Hemorrhagic Infarcts

ROBERT G. HART, M.D., AND J. DONALD EASTON, M.D.

MORE THAN A HUNDRED YEARS AGO, John Lidell observed that "red softening commences after 24–48 hours, dating from the apoplectiform attack" of cerebral embolism. While his pathological descriptions are arguably ambiguous, Lidell's observations surely are among the earliest descriptions of hemorrhagic infarct (HI). Our clinical-pathological concepts of HIs then lay relatively dormant until 1951, when Fisher and Adams emphasized the association of HI and embolism and proposed their well-known hypothesis about the mechanism of hemorrhagic transformation. HI remained an autopsy diagnosis until computed tomography (CT) and magnetic resonance imaging (MRI) permitted diagnosis during life. Recent studies, including two in this issue of STROKE, have refined our clinical concepts of HI. Treatment of acute stroke patients with thrombolytic agents and anticoagulants, both having secondary brain hemorrhage as their most feared complication, has rekindled interest in the occurrence and mechanisms of hemorrhagic infarction.

Hemorrhagic infarction describes multifocal, secondary bleeding into brain infarcts. Innumerable foci of capillary and venular extravasation either remain as discrete petechiae or merge to form confluent purpura (fig. 1). Pathologically, the distinction between pale and hemorrhagic infarcts is arbitrary in mild cases. Most recent infarcts show a few scattered petechiae, along their margins. Most pathologists do not designate an infarct as hemorrhagic unless a large part is involved with petechiae or unless petechiae are confluent.

Autopsy studies report that about 30% (range 18–42%) of recent brain infarcts are hemorrhagic, with the wide range in prevalence largely explained by varying definitions of mild HI and by ill-defined intervals from stroke to death. Autopsy studies emphasize a high prevalence of HI associated with embolic stroke: HIs occur in 51–71% of "embolic" strokes compared to 2–21% of "nonembolic" strokes. In most cases, the inability to diagnose embolic stroke with certainty, even at autopsy, clouds the interpretation of both autopsy and clinical data.

CT and autopsy studies convincingly link HI with infarct size. Lodder and colleagues in this issue question whether the association of HI and cardioembolic stroke at autopsy is explained by infarct size rather than by the stroke mechanism. If cardioembolic strokes are unduly large, HI could be a marker of large infarcts rather than the stroke mechanism per se. Earlier autopsy studies of HI did not report the interval from stroke to death, the cause of death, or the correlation of infarct size with HI, thus confounding analysis of the relationship of HI to infarct size independent of stroke mechanism. Using brain herniation to reflect infarct size, Lodder and colleagues conclude that "in the cases dying from brain herniation, HI was equally frequent in the group with a cardiac embolic cause of stroke, as it was in the group without such cause." However, alternative interpretation of these data yields a different conclusion. We would not consider the few petechiae termed "small HI" by Lodder and colleagues (their fig. 2, indicated by arrows) as HI. Considering only confluent petechiae (the unequivocal HI in their fig. 1), HIs were present in 42% (6 of 14) patients with cardioembolic sources who herniated compared with 15% (2 of 13) of patients without cardioembolic sources who herniated. It is our view that these important data of Lodder et al support the notion that cardioembolic strokes have a special, but certainly not exclusive, propensity for hemorrhagic transformation. Relatively dense HIs that occur deep within the distribution of the affected vessel are most often associated with a cardioembolic mechanism.

HIs are observed on less than 5% of initial CTs of patients with acute ischemic stroke but in an additional 10% if CT is repeated in the subsequent weeks. Hemorrhagic transformation visible on CT is delayed for variable intervals following stroke; early hemorrhagic transformation (within 48 hours of stroke onset) appears to be particularly frequent with presumed cardioembolic strokes. Horning et al performed serial CTs over a four week interval in 65 patients with acute ischemic stroke and reported hemorrhagic transformation in 17% within the first week after stroke, an additional 23% in the second week, 3% in the third week, and none in the fourth week. The overall 43% prevalence of HI is considerably higher than other clinical series of serial CTs and even exceeds the autopsy prevalence, suggesting patient population differences or potentiation of HI by their use of osmotic agents and low-dose heparin.

In one small series, enhancement of acute (within 28 hours) infarcts on CTs performed three hours after high-dose intravenous contrast infusion was predictive of later development of HI. HI are readily detected by MRI, but systematic comparison with CT has not yet been undertaken. Surprisingly, HI has not been associated with acute or chronic hypertension in most clinical and autopsy studies.

Given the dynamic nature of secondary hemorrhagic transformations and their relationship to large infarcts, it is difficult to directly compare prevalences of HI between CT and autopsy studies. Large infarcts would be over-represented in autopsy studies of recent stroke and postmortem examination would detect HI with greater sensitivity than CT; hence HI should occur more frequently in autopsy studies. On the other hand,
late-developing HI may especially occur in stroke survivors and result in higher CT detection rates.

About half (range 29–73%) of all HIs in clinical-CT studies are associated with presumed cardioembolic strokes.4, 6, 7, 10, 23 Of patients with presumed acute cardioembolic stroke, HI will be present on only 5% of CTs performed within the first 24 hours6, 14, 28, 29 but in about 20% (range 8–62%) of CTs performed 1–2 weeks after stroke.6, 10, 14, 24, 30 Hemorrhagic transformation is delayed for 6–12 hours after cardioembolic stroke, but usually occurs within 48 hours in nonanticoagulated patients.4, 9 The relatively early hemorrhagic transformation (within 48 hours) associated with presumed cardioembolic strokes compared to non-embolic infarcts partly explains why studies of early CT or of autopsies with early stroke deaths report a particularly high association of HI with cardioembolic stroke.

Serial CT studies of HI in patients with presumed cardioembolic stroke have yielded two additional clinical correlations: (1) most hemorrhagic transformations in nonanticoagulated patients are not associated with clinical worsening and (2) anticoagulation regularly accentuates the degree of HI, often with clinical deterioration. In one large collection of nonanticoagulated patients with presumed cardioembolic stroke and evolving HI documented by serial CTs, only 17% (2 of 12) experienced clinical deterioration associated with hemorrhagic transformation.4 Hemorrhagic transformation never occurred in the initial six hours after stroke onset, but the majority were present between 24–48 hours.31 Among anticoagulated patients with hemorrhagic transformation documented by serial CT, 56% (15 of 27) deteriorated.28 Severe secondary hemorrhage, resembling confluent hematomata, occurred in 41% (11 of 27) of anticoagulated patients but only 8% (1 of 12) of nonanticoagulated patients.9 Other clinical and autopsy studies have confirmed that anticoagulation during the period of hemorrhagic transformation accentuates the degree of secondary hemorrhage, often with clinical worsening, in patients with presumed cardioembolic stroke.4, 17 Anticoagulation does not appear to increase the likelihood of hemorrhagic infarction, but appears to accentuate the degree of hemorrhage.14, 26 The period of active bleeding is transient and anticoagulants administered after the appearance of HI on CT do not usually result in clinical or radiographic worsening.4, 24

What mechanism(s) allows blood to leak into some infarcts, but not into others? In mild-moderate HIs, hemorrhage is believed to result from diapedesis through ischemic endothelium, usually without vessel rupture. An ischemic insult of sufficient degree to induce a transient abnormality in vascular permeability appears to be a necessary substrate for HI. The extent of disruption of endothelial junctions and capillary rupture are related to the duration and degree of ischemia in primates with transient middle cerebral artery occlusion.32 A second essential condition is postulated to be restoration of circulation to the injured capillary bed during the interval of increased permeability, either by re-opening of the initial site of occlusion or by establishment of collateral circulation.4, 19

In other patients, variable degrees of necrosis of the vessel walls are present and the severe secondary hemorrhage appears unifocal, with mass effect and intraventricular extension.5, 6, 31 The bleeding in these patients clinically resembles intracerebral hemorrhage from a single locus, and some clinicians have suggested two distinct syndromes of hemorrhagic transformation: (1) multifocal hemorrhagic infarction and (2) secondary hematoma (apparently unifocal) within an infarct.5, 6, 33, 34 We suspect that, pathologically and mechanistically, the difference is of degree rather than of kind: Both are points along a spectrum of vascular injury, transiently increased permeability and secondary hemorrhage.

Hypothetically, the propensity of large infarcts to
undergo hemorrhagic transformation may be a reflection of the probability that the ischemia is sufficient to alter vascular permeability. In watershed infarcts, which may be large in volume and in which early reperfusion would be expected to occur, ischemia may be insufficient to substantially alter vascular integrity and dense HI is uncommon. \(^{17,25}\) HI is present in about one-third of patients with brain infarction due to vasospasm secondary to subarachnoid hemorrhage, with onset during remission of vasospasm. \(^{36}\)

In cardioembolic infarcts, hemorrhagic transformation is postulated to occur when distal migration of the embolic fragment from its initial site of arterial obstruction allows reperfusion of the damaged vascular bed (fig. 2). \(^{2,17-19}\) The relationship between re-opening of the site of occlusion and hemorrhagic transformation is strongly supported by both radiographic and pathologic data. \(^{2,16,17,18,38,59}\) However, persistent proximal occlusions have been found in 11–17\% of HIs associated with cardioembolic stroke, implicating other routes of reperfusion as well. \(^{10,17,19}\) The role of collateral circulation-reperfusion in hemorrhagic transformation has not been thoroughly studied except in experimental models.

Do strokes resulting from artery-to-artery embolism have the same predisposition for and mechanism of HI as those due to cardiogenic emboli? There are few clinical or pathologic data addressing this issue, due to the difficulty of defining this mechanism with certainty. We speculate that artery-to-artery embolism uncommonly results in sufficient ischemia to derange vascular permeability. However, with particularly large artery-to-artery emboli, the situation may well be analogous to cardioembolic stroke. \(^{17}\)

From analysis of these data, including those presented in this issue of STROKE, we conclude that cardioembolic strokes do indeed have a special propensity for hemorrhagic transformation, independent of infarct size. Further, the early re-opening due to distal migration of embolic fragments appears to result in a recognizable pattern of early (within 48 hours) hemorrhagic transformation with central or globular and relatively dense HI (fig. 3). \(^{2,17}\) Development of collateral circula-

![Figure 2. Hemorrhagic transformation in embolic stroke. Re-perfusion during the initial days due to distal migration of emboli from the initial site of occlusion may be a key factor in hemorrhagic transformation. From Toole, Cerebrovascular Disorders, with permission.][2]

![Figure 3. Subcortical hemorrhagic transformation may be particularly associated with presumed cardioembolic stroke. None of these four patients with presumed cardioembolic stroke received anticoagulation, one (upper right) deteriorated associated with hemorrhagic transformation. From the case collection of the Cerebral Embolism Study Group.][3]
spectrum of hemorrhagic infarction. Stroke 17: 1986 (this issue)
27. Cerebral Embolism Study Group. Brain hemorrhage and cardioembolic stroke: Clinical observations. (submitted)
33. Toole JF. Cerebrovascular Disorders. Raven Press (New York), 1984; p 187-198
Hemorrhagic infarcts.
R G Hart and J D Easton

Stroke. 1986;17:586-589
doi: 10.1161/01.STR.17.4.586

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/17/4/586.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/