Metabolic Penumbra in Intracerebral Hemorrhage

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Editorials

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In the past decade there has been considerable scientific discussion about the metabolic state of the tissue surrounding a brain hemorrhage. The scientific discussion has focused mostly on the question of whether brain ischemia is present in this “penumbral tissue,” which has great clinical relevance because the presence of ischemia would drive clinical treatment considerations such as blood pressure management and surgery.1 Ischemia has classically been considered to be the deprivation of oxygen to tissue caused by arterial occlusion, with a resulting increase in oxygen extraction fraction (OEF) followed by local tissue acidosis and eventually cell death. This model of ischemia has been used to define tissue at risk and is a core principal used for ischemic stroke. The exact PET thresholds that define ischemia2 have been proposed and are presently being used in research settings. In an important study, Zazulia and colleagues reported that the tissue immediately surrounding a brain hemorrhage did not exhibit classical ischemia as defined by PET OEF, and that small reductions in cerebral blood flow did not elicit much change in cerebral blood flow.4 This implies that ischemia is not present in the perihematomal tissue. PET OEF imaging in traumatic hemorrhage similarly shows no increase in OEF in the peritraumatic region.5 Nonetheless, the surrounding tissue displayed reductions in oxidative metabolism, with very low rates of oxygen use. This reduction in oxygen use is thought to be attributable to impaired mitochondrial function, which has preliminarily been confirmed in tissue samples taken during surgery from patients with brain hemorrhage. The impairment in mitochondrial function implies that a metabolic crisis is occurring in this tissue, despite the absence of brain ischemia. A similar nonischemic metabolic crisis has been documented in traumatic brain hemorrhage.7 The net effect of this information on treatment strategy has been for a recommendation to control blood pressure and cerebral perfusion pressure into conservative ranges and to not consider the surrounding tissue to be ischemic.

At the same time that we have been learning that the perihematomal tissue is not ischemic, there have been a number of observations about the exact nature of this nonischemic metabolic crisis. Measures of regional brain metabolism, neurochemistry, and electical activity have shed some light on the nature of this metabolic distress. Brain PET imaging in traumatic hemorrhage has revealed that an up-regulation of glucose uptake occurs in the penumbra.8 This increase in glucose use, termed hyperglycolysis, can be detected up to 5 days after the onset of hemorrhage. In this issue of Stroke, Zazulia and colleagues report that the perihematomal tissue is exhibiting a similar increase glucose uptake in the tissue surrounding the hematoma. This increase in glucose uptake occurred generally between 2 to 4 days after the onset of hemorrhage and resolved by 5 to 8 days after hemorrhage. This time course is similar to that reported by Bergsneider.9 The increase in glucose metabolism did not occur as a result of brain ischemia in brain trauma, and it does not appear that brain ischemia was present in the current study by Zazulia.9 Although the authors recognize potential limitations of their study, most notably the lack of concurrent PET measures of oxidative metabolism, the nonquantitative measures of glucose use, and lack of concurrent continuous electroencephalographic monitoring for seizures, the strengths of this article include high-resolution regional imaging done in a repeated fashion over time. Thus, this work is very important because it confirms that there is a disturbed glucose metabolism in perihematomal tissue and builds on the excellent work of the same center to define the lack of ischemia surrounding brain hemorrhage.

The regional increase in glucose utilization is thought to be due to one or more nonischemic mechanisms, such as regional inflammation, seizure activity, spreading depression or glutamate induced cytotoxicity. Using continuous EEG monitoring, several groups have documented frequent non-convulsive seizures after ICH.10,11 Since seizures can lead to increases in glucose consumption, one hypothesis is that the regional hyperglycolysis that is reported by Zazulia is due to seizure activity. Posthemorrhagic seizures occurring during a similar time frame, within 2 to 4 days after hemorrhage onset, have been demonstrated to be associated with worsening elevations in intracranial pressure, worsening mass effect and increased midline shift.10 In a similar fashion, electrical depolarization events in the form of direct current spreading depression have been documented using electrocorticography in regions adjacent to surgically evacuated hematomas.12 These DC depolarizations are repetitive events that classically elicit an increase in glucose utilization and secondary cellular injury. Given these complimentary clinical observations, one could reasonably speculate that electrical depolarization events, either seizures or DC events, could be occurring in the perihematomal tissue and leading to regional hyperglycolysis, as reported by Zazulia. Hence, the penumbral tissue is in a state of metabolic crisis, and constitutes a metabolic penumbra.

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Regional measures of neurochemistry, using cerebral microdialysis monitoring, have documented that perihematomal tissue has long-lasting signs of disturbed metabolism. Prolonged elevation of the excitotoxic amino transmitted glutamate have been reported in tissue adjacent to brain hemorrhage, and we are poised to determine whether modifying this disturbed metabolism will result in evidence for a metabolic rather than ischemic penumbra in intracerebral hemorrhage, and alterations of the lactate/pyruvate ratio have been reported in tissue adjacent to brain hemorrhage. There is now ample evidence of regional hyperglycolysis, the microdialysis studies suggest that there is ongoing injury occurring in this metabolic penumbral tissue. This ongoing injury therefore appears to be a new clinical target for intervention. One can imagine that use of drugs or other treatments to interrupt electric depolarizations, such as anticonvulsants, or interrupt glutamate toxicity may be useful to help protect this perihematomal tissue. Hence, the conceptual paradigm shift away from an ischemic penumbra to a metabolic penumbra holds much promise for the development of novel treatment strategies that are designed to improve the state of local metabolism that is based on supply of novel fuels, reduction of electric depolarization, or stereotactic removal of toxic blood. Some of these strategies are presently being tested in randomized controlled trials. There is now ample evidence for a metabolic rather than ischemic penumbra in intracerebral hemorrhage, and we are poised to determine whether modifying this disturbed metabolism will result in clinical improvement.

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