Spontaneous intracerebral hemorrhage: a review

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Spontaneous intracerebral hemorrhage (SICH) is a blood clot that arises in the brain parenchyma in the absence of trauma or surgery. This entity accounts for 10 to 15% of all strokes and is associated with a higher mortality rate than either ischemic stroke or subarachnoid hemorrhage. Common causes include hypertension, amyloid angiopathy, coagulopathy, vascular anomalies, tumors, and various drugs. Hypertension, however, remains the single greatest modifiable risk factor for SICH. Computerized tomography scanning is the initial diagnostic modality of choice in SICH, and angiography should be considered in all cases except those involving older patients with preexisting hypertension in thalamic, putaminal, or cerebellar hemorrhage. Medical management includes venous thrombosis prophylaxis, gastric cytoprotection, and aggressive rehabilitation. Anticonvulsant agents should be prescribed in supratentorial SICH, whereas the management of hypertension is controversial.

To date, nine prospective randomized controlled studies have been conducted to compare surgical and medical management of SICH. Although definitive evidence favoring surgical intervention is lacking, there is good theoretical rationale for early surgical intervention. Surgery should be considered in patients with moderate to large lobar or basal ganglia hemorrhages and those suffering progressive neurological deterioration. Elderly patients in whom the Glasgow Coma Scale score is less than 5, those with brainstem hemorrhages, and those with small hemorrhages do not typically benefit from surgery. Patients with cerebellar hemorrhages larger than 3 cm, those with brainstem compression and hydrocephalus, or those exhibiting neurological deterioration should undergo surgical evacuation of the clot. It is hoped that the forthcoming results of the International Surgical Trial in IntraCerebral Hemorrhage will help formulate evidence-based recommendations regarding the role of surgery in SICH.

KEY WORDS • intracerebral hemorrhage • epidemiology • pathophysiology • surgery • medical management

An SICH is defined in this review as a blood clot that arises in the brain parenchyma in the absence of trauma or surgery. An SICH can be classified as either primary or secondary depending on the underlying cause of the hemorrhage. Primary ICH accounts for approximately 70 to 80% of cases and is due to spontaneous rupture of small vessels damaged by hypertension or amyloid angiopathy. Secondary ICH is associated with a number of congenital and acquired conditions such as vascular anomalies, coagulopathies, tumors, and various drug therapies. Table 1 provides a summary of the important causes of SICH. Its most frequent sites are the basal ganglia, thalamus, subcortical white matter of the cerebral lobes, cerebellum, and brainstem.

Abbreviations used in this paper:
- AVM = arteriovenous malformation
- BBB = blood–brain barrier
- CAA = cerebral amyloid angiopathy
- CBF = cerebral blood flow
- CI = confidence interval
- CPP = cerebral perfusion pressure
- CT = computerized tomography
- GCS = Glasgow Coma Scale
- ICP = intracranial pressure
- ICH = intracerebral hemorrhage
- MABP = mean arterial blood pressure
- MR = magnetic resonance
- SAH = subarachnoid hemorrhage
- SBP = systolic blood pressure
- SICH = spontaneous ICH
- SPECT = single-photon emission CT
- tPA = tissue plasminogen activator

EPIDEMIOLOGY OF SICH

Incidence of SICH

Stroke is the third leading cause of death in the US. Each year in the US, an estimated 37,000 to 52,400 people suffer an ICH.13,119 This rate is expected to double by 2050 as a result of an aging population and changing racial demographics. Spontaneous ICH accounts for 10 to 15% of all strokes and is associated with a higher mortality rate than either ischemic stroke or SAH, with only 38% of affected persons surviving 1 year.31 In a study of all cases of SICH and SAH in the greater Cincinnati area during the year 1988, the investigators found that ICH is more than twice as common as SAH.15 They determined the incidence of SICH to be 15 per 100,000 individuals in the population compared with six per 100,000 for SAH. Variation in the incidence of SICH is seen among different sexes, age groups, and races. In African Americans (50 cases per 100,000) and Japanese (55 per 100,000) the incidence of SICH is twofold that in caucasians.16,118 Men are more likely to suffer an SICH than women and the likelihood increases with age.16 A circadian and circannual pattern of SICH onset in the morning and winter has been reported.10 A similar circadian rhythm has been reported for many cardiovascular
and cerebrovascular diseases. Peak incidence in the morning has been postulated to occur coincidentally with an increase in sympathetic tone or arterial blood pressure. A circannual winter peak may be due to responsiveness of the vascular system to environmental changes in temperature.

CAUSES OF SICH

Table 1 provides an outline of the major causes of SICH. Cerebrovascular damage to small arteries and arterioles due to chronic hypertension is recognized as the most significant cause of primary SICH (Fig. 1).37 Racial differences in hypertension and socioeconomic factors may explain the high incidence of SICH in certain ethnic groups.

Cerebral amyloid angiopathy is the other major cause of primary SICH and an important cause of lobar SICH in elderly populations.126 In CAA, β-amyloid protein is deposited in the media and adventitia of cortical and leptomeningeal blood vessels. Histological examination of brain tissue obtained during surgery or at autopsy is necessary for the definitive diagnosis of CAA. Although some investigators have emphasized the problem of intraoperative hemostasis in these patients, neurosurgery can be performed safely in those with CAA-related SICH.57 Hereditary ICH with amyloidosis, Dutch type, is a rare, autosomal-dominant type of CAA that results in recurrent, sometimes multiple, lobar hemorrhages.

Vascular anomalies are the second most common cause of SICH overall (Fig. 2). Aneurysms, AVMs, cavernomas, dural arteriovenous fistulas, and venous malformations all can result in secondary SICH. The hemorrhage due to a ruptured aneurysm almost always has a subarachnoid component and often extends into the ventricles. There should be a high index of suspicion in young patients with frontal or temporal lobe clots. Arteriovenous malformations are associated with an estimated mean annual hemorrhage risk of 4%.

Cerebral venous malformations are assumed to be congenital lesions resulting from aberrant venous maturation. These entities have also been termed venous angiomas or developmental venous anomalies. Although rarely associated with SICH, venous malformations are the most frequently occurring vascular lesion demonstrated in autopsy and radiological series.82 Their clinical significance remains controversial, with some authors reporting a negligible hemorrhage risk82 and others suggesting a higher risk.76 In a series of 63 patients with known venous malformations followed longitudinally by Naff, et al.,91 the risk of hemorrhage was 0.15% per lesion-year. We believe a conservative approach to their management should be adopted, because the risks of radiosurgery or resection probably outweigh the risk of hemorrhage.

Spontaneous ICH is not an uncommon presentation in cases of previously unsuspected brain tumor. Hemorrhage resulting from brain tumors can occur in up to 10% of all primary or metastatic tumors. Hemorrhage is more likely with certain types of tumors, including glioblastoma, hemangioblastoma, oligodendroglioma, and metastatic tumors. Metastatic tumors with a high propensity to hemorrhage are malignant melanoma, renal cell, prostate, and lung cancer. An indentation of the hematoma’s surface

| Table 1 |
| Summary of primary and secondary causes of SICH* |
| primary | secondary |
| hypertension | aneurysm | neoplasm |
| amyloid angiopathy | fusiform | primary |
| | mycotic | metastatic |
| | vascular malformation | coagulopathy |
| | AVM | acquired |
| | cavernous malformation | anticoagulation (Coumadin, heparin) |
| | venous angioma | thrombolitics (tPA, urokinase) |
| | dural arteriovenous fistula | blood dyscrasias (DIC, leukemia, thrombocytopenia) |
| neoplasm | platelet dysfunction (renal failure, medications) |
| primary | congenital |
| | hemophilia |
| | platelet disorders |
| metastatic | drugs or alcohol |
| | sympathomimeticians (ephedrine, phenylpropanolamine, |
| | pseudoephedrine) |
| | cocaine, amphetamine, Ecstasy |
| | hemorrhagic ischemic stroke |
| | dural venous sinus thrombosis |
| | vasculitis/vasculopathy |
| | moyamoya disease |
| | arterial dissection |
| | pregnancy |
| | eclampsia, venous sinus thrombosis |
| | other/unknown |

* DIC = disseminated intravascular coagulation.
Spontaneous intracerebral hemorrhage

fig. 2. Imaging studies obtained in a 26-year-old woman who presented with severe headache, vomiting, rapid progression to unconsciousness, and a blown left pupil. left: Axial CT scan revealing a large left temporoparietooccipital SICH with midline shift. At craniotomy for emergency clot evacuation, an AVM was observed, but no attempt at resection was made. right: Left vertebral artery angiogram obtained after clot evacuation confirmed a left posterior temporal AVM with a 2-cm nidus. Feeding arteries from the posterior cerebral artery and drainage into the transverse sinuses are shown. The patient was allowed to recover from the initial hemorrhage and then underwent resection of the AVM 1 month later.

revealed on pre-contrast CT scanning should prompt suspicion of a tumoral hemorrhage. Contrast-enhanced CT scanning or contrast-enhanced MR imaging usually identifies the tumor, although small areas of contrast enhancement can be obscured by hemorrhage. In young patients without hypertension follow-up imaging is warranted if initial studies are unequivocal regarding cause (Fig. 3).

Patients with liver failure or coagulopathy from any cause are at higher risk for SICH. The liver is responsible for synthesis of most clotting factors and fibrinogen, as well as playing a major role in metabolism of platelets.

Excluding neonatal intraventricular hemorrhage, structural vascular lesions are the most common cause of SICH in children. Hematological disorders and coagulopathies, as well as brain tumors, are also important causes. In a series of 68 children presenting with SICH to a single institution, vascular anomaly or underlying brain tumor was identified in 38 (56%), whereas hematological or coagulation disorders were present in 22 (32%). Because systemic hypertension is rare in this population, hypertensive SICH is also rare. An underlying structural lesion should be sought in all pediatric patients presenting with SICH. We recommend that MR imaging and angiography be undertaken in all pediatric patients suffering unexplained SICH as well as follow-up imaging if no cause is found.

Moyamoya disease is a rare disorder characterized by progressive occlusive changes in the anterior circulation of the circle of Willis and the abnormal development of collateral moyamoya vessels in the basal ganglia. Although cerebral ischemia is usually the initial symptom in children with the disease, SICH is the most common initial presentation in adults. Rupture of microaneurysms and failure of the abnormally dilated moyamoya vessels from hemodynamic stress are considered the cause of these hemorrhages. Long-term prospective evidence that revascularization surgery significantly prevents rebleeding in patients with hemorrhagic moyamoya disease is lacking.

Abuse of sympathomimetic drugs such as cocaine, amphetamine, or Ecstasy has been reported in association with SICH. The mechanism is believed to be secondary to induced arterial hypertension. Drug abuse may represent the most common cause of stroke in young adults. These drugs may also predispose unsuspected vascular anomalies to hemorrhage. In a study of 11 patients (mean age 31 years) with a history of abuse of one of these agents leading to SICH, 10 were found to harbor intracranial aneurysms or AVMs. Therefore, the traditional teaching that these were hypertension-related hemorrhages that did not require investigation for underlying vascular abnormality is no longer valid. Cerebral angiography or MR angiography should be a standard part of the workup of SICH in young adults, even in the presence of positive toxicology screen findings.

The most commonly implicated sympathomimetic medication related to SICH is phenylpropanolamine. Ephedrine, pseudoephedrine, and phencyclidine have also been described in association with SICH. Ginkgo biloba is an over-the-counter herbal extract used by many people in the US and Europe as a “memory aid,” several case reports have described an association between its use and ICH. A possible antiplatelet effect and Coumadin potentiation mechanism has been postulated.

Pregnancy and the puerperium can be associated with SICH due to dural venous sinus thrombosis and eclampsia. SICH occurs in one to five per 10,000 pregnancies. There are numerous other rare causes of SICH including cerebral artery dissection, infections, and a host of unusual bleeding diatheses.

Risk Factors

With a mortality rate of 40 to 50% in SICH, identification of modifiable risk factors might help lower its incidence. The role of hypertension as a risk factor for SICH is well established. Hypertension continues to be the single greatest modifiable risk factor for SICH. The incidence of SICH has, in fact, declined coincident with the widespread use of antihypertensive medications. The role of hypertension as a risk factor for SICH remains 3.9 to 13.3 times that for normotensive individuals. Juvaleza and colleagues have reported that recent moderate and heavy alcohol intake, hypertension, and anticoagulant treatment appear to be independent risk factors for SICH. Cigarette smoking seems to increase the risk for SAH, but is less strongly associated with SICH. Diabetes mellitus is more commonly associated with SICH than with SAH.

Anticoagulant treatment is a well-established risk factor for SICH, especially in elderly patients (Fig. 4). Conventional anticoagulation therapy increases the risk of ICH seven- to 10-fold. The use of thrombolytic agents can be complicated by ICH. In a metaanalysis of trials assessing treatment for ischemic stroke with tPA, the authors reported a 6.5% risk of SICH.

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In a recent metaanalysis of aspirin trials involving 55,462 participants, aspirin was associated with a slight absolute risk increase in hemorrhagic stroke. This was outweighed, however, by the overall risk reduction in myocardial infarction and ischemic stroke. Use of nonaspirin nonsteroidal antiinflammatory drugs does not seem to be associated with an overall increased risk of SICH. Symptomimetic drugs such as phenylpropanolamine and ephedrine, which are structurally similar to amphetamines, have been implicated in cases of SICH.

The apolipoprotein E genotype appears to have an important role in the pathogenesis of CAA, and this genotype is associated with an increased risk of recurrent lobar ICHs.

Recent attention has been focused on the association of hypocholesterolemia and an increased incidence of SICH. The mechanism underlying this relationship is not clear, but some investigators have proposed that the interaction of high diastolic pressure and low cholesterol levels weakens the endothelium of intracerebral arteries. Alternatively, there is some evidence that high plasma cholesterol levels may be associated with reduced risk of SICH. Hepatitis C virus infection may also be a risk factor for SICH as a result of subclinical clotting disorder or vessel wall friability resulting from hypocholesterolemia.

Prevention of SICH should emphasize treatment of hypertension, control of alcohol intake and sympathomimetic drug abuse, careful monitoring of anticoagulation levels in patients taking warfarin, and diligent selection of patients for thrombolytic treatment for myocardial infarction and acute ischemic stroke.

**CLINICAL FEATURES**

**Initial Presentation**

The classic presentation of SICH is sudden onset of focal neurological deficit progressing over hours with accompanying headache, nausea, vomiting, altered consciousness, and elevated blood pressure. Supratentorial hemorrhage is commonly accompanied by vomiting and altered consciousness but is rarely seen in ischemic stroke. Elevation in blood pressure occurs in as many as 90% of patients with SICH. Seizures occur in approximately 10% of patients.

The type of focal neurological deficit, of course, depends on hematoma location. Patients with supratentorial hemorrhage often present with contralateral sensory or motor deficits, aphasia, neglect, gaze deviation, and hemianopia. Infratentorial hemorrhages manifest with signs of brainstem dysfunction, cranial nerve abnormalities, ataxia, nystagmus, and dysmetria.

Blood may rupture into the ventricles and cause hydrocephalus. Rarely, blood finds its way into the subarachnoid space. A large hemorrhage can raise ICP to the level...
of the blood pressure until bleeding is tamponaded. Depending on clot location, this can result in brain herniation, compression of the brainstem, and death. Cerebellar clots greater than 3 cm in diameter have a poor prognosis if left untreated.

Risk of Hematoma Enlargement

In nearly one quarter of initially alert patients presenting with SICH, secondary deterioration in level of consciousness occurs within the first 24 hours after onset. Hematoma expansion and edema formation are believed to be the major factors involved (Fig. 4). In several large recent prospective and retrospective studies, investigators have evaluated the rate of hematoma enlargement after initial presentation and report rates ranging from 14 to 38% within the first 24 hours of admission. In their review of 627 patients with SICH, Fujii, et al., reported that CT scanning within 24 hours of admission demonstrated enlargement of the hematoma in 14% of patients. Five factors were found to be associated with enlargement: admission shortly after onset of symptoms, heavy alcohol consumption, irregularly shaped hematoma, reduced level of consciousness, and low level of fibrinogen.

Kazui, et al., used multiple logistic regression analysis of data obtained in 186 patients with SICH to identify factors related to the risk of hematoma enlargement. They identified four factors predisposing to hematoma enlargement: history of brain infarction, liver disease, fasting glucose level greater than 141 mg/dl with SBP greater than 200 mm Hg, and HgbA1c greater than 5.1% with SBP greater than 200 mm Hg. Enlargement of the hematoma was demonstrated in 22%. A long time interval between onset of symptoms to the first CT scanning study as well as small hematoma volume (< 25 cm³) strongly reduced the risk of hematoma enlargement.

In another report by Kazui, et al., the authors showed that, although CT scanning–documented expansion of ICH was common in the hyperacute stage, 17% of hematoma expansion occurred even after 6 hours of onset. Hematoma enlargement after 24 hours was rare. Early repeated CT scanning appears to increase the rate of detection of hematoma enlargement. It is our practice to perform repeated CT scanning within 24 hours of admission in patients in whom SICH is revealed on the initial CT scan. In the only prospective study of this phenomenon, Brott, et al., evaluated 103 patients with SICH and found no significant predictor of hemorrhage growth. Overall hemorrhage growth occurred in 38% of patients in whom CT scanning was conducted within 3 hours of symptom onset.

Mayer has proposed using ultra-early hemostatic therapy with recombinant activated factor VII as a potential method of minimizing this early hematoma growth. The author postulated that ultra-early hemostatic therapy for SICH could be used as the counterpart to thrombolytic intervention in cases involving acute ischemic stroke to prevent early neurological deterioration due to hematoma growth and late deterioration related to secondary effects of edema, ischemia, and inflammation. We have recently reported our experience using recombinant activated factor VII for rapid correction of coagulopathy in a small series of coagulopathic patients (including two with intraparenchymal hemorrhages) requiring urgent neurosurgical intervention (Fig. 5). The 30-day mortality and morbidity rates in patients with SICH could be used as the counterpart to thrombolytic intervention in cases involving acute ischemic stroke to prevent early neurological deterioration due to hematoma growth and late deterioration related to secondary effects of edema, ischemia, and inflammation.

Outcome After SICH

Despite advances in neurocritical care and neurosurgery, the prognosis for patients with SICH remains sobering. Of the estimated 37,000 Americans who suffered an SICH in 1997, 35 to 52% were dead by 1 month postictus and only 20% were living independently by 6 months. The volume of ICH, initial GCS score, and intraventricular extension of the hemorrhage are powerful predictors of 30-day mortality and morbidity rates in patients with SICH.

The 30-day mortality rate in one series of 188 patients was 44%, with most deaths occurring in the first 2 days after onset. Univariate logistic regression analysis in this series demonstrated that ICH volume, intraventricular hemorrhage volume, and initial GCS score were significant predictors of 30-day mortality, whereas age, sex, race, SBP, and location of hemorrhage were not. In patients in whom the hematoma volume was 60 cm³ or greater and the GCS score was 8 or less, the predicted 30-day mortality rate was 91% compared with only 19% in those in whom the volume was less than 30 cm³ and the GCS score was 9 or more.

In another study of 156 consecutive patients with SICH, potential risk factors for death and impaired outcome were studied prospectively. Risk of poor outcome was predicted by GCS score, volume of hematoma, age, amount of alcohol consumed within 1 week before hemorrhage, and presence of cerebellar hematoma. Of these factors, only alcohol consumption before SICH is potentially modifiable.

DIAGNOSTIC FACTORS

Computerized Tomography Scanning

Computerized tomography scanning is the initial diag-
nostic procedure of choice in acute stroke. Several clinical stroke scoring systems have been developed in an effort to help clinicians distinguish between hemorrhagic and ischemic stroke on the basis of clinical presentation alone. These stroke scoring systems, however, are inadequate for accurately differentiating between the two stroke types. Hematomas, even just a few millimeters in diameter, are rapidly and accurately identified on CT scans. Not only does CT scanning demonstrate the size and location of the SICH, but it can also suggest potential causes such as tumor, vascular malformation, or aneurysm. Related complications such as hydrocephalus, edema, herniation, and intraventricular extension are easily identified. The change in the CT scanning appearance of intracerebral hematomas over time has been well studied.

As mentioned previously, hemorrhage volume is one of the strongest predictors of outcome from SICH. Using a model of 30-day mortality based on GCS score and hemorrhage volume, outcome has been correctly predicted with 97% sensitivity and specificity. Many modern CT scanners are able to calculate hematoma volume directly by using special software. If direct volume measurements are not possible, a rapid, simplified method of determining hematoma volume has been described and validated. The formula used—(A × B × C)/2—is an approximation for the volume of an ellipsoid where A is the greatest hemorrhage diameter on axial CT scans, B is the largest diameter 90° to A, and C is the number of CT slices with hemorrhage multiplied by the slice thickness.

Magnetic Resonance Imaging

Magnetic resonance imaging and MR angiography are becoming increasingly useful in the diagnosis of SICH and may eventually replace CT scanning as the initial diagnostic test of choice in stroke. Magnetic resonance imaging is helpful for identifying brain tumors and is more sensitive in detecting cavernous malformations than CT scanning or angiography. The MR imaging appearance of SICH is complex and depends on hemoglobin breakdown products over time. Table 2 provides a summary of the sequential MR imaging signal intensity changes of ICH. Although SICH can be classified into distinct stages, there is considerable overlap and variation in duration of these stages.

Although MR imaging has been previously believed to be poorly sensitive for detecting hyperacute hemorrhage, the authors of more recent reports have shown that multi-sequence MR imaging is as reliable as CT scanning in the assessment of hyperacute SICH. In older studies a 24-hour time period was suggested before detectable amounts of paramagnetic deoxyhemoglobin would be present. The results of several small studies support the hypothesis that deoxyhemoglobin is present within the early hours after SICH and may be detected best by using susceptibility-weighted sequences. Multimodal MR imaging techniques such as diffusion- and perfusion-weighted sequences may add to its diagnostic reliability in hyperacute SICH.

Cerebral Angiography

Despite advances in imaging technology, conventional cerebral angiography remains the gold standard for diagnosis of vascular abnormality. A negative CT angiogram, MR image, and MR angiogram cannot completely exclude a vascular lesion and angiography is often needed for definitive diagnosis. Although the risk of angiography is low, the diagnostic yield must be weighed against the procedural risk at each institution. The site of hemorrhage, patient age, preexisting hypertension, and clinical status must all be considered collectively before choosing angiography. Elderly patients in whom the risk of surgery is unacceptable or neurological disability is severe should not undergo angiography if identification of an underlying vascular abnormality would have no effect on patient management. Surgery in a young patient with SICH and evidence of herniation should not be delayed by angiography (Figs. 2 and 6).

Fig. 5. Axial CT scans acquired in a 78-year-old man receiving Coumadin for atrial fibrillation who presented with a right temporoparietal SICH. Initial coagulation parameters were a prothrombin time of 28, international normalized ratio of 2.8, and an activated partial thromboplastin time of 36; after a 90-µg/kg dose of recombinant activated factor VII, the values immediately corrected to, respectively, 9.6, 0.9, and 32. The patient then underwent an uncomplicated craniotomy for clot evacuation. Left: Noncontrast scan obtained at presentation. Center: Scan obtained on postoperative Day 1. Right: Follow-up scan obtained 6 weeks postoperatively.
Spontaneous intracerebral hemorrhage

**TABLE 2**

<table>
<thead>
<tr>
<th>ICH Stage</th>
<th>Hemoglobin State</th>
<th>MRI Signal Intensity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyperacute (0–6 hrs)</td>
<td>oxyhemoglobin (intracellular)</td>
<td>= to ↓ ↑</td>
</tr>
<tr>
<td>acute (6 hrs–3 days)</td>
<td>deoxyhemoglobin (intracellular)</td>
<td>= to ↓ ↓</td>
</tr>
<tr>
<td>early subacute (3 days–1 wk)</td>
<td>methemoglobin (intracellular)</td>
<td>↑↑ ↓↓</td>
</tr>
<tr>
<td>late subacute (1 wk–1 mos)</td>
<td>methemoglobin (extracellular)</td>
<td>↑↑ ↓↓</td>
</tr>
<tr>
<td>chronic (&gt;1 mo)</td>
<td>hemosiderin &amp; ferritin</td>
<td>↓↓ ↓↓</td>
</tr>
</tbody>
</table>

* "= to ↓" = "equal to decreased;" ↓ = decreased; ↓↓ = significantly decreased; ↑ = increased; ↑↑ = significantly increased.
† Compared with gray matter.

excluded on the basis of hematoma location, patient age, or a history of preexisting hypertension. In fact, a significant number of elderly hypertensive patients are found to harbor potentially surgically treatable lesions. In a prospective study of 100 consecutive cases of nontraumatic SICH, the authors identified aneurysms or AVMs in 49% of cases. When a temporal lobe hematoma extended into the sylvian fissure or when it was associated with SAH, structural abnormalities were identified in more than 90% of cases. Although the diagnostic yield was lower in hypertensive patients, angiography still identified an AVM or aneurysm in 25% of hypertensive patients.

In another prospective study of angiography in 206 patients with SICH, the angiographic yield was 45% (66 of 148) in normotensive patients compared with 9% (five of 58) in hypertensive patients. A positive finding on angiography was identified in 53 (50%) of 105 patients younger than 45 years of age, compared with 18 (18%) of 101 patients older than 45 years. In grouping putaminal, thalamic, and posterior fossa hemorrhages together, the angiographic yield was 12 (48%) of 25 in younger normotensive patients compared with zero (0%) of 29 in hypertensive patients. Based on their results, Zhu, et al. recommended that the use of angiography should be considered in all patients with SICH except those older than 45 years of age with preexisting hypertension in thalamic, putaminal, or posterior fossa hemorrhage.

Imaging features that suggest an underlying structural abnormality include SAH, extracerebral hemorrhage, temporal lobe or perisylvian location, and intraventricular extension (Fig. 7). Halpin, et al. reported that CT scanning features in patients with SICH that warrant angiography include the presence of SAH, abnormal intracranial calcification, prominent vascular structures, and perisylvian hemorrhage location. In their study, angiography was positive in 32 (84%) of 38 patients in whom there was one or more of these CT findings. Follow-up angiography and MR imaging angiography should be considered in these high-risk patients if initial studies are negative.

**Laboratory Evaluation**

Laboratory evaluations should include a complete blood count, liver panel, coagulation profile, electrolytes, and toxicology screen. Underlying renal or liver failure, acquired or iatrogenic coagulopathy, infection, or drug use should be investigated.

**Histopathological Examination**

In a significant percentage of surgically treated cases, the cause of the SICH is unknown prior to surgical intervention. Often these hemorrhages are attributed to hypertension. Histological examination of surgical specimens obtained in a series of 84 cases of SICH in which the cause was unknown revealed a 25% rate of diagnosis involving specimens in which surrounding tissue was included. Biopsy sampling of adjacent hematoma wall or preservation of tissue fragments identified at the time of surgery can, therefore, be of important diagnostic value.

**PATHOPHYSIOLOGICAL MECHANISMS**

Intracerebral hemorrhage commonly occurs in the basal ganglia, thalamus, cerebral lobes, brainstem, and cerebellum. Primary tissue damage and distortion occur at the time of hematoma formation when the blood spreads between planes of white matter cleavage. Hemorrhage most commonly results from rupture of the small penetrating arteries damaged by the degenerative effects of chronic hypertension. In 1868, Charcot and Bouchard described the rupture of “microaneurysms” as the cause of SICH. Recent investigators have questioned the existence of such microaneurysms, suggesting that many of these structures are injection-related artifacts, complex vascular coils, subadventitial hemorrhages, or extravascular clots resulting from endothelial damage by the hematoma.
The authors of several studies have suggested that perilesional hypoperfusion can occur without ischemia as a result of reduced metabolic demand or diaschisis. In a study of 23 patients with SICH studied using SPECT scanning, perilesional blood flow was found to be lowest during the first 24 hours postictus, but it normalized as edema formed over the next 2 to 3 days. In a small study in which positron emission tomography was used, no zone of tissue hypoxia or “ischemic penumbra” was identified. However, analyzed serial SPECT scans obtained in patients with SICH and identified perilesional hypoperfusion. They were also able to demonstrate that some of the ischemic perilesional brain recovered its perfusion in the long term. There may be a window of opportunity early after SICH during which removal of the hematoma allows recovery of CBF and prevention of secondary ischemic insult.

Blood and plasma products mediate many secondary processes initiated after SICH. After SICH occurs, inflammatory mediators from the blood can induce an inflammatory reaction in and around the hematoma. Neutrophils, macrophages, leukocytes, and activated microglia can be found. The release of cytotoxic enzymes, free oxygen radicals, nitric oxide, and products of the phospholipid cascade is thought to contribute to secondary neural injury and cell death. Both necrotic and apoptotic neuronal death appear to play a role.

The vasculopathy of chronic hypertension affects the perforating arteries 100 to 400 μm in diameter, resulting in lipohyalinosis or focal necrosis. This helps explain the distribution of hypertensive hemorrhages in territories supplied by the lenticulostrate arteries (basal ganglia), the thalamoperforating arteries (thalamus), the perforating arteries of the basilar artery (pons), and the superior and anterior inferior cerebellar arteries (cerebellum). Lobar hemorrhages in the elderly are often considered to be a result of amyloid angiopathy, which preferentially involves the cortical and leptomeningeal blood vessels.

Unlike primary tissue injury from the hematoma formation, secondary brain injury and edema represent potential therapeutic targets. The roles of edema, ischemia, mass effect, direct cellular toxicity, inflammation, and apoptosis are being evaluated in experimental studies of SICH. There is controversy whether secondary ischemia contributes to brain injury after SICH. Thrombosis, clot retraction; coagulation cascade activation and thrombin production; erythrocyte lysis; cellular matrix, has been shown to be increased following SICH. Cushing believed that brain injury due to SICH was the result of local pressure compressing the microcirculation and causing ischemia around a hematoma. Astrup, et al., proposed the term “ischemic penumbra” to describe brain with CBF values above a lower limit of membrane dysfunction and cell death, but below an upper limit corresponding to electrophysiological dysfunction.

There are a number of animal models that have been used to study SICH and its effects on ICP, CBF, and ischemia. Findings included increased ICP associated with hematoma formation, decreased CBF adjacent to the hematoma, and histological ischemic changes in perihematomal brain tissue. Yang, et al., have suggested that the primary cause of edema formation in experimental models of SICH may be local tissue ischemia.

In more recent clinical studies, evidence does not clearly support the concept of perilesional ischemia in SICH. The authors of several studies have suggested that perilesional hypoperfusion can occur without ischemia as a result of reduced metabolic demand or diaschisis. In a study of 23 patients with SICH studied using SPECT scanning, perilesional blood flow was found to be lowest during the first 24 hours postictus, but it normalized as edema formed over the next 2 to 3 days. In a small study in which positron emission tomography was used, no zone of tissue hypoxia or “ischemic penumbra” was identified. However, analyzed serial SPECT scans obtained in patients with SICH and identified perilesional hypoperfusion. They were also able to demonstrate that some of the ischemic perilesional brain recovered its perfusion in the long term. There may be a window of opportunity early after SICH during which removal of the hematoma allows recovery of CBF and prevention of secondary ischemic insult.

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The vasculopathy of chronic hypertension affects the perforating arteries 100 to 400 μm in diameter, resulting in lipohyalinosis or focal necrosis. This helps explain the distribution of hypertensive hemorrhages in territories supplied by the lenticulostrate arteries (basal ganglia), the thalamoperforating arteries (thalamus), the perforating arteries of the basilar artery (pons), and the superior and anterior inferior cerebellar arteries (cerebellum). Lobar hemorrhages in the elderly are often considered to be a result of amyloid angiopathy, which preferentially involves the cortical and leptomeningeal blood vessels.

Unlike primary tissue injury from the hematoma formation, secondary brain injury and edema represent potential therapeutic targets. The roles of edema, ischemia, mass effect, direct cellular toxicity, inflammation, and apoptosis are being evaluated in experimental studies of SICH. There is controversy whether secondary ischemia contributes to brain injury after SICH. Thrombosis, clot retraction; coagulation cascade activation and thrombin production; erythrocyte lysis; cellular matrix, has been shown to be increased following SICH. Cushing believed that brain injury due to SICH was the result of local pressure compressing the microcirculation and causing ischemia around a hematoma. Astrup, et al., proposed the term “ischemic penumbra” to describe brain with CBF values above a lower limit of membrane dysfunction and cell death, but below an upper limit corresponding to electrophysiological dysfunction.

There are a number of animal models that have been used to study SICH and its effects on ICP, CBF, and ischemia. Findings included increased ICP associated with hematoma formation, decreased CBF adjacent to the hematoma, and histological ischemic changes in perihematomal brain tissue. Yang, et al., have suggested that the primary cause of edema formation in experimental models of SICH may be local tissue ischemia.

In more recent clinical studies, evidence does not clearly support the concept of perilesional ischemia in SICH.
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ly, gliosis.69 The end result is a hemosiderin-stained scar or a cavity containing old blood surrounded by fibrous tissue. An unusual form of chronic intracerebral hematoma has been defined by Roda and colleagues.106 Their term “capsulated intracerebral hematoma” refers to a chronically encapsulated intraparenchymal hematoma found in normotensive patients, usually caused by vascular malformations. These lesions exhibit progressive mass effect, edema, and ring enhancement. The self-perpetuating nature of these lesions has been compared with chronic subdural hematomas.

TREATMENT OF SICH

Macewan reported the first successful surgery for SICH in 1883. In general, there has been a pessimistic attitude among many medical professionals, including neurosurgeons, regarding treatment of SICH. As reported by Broderick and colleagues,14 this is reflected in the fact that more than 315 randomized clinical therapeutic trials for acute ischemic stroke and 78 trials for SAH were completed or ongoing as of 1995, whereas only the results of four small randomized surgical trials6,60,61,84 and four small medical trials of SICH had been published.55,99,121,135 The American Heart Association formed a task force that published practice guidelines in 1999 for the management of SICH and emphasized the desperate need for future randomized controlled trials.13

Medical Treatment

Critical Care. Because the risk of clinical deterioration after SICH is greatest during the 1st day, patients in whom this entity has been diagnosed should be monitored in an intensive care unit for a minimum of 24 hours. The goal of fluid status is to maintain euvoema with the use of isotonic crystalloid intravenous solutions. Enteral nutrition, via a feeding tube if necessary, should begin as soon as possible. Pneumatic sequential compression devices and elastic stockings decrease the risk of venous thrombosis and pulmonary embolism. Gastric cytoprotection should also be considered. Physical therapy, occupational therapy, speech therapy, and rehabilitation services should be consulted as soon as medically feasible.

Seizure Prophylaxis. The authors of retrospective studies have suggested that seizures are more frequent in hemorrhagic stroke than ischemic stroke and that the risk of epilepsy is greater in patients with lobar seizures after stroke.25,116 Most seizures occur within the first 24 hours after SICH.10

Cervoni, et al.,23 reviewed data obtained in 298 patients with SICH and found an 18% rate of seizures. Hematoma location was important because 35% of patients with lobar hemorrhages suffered seizures compared with only 8% of those with deep-seated hematomas. Epilepsy developed in 43% of patients affected by seizures occurring more than 2 weeks after the onset of SICH, whereas it developed in only 17% of those with seizures appearing within 2 weeks of onset. Passero, et al.,97 retrospectively reviewed data acquired in 761 patients with supratentorial SICH and reported a 30-day actuarial risk of post–SICH seizures of 8.1%. They found that the risk of early seizures in lobar SICH was reduced by prophylactic antiepileptic drug therapy.

Investigators recently reported the results of a large, prospective multicenter study designed to determine the incidence, outcome, and risk factors for seizures after both ischemic and hemorrhagic stroke. In 1897 patients analyzed, seizures occurred in 28 (16.6%) of 178 patients with hemorrhagic stroke compared with 140 (8.6%) of 1632 with ischemic stroke.10 The Kaplan–Meier survival analysis indicated the 1-year actuarial risk of seizures to be 20% in survivors of hemorrhagic stroke. Fifty-seven percent of seizures after hemorrhagic stroke occurred in the first 24 hours. Based on multivariate analysis, the only risk factor for seizures after hemorrhagic stroke was cortical location. Epilepsy occurred in 47 (2.5%) of 1897 patients. Epilepsy occurred in seven (100%) of seven patients with late-onset (> 2 weeks after SICH) seizures after hemorrhagic stroke.

The effect of surgical treatment for SICH on the occurrence and development of seizures has not been well studied. Given the results of the aforementioned report,10 we recommend undertaking anticonvulsant therapy in all patients who present with supratentorial SICH. No consensus exists on when anticonvulsant therapy can be discontinued following SICH, but most medications can be withdrawn after the 1st month in patients in whom no further seizure activity occurs. Those with late-onset seizures may require long-term anticonvulsant prophylaxis.23

Blood Pressure Management. Hypertension is common in patients who suffer SICH and in the early clinical course. There is disagreement as to the mechanism of this acute hypertensive state; however, major factors appear to be catecholamine release and the Cushing response.

Proponents of lowering blood pressure argue that doing so reduces secondary injury due to rebleeding and edema formation.69 Opponents, who favor leaving hypertension untreated, argue that preserving CPP is paramount to areas in the ischemic penumbra. Although induced hypertension can increase edema in experimental models, hypertension following SICH is not clearly related to the development of edema. Broderick, et al.,11 found no relationship between blood pressure and edema growth or neurological worsening in a study of 115 patients. Because of these complex issues, the management of hypertension in SICH remains controversial.3

The changes that occur in CBF in the setting of SICH are complex. An excellent review of the existing laboratory and clinical reports on this subject was recently provided by Qureshi and colleagues.106 Cerebral autoregulation refers to the ability to maintain constant CBF over a wide range of CPPs varying from approximately 60 to 150 mm Hg.115 Autoregulation can become deranged after a number of cerebral insults including ischemia, SAH, traumatic brain injury, and SICH. When CPP decreases below the lower limit of autoregulation, oxygen extraction increases in a compensatory fashion. After oxygen extraction is maximized, ischemia occurs. In most patients with chronic hypertension, the autoregulatory curve is at higher pressures, which may increase the risk of cerebral ischemia if blood pressure is normalized.103

There are no prospective randomized placebo-controlled studies in which investigators have compared the
effects of lowering blood pressure on immediate clinical status. Qureshi and colleagues reported, in a retrospective analysis of 105 patients admitted with SICH, that a rapid decline in MABP within 24 hours after presentation was independently associated with an increased mortality rate. These authors postulated two mechanisms for the deleterious effect of a rapid decline in MABP. First, a rapid decline in blood pressure may lead to a reduction in CPP and exacerbation of ischemic injury. Second, in regions with intact autoregulation, a compensatory vasodilation in response to the blood pressure reduction may result in exacerbation of intracranial hypertension.

In a study in which they used SPECT scanning, Kuwata, et al., found that a 20% reduction in SBP resulted in decreased mean CBF in the acute period following hypertensive ICH. Kaneko, et al., suggested a goal of SBP reduction of less than 20% in the acute period on the basis of CBF studies. In two other studies investigators have demonstrated that a controlled pharmacologically mediated reduction in blood pressure does not have deleterious effects on CBF.

In several studies improved outcomes have been reported with the use of antihypertension agents. Meyer and Bauer published a prospective nonrandomized unblinded trial involving use of the antihypertension agent reserpine in acute SICH. They concluded that antihypertension drugs improved the mortality rate; however, there were important limitations to the study. Dandapini, et al., also demonstrated improved mortality and morbidity rates with blood pressure reduction, although this study was retrospective and did not consider confounding variables such as hematoma volume and initial GCS score. In a retrospective review of 188 patients with ICH, Broderick and Brott found no difference in outcome in patients who received antihypertension agents compared with those who did not.

The intracranial hemodynamic effects of most antihypertension agents are poorly understood. Data acquired in clinical studies of patients with SICH are limited, but most vasodilators have the potential to raise ICP by increasing intracerebral blood volume. Short-acting, mixed α- and β-blockers such as labetalol should be used as first-line agents. Nitroprusside, the most commonly used agent for arterial vasodilators, such as hydralazine or angiotensin-converting enzyme inhibitors, demonstrated in a clinical study. In two other studies investigators have demonstrated that a controlled pharmacologically mediated reduction in blood pressure does not have deleterious effects on CBF.

Management of Intracranial Hypertension. Elevated ICP from SICH can result in herniation syndromes and death. Intuitively, monitoring and treatment of elevated ICP should reduce secondary injury. Improved outcomes, however, have not been clearly linked with monitoring and treatment of elevated ICP in SICH. Nevertheless, most authors recommend treatment when ICP exceeds 20 mm Hg with a goal CPP greater than 60 to 70 mm Hg. In general, ICP monitoring devices should be considered in all patients who present with a GCS score less 9 or in those patients in whom deteriorating clinical condition is believed to be due to elevated ICP.

Elevated ICP can have deleterious effects on CPP and, therefore, global CBF. Reduction in CPP and perihematoma ischemia may occur locally even in the absence of globally increased ICP. In experimental studies investigators have shown that a reduction in CPP leads to compensatory vasodilation, which increases intracranial blood volume, in turn, increasing ICP and further decreasing CPP. The physiological correction of this cycle is the systemic hypertension response that increases CPP, leading to arteriolar vasoconstriction, decreased intracranial blood volume, and lowered ICP. Rosner and Becker used the term “ischemic response” to describe this phenomenon that Cushing proposed in 1902. The impact of ICP treatment and hematoma evacuation on CBF has not been well studied, but some evidence exists that surgical evacuation and elevated ICP treatment can improve CBF.

Common strategies for managing elevated ICP include elevation of the head of the bed, hyperventilation therapy, osmotic therapy, sedation, and cerebrospinal fluid drainage. Mannitol is often given when surgery is not considered appropriate. Mechanical ventilation parameters should be adjusted to a PCO2 goal of 30 to 35 mm Hg. Intraventricular blood is associated with a high mortality rate. Venticulostomy, rather than fiberoptic ICP devices, should be used in patients with hydrocephalus or intraventricular hemorrhage (Fig. 8). Although ventriculostomy reduces ICP, frequent clots in the catheter and infections often diminish the beneficial effect on hydrocephalus and neurological status. We prefer to use prophylactic antibiotic medications in patients with ICP monitoring devices. Sedation with benzodiazepines, narcotic analgesics, or propofol can help control elevated ICP. Barbiturate coma or hemicraniectomy may be necessary if all other measures fail.

Unhelpful Therapies. Based on the results of two randomized trials that failed to demonstrate the efficacy of corticosteroid therapy in ICH, its use is not indicated. The authors of two other small randomized medical trials evaluating hemodilution and therapy with intravenous glycerol also did not find any significant benefit.

Surgical Treatment. Despite a nihilistic attitude among clinicians regarding SICH, most neurosurgeons believe evacuation of certain intracerebral hematomas can reduce the mortality rate and improve outcomes. The fact that approximately 7000 operations are performed annually in the US for SICH sup-
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Fig. 8. Axial CT scan acquired in an 82-year-old man with a history of hypertension who presented with headache, vomiting, and progressive deterioration in consciousness. A small left cerebellar SICH extending into the fourth ventricle is demonstrated. Obstructive hydrocephalus was successfully treated by ventriculostomy. The patient did not require evacuation of the hematoma and made a good recovery.

ports this belief.12 The efficacy of surgery for SICH, however, remains unproven in the year 2003.

Most of the published reports regarding surgical removal of these hemorrhages, many of which are in the Japanese literature, are nonrandomized case series for which definitive recommendations or guidelines cannot be made. There is considerable international variation in the indications and rate of surgery for SICH. In part because of its high incidence in Japan, there has been an increase in the number of clinical and experimental studies being reported over the past two decades.

The Cochrane Database of Systematic Reviews published a metaanalysis of surgery for primary supratentorial ICH in 2001.101 The authors analyzed the randomized and quasirandomized trials of medical management combined with intracranial surgery compared with medical management alone. Only four surgical trials comprising 260 patients met their criteria for inclusion.6,9,61,84 No trial had blinded outcome assessment and each trial used different scales for assessing functional status. The authors of the review concluded that the available evidence to date was insufficient to make a recommendation concerning the safety and efficacy of surgical treatment.

In a review of supratentorial SICH by Hankey and Hon published in 1997, the authors found a nonsignificant increase in the likelihood of death and dependency at 6 months in surgically treated patients. In a metaanalysis conducted by Fernandes, et al.,44 the authors suggested a benefit to surgery, with a reduction in the chances of death and dependency after surgery by a factor of 0.63. This analysis excluded a pre–CT scanning era trial and a Chinese trial because of methodological issues.

Patients with relatively normal consciousness (GCS Scores 13–15) rarely require surgery, whereas deeply comatose patients (GCS Scores 3–5) rarely benefit from surgery. Surgery is therefore usually considered to have the most potential benefit for the group of patients with GCS scores between 6 and 12 or in patients with deteriorating status.25 There is a neurosurgical bias toward more aggressive surgery for nondominant hemispheric hemorrhages, although the authors of outcome studies have indicated that despite language disability associated with dominant hemispheric lesions, functional outcome is not necessarily worse. Standard craniotomy for extirpation of primary brainstem or thalamic hemorrhages has been all but abandoned because of poor outcomes.17,46 Apparently successful cases of stereotactic aspiration of pontine hematomas have been reported, but the effect on prognosis remains unproven.

Although evidence favoring surgical intervention is lacking, there is good theoretical rationale for early surgery. Early hematoma evacuation may decrease the toxic effects of blood and plasma products, diminish surrounding edema and ischemia, and prevent hematoma expansion. Liquefaction of the clot by instillation of tPA and subsequent aspiration at 3 hours has been shown to reduce mass effect and perihematoma edema markedly at 24 hours in a pig model.127 Clot evacuation might be combined with pharmacological therapy targeting the inflammatory response shown to develop around the hematoma and leading to delayed cellular death in experimental animal models.49 Early evacuation might also be combined with hemostrict therapy such as recombinant activated factor VII to help prevent the risk of rebleeding (Fig. 5).79,89

Randomized Trials of Surgical and Medical Management. To date, there are nine prospective randomized controlled studies in which surgical and medical management of SICH has been compared.5,9,27,61,84,89,90,120,138 Overall, these studies fail to demonstrate a superiority of either medical or surgical management. The results are also limited by considerable methodological differences among the trials. A brief review of these trials follows.

McKissock, et al.,44 reported the first randomized study of surgery for SICH in 1961. They randomized 180 patients in a series of 303 potential cases. Ninety-one patients were “randomly allocated” to best medical treatment and 89 to surgery and best medical treatment, but the method of randomization was not described. Because this study was conducted well before the advent of CT scanning, diagnosis was established using angiography or ventriculography. Although the proportion of surgically treated patients who were dead or totally disabled 6 months after discharge was higher than the medically treated group (80 and 66%, respectively), the results may not be relevant to current practice. Almost no patients underwent surgery before 24 hours. In addition, neurosurgical, anesthesia, and critical care techniques have improved substantially since that time.
Juvela and colleagues\textsuperscript{61} reported a prospective study of 52 patients with supratentorial SICH randomized to surgery or best medical therapy for SICH. The median time from onset to craniotomy for evacuation was 14.5 hours. There were no statistically significant differences in mortality or morbidity rates between the two treatment groups, and these authors concluded that supratentorial SICH should be treated conservatively. Although the mortality rate of semicomatose or stuporous patients (GCS Scores 7–10) was statistically significantly lower in the surgical group, all surviving patients in this subgroup were severely disabled.

Auer, et al.\textsuperscript{5} randomly assigned 100 patients with supratentorial SICH to undergo stereotactic endoscopic evacuation of the blood clot within 48 hours after admission or to undergo medical therapy alone. At 6 months, the outcome was better in the surgically treated group with no or minimal deficits in 40% in this group compared with 25% in the medically treated group. The surgically treated group had statistically nonsignificant lower odds of death or dependency (odds ratio 0.45; 95% CI 0.19–1.04).

Batjer, et al.\textsuperscript{7} randomized 17 hypertensive patients with putaminal SICH of at least 3 cm to surgery or medical therapy. The results showed a trend toward a lower rate of death or level of dependence in the surgically treated patients (odds ratio 0.86; 95% CI 0.09–8.1), but the 95% CI included one.

Chen, et al.\textsuperscript{27} randomized 127 patients with hypertensive supratentorial and cerebellar hemorrhages to surgery or medical management. These authors included cerebellar hemorrhages, and although there was no statistically significant difference in mortality rates between the two groups, there was a trend toward an increased risk of death or dependency in those treated with surgery.

Zuccarello, et al.\textsuperscript{138} reported a small randomized feasibility study in which they evaluated the use of surgical evacuation, craniotomy, or stereotactic aspiration compared with medical treatment alone. Twenty patients were randomized; the median time from symptom onset to surgery was 8.5 hours. The likelihood of a good outcome (defined as 3-month GOS score > 3) was 56% in the surgical group and 36% in the medical treatment group, although this result did not reach statistical significance. The authors concluded that early clot removal in supratentorial SICH was feasible and warranted further investigation in randomized clinical trials.

Morganstern, et al.\textsuperscript{90} prospectively randomized 34 patients within 12 hours of onset. They reported a modest benefit in 6-month mortality rates in patients treated with craniotomy (19%) compared with medical therapy (24%).\textsuperscript{90} Outcome was measured by an investigator blinded to treatment allocation. In addition, only one patient underwent surgery within 4 hours and surgically treated patients harbored a significantly larger-volume hemorrhage, had lower GCS scores, and more frequently presented with deep-seated ICH.

In a later publication Morganstern, et al.,\textsuperscript{89} also reported preliminary results of a prospective single-center pilot study of surgery performed within 4 hours of SICH; their goal was to test the feasibility and safety of ultra-early clot evacuation compared with results of their previous 12-hour trial. This study was stopped for safety reasons after interim analysis of 11 patients in the 4-hour surgery arm showed a 6-month mortality rate of 36% compared with only 18% in the 12-hour surgical group. Because of the small number of patients in these pilot studies, the differences in mortality rates were not statistically significant. Rebleeding was more common in patients undergoing surgery within 4 hours (40%) than 12 hours (12%). Instead of preventing early hematoma expansion by coagulating the bleeding vessel, ultra-early surgery proved more difficult to achieve hemostasis. Morganstern and colleagues recommended using craniotomy within the first few hours after SICH with extreme caution because of the risk of rebleeding. This study did demonstrate the feasibility of ultra-early triage and surgery for patients with SICH much like protocols of thrombolytic therapy for acute ischemic stroke. In addition, patients with the smallest postoperative hemorrhage volumes experienced the best outcomes, arguing that removal of hematoma may ultimately be beneficial.

Teernstra and colleagues\textsuperscript{130} recently reported results from a multicenter randomized controlled trial of stereotactic drainage involving plasminogen activator compared with medical therapy. They randomized 36 patients to surgery and 35 to medical therapy, and found no statistically significant difference in mortality and morbidity rates at 6 months. A stereotactically placed catheter was used to install urokinase to liquefy and drain the hematoma in 6-hour intervals over 48 hours and resulted in a modest 18 ml reduction in hematoma volume over 7 days.

The International Surgical Trial in Intracerebral Hemorrhage, the largest multicenter randomized controlled trial of surgery for SICH, closed recruitment on February 25, 2003.\textsuperscript{85} Investigators randomized 1033 patients within 72 hours of supratentorial SICH to a surgery or medical therapy group. Although this important trial should help better define the role of surgery in SICH, it is likely to generate additional questions about patient selection, timing, and surgical technique.

Nonrandomized Surgical Studies. Although nonrandomized series of surgically treated patients with SICH are limited by methodological flaws and lack definitive conclusions, they do offer valuable information. In a nonrandomized report, Kaneko and colleagues\textsuperscript{64} reported good results after performing craniotomy for the evacuation of 100 putaminal hemorrhages within 7 hours of onset and 60 hemorrhages within 3 hours of onset. They reported only a 7% mortality rate and complete recovery or minor disability in 50%.

In a large nonrandomized study, Kanaya and Kuroda\textsuperscript{63} evaluated 7010 patients with putaminal hemorrhage. The mortality rate in alert and confused patients was significantly lower in medically treated groups; however, in patients who were stuporous or worse, the rate was significantly lower in the surgically treated group. They recommended surgical treatment if the hematoma volume was larger than 30 ml and the level of consciousness was somnolent to semicomatose.

In 1978 Backlund and von Holst\textsuperscript{7} proposed a new surgical technique for subtotal hematoma removal using CT scanning–guided aspiration with a special cannula. The authors of several case series have reported encouraging results when using stereotactic aspiration with fibrinoly-
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CONCLUSIONS

Despite the grim prognosis for patients suffering SICH, there are reasons for optimism. There have been improvements in medical treatment of hypertension and neurocritical care. Secondary brain injury, edema formation, and hematoma enlargement represent potential therapeutic targets. The roles of edema, ischemia, mass effect, direct cellular toxicity, inflammation, and apoptosis are being evaluated in experimental studies of SICH. Neurosurgical advances in minimally invasive techniques, endoscopy, and frameless stereotactic systems should improve results of surgery. It is hoped that the forthcoming results of the International Surgical Trial in IntraCerebral Hemorrhage will help formulate evidence-based recommendations regarding the role of surgery in SICH, although this trial is unlikely to end the controversy. Future randomized trials will still be needed to assess the effects of patient age, level of consciousness, comorbidities, hematoma volume, hematoma location, timing of surgery, and different surgical procedures.

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