Hemorrhagic Cerebral Infarction — A Prospective Study

C. R. Hornig, M.D., W. Dorndorf, M.D., and A. L. Agnoli, M.D.

SUMMARY In 65 cases of ischemic cerebral infarction, CT scans and quantitative assessments of the neurological disturbances were undertaken at specific intervals during the 4 week period after stroke. Forty-three patients underwent lumbar puncture to determine the serum/CSF albumin ratio. The etiology of the infarction was evaluated on the basis of angiographic, ultrasonic and cardiologic findings. A hemorrhagic transformation of the infarction occurred in 28 patients, eleven within the first week, and 15 within the second. Risks of hemorrhage were correlated with a severe neurological deficit, disturbance of consciousness, large infarction with a mass effect, enhancement of contrast medium in CT (especially if occurring early), involvement of the cortex, and distinct blood/CSF barrier disturbances. Cardiac embolism was a frequent etiology in patients with secondary hemorrhagic infarction, especially when transformation occurred within the first week after stroke.

In addition to a heterogeneous pattern of hemorrhage, frank hematoma predominated in those infarcts which underwent early transformation, while those transforming late often showed less hyperdense cortical hemorrhagic changes.

Deterioration evident on clinical evaluation was caused by the hemorrhagic transformation in three cases, in each instance within the first week after stroke.

THE RISK OF HEMORRHAGIC INFARCTION or frank secondary hemorrhage into initially ischemic cerebral infarction is a major issue influencing early use of anticoagulants for patients suffering from cerebral embolism of cardiac origin. Some authors favor early anticoagulation because of an assumed high risk of recurrent embolism within the first weeks after stroke. 13,14 Although secondary hemorrhage with anticoagulation has been observed, these authors deny it has any influence on the clinical course. Other authors recommend that early anticoagulation be avoided, as they have been confronted with severe intracerebral hematomas within ischemic infarction during the first days after stroke even in patients who have not received any anticoagulants. 6,7 In laboratory studies, dogs with experimental cerebral infarction developed secondary hemorrhage more frequently when they were given anticoagulants. 8 These experiences prompted the Cerebral Embolism Study Group to exclude patients suffering from large infarctions from early anticoagulation, since the risk of hemorrhage seems to increase with the size of the ischemic lesion. 9

Despite the studies to date, there remains a lack of information about the incidence, the clinical course and special risks of secondary hemorrhagic infarction. Detailed pathoanatomic studies naturally deal only with a segment of the patients concerned, 10-12 and computerized tomography (CT) has been found to be insufficient for imaging petechial hemorrhage. Presumably, this accounts for the discrepancy between the incidence of secondary hemorrhagic infarction in pathoanatomic 11,12 (18-42%) and CT studies (4, 3-9, 6%). 13-17 However, all the latter studies were performed retrospectively. In the 2 prospective CT studies, with only a small number of patients, and CT scans during the course of the disease, an incidence of 18-20% has been reported. 3,19 A comparative CT and pathoanatomic study demonstrated that 15 of 18 secondary hemorrhagic infarction could be detected by CT. 19 In view of these results, a prospective study of the risks, the incidence and the clinical course of secondary hemorrhagic infarction, identified by CT seemed to be desirable.

Patients and Methods

Over a period of 4 weeks serial CT scans before and after injection of contrast medium were performed (Stretton II, matrix 256 x 256, 60 ml Conray 60®) in 65 cases of supratentorial localized ischemic cerebral infarctions. The following parameters were evaluated in the CT scans: 1. maximum size of the infarction edema calculated by the formula: maximum length x maximum width x number of 1 cm slices 1:2; 2. maximum space occupied by the infarction edema; 3. occurrence of a visible hyperdensity within the infarction area as an expression of secondary hemorrhage; 4. enhancement of contrast medium; 5. involvement of cortical and subcortical structures in the infarction. The severity of neurological symptoms was expressed by a rating scale ranging from 1 to 29 points. The parameters evaluated by this score were consciousness, aphasia, orientation, hemianopia, facial power, motor strength of the arm and leg and sensory disturbances. CT scans as well as clinical examination were routinely performed on the 3rd, 7th, 14th, 21st and 28th day after stroke. All patients were admitted to the hospital within 24 hours after ictus. Most patients, especially all those with a hemorrhagic transformation of their infarctions by the 3rd day, had a CT scan on admission.

All patients had an ultrasonic examination of the extracranial carotid vessels; 35% underwent angiography. Evaluation of the patient’s cardiologic situation was based on the physical examination and the electrocardiographic findings in all cases and addition-
ally on an echocardiographical examination in 24 cases. Patients suffering from an ultrasonically or angiographically detected atherosclerosis of the cerebral vessels and without a probable source of embolism in the heart were considered to have a stroke of thrombotic etiology. Cardiac embolism was assumed in cases of atrial fibrillation or echocardiographically-proven sources of emboli in the heart and normal ultrasonic or angiographic findings of the cerebral vessels. For the rest, the etiology was classified as unknown.

All patients were treated with dextran or hydroxethylstarch infusions, and 65% received low dose heparin (2 × 5000 U/day). Partial Thromboplastin Time was determined routinely in those patients once a week and it was never prolonged. Most of the patients with an assumed thrombotic or an unknown etiology of

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**TABLE 1 Clinical and CT Characteristics of 28 Patients Suffering From Hemorrhagic Cerebral Infarction**
HEMORRHAGIC CEREBRAL INFARCTION/Hormg et al

their stroke were treated with Acetylsalicylacid (ASS) after dextran or hydroxyethylstarch infusions given for approximately 10 days after ictus.

Results

In 28 of 65 cases (43%), the infarction became hemorrhagic within four weeks (table 1). The transformation occurred mainly in the second week after stroke (15 patients). In 4 cases it occurred before the third day and in another 7 between the third and the 7th day after stroke (fig. 1).

Comparison of the patients with secondary hemorrhagic infarction with the remainder revealed some significant characteristics. The neurological deficit of patients with secondary hemorrhage was more severe as indicated by an average of 16.2 points of our rating scale compared to 12.7 points (p < 0.05, t-test). Accordingly, disturbances of consciousness were more frequent with 68% vs. 40% (p < 0.05, chi-square-test). Whereas embolism was the cause of 29% of secondary hemorrhagic infarction, it could be proved in only 14% of the remaining patients (fig. 2).

The CT scans also revealed some differences between hemorrhagic and nonhemorrhagic infarction. The maximum size of the edema of those infarctions which became hemorrhagic was on average larger (103 cm$^3$ vs. 55 cm$^3$; $p < 0.01$, t-test) and a mass effect was frequently recognizable (89% vs. 38%; $p < 0.001$, chi-square-test) (fig. 3 and 4). Whereas 93% of the secondary hemorrhagic infarctions involved the whole area supplied by a cerebral vessel or large parts of the cortex, 48% of the others were localized subcortically (p < 0.005, chi-square-test) (fig. 5). An enhancement of contrast medium could be observed in 86% of secondary hemorrhagic infarction but only in 46% of the rest (p < 0.005, chi-square-test). Enhancement was not only more frequent but also occurred earlier. Primary enhancement of infarctions occurring within the first week after stroke took place in 48% of secondary hemorrhagic but only in 25% of the remaining lesions (fig. 6).

The determination of the CSF-serum albumin ratio revealed a more distinct disturbance of the blood-CSF barrier of patients suffering from secondary hemorrhagic infarctions (0.0150 vs. 0.0103; p < 0.01, t-test). All of the CSF samples were obtained at a time when no blood was visible on CT scan (fig. 7).

Neither the presence or severity of arterial hypertension, low-dose heparin anticoagulation nor dextran therapy had any influence statistically on the transformation of infarctions to hemor-
rhagic within the first week after stroke involved the whole area supplied by a cerebral vessel, only 3 of the 17 that transformed later were of the same extent. Early hemorrhagic infarctions showed a more extensive mass effect. Cardiac embolism was the cause of seven of the 11 infarctions showing early hemorrhagic transformation but only of one of the late transforming infarctions \( p < 0.05 \), chi-square-test).

Three different patterns of hemorrhagic changes with infarction could be distinguished: 1. more or less extensive hematomas; 2. a heterogeneous hemorrhagic alteration and 3. a less hyperdense hemorrhagic change localized within the cortex involved in the infarction (fig. 8). Ventricular hemorrhage could be observed in three cases, two with hematomas and one with a heterogeneous pattern of bleeding. Secondary hemorrhage within the first week after stroke frequently occurred as hematoma (45%). Later transformation to hemorrhage was mainly as a less hyperdense cortical or heterogeneous hemorrhage (76%).

The hemorrhagic transformation was associated with a worsening in neurological symptoms in three patients. The pattern of hemorrhage was heterogeneous in one case and there was hematoma in two cases. Two of the patients suffered from a ventricular hemorrhage, a further case of ventricular hemorrhage due to hemorrhagic infarction showed no clinical deterioration. The transformation took place within the first week after stroke in all of the three cases, in two cases before the 4th day after stroke. The cause of the infarction was cardiac embolism in 2 cases and remained unknown in one case. The basal ganglia of all of the three patients were involved in the infarction on CT scan (fig. 9).

**Discussion**

Over a period of 4 weeks, 43% of 65 cerebral ischemic infarctions transformed to hemorrhage. This frequency of secondary hemorrhagic infarction corresponds to that observed in pathoanatomic studies limited to recent lesions. CT seems to be rather sensitive for detecting hemorrhage. This was inferred from the results of a comparative CT and pathoanatomic study in which 15 of 18 hemorrhagic infarctions could be detected by CT. The lower frequency of hemorrhagic infarction in CT found by other authors may have reflected the retrospective character of those studies. In prospective studies, it may reflect the small number of CT scans performed.

The risk of secondary hemorrhage was significantly increased in large infarctions with a mass effect and severe neurological disturbances. In two recent studies, secondary hemorrhagic infarctions were also found to be disproportionately large. The risk of hemorrhage was observed to be 12 times higher for infarction with a mass effect. Anticoagulants have been recommended for use in patients with embolic infarction and mild neurological symptoms. The lack of benefit in patients with a severe neurological deficit might be that the larger infarctions transform to hemorrhage. The reason for preferential hemorrhagic transformation of large infarction with a mass effect might relate to the more extensive edema, the compression of small vessels in the area surrounding the lesion and the stasis of blood flow. After the decrease of the edema, reperfusion of these vessels occurs and because these capillaries often
have a disrupted endothelium,\textsuperscript{22} a diapedesis of blood will occur. This process has been demonstrated in animal experiments.\textsuperscript{10, 23-25} Reperfusion of capillaries, which have been compressed by the edema and an increased vascular permeability caused by the ischemia also account for an extravasation of contrast medium and the disturbance of the blood/CSF barrier expressed by the CSF/serum albumin ratio. CT scanning of patients with secondary hemorrhagic infarction revealed an enhancement with contrast medium in 86\% and a distinct disturbance of the blood/CSF barrier. The coincidence of enhancement and secondary hemorrhage in patients with cerebral infarction has already been described.\textsuperscript{17, 19} A delayed enhancement after application of a high dose of contrast medium helps to predict a hemorrhage.\textsuperscript{18} Since the first occurrence of contrast enhancement generally has a peak frequency within the second week after stroke,\textsuperscript{26} it could be observed earlier in cases of secondary hemorrhagic infarction. A pathoanatomic study demonstrated that early enhancement is caused by necrosis of capillaries,\textsuperscript{19} which also leads to diapedesis after reperfusion.

A good collateral circulation was found to be essential for the transformation of ischemic infarction to hemorrhage in animal experiments.\textsuperscript{23, 24} After decrease of the edema, reperfusion by collateral circulation becomes effective. The frequent occurrence of hemorrhage within the second week after stroke might be
explained by this phenomenon. Pial collaterals seem to play an important role in reperfusion, because secondary hemorrhage within the second week after stroke was predominantly of a cortical or heterogenous pattern. The lower hyperdensity of these late hemorrhages is due to their petechial character. The predominant involvement of the cortex in the infarction that transformed to hemorrhage could be explained by this mode of pathogenesis. Accordingly, subcortically localized infarctions less frequently became hemorrhagic, because they often involve the terminal supply area of an artery with insufficient collateralization. On the other hand, subcortical infarctions are often small with the expectation from this small size of a lower risk of hemorrhage.

The second possible reason for the reperfusion of an ischemic area is the fragmentation of an embolus that has caused the ischemic event. It is well known that there is a coincidence of embolic etiology and the tendency to hemorrhagic transformation of cerebral infarction.11-13 16 Cardiac embolism was a frequent cause of secondary hemorrhagic infarction in our patients. In patients suffering from a thrombotic disease of the cerebral arteries, embolism from an atheromatous plaque might have caused the stroke.

Secondary hemorrhage worsened the clinical symptoms of 11% of the patients with hemorrhagic infarction. Whereas transformation to hemorrhage within the second week after stroke or later never caused a deterioration, probably because petechial bleeding predominated, the condition worsened of three of the 11 patients whose infarction transformed to hemorrhage within the first week after stroke. CT of these three patients always showed large infarction with a pronounced mass effect. Several authors reported on secondary hemorrhage leading to clinical deterioration. Hemorrhage in those cases predominantly formed hematomas and occurred within the first days after stroke.6, 7, 20, 28, 29

A possible source of the hemorrhage in those cases might be the small penetrating branches of the middle cerebral artery, since infarction of the three patients of our study as well as in one case reported in the literature involved the basalganglia.

It should be mentioned that low-dose heparinization had no significant effect on the transformation of ischemic infarction to hemorrhage. The existence and the severity of arterial hypertension in our study had no effect. The latter contrasts with the results of animal experiments, but is in agreement with observations concerning humans.12 20

The results of this prospective study indicate that anticoagulant treatment of patients with ischemic cerebral infarctions should be administered carefully because of the high risk of a secondary hemorrhage. In particular, it should be avoided within the first week after stroke, as secondary hemorrhage causing a clinical deterioration seems to be limited to this period. In the 13 patients with cerebral embolism of cardiac origin, the probability of a secondary hemorrhage resulting in a deterioration of the clinical picture was 15%.

On the other hand, the recurrence rate of embolism within the first weeks after stroke is estimated as between 0 and 9.5%. 3, 5, 6, 9, 30 Especially endangered are patients with large and contrast-enhancing infarction with a mass effect, severe neurological symptoms and distinct disturbances of the blood/CSF barrier.

References

A NUMBER OF STUDIES\(^1\)\(^-\)\(^2\) have demonstrated that hypertension is an important risk factor in stroke. The Framingham Study, confirmed by other population studies\(^3\)\(^-\)\(^4\) determined that systolic BP is a better predictor than diastolic BP of the risk of atherothrombotic brain infarction. On this basis, the concept, widely accepted in clinical practice, that diastolic pressure was the BP component more directly involved in all the clinical manifestations of cerebral vascular disease was criticized and the necessity of carefully treating systolic hypertension firmly stressed.

Although a few pathological studies\(^5\) have indicated a positive correlation between systolic BP values and severity of atherosclerotic (AS) lesions in the cerebral vessels, the site of action as well as the mechanism by which systolic hypertension may play a role in increasing the risk of ischemic stroke remains to be clarified. Moreover, rather than being a causative factor, increased systolic values could simply be an epiphenomenon of arterial damage. If so, therapeutic implications might be quite different.

The protocol of the Italian Multicenter Study of reversible cerebral ischemic attacks (RIA) provided the opportunity to contribute to the understanding of these problems for the following reasons: 1) careful and standardized BP data, obtained by means of a series of BP registrations throughout the baseline period of observation, were available; 2) patients with RIA conduct normal daily activities and therefore in such patients BP recordings are more closely representative of the real individual BP values than in restricted stroke patients; 3) all of the patients had undergone a thorough assessment of other risk factors for atherosclerosis; 4) all of the patients were studied by means of angiography: the extent and severity of the angiographic lesions were determined in a standardised manner and expressed by a score-index which can be used as a continuous variable.

On the basis of these considerations and utilizing some of the available data, we examined each BP component’s relative contribution to the presence, severity and extent of atherosclerotic lesions at extracranial level. None of the same variables was predictive of the severity of intracranial atherosclerosis.

The results of this clinical study may confirm the indication, coming from physiopathologic observations, of a predominant role of systolic hypertension in the process of maintenance and acceleration of atherosclerosis in the large pre-cerebral arteries.

**SUMMARY**

Utilizing the initial BP assessment in the 462 patients who entered the Italian Multicenter Study of reversible cerebral ischemia, an analysis of the effect of each BP component in respect of presence, extent and severity of atherosclerotic lesions, as displayed by angiography, was carried out separately for lesions located at either intra- or extracranial level.

In a multivariate statistical model, among the following variables: sex, age, systolic BP, diastolic BP, cholesterol and smoking, systolic BP was found the best predictor of extent and severity of atherosclerotic lesions at extracranial level. None of the same variables was predictive of the severity of intracranial atherosclerosis.

The results of this clinical study may confirm the indication, coming from physiopathologic observations, of a predominant role of systolic hypertension in the process of maintenance and acceleration of atherosclerosis in the large pre-cerebral arteries.
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Stroke. 1986;17:179-185
doi: 10.1161/01.STR.17.2.179

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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