefore be addressed within the context of a trial of BP reduction.

Treatment of Hyperglycemia

Multiple lines of evidence suggest that hyperglycemia is detrimental to the injured brain. Hyperglycemia is also associated with hematoma enlargement,^{6,7} an increased risk of spontaneous hemorrhagic transformation of ischemic infarcts,^{166,167} and an increased risk of hemorrhagic transformation after systemic^{168,169} and intra-arterial thrombolysis.^{170,171} A prospective randomized control trial to define the appropriate glycemic targets in ischemic and hemorrhagic stroke, and the best strategies to achieve those targets, is needed. This trial must also address the benefits of glucose normalization in light of the potential neuroprotective/anti-inflammatory benefits of insulin.

Normalization of Body Temperature

Fever is common in patients with ICH, and even minimal elevations in body temperature are associated with worse stroke outcome.¹⁷² Small studies show that standard treatment with antipyretics, at least in ischemic stroke, usually have minimal effects on core body temperature.^{173,174} Prospective randomized control trials to determine the best strategy for lowering core body temperature and, more importantly, whether normalization of body temperature (or induction of hypothermia) translates to improved functional outcome should be undertaken.

Administration of Anti-Epileptic Drugs

Recent clinical data show that electrographic seizures occur in 28% of patients with ICH. Patients experiencing electrographic seizures were more likely to evidence neurologic worsening and there was a trend toward worse functional outcome.⁶² The clinical benefit of prophylactic anti-epileptic drug administration in patients with ICH needs to be assessed.

Safety of DVT Prophylaxis

Patients with ICH are at high risk for DVT and pulmonary embolism. Administration of prophylactic anticoagulants is likely to be of benefit in this patient population, but the timeframe for safe administration of these agents is largely undefined. Given that serial imaging studies will be performed in a trial of BP management, such a study would be able to address the risk of ICH enlargement in patients receiving prophylactic anticoagulant therapy.

Reversal of Antithrombotic/Fibrinolytic-Induced ICH

Trials of thrombolysis for myocardial ischemia provided the initial experience with thrombolytic-induced ICH. In these studies, the risk of ICH in patients treated with thrombolytics was related to the BP at the time of therapy and to the degree of systemic fibrinolysis.^{94,175} The frequency of early hematoma expansion in patients treated with warfarin or acute thrombolytic therapy may be substantially higher¹⁷⁶ than the rebleeding rate in spontaneous ICH, and the approach to limiting hematoma expansion in these patients needs to be addressed. Given the incidence of hematoma expansion and the strong and well-established relationship between ICH volume and outcome,⁴⁹ it is plausible that ultra-early hemostatic therapy directed at preventing or minimizing early hematoma expansion may improve outcome in patients with ICH.¹⁷⁷ As an additional benefit, early treatment with an effective hemostatic agent may make early surgical clot evacuation safer and more feasible.

Regardless of the results of the trial of recombinant activated factor VIIa, it seems likely that further research to develop and refine medical treatments that can effectively limit early hematoma expansion will be needed. Potentially fruitful areas of inquiry might include: (1) the accurate identification of patients at high risk for ICH expansion; (2) the development and refinement of safe and highly effective agents, either alone or in combination, to attain hemostasis; (3) the development of adjunctive medical management protocols that can limit hematoma growth or enhance the efficacy of a hemostatic agent; and (4) the development of management strategies specifically directed toward coagulopathy-associated ICH.

Development and Evaluation of Hemostatic Agents in Coagulopathy-Associated ICH

Specific questions to address:

1. How is warfarin-induced coagulopathy best reversed? What drugs and blood products should be administered, in what doses, by what route, and for how long?
 - a. Fresh frozen plasma
 - b. Vitamin K
 - c. Activated factor VIIa

2. Should patients with a recent history of antiplatelet use (aspirin, clopidogrel, dipyridamole) who present with ICH routinely be given platelets? Should all such patients with ICH be given platelets? Should platelet function be assessed in patients presenting with ICH to determine the need for platelet transfusion?

To best-determine the relevant hematologic measures to indicate hemostasis, involvement of the hematology community will be essential for this trial.

Given that hematoma enlargement is seen in patients without antithrombotic-induced coagulopathy, strategies to prevent spontaneous ICH growth must also be evaluated. Appropriate studies, in addition to the use of hemostatic agents, should include the following:

1. Identification of patients at risk. Even if an effective hemostatic agent is identified, restricting therapy to patients at highest risk for hemorrhage expansion may improve the safety and cost-effectiveness of treatment.¹⁷⁷ In addition to the risk factors for hematoma expansion identified in observational studies,^{5,9} novel imaging modalities, such as gradient echo magnetic resonance or computed tomographic angiography, may help to select patients most likely to benefit from early hemostatic therapy by documenting expansion of hematoma.^{7,151}

2. Adjunctive medical management. Acute physiological derangements that occur commonly during the acute phase of ICH, such as hypertension and hyperglycemia, have been linked to ICH growth.^{5,7,9} A better understanding of how these physiological derangements predispose to hematoma growth should aid in the development of medical interventions to limit hematoma growth.

After ICH, the hematoma exerts detrimental effects on the surrounding brain related to its displacement of tissue and occupation of space. The clinical utility of currently used hyperosmolar agents needs to be rigorously evaluated. In addition, therapies such as induction of mild hypothermia and the administration of cytoprotective drugs should be studied.

Excluding patients in whom medical therapy is withdrawn, the cause of death in most patients with ICH is cerebral herniation. Standard medical therapy for the reduction of cerebral edema, and hence mass effect, includes administration of hyperosmolar agents, such as mannitol and hypertonic saline. Whereas these agents can certainly produce transient decreases in ICP, the long-term risks and benefits of such treatment are largely unknown. A recent observational study suggests that the use of mannitol in hemorrhagic stroke is associated with no benefit, and potentially harm.¹⁷⁸ A prospective randomized control trial is needed to determine if hyperosmolar therapy improves clinical outcome in ICH. Details regarding the optimal route, dose, frequency, and duration of drug administration need to be determined and specified. The utility of ICP monitoring in ICH and the most appropriate site to monitor ICP in patients with focal brain lesions needs to be evaluated. Novel monitoring techniques, including assessment of tissue oxygen, microdialysis for markers of tissue injury, and local cerebral blood, should be incorporated into clinical therapy and correlated to outcome.

Induction of mild hypothermia could improve outcome from ICH through several different mechanisms of action. Reduction in brain temperature leads to a reduction in the metabolic needs of the brain.^{179,180} Hypothermia also attenuates the cerebral inflammatory response and limits the formation of edema, which would help prevent local increases in tissue pressure.^{124,181,182} Induction of hypothermia could be used as a primary therapy for ICH or as an adjunct to surgical clot removal. In patients experiencing cardiac arrest, induction of hypothermia dramatically improves functional recovery.^{183,184} The neurologic benefits of hypothermia have been proven in animal models of cardiac arrest and ischemic stroke. Experimental studies of hypothermia in ICH have been much more limited.

Very little experimental information exists regarding the use of cytoprotective agents in ICH; moreover, the mechanisms of cell death after ICH is unclear. Although there is little evidence to support the notion of a perihematomal ischemic penumbra early after ICH, whether such a penumbra exists at a later time point (when edema is most robust) and whether breakdown products of hemoglobin contribute to cell death are unknown. Most experimental and clinical studies of neuroprotective agents focus on a single drug that affects a single metabolic pathway in the injury cascade. Given the multiplicity of potential mediators of cell injury, the rationale for combination or “cocktail” therapy using different therapeutic agents designed to affect multiple different metabolic pathways involved in the secondary injury process is sound. Preliminary studies with drug cocktails in experimental ischemic stroke appear promising.^{185,186} It would also be possible, and potentially very effective, to consider the combination of cytoprotective therapy and hypothermia. Such strategies appear to be very effective in experimental models of ischemic stroke.^{187,188} Whether similar benefits would be seen in ICH is unknown. The potential benefits of drug “cocktails” and the complexities of designing clinical trials to test such cocktails have been addressed for ischemic stroke.¹⁸⁹ Briefly, clinical studies of combination therapy would require very large numbers of patients to adequately power the endpoints given the number of statistical permutations that arise for each intervention, drug, and drug dose used in the “cocktail.”

Surgical Priorities

A randomized clinical trial of minimally invasive techniques for clot removal is critically important. There are considerable data from non-US groups suggesting catheter placement into an ICH is safe and capable of removing clot.¹⁸⁸ There are also data suggesting that intrahemorrhage catheter-based thrombolysis with urokinase is safe and may be efficacious.¹⁸⁹ There is also evidence that intrahematoma rTPA infusion is safe and efficacious in removing clots.¹⁹⁰

Mechanical Clot Removal Devices

Within a few hours of the onset of an ICH, the clot consists of ≈20% of liquid blood and 80% denser clot by volume.^{191,192} These physical attributions make it difficult for simple aspiration. A variety of instruments and pharmacological agents have been developed to fragment and liquefy these

consolidated clots and increase the volumetric yield of aspiration. In 1978, Backlund and von Holst described a new instrument for stereotactic evacuation of hematomas, which consisted of a 4-mm cannula in which there was an Archimedes screw. Suction was applied to aspirate the clot into the cannula, and the rotating screw would morcellate the hematoma.¹⁹³ Using this technique, other authors were able to evacuate almost completely intracerebral hemorrhages in 13 of 16 patients in their series. However, 81% of these patients died.¹⁹⁴ After these pioneering reports, several modifications to the device were described.^{191,195} Other innovative devices included a specially designed ultrasonic aspirator,¹⁹⁶ a modified nucleotome,^{188,197} and a double-track aspiration system.^{189,198}

Adjuncts to Surgical Targeting

In 1989, Auer reported the results of a randomized clinical trial of 100 patients subject to ultrasound-guided endoscopic evacuation with laser coagulation within 48 hours for ICH >10 mL volumes versus medical therapy alone.¹⁹⁹ There was a decreased mortality at 6 months in the surgical group (42%, versus 70% in the medical therapy group). A trend toward better outcomes in the surgical group was also observed, and endoscopic evacuation of smaller hematomas led to significantly better quality of life compared with those treated medically. Surgical benefit was limited to patients with lobar hematomas and patients younger than 60 years. Unfortunately, there are no follow-up studies in the literature from this or other groups regarding the use of this technique.

Intra-operative and Peri-operative Real-Time Imaging

Innovative and new potential future surgical treatments for ICH require the refinement of real-time imaging technologies to allow for real-time feedback of the progress of hematoma evacuation and allow for accurate placement of the devices. It is imperative to study these imaging adjuncts in clinical trials. Real-time 2-dimensional ultrasound, intra-operative CT fluoroscopy, and intra-operative MRI appear the most promising.^{200–203}

Local Delivery of Protective/Restorative Agents Improve Outcome and Restore Biology

Locally applied agents have been shown in other clinical situations to induce faster and more complete hemostasis than conventional substances. One of these is a fibrin sealant, which consists of pooled human fibrinogen and thrombin with or without factor XIII.^{203,204} Two other popular agents are FloSeal Matrix (particulate gel foam plus thrombin; Baxter Healthcare Corp)²⁰⁵ and CoSeal (a polymeric sealant; Baxter Healthcare Corp).²⁰⁶ In addition, there is evidence from a prospective series that rebleeding occurs after surgical evacuation, especially if performed early.²⁰⁷ Rebleeding after surgery was also reported in nonprospective clinical series and has been reported to be as high as 7.4% even in series of ICH treated with stereotactic aspiration.¹⁸⁹ One possible solution to this issue is to consider superselective injection of a hemostatic agent at the site of dye extravasation on an angiogram as a treatment strategy.

We propose testing whether intracavitary administration of these agents reduces rebleeding after clot evacuation. In addition, we heartily suggest examining the effect of intra-arterial administration of factor VIIa to promote postsurgical hemostasis compared with untreated patients and patients treated with intravenous factor VIIa. Testing these hypotheses is important because postoperative rebleeding negatively impacts on outcome and might account for negative or even marginal data from previous trials in which postoperative CT scanning is not routine. However, administration of procoagulants, especially those containing thrombin, might adversely effect outcome by enhancing edema formation or contributing to microvascular failure.

Regional Hypothermia

Although the data on hypothermia's protective effects in experimental ICH are controversial,^{124,208} it is possible that it would prove more efficacious if the deleterious side effects of hypothermia could be minimized. There now exist several devices in various stages of preclinical development that hold the hope of creating regional brain hypothermia without whole-body cooling.²⁰⁹ Studies will need to compare the safety and efficacy of these devices in the setting of ICH. Each of these devices requires a minor surgical procedure to be performed in addition to clot evacuation or conservative management.

Does Intracavitary Microdialysis for Markers of Ongoing Injury Provide Guidance for Future Therapies?

Recent data suggest that microdialysis can be safely performed in a variety of neurosurgical patients.²¹⁰ Moreover, it appears that in the setting of subarachnoid hemorrhage, interstitial fluid might guide therapeutic manipulations.²¹¹ Future studies will be needed to test whether microdialysate from juxta-cavitary regions guides therapy and correlates with novel imaging.

Polymer-Based Sustained-Release Technology With or Without Remote Staged Activation as an Alternative to Topical or Convection-Enhanced Techniques for Delivery of Cytoprotective or Regenerative Therapies

Despite evidence that the blood-brain barrier is disrupted after ICH, there remains the possibility that cytoprotective or regenerative (especially cellular) therapies might be better-delivered in the cavity. Unfortunately, the clot cavity is most readily accessed early at the time of clot evacuation. This may not be the most efficacious time for delivery of a proposed therapy. There currently exists a whole host of options for time-released delivery of agents either regionally or to the entire cerebrum. These options include the use of polymeric wafers²¹² or convection catheters connected to reservoirs.²¹³ Future studies will need to define which therapies are best-delivered at which time and with which device.

Delayed Restorative Surgical Procedures

The initial hemorrhagic insult of ICH may lead to irreversible loss of neurons and functional neuronal units despite best

medical and surgical care. Strategies to limit infarct volume in animal models of ischemic stroke using growth factors and transplantation of stem cells have shown functional benefits.^{214,215} Similar utilization of stem cells delivered by a variety of routes to the residual hematoma cavity and administration of growth factors may potentiate the restorative capacity of the human brain leading to improved functional outcome.

Delayed Implantation of Bionic Interfaces

ICH predominantly affects axons and white matter and may result in a disconnection between preserved/intact overlying cortex and brain stem. Electrode arrays and neural stimulation have shown promise in rodents in inducing sensory-evoked behaviors.²¹⁶ These similar techniques and cortical body computer interfaces may allow for a "white matter" bridge from cortex.

Clinical Research Methodology Challenges

We have identified 3 major challenges to the proper design and successful completion of future randomized treatment trials of ICH: (1) recruitment and process of informed consent; (2) standardization of management interventions, as well as organization and experience of trial team; and (3) stratification of disease severity and choice of the most relevant outcome parameters.

Patient Recruitment and Consent Process

Recruitment and informed consent of patients with ICH into randomized trials is quite challenging because the patients are often very ill or near death and require rapid and aggressive medical management. Failure to recruit patients into randomized studies is difficult from the perspective of the patient and family, as well as the treating physician. First, ICH patients usually present with severe neurologic deficits, including progressive worsening in the level of consciousness, markedly elevated BP, and respiratory difficulties. Often, by necessity, these therapies are started soon after arrival in the emergency department and before any discussion of a study with the family.

Because of the severity of the deficit, and frequent intubation with sedation, the majority of ICH patients cannot provide informed consent. Thus, the family or legal representative must provide this consent. The process of community consent for trials of hypothermia in cardiac arrest and head trauma could be used in randomized trials of ICH. Randomization to a study that involves aggressively doing something (surgery) as compared with medical therapy can be a difficult concept for families and physicians when the patient has a high risk of very rapid deterioration or death.

Recruitment is also more difficult for ICH as compared with ischemic stroke because it is less common, comprising only 10% of all strokes. Additionally, the more restrictive the inclusion and exclusion criteria for a given trial (eg, severity of deficit at baseline, volume of ICH, age, presence of intraventricular hemorrhage (IVH), time to treatment), the more difficult recruitment will be. It is likely that many more centers will be needed to recruit a given number of patients

TABLE 2. Some Factors Ideally Controlled for in Standardized Treatment Protocols for ICH

Coagulation abnormalities
Hydrocephalus management
Blood pressure and hemodynamic management
Intracranial pressure
Fever management
Serum glucose
Seizure management
Use of sedation
Pulmonary issues
Fluid and electrolytes issues
Gastrointestinal/nutritional issues
Infection monitoring and management
Deterrence of complications of immobility

with ICH as compared with the same number of patients with ischemic stroke.

In addition to neurologists, neurosurgeons, who are most frequently asked to see ICH patients in the emergency department, will need to be the most important drivers of recruitment into successful randomized trials of ICH. Neurosurgical leadership in trials of traumatic brain injury and subarachnoid hemorrhage is a model for successful recruitment in future treatment trials of ICH.²¹⁷ Neuro-intensivists play an important role in care of ICH patients at some centers but, without the willingness and hands-on leadership of neurosurgeons, randomized trials of ICH will be relegated to medical therapies alone. Emergency physicians should be encouraged to play a role in future treatment trials of ICH.

Standardization of Management Interventions and the Organization and Experience of the Trial Team

Most ICH studies lack standardization of medical and surgical treatment. With respect to medical management, numerous factors may bear a relationship to outcome with ICH (Table 2). Failure to control such factors may confound interpretation of future treatment trials of ICH. Thus, any study on the efficacy of a particular intervention for ICH should standardize the medical management of key modifiable medical factors and fully describe the spectrum of intervention.^{218–220}

The experience of the treating physicians and nurses likely has an impact on the outcome from ICH. The volume of hospital admissions for aneurysmal subarachnoid hemorrhage has been shown to correlate with outcome.²²¹ Because the spectrum of disease severity and management issues is similar with ICH, it would be expected that such a correlation exists with ICH as well. Similarly, it has been shown that admission to a neurological/neurosurgical intensive care unit is associated with reduced mortality after ICH.²²² Multicenter studies on ICH should involve thoughtful center and investigator selection based on extent of experience of the investigators, the model, continuous availability for skilled multidisciplinary (cross-specialty) collaboration, and the organization of the clinical care environment for the proposed study patients.²²³

Stratification of Disease Severity and Choice of the Most Relevant Outcome Parameters

Volume of ICH and volume of IVH are highly associated with mortality and disability. Although this relationship between severity of disease and outcomes has been well described, the effect of clot removal on outcome has not been directly tested in an interventional study. Stratification by hematoma size will insure an equal mix of high and low mortality risk in the test populations of a randomized trial. The use of predicted mortality/morbidity has also been used successfully to compare outcomes.⁵⁶

Because hemorrhage extension is an ongoing and variable process, growth of ICH/IVH cannot be used as a stratification factor in the first hours after onset. Stability of ICH volume on serial imaging could be used as entry criterion for a given trial.

In addition to volume of ICH and IVH, Glasgow Coma Scale on initial evaluation has a strong relationship to mortality. Specifically, age, location, gender, and race clearly are not independently associated with excess mortality. It should be noted that brain stem and infratentorial locations might be associated with a higher likelihood of poor functional recovery; however, these locations represent 10% or less of all hemorrhages.

Selection bias may influence the generalizability of results of clinical trials for ICH. Many young patients with impending herniation, as well as many severely affected older patients, are never randomized. Randomized trials of ICH need to characterize the population undergoing study as compared with the broader universe of all patients with ICH. Mortality after ICH is high with protracted recovery among survivors. Some^{207,224} have suggested that long-term assessment of functional outcome, in addition to mortality, is important. Ongoing studies have struggled with the appropriate cutoff for functional outcome using modified Rankin scale or other measures. Because attainment of a Rankin score of 0 to 1 in a patient with ICH is rare, use of Rankin score of 0 to 2 (favorable outcome) or Rankin score of 4 to 6 (severe disability or death) may be more appropriate. Another option may be to consider outcome after ICH, taking into account the baseline severity. This approach has been adopted by the STICH investigators.²²⁵

Study of surrogate markers of functional outcome, such as residual volume of ICH after therapy or percent change of ICH volume from baseline, is an important area of future research. Surrogate markers should be particularly focused on measuring expected effect of a particular intervention (eg, evaluation of clot removal techniques by change in volume of ICH) or disease progression.

Some young patients with ICH can recover well by stroke and disability outcomes scales but still may have significant impairment of quality of life.²²⁶ Measurement of quality of life may be complicated in very severely compromised patients with communication and cognitive deficits. Studies of quality of life modeling after ICH are needed to complement current outcome instruments.

Consideration of Withdrawal of Care and Do Not Resuscitate Status

Outcome and mortality in ICH studies may be contaminated by do not resuscitate status. Some have found that withdrawal of care and aggressiveness of care in ICH may not accurately reflect the disease's natural history.²²⁶ This should be considered in designing ICH trials.

Appendix

Workshop Leadership Committee: Chair, Lewis B. Morgenstern, University of Michigan, Ann Arbor; Chair, Marc R. Mayberg, Cleveland Clinic Foundation, Cleveland; Katherine Woodbury-Harris, NINDS, Rockville; John R. Marler, NINDS, Rockville.

Group I—Current State of ICH Research: Chair, Michael N. Diringer, Washington University, St. Louis; Co-Chair, David W. Newell, University of Washington, Seattle; Michael DeGeorgia, Cleveland Clinic Foundation, Cleveland; Hunt Batjer, Northwestern University, Chicago.

Group II—Basic Science Foundations of ICH Research: Chair, Gregory J. del Zoppo, Scripps Research Institute, La Jolla; Co-Chair, Julian T. Hoff, University of Michigan, Ann Arbor; Kyra J. Becker, University of Washington, Seattle; James C. Grotta, University of Texas, Houston; Kenneth R. Wagner, University of Cincinnati.

Group III—Medical Targets for ICH Research: Chair, Kyra J. Becker, University of Washington, Seattle; Co-Chair, Adnan I. Quereshi, University of Medicine and Dentistry of New Jersey, Newark; Stefan A. Mayer, Columbia University, New York; Christopher S. Ogilvy, Massachusetts General Hospital, Boston.

Group IV—Surgical Targets for ICH Research: Chair, Mario Zuccarello, University of Cincinnati; Co-Chair, James C. Grotta, University of Texas, Houston; Peter A. Rasmussen, Cleveland Clinic Foundation, Cleveland; E. Sander Connolly, Columbia University, New York; A. David Mendelow, University of Newcastle, Newcastle Upon Tyne.

Group V—Imaging Targets for ICH Research: Chair, Steven M. Greenberg, Massachusetts General Hospital, Boston; Co-Chair, Howard Yonas, University of Pittsburgh; Chelsea S. Kidwell, University of California, Los Angeles; Larry R. Wechsler, University of Pittsburgh.

Group VI—Clinical Methodology Challenges in ICH Research: Chair, Joseph P. Broderick, University of Cincinnati; Co-Chair, Issam A. Awad, Northwestern University, Chicago; Penelope M. Keyl, East Sandwich MA; Daniel F. Hanley, Johns Hopkins, Baltimore; Jeffrey I. Frank, University of Chicago.

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