Cerebral Blood Flow Determination Within the First 8 Hours of Cerebral Infarction Using Stable Xenon-Enhanced Computed Tomography

Richard L. Hughes, MD, Howard Yonas, MD, David Gur, ScD, and Richard Latchaw, MD

Cerebral blood flow mapping with stable xenon-enhanced computed tomography (Xe/CT) was performed in conjunction with conventional computed tomography (CT) within the first 8 hours after the onset of symptoms in seven patients with cerebral infarction. Six patients had hemispheric infarctions, and one had a progressive brainstem infarction. Three patients with very low (<10 ml/100 g/min) blood flow in an anatomic area appropriate for the neurologic deficit had no clinical improvement by the time of discharge from the hospital; follow-up CT scans of these three patients confirmed infarction in the area of very low blood flow. Three patients with moderate blood flow reductions (15-45 ml/100 g/min) in the appropriate anatomic area had significant clinical improvement from their initial deficits and had normal follow-up CT scans. One patient studied 8 hours after stroke had increased blood flow (hyperemia) in the appropriate anatomic area and made no clinical recovery. (Stroke 1989;20:754-760)

Computed tomography (CT) of the head characteristically is normal during the first few hours after cerebral infarction, when decisions about therapy must be made. The role of CT during this period has been to exclude hemorrhage or other mass lesion as the cause of the clinical event and to provide other information, including evidence of previous infarction, that can guide treatment decisions.

The lack of a practical method to determine the size, cause, and prognosis of an acute neurologic deficit during the first few hours after onset has been a major problem in clinical trials of treatments for stroke. Even after extensive evaluation during a patient’s clinical course, there is often uncertainty about the mechanism, size, or location of an ischemic injury.1

The use of stable xenon-enhanced CT (Xe/CT) to map local cerebral blood flow (LCBF) has produced LCBF measurements with a relatively high degree of spatial resolution. Because a conventional CT scanner is used to record the build-up of xenon in the brain, direct anatomic reference (CT) is available to confirm the location of normal or abnormal LCBF values. The accuracy of this method is supported by animal studies2,3 and by preliminary clinical reports.4-6 The details of this methodology have been presented elsewhere.7,8

We reviewed Xe/CT scans obtained within the first 8 hours after an acute cerebral infarction in six patients with hemispheric cerebral infarction and in one patient with a progressive brainstem infarction. A standardized Xe/CT system integrated within a GE 9800 CT scanner (General Electric Corporation, Medical Systems Division, Milwaukee, Wisconsin) was used for all seven patients. Xe/CT scanning added approximately 15 minutes to the time required to complete a conventional CT scan. Cerebral blood flow (CBF) maps were available within 15 minutes after the study was completed. By altering the window and level (equal to LCBF in milliliters per 100 g per minute) settings on the CT terminal, areas of normal and abnormal LCBF were identified in minutes. The 2-cm regions of interest were selected when the Xe/CT studies were originally obtained. These were retrospectively reviewed and are representative and reproducible CBF values. Regions of physiologically low LCBF due to excessive amounts of cerebrospinal fluid can be appropriately identified using the corresponding CT image.

Case Reports

A clinical summary of the seven cases is given in Table 1.

Case 1

A 66-year-old right-handed woman had undergone bilateral carotid endarterectomies 11 years earlier and had a right superficial temporal artery-to-middle
cerebral artery bypass 4 years after that. She was admitted for two left hemisphere transient ischemic attacks (TIAs). An angiogram demonstrated bilateral carotid stenosis. Preoperative CT and Xe/CT scans demonstrated an old right hemisphere infarction.

Immediately after a left carotid endarterectomy, she had right hemiplegia and right homonymous hemianopsia. An Xe/CT scan obtained in conjunction with the CT study within 4 hours of her admission to the recovery room demonstrated LCBF values ranging from 3 to 6 ml/100 g/min in 1–2-cm regions of interest within the territories of the left middle and anterior cerebral arteries (Figure 1, upper left and lower left). The posterior temporal and parietal cortex overlying these areas had higher LCBF values of >20 ml/100 g/min.

Initially alert, she worsened over the next few days and had signs of herniation on postoperative

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Deficit</th>
<th>Hours to CT and Xe/CT</th>
<th>LCBF (ml/100 g/min)</th>
<th>Follow-up CT Results</th>
<th>Day</th>
<th>Improvement at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/66/F</td>
<td>R hemiplegia, R hemianopsia, aphasia</td>
<td>4</td>
<td>&lt;10</td>
<td>+</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>2/67/M</td>
<td>Quadriaparesis</td>
<td>2</td>
<td>&lt;10</td>
<td>+</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td>3/60/F</td>
<td>L hemiplegia, dysconjugate gaze</td>
<td>1</td>
<td>&lt;5</td>
<td>+</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>4/71/M</td>
<td>L hemiplegia</td>
<td>2</td>
<td>14–44</td>
<td>NA</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>5/65/F</td>
<td>L hemiplegia, L hemianopsia</td>
<td>1</td>
<td>17–27</td>
<td>−</td>
<td>7</td>
<td>Yes</td>
</tr>
<tr>
<td>6/62/M</td>
<td>R hemiparesis, aphasia</td>
<td>3</td>
<td>32–61</td>
<td>−</td>
<td>11</td>
<td>Yes</td>
</tr>
<tr>
<td>7/70/F</td>
<td>R hemiparesis</td>
<td>8</td>
<td>67–113</td>
<td>NA</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

Xe/CT, stable xenon-enhanced computed tomography; CT, conventional computed tomography; Pt., case; F, female; M, male; R, right; L, left; +, positive; −, negative; NA, not available.

FIGURE 1. Case 1. Upper left: Conventional computed tomogram (CT scan) demonstrating vague decrease in density within left hemispheric white matter. Lower left: Stable xenon-enhanced CT scan (Xe/CT scan) 4 hours after infarction. Blood flow in 2-cm regions of interest in ml/100 g/min. Lower right: Xe/CT scan gray scale adjusted to level of 10 ml/100 g/min demonstrating areas of very low blood flow (<10 ml/100 g/min) as black. Upper right: Follow-up CT scan on Day 3.
Day 3. Regions that had LCBF values of <10 ml/100 g/min had reduced CT attenuations consistent with infarction (Figure 1, lower right and upper right). Although the signs of herniation resolved, she remained hemiplegic and aphasic. She was discharged to a nursing home.

**Case 2**

A 67-year-old right-handed man had poorly described problems walking for 2 days; then, upon awakening, he had progressive weakness of all four limbs and dysarthria. In the emergency room his left pupil was larger than his right, although both reacted to light. He had impaired vertical gaze, a decreased left corneal reflex, dysarthria, moderate weakness of his right arm and leg, and plegia of his left face, arm, and leg.

A CT scan performed within 2 hours after his awakening was normal (Figure 2, upper left). A Xe/CT scan showed mean LCBF values of <10 ml/100 g/min within the mesencephalon, the pons, and the medial left cerebellar hemisphere and a generally reduced blood flow to the cerebral hemisphere (Figure 2, lower left and lower right).

The next morning, although he maintained respiration and blood pressure, he was flaccid and had no pupillary reaction, corneal reflexes, or oculocephalic response. He remained in this state for 2 weeks, when a second CT scan was performed. It showed a region of low density consistent with infarction within the areas of the mesencephalon, the pons, and the cerebellum that had exhibited very low LCBF values on the Xe/CT study performed upon hospital admission (Figure 2, lower left, lower right, and upper right). The patient was transferred to a chronic-care facility.

**Case 3**

A 60-year-old woman began to have constant, dull, aching headaches that interfered with her sleep. A large basilar tip aneurysm was seen on CT images and was confirmed with angiography. The aneurysm was clipped surgically, but in the recovery room she had a left hemiplegia. Her pupils were equal and reactive, and her left eye was deviated downward. A CT scan demonstrated a small amount of blood along the falx and within the third ventricle (Figure 3, upper left). A Xe/CT scan performed approximately 1 hour after the operation while the patient was still intubated and awakening from the anesthesia showed reduced LCBF to the cerebral cortex bilaterally, with mean values of approximately 20–30 ml/100 g/min, and a 1 x 2-cm region in which LCBF was <5 ml/100 g/min in the right thalamus (Figure 3, lower left and lower right). A CT scan performed 7 days later confirmed that the small area of very low blood flow represented a lacunar infarction in the right thalamus (Figure 3,
upper left), which was presumably related to the occlusion of a perforating vessel during the clipping of the aneurysm. Upon discharge, she remained hemiparetic and had disconjugate eye movements.

Case 4
A 71-year-old right-handed man with a right carotid bruit underwent a right neck dissection and laryngectomy for squamous cell cancer of the larynx. In the recovery room, he was completely flaccid on the left side. A CT scan performed within 2 hours was normal. A Xe/CT scan performed at that time demonstrated reduced LCBF (as low as 14 ml/100 g/min) in the region of the right lenticulostriate arteries and mild reduction (20–44 ml/100 g/min) in the remaining area of the right middle cerebral artery.

When discharged 4 weeks later, he had regained enough strength to have a near-normal grip, and he could walk with assistance. A follow-up CT scan was aborted because the patient had severe retrosternal pain.

Case 5
A 65-year-old right-handed woman had a 1-hour episode of left-sided weakness and slurred speech. During a right carotid angiogram, she became agitated and her speech again became slurred. She had weakness on the left side of her face, a left homonymous hemianopsia, and no movement of her left arm. She neglected her left side.

A Xe/CT scan performed within 1 hour of the angiogram demonstrated LCBF values of 17–27 ml/100 g/min in 2-cm regions of interest in the right hemisphere; by comparison, values in homologous left hemispheric regions were 31–37 ml/100 g/min.

She was treated with isovolemic hemodilution using low-molecular-weight dextran for 1 week. No evidence of infarction in the affected right hemispheric area was seen on CT images obtained at the end of that week. Upon discharge, she had a left homonymous hemianopsia, occasional neglect of her left side, and only mild weakness of her left arm.

Case 6
A 62-year-old right-handed man had two brief episodes of transient right-handed weakness. A left internal carotid endarterectomy was performed without incident, but in the recovery room he became progressively lethargic, aphasic, and had weakness of his right face and arm. No significant focal or generalized alterations in measured values of LCBF were seen on the Xe/CT scan (Figure 4).

A CT scan on postoperative Day 11 was normal. He was discharged with only mild-to-moderate weakness of his right arm.

Case 7
A 70-year-old right-handed woman had three brief hemispheric TIAs. A left carotid endarterec-
Discussion

The patterns and absolute LCBF values in these seven cases fall into three categories (Table 2). In the first category are Cases 1–3: patients whose Xe/CT CBF study showed cortical regions with LCBF values of <10 ml/100 g/min, whose follow-up CT studies showed infarction in those regions, and who had clinically severe and irreversible deficits in those regions. Similar correlations between LCBF values of <10–15 ml/100 g/min and irreversible infarction were found in a study using positron emission tomography (PET) and experimental measurements of CBF and metabolism that repeatedly

tomy with electroencephalographic monitoring was performed. In the recovery room, the patient had weakness on her right side and therefore underwent reoperation. A fresh thrombus was removed from the area of the original surgical procedure. A CT image obtained within 8 hours after the first endarterectomy demonstrated only an old left frontoparietal lucency. However, Xe/CT demonstrated an increase in LCBF to 113 ml/100 g/min in cortical regions of the left middle cerebral artery (Figure 5), while LCBF values in similar areas of the right hemisphere were 41–76 ml/100 g/min.

When discharged she was able to walk, but there was no movement in her right arm.
far in excess of metabolic need. Acute hyperemia
also has significant disadvantages. First, the study
requirement is complicated by the euphoric or hyper-
esthetic sensation that frequently accompanies the
inhalation of 32% xenon. Second, at present no
more than three brain levels can be studied at one
time, potentially missing small changes in LCBF. Third,
even in the total absence of blood flow, Xe/CT does not record a value of 0 ml/100 g/min, but
instead gives values of approximately 0.5–2 ml/100 g/min, because of the assignment of a value of 0 to
any single voxel in which the rate constant is
negative. Thus, small positive values from system
noise are not cancelled out by correspondingly
small negative values. Despite this limitation, Xe/CT-derived CBF values in low-flow studies appear
to have greater significance than other clinically
applicable CBF methods, which, in general, have
been limited in their ability to record very low CBF
values. Fourth, the quantitative value of Xe/CT has
come under question because of the tendency of
xenon gas to increase CBF.17,18 However, absolute
values of CBF obtained by Xe/CT have not been
notably different from CBF values obtained by
other methods.4–6,9,12–14,18–22 Although concern over
a possible “steal” phenomenon caused by xenon-
induced blood flow activation has been expressed,
o evidence for a “steal” phenomenon in acute
ischemia exists; moreover, we have not observed a
single example of either transient or permanent
worsening of a neurologic deficit in the more than
2,500 Xe/CT studies that we have done.

Because no well-defined therapy for stroke has
emerged, it is difficult to state the clinical implica-
tions of identifying recently ischemic brain regions
that within several hours of ischemia had essentially
no, low-normal, or high blood flow. Because many
current strategies for stroke therapy involve efforts
to increase CBF, the greatest likelihood of providing
clinical benefit may be in the group with low-
normal CBF or perhaps in persons with strokes
with a significant ischemic penumbra (i.e., a large
area of low-normal LCBF). The late reintroduction
of CBF to infarcted tissues with essentially no
blood flow cannot be of clinical benefit, and it
carries the risk of hemorrhagic transformation or
exacerbation of cerebral edema. Efforts to augment
CBF in an already hyperemic region obviously can
be of no benefit. Thus, as treatments for stroke are
being clinically examined, the inclusion of CBF
determinations in the study protocol could clarify
which patients are likely to receive clinical benefit.

Further efforts to evaluate the utility of Xe/CT
and other CBF methodologies in the early diagnosis
and management of patients with acute cerebral
infarction are warranted.

Acknowledgments
The authors would like to thank Dr. Michael P.
Earnest and Dr. Lawrence R. Wechsler for their
thoughtful comments.

| Table 2. Cases of Cerebral Infarction Studied by Stable Xenon-
Enhanced Computed Tomography Categorized by LCBF |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

LCBF, local cerebral blood flow in appropriate anatomic area; +, positive; −, negative; NA, not available.

Cases 4–6 constitute the second category: patients
who had normal or low LCBF values, no evidence
of low-density areas on follow-up CT scans, and a
better clinical outcome. It is probable that these
individuals had an ischemic insult that was less
severe and/or of shorter duration. It is possible that
CT scanning later would have demonstrated their
infarctions. Although very few PET studies have
been obtained during the initial hours after infarc-
tion, examinations obtained within 48 hours after
stroke onset also indicate that these individuals
generally have a more favorable course.12

Case 7 is our only example of a third category:
patients whose LCBF values are significantly greater
than normal, suggesting that reperfusion after a
significant ischemic challenge had occurred.13
Higher-than-normal CBF values indicate an abso-
lute “luxury perfusion” with blood flow probably
far in excess of metabolic need. Acute hyperemia
has been associated with severe neurologic deficits
when accompanied by reperfusion in animals that
died with "large infarcts and considerable swelling
of the brain,"14 but in one clinical series cortical
hyperemia was not consistently followed by the late
appearance of low-density areas on CT scans.15 The
prognostic significance of identifying a cortical region
of the brain with such LCBF values remains unclear.

Two important observations can be made from
our initial series. One is that CBF examinations can
be obtained within the first few hours after stroke
onset. Because the Xe/CT method uses a CT scanner,
this study can be done immediately after the
emergency CT scan excludes a mass lesion or
infracranial hemorrhage as the cause of a neurologic
deficit. The other observation is that Xe/CT can
record very low LCBF values (<10 ml/100 g/min),
even in small and centrally located brain regions.
Experience with animal models13 and with clinical
cases of focal cerebral ischemia4–6 and brain death16
suggests that this technology is able to record very
low LCBF values that are consistently accompa-
nied by irreversible infarction.

Although Xe/CT provides some advantages, it
also has significant disadvantages. First, the study
demands registration of baseline and xenon-
enhanced images. Thus, there can be no head
motion during the 6-minute scanning period. This
requirement is complicated by the euphoric or hyper-
References

2. Gur D, Yonas H, Jackson DL, Wolfson SKJ, Rockette H, Good WF, Cook EE, Arena VC, Willy JA, Maitz GS: Simultaneous measurement of cerebral blood flow by the xenon/CT method and the microsphere method. Invest Radiol 1985;20:672-677

KEY WORDS • cerebral blood flow • cerebral infarction • xenon

Cerebral blood flow determination within the first 8 hours of cerebral infarction using stable xenon-enhanced computed tomography.
R L Hughes, H Yonas, D Gur and R Latchaw

*Stroke*. 1989;20:754-760
doi: 10.1161/01.STR.20.6.754

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/20/6/754

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/