CT Enhancement After Prolonged High-Dose Contrast Infusion in The Early Stage of Cerebral Infarction

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SUMMARY To demonstrate the BBB break-down on the CT image in the acute stage of cerebral infarction, a 3 hour continuous drip infusion of 200 ml of meglumine amidtrizoate, rather than the conventional bolus injection, was used. In this study, 22 examinations were carried out in 18 patients in whom cerebral infarction due to temporary or permanent obstruction of the cerebral artery was diagnosed by CT and angiography on admission. With each examination, the first CT was obtained prior to contrast infusion, and second immediately after the end of 3 hours of continuous contrast infusion. The EMI number was calculated at 3 regions of interest in the infarct. Within 3 days after stroke episode, 4 out of 5 patients with temporary vascular obstruction demonstrated enhancement, as well as 6 out of 9 patients with permanent vascular obstruction. Between 4 and 14 days after the stroke episode, all of 8 patients showed enhancement.

To further clarify the extravasation of the contrast medium during the first 3 days of a cerebral infarction, a third CT scan was performed 3 hrs after finishing the contrast infusion in 4 patients. In these latter patients, blood was sampled at the time of each of the 3 CT series. The EMI number of the blood samples was also measured. In all 4 patients, the Gado's tissue-blood ratio (the EMI number of the CT lesion divided by that of the blood sample) was higher than 17.2% in the second, and higher than 54.7% in the third CT scan. Thus break-down of the BBB which was demonstrated by prolonged contrast infusion is an earlier event in human cerebral infarction than is usually accepted.

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of interest on the CT image was calculated for each scan. Peripheral blood samples (30 ml) were obtained after each scan, transferred to a condom, immersed in a water-filled phantom, scanned, and their mean EMI numbers were calculated. The serum concentration of contrast medium (mg I/ml) was determined for each blood sample. The values of contrast enhancement in the blood samples, the region of interest being in the infarcted cerebral cortex and the white matter, were calculated and the changes in these values were studied (fig. 1). The ratio of contrast enhancement in the infarcted brain tissue and in blood (Gado's tissue-blood ratio) was calculated and multiplied by 100. Changes in this ratio at the second, third and fourth scan were studied to assess extravasation of the contrast medium (fig. 2).

Results

Findings Obtained Within 3 Days of the Stroke

In all 14 patients, we noted hypodense infarcted areas on CT images obtained before contrast infusion (fig. 3, 4). In 4 of 5 patients with temporary cerebrovascular obstruction in whom admission angiograms failed to reveal cerebrovascular obstruction, the infarcted brain enhanced on scans obtained immediately after completing the 3-hr drip infusion (fig. 3). All 5 patients showed a mass effect on the CT image (table 1), but no cerebral hemorrhage was observed in the subsequent plain CT scans 3–5 days after the examination, except for one patient in whom hemorrhagic infarctions occurred 16 days after the 3-hr continuous drip infusion. In 6 of 9 patients with angiographic evidence of cerebrovascular obstruction, mild to moderate enhancement was noted, primarily along the cerebral cortex and at the periphery of the lesion (table 1 and fig. 4). In these patients, mass effect was also present. In patients with complete cerebrovascular obstruction, serial films of the angiogram showed that the contrast medium reached the ischemic brain tissue via collateral circulation.

Findings Obtained Between 4 and 14 Days After the Stroke

In all 8 examinations, of whom 5 showed angiographic evidence of cerebrovascular obstruction, we noted moderate to marked contrast enhancement and a positive mass effect (table 2).
Assessment of Contrast Extravasation

In 4 patients (Nos. 1—4), we obtained a third scan 3 hours after contrast infusion. In one (No. 1) we performed a fourth scan after 20 hours. Blood was sampled after each scan. We found a good linear relationship between the contrast enhancement values (EMI number) and the iodine concentration (mg I/ml) in nine blood samples (fig. 5).

In patient No. 1, who had temporary cerebral ischemia, the value of contrast enhancement in the area of cerebral infarction increased between the 2nd and 3rd scan, from 42.17 to 46.55 in the cortex and from 43.05 to 46.88 in the white matter. The blood value, on the other hand, decreased from 63.00 to 50.26 (figs. 1, 3). In patients 2, 3 and 4, who had permanent cerebral ischemia, the value of contrast enhancement in the...
TABLE 1 Patients With or Without Contrast Enhancement and with Positive or Negative Mass-effect within 3 Days of the Stroke Episode

<table>
<thead>
<tr>
<th>Mass Effect</th>
<th>Temporary Cerebro-vascular Obstruction</th>
<th>Permanent Cerebro-vascular Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enhancement</td>
<td>No Enhancement</td>
</tr>
<tr>
<td>Positive</td>
<td>marked, homogeneous* (1)*</td>
<td>1 (1)*</td>
</tr>
<tr>
<td></td>
<td>marked, peripheral and heterogeneous (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>marked, peripheral and heterogeneous (2)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0 (1)</td>
<td>0 (1)</td>
</tr>
</tbody>
</table>

*Degree and pattern of enhancement.
†Days since stroke.

Time Course of the Plasma Concentration for Contrast Medium

We recorded the time course of the plasma concentration of contrast medium after conventional bolus injection (100 ml) (n = 4) and after the start of 3-hrs continuous drip infusion (200 ml) (n = 4) of 66% meglumine amidtrizoate (fig. 6). When the contrast medium was given by infusion, the concentration increased and decreased gradually, during and after the infusion. Consequently, a high blood concentration of the medium was maintained for an extended time period. On the other hand, in patients who received the bolus injection, the plasma concentration of the medium was high immediately after the injection and fell rapidly thereafter.

Discussion

There is a wide consensus that the infarcted area is enhanced on CT scans taken between 2-4 weeks after the stroke episode. However, some authors have reported that approximately 50-60% of stroke patients showed enhancement within 14 days of the ictus. In patient No. 1, the Gado tissue-blood ratio of the infarcted brain tissue increased from 66.94 to 154.03% (cortex) and from 68.33 to 132.08% (white matter) between the second and fourth scan (fig. 2). In the other 3 patients, this ratio also increased from 17.24-29.24% to 54.74-100.19% in the cortex and from 0.916 to 9.73 or 57.49% in the white matter between the second and third scan. These findings suggest that while the concentration of the contrast medium in the blood circulation decreased, it increased or remained relatively unchanged in the extravascular compartment of the brain tissue. Therefore, it was possible to document that extravasation of the contrast medium occurred in the infarcted brain after both temporary and permanent cerebrovascular obstruction.

Animal models suggested the extravasation of plasma constituents due to BBB change to be a slow process in cerebral infarction. If pinocytotic vesicular
transportation is assumed to be a main mechanism of BBB disruption in the ischemic brain,\textsuperscript{21-23} the slowness in the extravasation of contrast medium can be explained. However, the blood concentration of contrast medium dropped rapidly in our patients after conventional bolus contrast injection. Therefore, in some of our patients we used continuous 3-hr drip infusion to obtain a sustained high blood concentration of contrast medium (fig. 6).

We found that 10 (71\%) of the 14 patients examined within 3 days, and all 8 patients examined between 4-14 days after the ictus manifested enhancement of the cerebral infarction (tables 1, 2). Of 5 patients with temporary cerebrovascular obstruction, 4 (80\%) manifested definite enhancement during the 3 days following the ictus. The finding in humans of prominent enhancement due to BBB destruction in the acute stage after temporary cerebrovascular obstruction coincides with observations we made in our animal models using Evans blue\textsuperscript{12} and \textsuperscript{131}I-albumin (RISA)\textsuperscript{13} as a tracer. Hornig et al.\textsuperscript{24} who measured the serum protein concentration in the CSF of patients with acute cerebral infarction, found that BBB breakdown for serum protein occurred in the early phase of cerebral ischemia, in most cases within 14 days of the ictus.

Hayman et al.\textsuperscript{20} reported that 4 of 7 patients, in whom contrast enhancement occurred in the early phase of cerebral infarction, died from hemorrhagic infarction. In our series, only 2 out of 14 patients, with contrast injection to the infarcted brain within 3 days of the ictus, experienced slight cortical hemorrhagic infarc-

tion several weeks after the examination, and no patient died from hemorrhagic infarction. This incidence is compatible with that in the reported natural course of this disease.\textsuperscript{5, 20}

Enhancement on the CT scan has been related to the concept of luxury perfusion of hypervascularity of the infarcted brain (intravascular event).\textsuperscript{24-26} Alternatively, contrast enhancement has been ascribed to extravasation of contrast medium due to hyperosmolar BBB damage by the contrast medium of the already injured cerebrovascular endothelial cells.\textsuperscript{1-2, 22, 24, 27-29} In our four patients examined in the 3-day period after the ictus, the existence of an extravascular compartment of contrast medium in the infarcted brain, i.e. contrast-extravasation, has to be considered, because the grade of contrast enhancement in the lesion increased immediately after the completion of the 3-hr drip infusion and further 3 hrs after completion. On the other hand, in these patients, the enhancement value of the scanned blood samples decreased (fig. 1). Furthermore, the enhancement ratio of infarcted brain tissue to blood (Gado's tissue/blood ratio)\textsuperscript{15} exceeded 17.24\% in the cortex immediately after the 3-hr drip infusion; it was more than 54.74\% 3 hrs later (fig. 2). If blood in the normal brain occupies 3-4\% of total brain volume, the

![Graph showing values of contrast enhancement and iodine concentration](image_url)
CT ENHANCEMENT OF ACUTE CEREBRAL INFARCTION/Itto et al

Remarkably high tissue/blood ratio of the infarcted brain tissue at 3 hrs after completion of the drip infusion is highly suggestive of the extravascular presence of contrast medium. However, we do not know whether the contrast medium is located within and/or outside the vascular endothelial cells.

During the 3 days after the ictus, 2 of our 5 patients with temporary ischemia and 6 of 9 patients with permanent vascular obstruction showed no or only mild enhancement. Among them, mass effect on the CT image was observed in the 2 patients with temporary obstruction and in 4 of 6 patients with permanent obstruction (table 1). These findings are compatible with cytotoxic edema in the acute phase of experimental cerebral ischemia. According to Wall et al, in 21 of 26 patients (81%), high resolution CT scans revealed focal low density areas corresponding to the infarcted gray matter as early as 24 hours after the ictus. Only 5 of 15 patients showed contrast enhancement at the same time. These findings suggest the early appearance of cytotoxic edema in acute cerebral ischemia.

Haley reported 3 patients who manifested temporary consciousness disturbance due to encephalopathy which seemed to be induced by carotid injection of 51 ml meglumine iothalamate. According to Kendall et al, symptomatic recovery from cerebral infarction was slower in patients who had meglumine iothalamate for contrast CT than in patients in whom contrast was not used. They ascribed the adverse effect of contrast medium extravasation to its chemical effects on the brain parenchyma. On the other hand, the i.v. injection of a large amount of iodine contrast medium did not increase the mortality rate of baboons subjected to experimental cerebral ischemia, nor did it have a harmful effect on patients with cerebral infarction who manifested marked enhancement.

In the present study, we noted no adverse side effects in any of our patients in whom 200 ml of 66% meglumine amidtrizoate was i.v. infused over a 3 hr period. Prolonged contrast infusion of this amount did not exceed iodine content of blood in patients with the conventional bolus contrast injection (fig 6). However, some chemical adverse effect of the extravasated contrast medium could not absolutely be ruled out. In the future, a high dose of non-ionic contrast medium could safely be used.

References

30. Wall SD, Brant-Zawadzki M, Jeffrey RB, Barnes H: High fre-
Mechanism of In-Hospital Cerebral Ischemia

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SUMMARY Of 171 patients evaluated prospectively and consecutively for cerebral ischemia, 26 (15%) developed symptoms while hospitalized. Cerebral ischemia complicated operative procedures in 12 patients, unsuccessful cardioversion in one and coronary angiography in another. Twelve patients had apparent cerebral embolism and 14 patients had cerebral thrombosis as a mechanism of their symptoms. Hospitalized patients who suffered cerebral ischemia had one or more of the following: risk factors for stroke including cardiac source of embolus, previous stroke, diagnostic or therapeutic procedures for vascular disease, or chronic hypertension complicated by acute hypotension.

IN-HOSPITAL STROKE ACCOUNTS for a significant proportion of spontaneous stroke disease. In The National Survey of Stroke, 8.7% of strokes assessed in 1975-76 took place while the patient was in the hospital for some other condition.1 In a population-based study,2 Schoenberg et al found that 6.5% of all first strokes occurred while patients were in the hospital for a surgical procedure or a medical problem. We therefore carried out hospital-based prospective evaluation to assess possible factors related to in-hospital stroke.

Materials and Methods

We prospectively and consecutively assessed 203 patients with symptoms of acute stroke at Temple University Hospital between July 1, 1982 and February 28, 1983. One hundred and seventy-one patients had cerebral ischemia and 32 had hemorrhagic stroke. Of the 171 patients with cerebral ischemia, 47 had a transient ischemic attack (TIA) and 124 had a completed infarction. Twenty-six patients developed symptoms of cerebral ischemia in the hospital while no cases of primary hemorrhagic stroke occurred in hospitalized patients. Patients with onset of symptoms while hospitalized were admitted for other medical or surgical disorders or for evaluation of asymptomatic carotid bruit. None of these patients were having symptoms of cerebral ischemia at the time of their admission. All patients were followed by the authors throughout their hospital course. Followup, after discharge, was obtained in 10 of the 19 surviving patients. The 26 patients all had routine admission laboratory studies including complete blood count, serum chemistries, prothrombin time, partial thromboplastin time, platelet count, rapid plasma reagent test, electrocardiogram, chest x-ray, urinalysis, as well as computed tomographic (CT) brain scan. Patients were screened by neurological consultation as well as by review of CT scan results. CT scan was judged to be an absolute requirement for entrance into our study. Further cardiac evaluation and assessment of extracranial cerebrovascular disease was obtained as outlined in table 1. An autopsy was obtained in one instance.

To determine whether cerebral ischemia was thrombotic or embolic, we used the criteria of the Harvard Cooperative Stroke Registry.3 Evidence for thrombosis of the large artery type included: premonitory TIAs; evidence of large vessel occlusive disease or CT evidence of a bland infarct that was not confined to the distribution of a single surface artery. As an additional criterion, we included cerebral ischemia in the presence of hypotension defined as a drop in mean arterial blood pressure (mABP) of greater than 25% which is when cerebral autoregulation becomes disrupted.4 Lacunar stroke was based on clinical presentation and CT scan. Embolism was invoked in patients with one or more of the following features: sudden neurological signs with cardiac source of embolus; branch occlusion of an intracerebral artery by arteriography; infarction of a superficial cerebral artery territory by CT scan; CT evidence of secondary hemorrhage or multiple infarcts in different vascular territories.

Results

Eleven men and 15 women patients had cerebral ischemia while in the hospital. Their mean age (± std. dev.) was 61.8 ± 11.5 years (range, 35 to 85 years) and 50% were black, 50% white. Five patients had TIAs and 21 patients had completed infarction (table 2). Twelve patients had embolic events and 14 thrombotic. The risk factors for each group are outlined in table 3. As expected, the embolic group had a higher

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