Delayed High Dose Contrast CT: Identifying Patients at Risk of Massive Hemorrhagic Infarction

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A prospective clinical study was done on 20 patients referred for computed tomography within 28 hr of a cerebral ischemic event. The patients were scanned before, immediately after, and 3 hr after a high dose of intravenous contrast medium was administered to produce prolonged high blood iodine levels. In seven patients the delayed scan demonstrated a heretofore undescribed type of contrast enhancement which represents the early massive vasogenic edema seen in experimental animals before confluent hemorrhagic infarction. Four of the seven patients developed hemorrhagic infarction. None of the remaining 11 patients with cerebral infarctions and conventional postenhancement CT patterns showed hemorrhage on follow-up CT scans or at autopsy. Two patients with transient ischemic attacks had normal CT scans. It may now be possible to predict patients in whom there is high probability of hemorrhagic infarction before blood appears on CT. Treatment of these patients should probably be aimed at preventing the devastating effects of the vasogenic edema. We speculate that heparinization or bypass surgery to reestablish circulation may be contraindicated in this group.

Previous contrast-enhanced computed tomographic (CT) studies have indicated that enhancement is rarely if ever apparent in cerebral infarcts within 5 days of onset [1–3]. It has been recommended, therefore, that enhancement be used only during the period of neovascularization (5 to 20+ days after onset) when contrast extravasation can be used to detect 'isodense' cerebral infarction. Thus contrast CT has not been routinely used during the critical hours immediately after onset when vital therapeutic decisions must be made.

The reported absence of early CT enhancement in humans after standard doses of contrast media contradicts work in primate models of cerebral infarction (in which transient arterial occlusion and subsequent microembolization were induced) that document vasogenic edema of early onset [4]. Since enhancement was consistently seen in the primate on CT as soon as 90 min after fragmentation of the carotid embolus, the reported lack of early enhancement in human infarction became suspect.

Our investigation was undertaken to determine whether a CT scan immediately after a higher dose of contrast medium (80 g iodine) or a delayed scan (3 hr later) could reveal early vasogenic edema (i.e., persistent contrast enhancement) in patients with cerebral infarction.

Subjects and Methods

At the U.S. Veterans Administration Medical Center, during a period of 13 months, we examined 23 adult male patients who were referred for CT during the first 28 hr after a well documented cerebral ischemic episode. Each patient’s entry into the study was determined by the referring physician. Three were subsequently excluded from the series because, despite Valium sedation, patient motion prevented us from obtaining adequate cranial scans. Patients in poor clinical condition who might have a cause other than cerebral
infarction for the sudden onset of neurologic dysfunction were often enrolled by clinicians in this series. In this respect our study differs from other reports on CT of cerebral infarction which failed to mention clinical outcome [1, 3], excluded the 25% or more of patients [5] who died within 30 days after onset [2], or preselected a population of infarctions with an astonishing low 1.2% mortality rate [6].

Each of the 20 patients was scanned before contrast infusion. Then 270 ml of diatrizoate meglumine (Reno-M-DIP) was administered intravenously in 2–3 min. Immediate contrast CT scanning began at that point. During the first 5–9 min of the scanning, an additional rapid drip of 300 ml of the same contrast substance was given. One or more delayed high dose scans were obtained at intervals thereafter.

The delayed high dose scans were overlapped to enable accurate comparison with immediate scans. All studies were done on an EMI 1010 scanner and identical window settings were used for filming all scans. Each examination was then evaluated and placed in one of four groups according to enhancement pattern. They were further correlated with the medical records and additional follow-up preinfusion and delayed high dose scans to discover whether their appearance might be useful for predicting the ultimate clinical outcome. This information is summarized in tables 1–3. The findings on high dose contrast immediate and delayed scans were compared with data reported in CT of acute cerebral infarction after standard contrast administration. [1–3]. The clinical status at time of scan was assigned using the modified Mathew System suggested by Frithz and Werner for all eight patients who died [5]. Six of the eight underwent autopsy.

After the brain was fixed in formalin, it was sectioned at the CT plane of interest at appropriate levels were processed for whole-organ sections. Brain slices (12 μm), chosen after evaluation of CT findings, were stained with alum hemotoxylin, eosin-phloxine-orcein G, modified Snook silver stain, and Luxol Fast Blue/Periodic Acid Schiff. All of these preparations and the gross specimens were reviewed and correlated with the findings on the pre-, post-, and delayed high dose contrast scans. A detailed analysis of microscopic findings will be the subject of a separate report.

For the purposes of this study, a hemorrhagic infarct is defined as a grossly visible area of confluent hemorrhage. Very small perivascular hemorrhages that can be seen in most recent infarctions were not considered to indicate hemorrhagic infarction. Vasogenic edema is defined as a leakage of a protein-containing plasma filtrate from vessels into the extracellular spaces of the brain caused by a defective blood brain barrier. Cytotoxic edema, which occurs in infarction, is swelling of brain cells. (A third type of edema, not seen in infarction, is interstitial edema, which is primarily found in hydrocephalus when fluid moves from the ventricles into the brain [7].)

Results

Immediate and delayed postinfusion scans were divisible into four groups. There was a focal absence of gray matter

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**TABLE 1: Group 1: Delayed Wedge Enhancement**

<table>
<thead>
<tr>
<th>Case No. (Age)</th>
<th>Onset Until Scan (hr)</th>
<th>Etiology</th>
<th>Blood Pressure at Scan</th>
<th>Scan Delay (hr)</th>
<th>Outcome</th>
<th>Subsequent CTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (54)</td>
<td>9</td>
<td>Mitral stenosis, atrial fibrillation</td>
<td>100/70</td>
<td>1½, 3</td>
<td>No hemorrhage, clinical improvement</td>
<td>8, 19</td>
</tr>
<tr>
<td>2 (66)</td>
<td>17</td>
<td>Atrial fibrillation</td>
<td>200/85</td>
<td>3</td>
<td>Massive hemorrhage, died 4 days later</td>
<td>0</td>
</tr>
<tr>
<td>3 (58)</td>
<td>20</td>
<td>Atrial fibrillation and ventricular failure</td>
<td>130/100</td>
<td>3</td>
<td>Massive hemorrhage, died 10 days later</td>
<td>0</td>
</tr>
<tr>
<td>4 (78)</td>
<td>24</td>
<td>Atrial fibrillation</td>
<td>160/100</td>
<td>1, 3</td>
<td>Recovered from aphasia completely within 4 months</td>
<td>0</td>
</tr>
<tr>
<td>5 (63)</td>
<td>*</td>
<td>Multiple infarcts, prior right carotid occlusion</td>
<td>160/90</td>
<td>3½</td>
<td>Massive hemorrhage, died 11 days later, surgery 26 hr post scan</td>
<td>2</td>
</tr>
<tr>
<td>6 (52)</td>
<td>*</td>
<td>Systemic emboli at autopsy</td>
<td>90/60</td>
<td>3</td>
<td>Patchy hemorrhage, died 12 hr later</td>
<td>0</td>
</tr>
<tr>
<td>7 (64)</td>
<td>28</td>
<td>Arrhythmia</td>
<td>170/108</td>
<td>2½</td>
<td>Moderate recovery, hemiparesis</td>
<td>13</td>
</tr>
</tbody>
</table>

* Neurologic status deteriorated in the 24 hr immediately before scan. Onset of clinical symptoms was 5 days before scan.

**TABLE 2: Group 2: Immediate Contrast Enhancement**

<table>
<thead>
<tr>
<th>Case No. (Age)</th>
<th>Onset Until Scan (hr)</th>
<th>Etiology</th>
<th>Blood Pressure at Scan</th>
<th>Scan Delay (hr)</th>
<th>Outcome</th>
<th>Subsequent CTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (54)</td>
<td>3</td>
<td>Middle cerebral artery bifurcation embolus</td>
<td>130/90</td>
<td>...</td>
<td>Hemiparesis persisted</td>
<td>45, 93</td>
</tr>
<tr>
<td>9 (61)</td>
<td>4</td>
<td>Atrial fibrillation</td>
<td>108/92</td>
<td>...</td>
<td>Hemiparesis persisted, died 5 days later</td>
<td>3</td>
</tr>
<tr>
<td>10 (67)</td>
<td>16</td>
<td>Cerebrovascular accident *</td>
<td>170/90</td>
<td>1, 3</td>
<td>Hemiparesis and aphasia persisted</td>
<td>5</td>
</tr>
<tr>
<td>11 (72)</td>
<td>22</td>
<td>Cerebrovascular accident *</td>
<td>130/90</td>
<td>1, 3½</td>
<td>Hemiplegia and aphasia persisted</td>
<td>5</td>
</tr>
<tr>
<td>12 (54)</td>
<td>24</td>
<td>Atrial tumor with embolus</td>
<td>110/70</td>
<td>...</td>
<td>Persistent aphasia, died 45 days later</td>
<td>3, 24</td>
</tr>
<tr>
<td>13 (69)</td>
<td>28</td>
<td>Cerebrovascular accident *</td>
<td>140/90</td>
<td>1, 3</td>
<td>Hemiplegia persisted</td>
<td>9</td>
</tr>
</tbody>
</table>

* Specific cause not noted in clinical records.
enhancement in all patients with verifiable infarction (groups 1–3) but this was the only finding in patients classified as group 3.

Group 1 (table 1)

A large, inhomogeneous zone of contrast enhancement appeared on delayed scans in areas of infarction which demonstrated normal or decreased attenuation coefficients on preinfusion scan. The area of enhancement developed during the delay period and intensified between the 1 and 3 hr delayed scans. In two cases a small dense nodule of enhancement was evident on the immediate postinfusion scan located at what, on delayed scan, proved to be the margin of the enhancement (table 1, cases 5 and 6; figs. 1 and 2). In six cases the enhancement was wedge-shaped, sharply marginated, and contained foci of very dense contrast. Its base was at the cortex and its apex extended into the white matter toward the ventricle. The sulci at the base and the ventricle near the apex did not become compressed during development of delayed enhancement. Mild generalized "mass effect," if evident on preinfusion examination, did not change during the postinfusion scan, proved to be the margin of the enhancement (table 1, cases 5 and 6; figs. 1 and 2). In six cases the cortical part of the wedge enhancement was located at the periphery of the middle cerebral artery territory. In one case the basal ganglia and centrum semiovale developed delayed enhancement without cortical involvement (table 1, case 7).

In four of the seven cases the area of delayed enhancement was subjected to pathologic examination. Three patients were autopsied (12 hr, 4 days, and 10 days after scan) and one underwent surgery (1 day after scan). In the three autopsied cases, gross hemorrhagic infarction had occurred in the wedge zone of delayed enhancement. In one of these, at autopsy 12 hr after the scan, only part of the wedge demonstrated hemorrhage, the rest demonstrating severe gray and white matter damage. The fourth patient, at surgery 26 hr after CT examination, had a huge hemorrhagic infarction. This was the only patient with hemorrhage on the preinfusion scan (table 1, case 5; fig. 2).

Two patients (table 1, cases 1 and 7) in the group survived and recovered function; subsequent CT scans showed no evidence of hemorrhagic infarction. A follow-up scan could not be obtained in case 4; however, there was clinical recovery.

Group 2 (table 2)

There was immediate and persistent contrast enhancement of parts of the gray matter in infarcted zones. Delayed contrast scans demonstrated no evidence of the delayed enhancement described in group 1 (fig. 5). Pathologic correlation was available in case 5 when an autopsy was done 45 days after onset of cerebral infarction. The zones of cortex that showed dense persistent enhancement did not differ from other areas of anemic infarction which were either undetected or demonstrated only absence of normal cortical enhancement. In this case and the five others in group 2, there was no significant improvement in neurological deficit.

Group 3 (table 3)

Absence of normal pattern of cortical enhancement was the only finding. Two patients expired (30 min and 10 days after scan). Pathologic examination revealed anemic infarction in each of the three other cases.

Group 4

The pre-, post-, and delayed 1 and 3 hr high dose scans were normal in the two group 4 patients, examined 2 and 24 hr after transient ischemic attacks which occurred as incidental events prior to a scheduled CT examination.

Review of Fatal Cases

Group 1

Case 2. A 66-year-old man with a history of right middle cerebral artery infarct was admitted in a coma after a seizure. He had atrial fibrillation and bilateral hemiparesis. CT demonstrated delayed wedge enhancement. He was treated for 2 days with heparin which was discontinued when he developed gastrointestinal bleeding. Four days after admission, without regaining consciousness, he

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Onset Until Scan (hr)</th>
<th>Etiology</th>
<th>Blood Pressure at Scan</th>
<th>Scan Delay (hr)</th>
<th>Outcome</th>
<th>Subsequent CTs (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (43)</td>
<td>1½, 24</td>
<td>Marantic emboli to middle cerebral artery branches on angiography</td>
<td>150/100</td>
<td>2, 2½</td>
<td>Steady neurologic deterioration, died 10 days later</td>
<td>0</td>
</tr>
<tr>
<td>15 (43)</td>
<td>4</td>
<td>Occluded cortical middle cerebral artery branches 10 days later</td>
<td>100/70</td>
<td>2, 4</td>
<td>Marked improvement in hemiparesis and speech</td>
<td>7</td>
</tr>
<tr>
<td>16 (87)</td>
<td>14</td>
<td>Atrial fibrillation</td>
<td>100/85</td>
<td>2½</td>
<td>Died 1 hr later</td>
<td>0</td>
</tr>
<tr>
<td>17 (64)</td>
<td>20</td>
<td>Atrial fibrillation</td>
<td>190/90</td>
<td>1½, 5</td>
<td>Excellent recovery of hemiparesis</td>
<td>8</td>
</tr>
<tr>
<td>18 (57)</td>
<td>24</td>
<td>Postoperative carotid endarterectomy</td>
<td>132/70</td>
<td>3</td>
<td>Aphasia improving</td>
<td>11</td>
</tr>
</tbody>
</table>
died of a pulmonary embolus. Autopsy demonstrated hemorrhagic infarction of the area of delayed wedge enhancement (fig. 4).

Case 3. A 58-year-old diabetic male with renal insufficiency and congestive heart failure from previous myocardial infarctions was being treated for atrial fibrillation when he suddenly became comatose and developed a right hemiparesis. CT demonstrated delayed wedge enhancement. His cardioneurological status improved, and 3 days later he was transferred from the intensive care unit. He aspirated, became septic, and developed renal and hepatic failure. Antibiotic therapy was ineffective and he died 10 days later. At autopsy a hepatitis B surface antigen was discovered in addition to cardiac thrombi, infarction of both kidneys, and hemorrhagic infarction of the area of delayed wedge enhancement seen on CT (fig. 3).

Case 5. A 63-year-old male alcoholic with advanced cirrhosis, secondary marrow suppression, and a platelet count of 14,000 was admitted in coma, septic, and experiencing periods of significant hypotension. Antibiotic therapy was ineffective. Five days after admission his neurologic condition "deteriorated." CT demonstrated delayed wedge enhancement. Three-vessel angiography 1 day later showed only occlusion of the right internal carotid artery (which had been present years earlier). Repeat CT 26 hr later revealed hemorrhage in the area of delayed wedge enhancement. He was treated with platelet transfusions. A decompression craniotomy was performed. He continued to decline until death 11 days later (fig. 2).

Case 6. A 52-year-old man had widespread metastatic clear cell carcinoma that had destroyed renal function and invaded the myocardium causing congestive heart failure. He was admitted with hypercalcemia, gastrointestinal bleeding, and severe sepsis. After 5 days he suddenly became more confused and lapsed into coma. CT scan demonstrated delayed wedge enhancement. He died 12

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**Fig. 1.**—Case 6. A–C. Immediate high dose contrast CT. "Nodular" enhancement (arrowheads) in watershed zone between three major cerebral arteries; absence of enhancement in the adjacent cortex at left convexity in B. D–F. Delayed high dose scans 3 hr later. Wedge enhancement which developed without distorting adjacent ventricle. "Nodular" enhancement has enlarged in E and F (arrowheads). G–I. Autopsy specimens 12 hr after scan. Hemorrhagic infarction at left convexity. Microscopic evidence of infarction and white matter necrosis throughout zone of wedge enhancement was found.
Fig. 2.—Case 5. A, Precontrast CT. Area of hemorrhage at right cerebral convexity. B, Immediate high dose contrast CT. "Nodular" enhancement in watershed zone (arrow). C, Delayed high dose scan 3.5 hr later. Wedge enhancement surrounds hemorrhagic area and extends inferiorly (in scans not shown) to involve large areas of brain which had appeared normal on precontrast and immediate high dose scans. Adjacent sulci are not compressed. D, 24 hr later, CT immediately after angiography. Large zone of hemorrhage is evident which was confirmed as hemorrhagic infarction at surgery 2 hr later.

Fig. 3.—Case 3. A, Precontrast CT. Obliteration of right sylvian fissure. Compression of right lateral ventricle. B, Immediate high dose contrast CT. Absence of gray matter enhancement in right operculum and posterior lateral right thalamus. C, Filtered delayed high dose scan 3 hr later. Wedge enhancement which includes lentiform area. Zone of cortical nonenhancement. Mass effect did not increase as enhancement developed. D, Autopsy specimen obtained 8 days later. Hemorrhagic infarction in area of delayed enhancement and anemic infarction (with very small punctate zones of hemorrhage) in areas of gray matter nonenhancement.

Fig. 4.—Case 2. A, Precontrast CT. Old right middle cerebral infarction; generalized compression of left lateral ventricle. B, Immediate high dose contrast CT. Vascular images in left sylvian area. C, Delayed high dose scan 3 hr later. Massive wedge enhancement without additional mass effect. D, Autopsy specimen obtained 4 days later. Hemorrhagic infarction in area of delayed enhancement.
infarction was admitted with nerve paralysis, and confusion. He had congestive heart failure secondary to bradycardia from an atrioventricular block. CT showed bilateral white matter cerebral edema and right posterior parietal cortical nonenhancement. Vital signs were stable during CT examination and the patient returned to the intensive care unit in satisfactory condition. One hour later he had cardiac arrest and died. At autopsy, a large bilateral pulmonary embolus was found. Anemic infarction was noted in the right parietal area and cerebellum.

Discussion

Human cerebral infarction is caused by a variety of factors which, separately or in combination, cause an inhomogeneous cerebral damage which kills 200,000 Americans each year [8]. There is no effective treatment currently available for this condition [9] and it is unlikely that appropriate therapy will be devised without first reaching a clear understanding as to why these patients die.

Data concerning human cerebral infarction has been garnered from serial angiograms of patients examined within 24 hr of cerebral embolization which shows that: (1) rapid fragmentation of initially demonstrable clot occurs in 38% of cases within 3 days after infarction, thus predisposing the patient to edema and hemorrhagic infarction [10] and (2) fragmentation of an embolus can cause extravasation of angiographic contrast medium and subsequent hemorrhagic infarction [11].

CT scans without contrast infusion have been used to demonstrate zones of acute cerebral edema and hemorrhagic infarction. However, numerous very small hemorrhages in an edematous area can appear isodense because of volume averaging [12]. Furthermore, zones which will subsequently become hemorrhagic are not detected. Nineteen cases in the literature have been examined with contrast (30–40 g iodine) CT within 48 hr after onset [1, 2]. There was immediate enhancement in only four of these cases [1].

The incidence of hemorrhagic infarction in our series was 21% (four of 18 patients with infarction). This is statistically comparable to the 18% reported by Fisher and Adams [13].
In 373 consecutive autopsies of patients with cerebral infarction. In the series of Davis et al. [6], the incidence of hemorrhagic infarction detected by CT performed within 48 hr after onset was 23.4% (four of 17 patients). In that series, two patients developed hemorrhagic infarction 24 hr after their initial CT scan had shown no hemorrhage.

The development of hemorrhagic complications depends on the reestablishment of flow through damaged vessels and a number of other considerations. The number of embolic rather than thrombotic cerebral infarctions in a series increases the incidence of hemorrhagic infarction, since 80% of embolic infarctions are hemorrhagic at autopsy [14]. Lengthening the initial ischemic event from 6 to 24 hr before reperfusion can increase the incidence of hemorrhagic infarction from 40% to 60% in cats [15]. Increasing the collateral cerebral blood flow by hypercarbia or systemic hypertension in the primate 48 hr after permanent segmental occlusion of the middle cerebral artery transforms many anemic infarctions to hemorrhagic infarctions or hematomas. (These factors have no effect on acute anemic cerebral infarction less than 48 hr old [16].)

The use of heparin in acute cerebral infarctions produced by stationary emboli in dogs increased both the incidence of hemorrhage and the overall mortality [17]. In this study, one patient with hemorrhagic infarction received heparin (table 1, case 2) and another had severe platelet deficiency (table 1, case 5). (The occurrence of hemorrhagic infarction in association with thrombocytopenia has been reported [18].)

The administration of high doses of intravenous contrast material in primate models of cerebral infarction (fragmenting and stationary emboli) has not caused hemorrhagic transformation of anemic infarction or increased mortality [4, 19]. In fact, the intravenous administration of hyperosmolar solutions during the acute phase of cerebral infarction has been found to protect animals from the effects of cerebral infarction and produce a statistically significant reduction of histologically detectable residual brain damage [20, 21]. In human cerebral infarction studies, the effect of hyperosmolar solutions (glycerol, urea, contrast media) is more difficult to assess. To determine the effect of contrast media on the clinical outcome of patients with cerebral infarction, a prospective randomized study must be done in which patients with comparable initial clinical deficits receive either a contrast or a noncontrast CT scan. Uniform post-scan therapy and vigilant reporting of subsequent infarctions which might affect outcome would be necessary. The number of cases in such a study would have to be large, since there are no criteria for accurately predicting the etiology of infarction (i.e., thrombosis vs. embolization). Until such a study is done, the effects of contrast media on cerebral infarction in humans cannot be scientifically evaluated.

In this connection, a limited retrospective study of consecutive patients with cerebral infarction has been carried out [22, 23]. It evaluated two groups: those with CT contrast enhancement in the area of infarction, and those in whom contrast was not given. Since it did not randomize entry into the study or match initial severity of the infarctions in each group, more patients with normal precontrast scans were in the uninfused group; patients with larger lesions and mass effect were in the group that received contrast. (In addition, there was no statistical correction for the 10% of patients who were lost to follow-up.) The authors concluded that contrast infusion might have adversely affected the clinical outcome of the cerebral infarction, but their data showed no statistically significant evidence to support this conclusion.

**Group 1**

Correlation of delayed high dose scan and pathologic specimen in four cases demonstrated that zones of infarction in which there was slow perfusion and blood brain barrier damage (delayed enhancement) have severe tissue necrosis (seen 12 hr after scan in fig. 1) which may progress to hemorrhagic infarction (cases examined 1, 4, and 10 days later; figs. 2–4). Consider how the significance of the CT observation of early, extensive vasogenic edema (delayed enhancement) in humans correlates with the findings of other workers:

1. In gerbils, a suppression of EEG activity after occlusion of the carotid artery temporarily returned when circulation was restored. However, marked suppression of EEG (more pronounced than that recorded immediately after carotid occlusion) occurred as vasogenic brain edema developed in the reperfused hemisphere. It was concluded that edema was detrimental to the neuron as well as the neuropil and caused subsequent progression of tissue damage. Two theories were advanced for the development of vasogenic edema in the reperfused vascular bed. First, that the loss of autoregulation in the tissue allows hyperemia to develop when circulation is restored and this, in turn, is accompanied by vasogenic edema which causes brain damage. Second, that chemical metabolites from damaged tissue cause blood brain barrier damage by increasing vascular pinocytic transport [24].

2. Rhesus monkeys with microemboli-induced wedge-shaped zones of vasogenic edema demonstrate tissue necrosis of areas that were never ischemic, demonstrating that the damage was caused by edema [25, 26]. The edema occurred within a specific time. Extravasation was observed 15–60 min after microembolization. It could not, however, be detected 2 or 4 hr after microembolization (when extensive vasogenic edema had already developed in the white matter, and which presumably had impaired perfusion of the tracer).

3. The temporal sequence of blood brain barrier leakage was also defined by Olsson et al [27] who noted blood brain barrier damage 2 hr after recirculation (after a 4-hr-long occlusion of the middle cerebral artery) in the monkey. However, blood-brain barrier damage could not be demonstrated at 2 min or at 24 hr after circulation had been reestablished indicating that vasogenic edema begins some time after flow is reinstated and persists for a discrete interval [27].

The time during which this phenomenon occurs in humans is not well understood, but our study shows that massive contrast extravasation indicating vasogenic edema (group 1) can be detected 9–24 hr after the clinical onset of (or sudden clinical deterioration in) a cerebral infarction.
4. The sites of ischemic vascular damage have been explored. Rapidly developing ultrastructural changes in cerebral capillaries and arterioles in several animal species subjected to brain ischemia for periods of 5 min to 7 hr have been observed. It is postulated that these microvascular changes may be the cause of the damaging vasogenic edema [29]. Permeability changes in larger cerebral vessels ('arterioles or venulae') induced by transient occlusion of the middle cerebral artery in monkeys allowed diapedesis and extravasation of red blood cells (perivascular hemorrhage). In this animal model no morphologic changes were seen in the microvasculature [29]. In human hemorrhagic cerebral infarctions, hemorrhage occurs along small vessels and capillaries which are distended with blood but are not necessarily necrotic [14].

Group 2

The CT pattern of immediate and persistent enhancement that did not progress to wedge enhancement was correlated with a zone of anemic infarction in one patient (fig. 5). In earlier animal work, we have demonstrated this CT pattern of immediate persistent gray matter enhancement in baboons infarcted with a fragmenting microfil embolus. Anemic infarction was demonstrated at autopsy in all but one animal who recovered and whose autopsy was normal [4].

Areas that enhanced immediately represent well perfused zones with blood-brain barrier damage which may be transient. Although ischemic infarction is likely in these zones, this pattern (in contrast to that of group 1) does not seem to provide a reliable predictive sign of irreversible brain damage. The areas of brain exhibiting this pattern were not extensive.

Group 3

The CT pattern of absent normal enhancement of gray matter in this series was correlated with anemic infarction at autopsy in two patients and small zones of petechial hemorrhage within a zone of anemic infarction in the autopsy of another patient (fig. 3). This CT pattern correlated with anemic infarction in 13 baboons infarcted with stationary emboli in the middle cerebral artery [19]. In that study, low density zones appeared on CT 12–24 hr after embolization, although immediate and delayed high dose contrast CT scans at 6 hr failed to demonstrate enhancement within the zone of anemic infarction. The inability of the delayed high dose technique to detect edema caused by a stationary embolus probably indicates that even prolonged high blood iodine levels [Hayman LA, Nell J, Feldman S, unpublished data] are inadequate to detect infarcted areas which have virtually no perfusion. This pattern is best seen on the immediate contrast CT. The delayed high dose scan was useful in documenting that contrast extravasation had not occurred.

Group 4

No CT abnormality was demonstrated in patients with transient ischemic attacks. The absence of gross morphologic changes in these patients should discourage the use of contrast CT for evaluation of patients with a clinical presentation classically associated with transient ischemic attacks.

Conclusion

The CT technique described in the present paper enabled us to separate patients with severe vasogenic edema who were at risk of hemorrhagic infarction (delayed enhancement in the infarcted zone, group 1) from patients without severe vasogenic edema (anemic infarction) who developed immediate and persisting patchy gray matter enhancement (group 2) or only noneenhancement of involved gray matter (group 3). We realize that there may not be an effective treatment beyond supportive measures for either type of infarction, but it would seem prudent to avoid anticoagulation, reanastomosis, or endarterectomy when vasogenic edema which has been experimentally shown to precede the hemorrhage is detected on a delayed high dose CT scan. In addition, the ability to ascertain which patients are at risk from vasogenic edema and subsequent hemorrhage enables informed selection of patients for future experimental therapeutic regimens. The use of high dose contrast in acute infarction has not affected the course of cerebral infarction in two experiments with primate models and its use does not seem to have changed the outcome as predicted by the criteria used by Frithz and Werner [5] in the 20 cases examined in this series.

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