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Iodine-Enhanced CT Patterns After Cerebral Arterial Embolization in Baboons

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The pathophysiology of iodine-enhanced computed tomography (CT) patterns produced by embolic arterial cerebral infarction in the baboon is reported. The appearance of iodine patterns in zones of nonperfusion, blood-brain barrier damage, loss of autoregulation, and neovascularity is demonstrated. The iodine CT patterns were correlated with stable xenon CT flow studies, regional cerebral blood flow studies, clinical course, and pathology.

Iodine-enhanced computed tomography (ICT) is now commonly used to evaluate cerebral infarction. Intervenous administration of a 0.6 gm/kg iodine bolus immediately before CT rarely produces enhancement in acute infarction (0–7 days). However, 7–30 days after cerebral infarction, 60% of patients show enhancement [1]. Contrast enhancement has actually been demonstrated as late as 6 months after infarction [2, 3]. Such observations in human subjects have yet to be satisfactorily supplemented by experimental studies in suitable animal models to explain the pathogenesis and clinical significance of CT contrast enhancement. Our investigation using nonhuman primates examines these points.

In previous CT studies of arterial cerebral infarction in the monkey, resolution of the CT images was suboptimal for technical reasons [4–7] and iodine infusion was of little value since the embolus remained lodged in the horizontal middle cerebral artery, thereby almost completely preventing entry of iodine into the infarcted zone. Through improvement of CT technology and the use of emboli that fragment, a reliable and reproducible model of cerebral infarction has been produced in the baboon for studying the pathogenesis of the contrast enhancement accompanying brain ischemia.

Materials and Methods

Seven baboons (*Papio anubis*) weighing 5–5.5 kg were used. Light anesthesia was induced by intramuscular injection of ketamine hydrochloride (2 mg/kg of body weight). The rate of administration of sodium pentobarbital was controlled by monitoring the electroencephalogram and maintaining dominant alpha rhythm without permitting preponderance of slow activity.

End-tidal partial pressures of carbon dioxide ($PECO_2$) and oxygen (PEO_2) were recorded continuously with a Godart capnograph (Instrumentation Associates, Inc., New York, N.Y.)

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TABLE 1: **Possible Consequences of Cerebral Embolization**

Consequence	Time of Appearance After Embolization	State of Tissue	Xe^s CT Flow	ICT	Illustrative Figures (No.)
Absence of perfusion	Immediately +	Nonviable	Absent perfusion (white & gray matter)	Absent enhancement (only gray matter)	1–3
Blood brain barrier damage	1 hr +	Spectrum from viable to nonviable	Decreased perfusion	Enhancement (requires delayed scans)	3, 4
Stasis with slow flow	Immediately +	Spectrum from viable to nonviable	Decreased perfusion	Enhancement (requires delayed scans)	4, 5
Peripheral neovascularity	7 days +	Nonviable	Decreased perfusion	Ringshaped enhancement	6
No change	Immediately (if good collateral); delayed (if recovery occurs)	Viable	Normal perfusion	Normal	7
Luxury perfusion	½ hr +	Viable	Increased perfusion	Obscured by enhancement of blood brain barrier damage	2B

and Beckman (160) gas analyzer (Beckman Instruments, Inc., Fullerton, Calif.) and the blood pressure was recorded with a strain gauge from a catheter placed in the aorta via the femoral artery. Arterial blood samples were collected for determination of hematocrit and hemoglobin values before and after each CT study. During the CT examination the animals were immobilized with pancuronium bromide (0.1 mg/kg) and ventilated by means of a positive pressure respirator connected to a chronic tracheostomy.

The main trunk of the middle and/or anterior cerebral artery was occluded with emboli of a silicone rubber compound Microfil (Canton Bio-Medical Products, Inc., Boulder, Colo.) as originally described by Molinari et al. [8] with one important exception, that is, that the compound had aged for 18 months. Aging caused it to become brittle, enabling it to fragment easily after insertion. A 4–5 × 1.6 mm cylindrical embolus of this aged material was injected through a catheter placed in the internal carotid artery. In all animals these emboli subsequently fragmented and occluded multiple distal branches. The emboli were localized during life by CT and confirmed at necropsy.

Each animal was scanned before, immediately after, and 20 min after intravenous bolus injection of 1.2 gm iodine/kg of diatrizoate meglumine (Reno-M-DIP, Squibb). One animal was scanned 60 min after iodine administration. The sections were made at 1.5 min intervals for a series of four scans with a 30 sec pause for computer processing between scans. An EMI 1010 CT unit was specially modified by means of 180 mm wedges and a 4 mm collimator. The x-ray beam was adjusted to 100 kVp with a 40 mA, 60 sec scanning mode.

All seven animals were scanned within 0–7 hr after embolization. In order to maintain a constant scan level before and after embolization, a previously placed carotid cannula was used for introduction of the embolus. One animal was sacrificed 2 hr, one 6 hr, and one 24 hr after embolization. Three more animals had repeat scans 1 week after embolization and two of these were then sacrificed. The survivor was scanned after 3 and 4 weeks and then sacrificed. The seventh animal was scanned at 6 weeks and then sacrified.

Before each ICT, stable xenon (Xe^s) CT clearance studies were performed in each of the seven animals. A quantity of 100% O_2 was inhaled for 30 min before a 15 min period during which 80% Xe^s (Zeron IWECO Gas Co., Houston, Tex., a distributor of Lindy Gas) was substituted. Scans were made at 5 min intervals during this "saturation" period. Once the Xe^s had equilibrated as judged by stability of Hounsfield units, the O_2 was reintroduced and scans carried out at 60 and 90 sec intervals for 20 min during the "desaturation" period. The PEo_2 and $PEco_2$ in the expired air were measured by an oxygen polarograph and a Godart capnograph, type 146 (Instrumentation Assoc., Inc., New York, N.Y.) The end-tidal Xe^s was monitored by means of a Gow-Mac thermoconductivity sensor (Gow-Mac Instrument Co., Bound Brook, N.J.).

All CT examinations were correlated with regional cerebral blood flow measurements using the ^{133}Xe inhalation method [9] wherein external probes are placed over both hemispheres and the brainstem–cerebellar region to evaluate cerebral hemodynamic changes.

Clinical and neurologic findings were recorded every 24–48 hr after embolization until the animal was sacrificed. At necropsy the brain was removed and its arteries irrigated with a 5%–10% solution of trypan blue at a pressure of 100 mm of water in order to demonstrate any damage to the blood-brain barrier. The brain was then suspended in 10% formalin and photographed. Parts of lesions and corresponding tissues from the unaffected contralateral hemisphere were prepared for paraffin embedment. Embedded tissues were sectioned and stained with hematoxylin and eosin, Gomori trichrome, Gomori for reticulin fibers, Luxol fast blue for myelin fibers, or phosphotungstic acid hemotoxylin for glial fibers.

Results

In each baboon the modified Microfil embolus that was injected subsequently fragmented. The combined and independent effects of transient occlusion of the main trunk and subsequent distal branch occlusions caused by daughter emboli produced complex ICT patterns remarkably similar to those seen clinically in human subjects suffering from cerebral infarction. The ICT patterns were complex because there were multiple emboli, each of which could cause one or more of six reactions.

Table 1 summarizes the six possible consequences of cerebral embolization. Pertinent iodine- and Xe^s-enhanced

CT scans are indicated in column 6. These scans illustrate the consequence(s) and pattern(s) described below and are best understood if the text is read first.

Absence of Perfusion

When a vessel was obstructed there was diminished or absent perfusion of brain tissue, depending on the amount of collateral circulation present. When severe enough, ICT showed complete absence of iodine in the gray matter of the involved territory. Xe^s CT was an even more sensitive indicator of perfusion abnormality, being able to detect absence of perfusion to white as well as gray matter. (Absence of perfusion to white matter was not recognizable on immediate or 20 min delayed ICT scans). Pathologic specimens injected postmortem with trypan blue displayed the zone of nonperfusion (figs. 1–3).

Blood-Brain Barrier Damage

When the embolus occluded a major artery only temporarily and then fragmented, showering small emboli distally, both of these events contributed to the ICT pattern. The nonperfusion of cortical or basal ganglia structures (described under Absence of Perfusion) was produced by the distal fragments. In addition there was extravasation of contrast substance from vessels presumably damaged by the ischemia produced by the embolus before it fragmented. This was seen as cortical and/or basal ganglia (gray matter) enhancement that increased on delayed scans (figs. 3 and 4). This phenomenon was seen in all animals. However, it was not a reliable indicator of permanent neurologic deficit since one animal recovered completely from a hemiparesis that was associated with subtle but progressive enhancement of the motor cortex. Since each iodine scan in our series was preceded by Xe^s scans, there was at least 1 hr

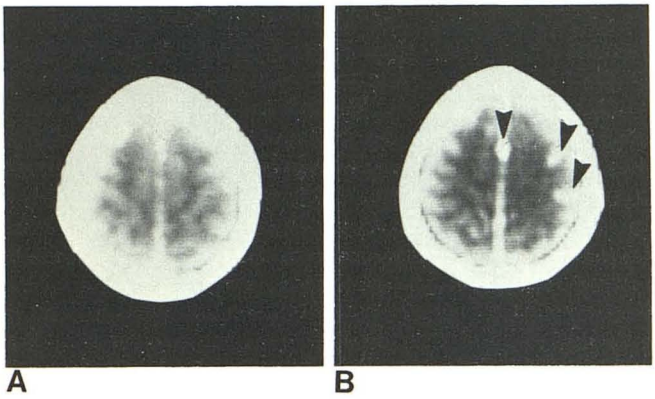

Fig. 1.—ICT scans 1 week before (**A**) and immediately after (**B**) embolization of anterior cerebral and left middle cerebral arteries. (Nonhuman primates have only one anterior cerebral artery.) Gyral pattern over infarcted left hemispheric convexity absent. Embolic fragments in distal branches (*arrowheads*). Apparent large size of emboli is CT artifact from relatively high density silicone rubber in contrast with density of surrounding brain tissue.

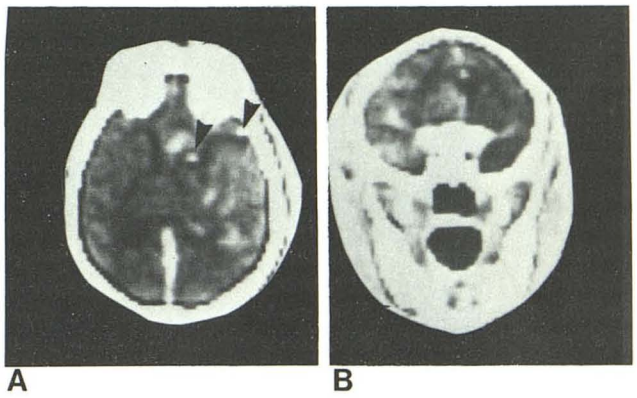

Fig. 3.—6 hr after embolization of left middle cerebral artery. ICT scans in axial (**A**) and coronal (**B**) planes. Enhancement of cortex and basal ganglia supplied by artery. (Delayed scans showed intensifying enhancement.) Gray matter enhancement absent in areas supplied by branches totally occluded by distal emboli (*arrowheads*). Concomitant edema produced transfalcine herniation and death.

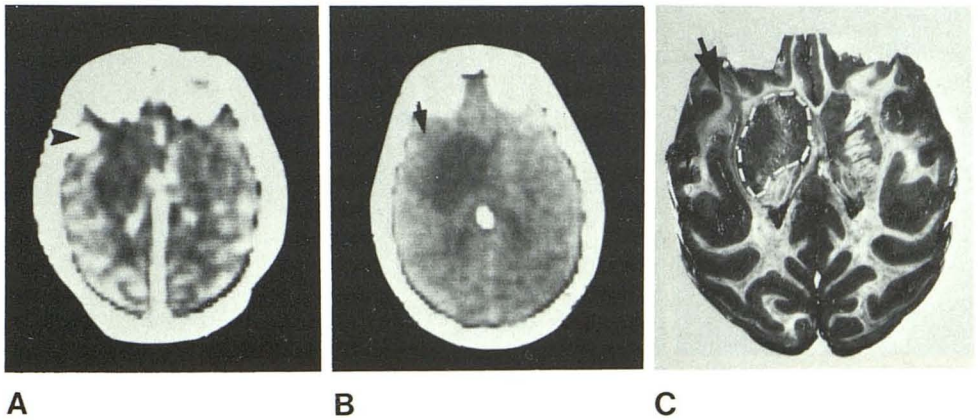

Fig. 2.—4 weeks after embolization of right middle cerebral artery. **A**, ICT scan. No contrast enhancement of right basal ganglia. Abnormally prominent enhancement of cortex on right secondary to leakage across damaged blood-brain barrier. (*Arrowhead* marks upper rim of neovascularity in fig. 6A). **B**, Xe^s scan at same level. Xenon absent in right basal ganglia. Compare cortex on right with left. Less xenon has entered anterior right temporal cortex (*arrow*) adjacent to basal ganglia infarct (slow flow) while more xenon enhancement occurred in posterior right temporal cortex (luxury perfusion). **C**, Pathologic specimen at same level. Corresponding necrosis of right basal ganglia (outlined in white) and in adjacent temporal lobe (*arrow*).

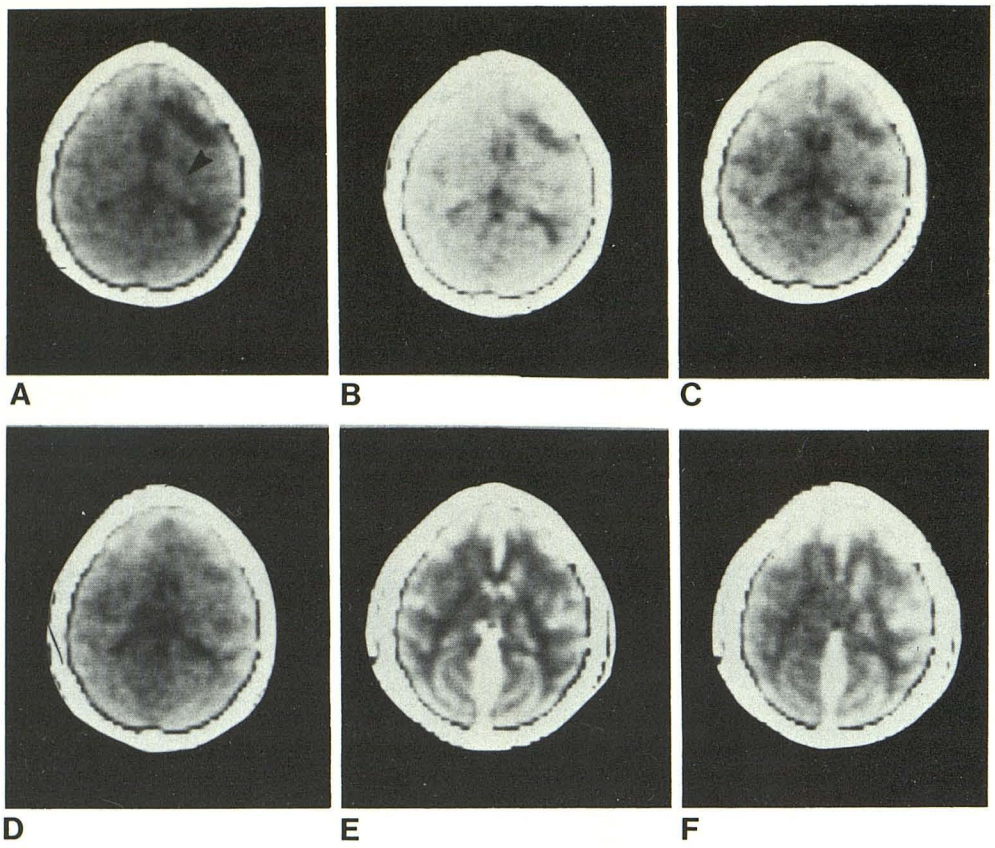

Fig. 4.—Left middle cerebral embolus (which subsequently fragmented) placed after positioning animal in scanner and inhaling 0_2. Inhalation of 80% Xe^s begun immediately after embolization. **A**, Saturation phase, Xe^s scan. Perfusion absent in left internal capsule (*arrowhead*) and zones adjacent to frontal and occipital parts of left lateral ventricle. **B**, Equilibrated Xe^s scan (20 min after embolization). Xenon diffusion into internal capsule and margins of infarcted zones. Desaturation phase Xe^s scans at 2 **(C)** and 3 **(D)** min after 100% O_2 administration. Delayed clearance of xenon from left middle cerebral cortex (slow flow). **E**, ICT scan at same level 1.5 hr after embolization. Enhancement of caudate nucleus and lateral aspect of left thalamus. **F**, Delayed ICT (26 min after contrast injection). Increased enhancement of cortex and basal ganglia in left middle cerebral artery territory secondary to contrast leakage.

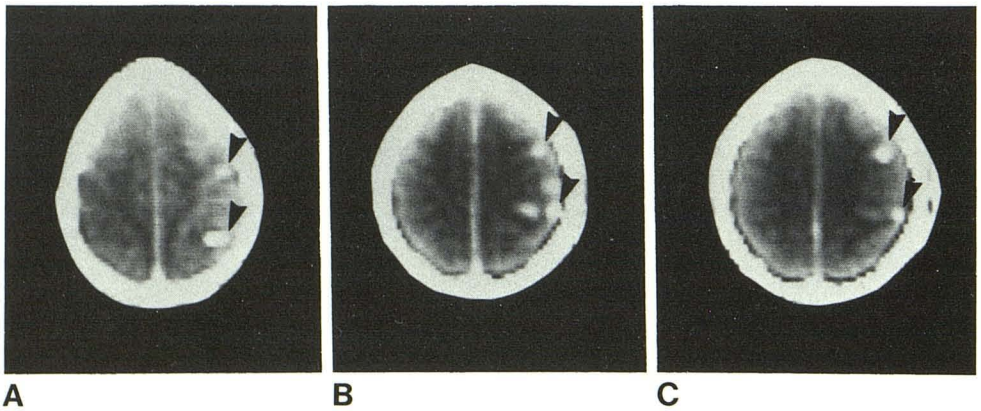

Fig. 5.—ICT scans. **A**, 4 hr after two embolic fragments (*arrowheads*) lodged in distal branches of left middle cerebral artery. Diffuse cortical iodine enhancement in middle cerebral territory. **B**, 2 weeks later (with slightly different head position). Same emboli (*arrowheads*) and two focal zones of cortical enhancement resembling metastatic "nodules." **C**, 15 min later. Only emboli (*arrowheads*) appear. Speculatively, "nodules" may have disappeared because they represented areas that lost autoregulatory ability. Disappearance of contrast over 15 min period and normal appearance of microscopic specimen distinguishes this "enhancement" from that of blood-brain barrier damage.

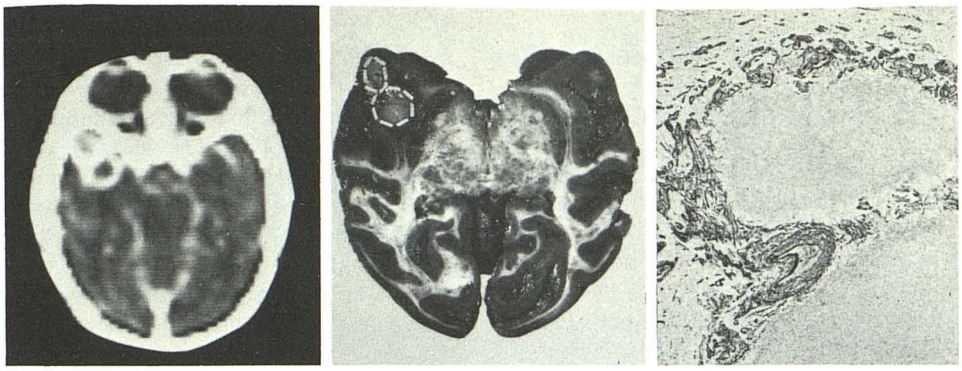

Fig. 6.—4 weeks after right middle cerebral artery embolization. **A**, ICT. Biannular enhancement surrounds embolic fragment in horizontal middle cerebral artery. **B**, Pathologic specimen shows corresponding necrosis (outlined in white). **C**, Microscopic section of rings. Neovascularity surrounds areas of necrosis.

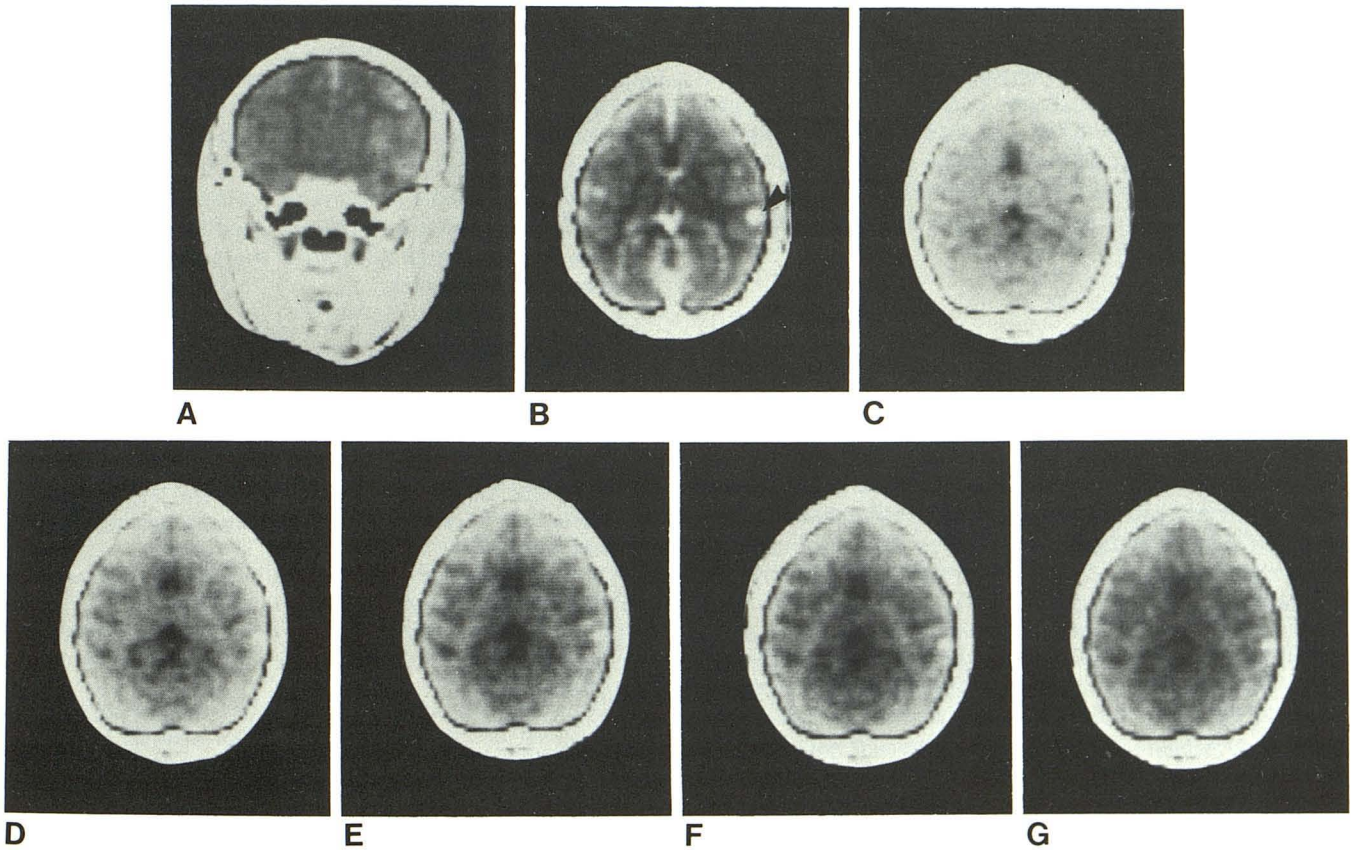

Fig. 7.—**A**, Coronal ICT scan 4 hr after left middle cerebral embolization. Iodine enhancement apparent throughout distal left middle cerebral distribution except for lenticulostriate territory. **B**, Normal axial ICT 2 weeks later. Mild left hemiparesis seen after embolization has resolved. Embolic fragment (*arrowhead*). **C–G**, Normal serial Xe^s desaturation scans also 2 weeks after embolization. Symmetrical disappearance of xenon indicator from gray matter with usual delay in disappearance from white matter (which normally has slower blood flow than cortex) causes apparent "selective enhancement" of internal capsules (**F** and **G**).

interval between embolization and ICT. It is possible that blood-brain barrier damage might be detected by ICT even sooner than we have shown.

It should be noted that damage to the blood-brain barrier cannot be detected by Xe^s scans because Xe^s normally crosses the intact blood-brain barrier. Xe^s CT was able to detect perfusion in the damaged zones that were seen as blood-brain barrier damage subsequently on ICT.

Stasis With Slow Flow

When the embolus caused capillary and venous engorgement with slight reduction of flow in the gray matter of the affected territory, ICT demonstrated a *transient focal cortical blush* that disappeared on 15 min delayed scans. Postmortem examination of this area revealed normal vascular walls without extravasation of trypan blue and normal appearance of surrounding neurons and glia (figs. 4 and 5).

We believe this phenomenon is frequently encountered but it was seen on only one ICT scan because the diffuse enhancement resulting from concomitant blood-brain barrier damage obscured the enhancement caused by flow abnormality. Xe^s CT was excellent for detecting reduced perfusion.

Peripheral Neovascularity

When the embolus caused tissue necrosis, regeneration of numerous vessels from the periphery having no effective blood-brain barrier (neovascularity) developed within the first week. This was manifested by a dense ICT ring of enhancement ascribable to the increased number of vessels, slow flow within them, and leakage of contrast substance across the blood-brain barrier (the latter accounts for most of the effect). This pattern was confirmed by examination of pathologic specimens at 7 days, 28 days, and 6 weeks after infarction (fig. 6).

No Change

When an embolus occluded a vessel with excellent collateral circulation, the ICT, Xe^s CT, and regional cerebral blood flow values remained normal, as did the clinical, electroencephalographic, and pathologic findings. In some instances the embolus caused only transient abnormalities. In these, clinical recovery was paralleled by reversion of Xe^s CT and ICT to normal (fig. 7).

Luxury Perfusion

When an embolus induced luxury perfusion (increased blood volume and increased cerebral blood flow at the margin of the infarction), Xe^s CT demonstrated the increased regional clearance (fig. 2B). The enhanced regional ICT pattern may have been due in part to increased regional cerebral blood flow but this could not be detected because of associated extravasation of iodine secondary to blood-brain barrier damage.

The generalized, bilateral ventriculomegaly seen by Drayer et al. [5] after lodgment of a stationary embolus in the horizontal limb of the middle cerebral artery was not seen in this series. However, displacement of the ventricle by regional edema was seen after several hours. Focal atrophic ventricular enlargement developed as early as 1 week after embolization. In all animals ICT demonstrated cerebral infarction better than precontrast scans, which never revealed the full extent of ischemic damage and frequently failed to demonstrate any abnormality at all, especially when infarction was more distal and involved only cortex.

Discussion

Contrast-enhanced computed tomography (using iodine and/or Xe^s as contrast medium) provides a sensitive, noninvasive means of monitoring pathophysiologic events after cerebral infarction. The modified Microfil embolization technique can be used in the baboon to demonstrate ICT patterns that can be seen in patients examined by delayed ICT within 28 hr after cerebral infarction (L. A. Hayman, unpublished data).

ICT is limited insofar as it does not identify the absence of perfusion of white matter. It can demonstrate blood-brain barrier damage as a diffuse enhancement of involved cortex and basal ganglia (gray matter). This enhancement often accentuates areas of nonperfused gray matter but obscures areas of luxury perfusion or stasis. Delayed ICT scans are necessary to distinguish blood-brain barrier damage (associated with progressively increasing enhancement) from flow abnormalities (characterized by transient enhancement). Occasionally delayed ICT scans are necessary to detect enhancement secondary to blood-brain barrier damage probably because the iodine is slow to reach the damaged vessels through a limited collateral network.

Xe^s CT is excellent for evaluation of changes of hemodynamics in the white and gray matter. Unlike ICT, Xe^s CT does not detect damage to the blood-brain barrier. Used in concert, these two complementary techniques provide an improved overall understanding of the pathogenesis of embolic cerebral infarction.

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