Ischemic Brain Injury After Intracerebral Hemorrhage
A Critical Review

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Intracerebral hemorrhage (ICH) is the second most common cause of stroke and accounts for 8% to 15% of strokes in Western societies with an estimated incidence of 10 to 25 per 100 000 persons. Despite advances in the field of stroke and neurocritical care, the 30-day mortality has not changed significantly over the past 20 years. Indeed, ICH has the highest rates of dependence or death among stroke types and proven treatments are lacking.

Clinical trials aimed at limiting hemorrhage growth, procoagulant agents for hemostasis, and surgical evacuation have not translated into improved clinical outcomes. Antihypertensive therapy for the purpose of reducing hematoma growth has been a mainstay of acute management. Guidelines recommend maintaining mean arterial pressure <130 mm Hg during the acute phase; however, controversies exist given the lack of randomized clinical trial data and uncertainties about the rapidity and target level of blood pressure (BP)-lowering. Recent Phase 2 clinical trials evaluating acute BP control have shown promise in reducing hematoma expansion with an adequate safety profile and Phase 3 trials are underway.

Besides hematoma growth, other pathophysiological processes occur in the setting of ICH and may serve as potential therapeutic targets. In the acute period after ICH, a rapid rise in intracranial pressure (ICP) from an expanding hematoma may reduce cerebral perfusion pressure. In this setting, interventions aimed at BP-lowering and hemostasis may theoretically induce thrombosis or exacerbate brain ischemia, particularly in patients with pre-existing cerebrovascular disease. A recent publication suggests that aggressive BP-lowering may actually cause acute brain ischemia and worsen outcomes after ICH.

In this review, we outline the data on secondary acute ischemic injury after ICH, review the prevalence of remote ischemic lesions and risk factors associated with their occurrence, explore potential mechanisms and clinical impact of these lesions, and discuss future directions in this arena of research.

Prevalence of Secondary Ischemic Injury After ICH

After arteriolar rupture and parenchymal hemorrhage in the brain, a combination of local compression, cytotoxic injury, inflammation, and surrounding edema ensues. Imaging studies in patients with ICH have demonstrated these effects at varying stages of hemorrhage and within and surrounding the hematoma bed. Although there is restricted diffusion within the hematoma during the first 2 weeks, an effect of increased viscosity and susceptibility effects from blood breakdown products, much more attention has been paid to the potential for ischemia in the surrounding tissue.

That aggressive BP-lowering might promote cerebral ischemia adjacent to the hematoma has been cited as a potential hazard of aggressive antihypertensive therapy; however, imaging studies using single-photon emission CT, positron emission tomography, and CT and MR single-photon emission computed tomography and perfusion studies have failed to show any significant rim of perihematomal ischemia. There appears to be decreased cerebral blood flow in the perihematomal region but it is accompanied by a decreased cerebral metabolic rate of oxygen and lowered, not elevated, oxygen extraction fraction. Thus, the data suggest that perihematomal hypoperfusion in ICH is a consequence of hypometabolism, which may be mediated by toxic effects from the hematoma itself. Other studies, however, using single-photon emission computed tomography and jugular venous oxygen tension have observed reduced hemispheric cerebral blood flow and impaired cerebral autoregulation in the setting of aggressive BP-lowering. It is also known that complex phasic variations in cerebral blood flow and metabolism may exist after ICH such that very aggressive BP-lowering or persistent modest lowering in the later periods of metabolic normalization may lead to cerebral ischemia both in the perihematomal and distant brain regions.

Diffusion-weighted imaging (DWI) offers greater spatial resolution (1–2 mm) than single-photon emission CT, positron emission tomography, or CT-based techniques (5–10 mm); can detect very small foci of acute neuronal injury; and is a sensitive marker of acute brain ischemia. The occurrence of DWI lesions, remote from the primary site of injury and delayed from the ictus, has been described in other types of brain injury including ischemic stroke, transient ischemic attack, and subarachnoid hemorrhage. Its recent application in ICH suggests that remote ischemic lesions are found in approximately 25% of patients. The lesions
Mechanisms and Pathophysiology

Mechanisms of secondary ischemic injury after ICH are uncertain. However, based on the recent publications, it appears that several potential factors have been consistently associated with acute ischemic lesions. These include BP-lowering, markers of microvasculopathy, and ICP elevation (Table). We theorize that these mechanisms interact in complex ways (Figure 2). Acting on a background-enhanced thrombotic milieu (‘stroke-prone’ state) after ICH, vulnerable patients with pre-existing cerebral microangiopathy due to atherosclerotic risk factors and/or cerebral amyloid angiopathy (CAA) may have lower thresholds for brain ischemia. In such patients, elevations of ICP, failure of autoregulation, and aggressive early BP-lowering could provoke acute brain ischemia.

BP-Lowering

Three studies have independently suggested a relationship between degree of BP-lowering and DWI lesions, whereas 2 have not found an association. In the positive studies, change in BP, in absolute and relative terms, correlated with presence of DWI lesions. This relationship may be heightened in the first few hours after BP treatment (Figure 3).

Cerebral blood flow is regulated across a wide range of mean arterial pressure or cerebral perfusion pressure in the normal state. Cerebral autoregulation is right-shifted in chronic hypertension and may be lost in the setting of acute brain injury such that cerebral blood flow responds linearly to cerebral perfusion pressure. Elevated ICP and use of vasoactive substances with the potential of exacerbating ICP may further compromise cerebral perfusion pressure in patients with ICH.

Table. Summary of Recent Publications on DWI Lesions After ICH

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Design</th>
<th>Timing of MRI</th>
<th>Age, y</th>
<th>Race</th>
<th>ICH cause</th>
<th>Prevalence of DWI lesion</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimberly et al</td>
<td>78 (87% ICH)</td>
<td>Retrospective case–control</td>
<td>Median, 4 d</td>
<td>White?</td>
<td>100% CAA</td>
<td>15%</td>
<td>Total MBs, Prior stroke, Craniotomy</td>
</tr>
<tr>
<td>Prabhakaran et al</td>
<td>118 (100% ICH)</td>
<td>Retrospective</td>
<td>Median, 1 d</td>
<td>Nonwhite 67%</td>
<td>70% HTN</td>
<td>23%</td>
<td>CAA etiology, BP-lowering</td>
</tr>
<tr>
<td>Gregoire et al</td>
<td>114 (100% ICH)</td>
<td>Multicenter case–control</td>
<td>Median, 7 d</td>
<td>White?</td>
<td>34% CAA</td>
<td>13%</td>
<td>Leukoaraiosis, IVH</td>
</tr>
<tr>
<td>Garg et al</td>
<td>95 (100% ICH)</td>
<td>Prospective</td>
<td>Median, 2 d</td>
<td>Nonwhite 62%</td>
<td>62% HTN</td>
<td>41%</td>
<td>Total MBs, ICH volume</td>
</tr>
<tr>
<td>Menon et al</td>
<td>138 (100% ICH)</td>
<td>Prospective</td>
<td>Median, 2 d and 35 d</td>
<td>Nonwhite 73%</td>
<td>62% HTN</td>
<td>Acute: 35%</td>
<td>Leukoaraiosis MBs &gt;2</td>
</tr>
<tr>
<td>Kang et al</td>
<td>97 (100% ICH)</td>
<td>Prospective</td>
<td>Median, 3 d</td>
<td>Asian</td>
<td>83% HTN</td>
<td>27%</td>
<td>1 mo: prior stroke, Baseline MB</td>
</tr>
</tbody>
</table>

*DWI indicates diffusion weighted imaging; ICH, intracerebral hemorrhage; MB, microbleeds; CAA, cerebral amyloid angiopathy; HTN, hypertension; BP, blood pressure; IVH, intraventricular hemorrhage.*
Cerebral Microangiopathy

Five of the studies consistently reported an association with either microhemorrhage burden on gradient-echo imaging or white matter hyperintensity burden on fluid-attenuated inversion recovery sequences.27–30 A history of stroke was associated with DWI lesions in another study.31 As markers of chronic cerebral vasculopathy, these factors may identify those with significant pre-existing cerebrovascular disease and who are more prone to ischemic injury after ICH.

Ischemic stroke and ICH share many risk factors and pathological substrates. The characteristic locations of hypertensive ICH include the basal ganglia, thalamus, pons, and cerebellum, many of which are common sites for lacunar ischemic infarction. They also share many vascular risk factors including hypertension, diabetes mellitus, dyslipidemia, and smoking.33 It is well established that these risk factors lead to distinct pathologies affecting arterioles (typically perforators) including fibrinoid changes, lipohyalinosis, necrosis, and microaneurysm formation. These changes can predispose them to occlusion and/or rupture.34 Further evidence of the link between ischemic stroke and ICH is drawn from the observations that patients surviving ICH have comparable risks for subsequent ischemic and hemorrhagic stroke.35,36

In contrast to hypertensive vasculopathy, which affects the deep and subcortical arterioles, CAA affects small superficial and leptomeningeal arterioles. Beta-amyloid protein deposition in these vessel walls leads to degenerative changes that predispose them to vessel fragility and rupture.37 Just as hypertensive vasculopathy can manifest as ICH, ischemic infarction, leukoaraiosis, and vascular dementia, patients harboring CAA pathology can have multiple cerebrovascular presentations including ICH, vasculitis and ischemic stroke, leukoencephalopathy, and dementia.38 Indeed, white matter disease is increased and cerebral blood flow responses are impaired in patients with CAA compared with control subjects.39,40

Thus, a chronic microangiopathy, either due to hypertension or CAA, may pre-exist in many patients with ICH. These underlying disease processes may place such patients at risk for both ischemic and hemorrhagic stroke. Vascular biological substrates may also play critical roles in determining the response to hemodynamic alterations after ICH and precipitate secondary ischemic injury. For instance, pre-existing microvascular flow impairment may be exacerbated by aggressive BP-lowering and/or thrombotic activation after ICH and result in small ischemic infarcts.

Further support of an underlying microangiopathy in both hemorrhagic and ischemic stroke comes from a recent report of subclinical incident microhemorrhage occurrence (unrelated to hemorrhagic transformation) after acute ischemic stroke. In a serial brain MRI study of 237 patients with ischemic stroke, 12.7% of patients developed new microhemorrhages within days of the initial scan.41 A common microvascular disarray might underlie both hemorrhagic and ischemic stroke and promote a “stroke-prone state” after any acute cerebrovascular insult.24 These may be mediated by endothelial dysfunction, active inflammation, and breakdown of the blood–brain barrier in ICH.42 We, therefore, speculate that hypertensive and CAA-mediated changes in the microvasculature lead to hemorrhagic or ischemic stroke in isolation in most patients but can occur in rapid sequence or simultaneously in some patients.

Other Mechanisms and Provoking Factors

As noted, ICP elevation in moderate- or large-volume hemorrhages or those associated with intraventricular hemorrhage...
and hydrocephalus may lower the threshold for ischemia in the setting of relatively modest but rapid BP-lowering. Volume of ICH and intraventricular extension, probably as surrogate markers of ICP, have been associated with DWI lesions.30,31 Alternatively, many patients with ICH with vascular risk factors may ingest antithrombotic agents and harbor large-artery stenosis or cardiac sources of embolism at baseline. Thus, ischemic stroke may simply be occurring in high-risk patients in the setting of antiplatelet therapy withdrawal.43

Another possibility is that frank hemorrhagic transformation of an embolic ischemic stroke may be misdiagnosed as spontaneous ICH with remote DWI lesions providing evidence of embolism. This would unlikely explain such a large proportion of patients with this finding, however. Other unlikely mechanisms include local vascular compression due to the mass effect from the hematoma. A small percentage of patients also undergo craniotomy, during which low BPs, anesthetic agents, manipulation of arteries, and thrombotic activation with surgery may promote ischemia. Vasospasm, which is common after subarachnoid hemorrhage, is not known to occur after spontaneous ICH in the absence of an unusual amount of subarachnoid blood or a reversible vasculopathy that may present with ischemic and hemorrhagic stroke (ie, Call-Fleming or reversible cerebral vasoconstriction syndrome). Finally, given the delayed incident lesions at 1 month, there may be a period of thrombotic or inflammatory activation that leads to subclinical and clinical events soon after ICH, like in other acute brain injury states. In animal models of subarachnoid hemorrhage,44 trauma and traumatic brain injury,45 platelets have been shown to aggregate and cause microvascular occlusion due to an inflammatory prothrombotic environment.

Impact on Long-Term Outcomes
Given the data on the prevalence of ischemic lesions after ICH, the next logical question is: do they matter? Silent brain infarcts are frequently observed on brain imaging of elderly individuals, serve as markers for the extent or severity of cerebrovascular disease, and predict subsequent risk of stroke and vascular dementia.46-48 Early subclinical DWI lesions after acute ischemic stroke also increase the subsequent risk of recurrent ischemic stroke, transient ischemic attack, and vascular death.49 Silent infarcts may also interact with the index infarct volume and worsen the degree of motor impairment in patients with stroke.50

Two longitudinal studies have evaluated the influence of DWI lesions on subsequent functional outcomes after ICH. At 3 months, those with DWI lesions were 5-fold more likely to have poor functional outcomes (defined as modified Rankin Scale score 4–6 indicating dependence or death) adjusting for known predictors (age, initial stroke severity, and ICH score).10 Another single-center study evaluated outcomes at 1 year and noted that those with DWI lesions were >6-fold more likely to have poor outcomes at follow-up than those without, independent of stroke severity.51 A third prospective study of 97 patients with ICH followed for median 42 months demonstrated that DWI lesions signi-
cantly increased risks of ischemic stroke and combined ischemic stroke, ICH, and vascular death.28

The mechanisms by which small ischemic lesions worsen outcome after ICH are uncertain. These may reduce neuroplasticity and retard restorative ipsi- and contralesional synaptic networks. Some lesions may be strategically symptomatic but only become recognized after the initial clinical presentation, influenced mostly by the hematoma itself, recedes in the subacute period. Lastly, DWI lesions in ICH may simply be markers for “frail” patients who are destined for poor recovery and elevated risk of recurrent stroke.

Implications for Current Practice
These studies cumulatively support (1) a considerable (approximately 25%) prevalence of DWI lesions; (2) a strong correlation with BP-lowering; and (3) a negative impact of DWI lesions on functional outcomes after ICH. Thus, it may be time to reconsider our approach to this disease and to re-evaluate ongoing clinical trials aimed at BP-lowering after ICH. Aggressive BP-lowering has become standard practice at many centers at the time the pivotal clinical trials to determine its clinical impact are still underway; a more refined approach with careful titration of antihypertensive therapy and using individualized targets may be necessary.

Randomized clinical trials of BP-lowering should incorporate MRI to evaluate for secondary ischemic lesions and assess their influence on functional outcomes. We postulate that DWI lesions may modify the effect of BP-lowering on functional outcomes after ICH such that it may be hazardous in those with DWI lesions and beneficial in those without.

Future Directions
Given these potential implications and yet many open questions, it is imperative that research in this area continue. First, imaging techniques including perfusion and functional imaging may help quantify the hemodynamic effects of acute BP-lowering after ICH and evaluate the impact of “silent” lesions on functional recovery. Second, serial MRI studies are needed to define the timing of ischemic lesions because subacute infarcts may be amenable to prevention. Third, detailed outcomes assessments are currently lacking but would provide insights into subtle cognitive or quality-of-life effects not appreciated by crude outcome measures such as the Rankin Scale. Fourth, pilot studies should assess the prevalence of DWI lesions at different target BP levels and the safety of ischemic stroke prevention strategies such as aspirin and statin therapy after ICH.

New targets for therapeutic intervention in ICH are sorely needed. Current guidelines for BP reduction and hemostatic therapy to limit hematoma growth at the possible expense of cerebral hyperperfusion and arterial thrombosis, respectively, may be doing more harm than good. If an active biological link between hemorrhagic and ischemic brain disease exists and imaging-based techniques can identify those at risk for either or both conditions, then the relative value of secondary prevention strategies such as lipid-lowering, long-term BP control, glycemic regulation, and antithrombotic agents gains even greater importance for individualized application in vulnerable patients. Early use of antiplatelet and statin ther-
apis to prevent secondary neuronal injury during a proinflammatory, “stroke-prone” period even at the expense of hemorrhage growth or recurrent hemorrhage may be more beneficial than currently believed. Furthermore, risk factors such as carotid artery stenosis, atrial fibrillation, and underlying hypercoagulable states may need to be considered in the diagnostic evaluation of ICH. In summary, the emerging data lying hypercoagulable states may need to be considered in the such as carotid artery stenosis, atrial fibrillation, and under-

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