See related article, page 67.

The study by Garg et al\(^1\) reports the frequency of decreased diffusion using diffusion-weighted imaging and an apparent diffusion coefficient map in patients with intracerebral hemorrhage (ICH) undergoing MRI. Only areas of decreased diffusion that were not contiguous with the hematoma were analyzed. A total of 36 (38%) of 95 patients with ICH had evidence of decreased diffusion on MRI scans performed at a median time interval ranging from 1.6 to 2.3 days after symptom onset. Prabhakaran et al\(^2\) similarly reported diffusion-weighted abnormalities in 23% of the 118 patients with spontaneous ICH who underwent MRI scans within 28 days of admission. Because these patients did not have MRI scans before onset of ICH and minor neurological deterioration was not always detected, the characteristics of MRI changes are the only proof of temporal correlation with occurrence of ICH. However, the exact time interval between ICH onset and the development of new diffusion changes cannot be accurately determined. Garg et al\(^3\) also found that evidence of decreased diffusion was associated with a 5× higher odds of death or dependency at 3 months among patients with ICH after adjusting for the ICH score.

Diffusion-weighted MRI provides image contrast that is dependent on the molecular motion of water. Molecular motion of water is restricted (decreased diffusion) in the intracellular compartment (particularly with fragmented intracellular components) and in the extracellular space compressed by cellular swelling.\(^3\) Disruption of energy metabolism accompanied by failure of the Na\(^+\)/K\(^+\) adenosine triphosphatase pump and other ionic pumps results in movement of water from the extracellular to the intracellular compartment. Cytotoxic edema also results in a reduction in cerebral blood flow.\(^4\) Therefore, decreased diffusion can be seen in ischemic stroke,\(^4\) traumatic brain injury,\(^5\) and encephalitis.\(^6\) Evidence of decreased diffusion in areas distinct from the hematoma supports the concept of cellular injury in noncontiguous regions (distant injury).\(^6,7\) However, the underlying process for decreased diffusion remains unclear. The presence of decreased diffusion is considered a sensitive marker of acute (<2 weeks) cerebral infarction.\(^4\) However, patients with traumatic brain injury, in particular those with focal contusions, have decreased diffusion without any prominent reduction in cerebral blood flow.\(^5\)

Therefore, 3 mechanisms can be postulated for decreased diffusion observed on MRIs of patients with ICH: (1) these changes are secondary to ischemia around the perihematoma region; (2) the occurrence of new lacunar infarctions due to coexistence of small vessel disease; or (3) cytotoxic edema secondary to mechanical disruption and secondary mediators. The first possibility is probably the least likely because perihematoma ischemia has not been detected in either experimental or clinical studies.\(^8\) An acute hypometabolic and hypoperfusion (hibernation) phase, with mitochondrial dysfunction and metabolic failure, has been demonstrated in the perihematoma region.\(^5\) Occurrence of lacunar infarction is consistent with the notion that ICH is a severe manifestation of a progressive brain blood vessel disorder.\(^9\) However, the rate of subsequent cardiovascular events was 4%, 2%, and 1% per patient-year for all stroke, ICH, and ischemic stroke, respectively, in a previous study,\(^10\) which is much lower than the rate observed in the current study. The possibility of hematoma inducing injury by mechanical disruption of the neurons and glia in the immediate vicinity followed by larger-scale mechanical deformation, neurotransmitter release, mitochondrial dysfunction, and membrane depolarization remains a possible explanation for lesions with decreased diffusion.\(^9\)

Garg et al\(^1\) found a relationship between decrease in systolic blood pressure within 96 hours of symptom onset and occurrence of decreased diffusion. However, interpretation of the relationship and more importantly implications for treatment of an acute hypertensive response require a better understanding of the underlying etiology for decreased diffusion observed in patients with ICH. Currently, there are 2 ongoing trials recruiting patients with ICH and acute hypertensive response. The Second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) is investigating whether early intensive blood pressure-lowering therapy can reduce death and disability compared with current guideline-based management among patients with ICH (www.strokecenter.org/trials/TrialDetail.aspx?tid=751). The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II funded by National Institute of Neurological Disorders and Stroke (NINDS) is currently underway in the United States, Japan, South Korea, and Taiwan.\(^1\) The goal of the Phase III study is to definitively determine the efficacy of early, intensive, antihypertensive treatment using...
intravenous nicardipine initiated within 3 hours of onset of ICH and continued for the next 24 hours in subjects with spontaneous supratentorial ICH. The primary hypothesis of this large (N=1280), streamlined, and focused trial is that systolic blood pressure reduction to ≤140 mm Hg reduces the likelihood of death or disability at 3 months after ICH, defined by modified Rankin Scale score of 4 to 6, by at least 10% absolute compared with standard systolic blood pressure reduction to ≤180 mm Hg. A substudy, The CTA Spot Sign Score Acute Cerebral Hemorrhage (SCORE IT; Jonathan Rosand, MD, Principal Investigator), also funded by the NINDS, will perform an analysis of all CT perfusion images and MRI acquired in the recruited subjects. Imaging data acquired through the substudy may provide us with a better understanding of the MRI findings reported in the study by Garg et al.1

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