Ischemic Core and Penumbra in Human Stroke

Anthony M. Kaufmann, MD, MSc, FRCSC; Andrew D. Firlik, MD; Melanie B. Fukui, MD; Lawrence R. Wechsler, MD; Charles A. Jungries, MD; Howard Yonas, MD

Background and Purpose—The ischemic core and penumbra have not been thoroughly characterized after acute cerebral thromboembolic occlusion in humans. Differentiation between areas of potentially viable and irreversibly injured ischemic tissue may facilitate assessment and treatment of stroke patients.

Methods—Cerebral blood flow (CBF) was measured in 20 patients with acute middle cerebral artery (MCA) occlusion between 60 and 360 minutes after stroke onset, with the stable xenon computerized tomography (CT) technique. Threshold displays were generated at a single level, and the percentages of hemisphere with CBF ≤6, ≤10, 11 to 20, 21 to 30, and >30 cm³ · 100 g⁻¹ · min⁻¹ were measured. The corresponding images on 12 available follow-up CT scans were similarly assessed to determine the area of final infarct. Comparisons were analyzed with a paired Student’s t test and Pearson’s correlation coefficient.

Results—Discrete and confluent areas of CBF ≤20 cm³ · 100 g⁻¹ · min⁻¹ were identified in all patients, ipsilateral to the symptomatic MCA territory. The average area of CBF ≤20 cm³ · 100 g⁻¹ · min⁻¹ within the ipsilateral hemisphere was 66±17% compared with 36±12% contralaterally (P<0.001). A difference in the extent of low CBF was due primarily to areas with CBF ≤10 cm³ · 100 g⁻¹ · min⁻¹ (48±18% versus 16±7%, P<0.001). The area of most severe ipsilateral ischemia (>6 cm³ · 100 g⁻¹ · min⁻¹) best corresponded to the final area of infarction (37±18% versus 40±24%; correlation coefficient, 0.866; P<0.01). The acute ischemic core destined to infarction was not surrounded by a widened rim of moderate ischemia because the area with CBF 11 to 20 cm³ · 100 g⁻¹ · min⁻¹ was similar bilaterally (19±4% versus 20±7%, P=0.792, thus not significant).

Conclusions—Our study in acute human stroke involving MCA occlusion indicates that a severely ischemic core (CBF ≤6 cm³ · 100 g⁻¹ · min⁻¹), observed between 1 to 6 hours after stroke onset, corresponds to the cerebral tissue destined to infarction. The ischemic penumbra with flow values between 7 and 20 cm³ · 100 g⁻¹ · min⁻¹ surrounding the ischemic core is very narrow. Therefore, strategies to improve the outcome of many patients with acute MCA occlusion must either include interventions to reverse the ischemic process within a few minutes of onset or increase the cerebral tolerance of ischemia and thereby prolong the potential therapeutic window. (*Stroke. 1999;30:93-99.*)

Key Words: cerebral blood flow ■ cerebral infarction ■ cerebral ischemia ■ penumbra ■ tomography, emission computed

The current goal of acute stroke therapy is to protect cerebral tissue before development of irreversible injury. A transition from reversible to irreversible injury is dependent primarily on the severity and duration of ischemia.1 Efforts to reestablish tissue perfusion in a timely fashion are therefore expected to be beneficial. Indeed, human studies of thrombolysis have shown improved outcome for carefully selected patients compared with placebo-treated control subjects.2–4 However, these studies have not identified a reduction in size of infarction because there has been no pretreatment delineation of the tissue at risk. Furthermore, clinical and computerized tomographic (CT) findings do not reflect the extent or severity of acute cerebral ischemia.5–7 To better evaluate acute stroke interventions, it is necessary to establish imaging techniques that demonstrate the therapeutic target and differentiate this from areas of already established infarction.8

Experimental data have demonstrated a gradual progression of a reversible degree of ischemia toward infarction.1,9–14 A central core with severely compromised cerebral blood flow (CBF) is thought to be surrounded by a rim of moderate ischemic tissue with impaired electrical activity but preserved cellular metabolism and viability.15–21 This “penumbra” has a variable outcome, and tissue salvage may be achieved when reperfusion is established within a 6- to 8-hour period.12,22–28 Positron emission tomography (PET) studies have also demonstrated a gradual reduction in cerebral metabolic activity within regions of acute focal ischemia.12,21,27 Retained cerebral metabolism has been demonstrated for ≤17 hours in severely ischemic areas that subsequently progress to infarc-
tion. However, such cellular activity does not necessarily indicate functional viability. Indeed, tissue injury in the severely ischemic core may progress to infarction within 1 to 2 hours.

Although PET imaging has greatly increased our understanding of the stroke process, its availability and practicality in acute clinical settings are limited. There is a need to establish readily available imaging techniques that may delineate the extent and severity of cerebral ischemia during the first minutes and hours after stroke onset. Such data may define the areas of brain destined to infarction and distinguish potentially viable tissue at risk (ie, therapeutic target). Delination of this tissue will facilitate evaluation of future treatments. Management decisions may then be individualized among the inhomogeneous group of acute stroke victims.

In the present study, we examine quantitative measurements of CBF in the first 6 hours after middle cerebral artery (MCA) territory stroke onset in humans. The extent and severity of ischemia were determined and compared with the final area of infarction. These data characterize the ischemic core and penumbra and support the concept of an ischemic threshold in human stroke.

### Subjects and Methods

We retrospectively reviewed a consecutive series of patients with MCA ischemic stroke who underwent quantitative CBF measurements within 6 hours of stroke onset. A precise onset time was necessary for patient inclusion; therefore, individuals who awoke with stroke symptoms were excluded. Patients were also excluded if preliminary conventional CT scans demonstrated intracranial hemorrhage, mass lesion, or early CT evidence of infarction over one third of the affected MCA territory. Therefore, all these patients were potential candidates for thrombolytic interventions. Although none received intravenous thrombolytic therapy, all were initially assessed as potential candidates for an institutional intra-arterial thrombolysis (IATL) protocol with urokinase within the first 6 hours of acute MCA stroke presentation. However, therapeutic decisions regarding the use of IATL in the present series of patients were made at the discretion of the attending stroke neurologist or neurosurgeon independently of the acute CBF imaging results (Table 1).

### Xenon-Enhanced CT CBF Technique

Xenon-enhanced CT (XeCT) is a quantitative CBF imaging technique with a high degree of sensitivity and spatial resolution. Its accuracy has been validated against other quantitative CBF techniques, including radiolabeled microspheres, $^{133}$Xe, and iodoantipyrine CBF techniques. Previous investigations have determined that the normal CBF in human mixed cortical tissue is $50\pm20$

### Table 1. Twenty Patients With Acute MCA Occlusion Stroke

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Side</th>
<th>Timing XeCT</th>
<th>Treatment</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>R</td>
<td>140</td>
<td>Angiogram; M1 and A2 occlusion; puncture M1 during attempted IATL</td>
<td>SAH; LD for hydrocephalus</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>M</td>
<td>R</td>
<td>240</td>
<td>Angiogram; M1 occlusion; anticoagulation</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>F</td>
<td>L</td>
<td>240</td>
<td>Angiogram; IATL of M1; complete reopening M1, partial distally</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>F</td>
<td>R</td>
<td>240</td>
<td>Angiogram; IATL of M1; partial reopening</td>
<td>Hemorrhagic conversion; surgical decompression</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>F</td>
<td>L</td>
<td>360</td>
<td>Antiocoagulation</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>6</td>
<td>84</td>
<td>F</td>
<td>R</td>
<td>360</td>
<td>Medical</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>F</td>
<td>L</td>
<td>210</td>
<td>Angiogram; IATL of M1; partial reopening</td>
<td>Swelling; mannitol</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>M</td>
<td>R</td>
<td>210</td>
<td>Angiogram; IATL of M1; partial reopening</td>
<td>Hemorrhagic conversion; surgical decompression</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>M</td>
<td>L</td>
<td>360</td>
<td>Antiocoagulation</td>
<td>Swelling; mannitol</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>M</td>
<td>L</td>
<td>150</td>
<td>Angiogram; ICA and M1 occlusion; IATL; no reopening</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>11</td>
<td>69</td>
<td>F</td>
<td>L</td>
<td>180</td>
<td>Angiogram; ICA and M1 and A1 occlusion; IATL; partial reopening</td>
<td>Hemorrhagic conversion; surgical decompression; died</td>
</tr>
<tr>
<td>12</td>
<td>81</td>
<td>F</td>
<td>R</td>
<td>345</td>
<td>Angiogram; M1 occlusion; anticoagulation</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>13</td>
<td>79</td>
<td>M</td>
<td>L</td>
<td>120</td>
<td>Angiogram; IATL of M1; complete reopening</td>
<td>Deep ICH; no cortical infarct</td>
</tr>
<tr>
<td>14</td>
<td>61</td>
<td>F</td>
<td>R</td>
<td>120</td>
<td>Angiogram; IATL of M1; partial reopening</td>
<td>Deep ICH; subsequent swelling; surgical decompression 2 times</td>
</tr>
<tr>
<td>15</td>
<td>62</td>
<td>M</td>
<td>L</td>
<td>210</td>
<td>Angiogram; ICA and M1 occlusion; IATL; partial reopening</td>
<td>Hemorrhagic conversion; surgical decompression</td>
</tr>
<tr>
<td>16</td>
<td>72</td>
<td>M</td>
<td>R</td>
<td>160</td>
<td>Angiogram; ICA and M1 occlusion; anticoagulation</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>17</td>
<td>62</td>
<td>F</td>
<td>L</td>
<td>210</td>
<td>Angiogram; M3 occlusion; no thrombolysis</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>18</td>
<td>50</td>
<td>M</td>
<td>L</td>
<td>155</td>
<td>Angiogram; ICA and M1 occlusion; IATL; partial reopening</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>19</td>
<td>84</td>
<td>F</td>
<td>R</td>
<td>360</td>
<td>Medical</td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>20</td>
<td>81</td>
<td>M</td>
<td>L</td>
<td>60</td>
<td>Angiogram; IATL of M1; partial reopening</td>
<td>Uncomplicated</td>
</tr>
</tbody>
</table>

SAH indicates subarachnoid hemorrhage; LD, lumbar drain; and ICA, internal carotid artery.

*CBF was measured by stable XCT technique within 6 hours of presentation.
cm$^3 \cdot 100$ g$^{-1} \cdot \text{min}^{-1}$, whereas cortical gray and deep white matter have CBFs of $80\pm14$ and $20\pm5$ cm$^3 \cdot 100$ g$^{-1} \cdot \text{min}^{-1}$, respectively.

All patients underwent conventional CT and XeCT imaging on a standard CT scanner in which an independent system for stable xenon gas delivery and CBF calculation was added (XeCT System, Diversified Diagnostics Products). While patients inhaled a 33% xenon/67% oxygen mixture (Praxair Pharmaceutical Gases) for 4.3 minutes, CT images with 1-cm slice thickness were obtained at 3 levels through the brain. Acquisition of XeCT data and its display were typically completed within 20 minutes.

**Interpretation of XeCT Scans and Late Infarct**

The CBF data obtained at 60 to 360 minutes after stroke onset and before any therapeutic interventions were analyzed by means of the XeCT computerized program. Analysis was limited to the middle scan level, which allowed maximal representation of the MCA territory and provided the potential to coregister with follow-up CT images. Several CBF ranges were selected, including 0 to 6, 0 to 10, 11 to 20, 21 to 30, and $30$ cm$^3 \cdot 100$ g$^{-1} \cdot \text{min}^{-1}$. The areas of cerebral tissue with these specified values were superimposed on the image most closely corresponding to the XeCT middle level was selected. Infarction on CT was defined as a distinct area of brain lucency. These areas were measured by the same 2-dimensional computer tracing plot apparatus and accompanying CT scan images. These highlighted areas were then measured with a 2-dimensional computer tracing plot apparatus and recorded as a percentage of cerebral hemisphere area. The lateral ventricles were excluded from all measurements, and no areas of preexisting infarction were encountered.

Available follow-up CT scans were reviewed, and the 1-cm slice image most closely corresponding to the XeCT middle level was selected. Infarction on CT was defined as a distinct area of brain lucency. These areas were measured by the same 2-dimensional tracing technique, without reference to the previous XeCT CBF area measurements. Comparisons were analyzed with a paired Student’s $t$ test and Pearson’s correlation coefficient. Patient numbers are maintained throughout all figures and tables.

**Results**

**Acute XeCT Measurements**

The CBF ranges were determined in all 20 patients and recorded as a percentage of hemisphere area on a single image level (Table 2). The extent of severe ipsilateral ischemia (ie, $\leq 10$ cm$^3 \cdot 100$ g$^{-1} \cdot \text{min}^{-1}$) varied between individuals, ranging between 14% and 72% of the ipsilateral hemisphere, reflecting differences in naturally occurring collateral circulation. Side-to-side asymmetries of CBF were also variable and dependent on the extent of this severe ischemia ($48\pm18$% ipsilaterally versus $16\pm7$% contralaterally, $P<0.001$). There was a homogeneous distribution of CBF 11 to $20$ cm$^3 \cdot 100$ g$^{-1} \cdot \text{min}^{-1}$ that corresponded to the sulcal and hemispheric deep white matter, and this area was similar bilaterally in all 20 patients ($19\pm4%$ versus $20\pm7%$, $P=0.792$). There was, however, no widened rim of such “moderate ischemia” surrounding the ischemic core (Figure 1).

![Figure 1](http://stroke.ahajournals.org/)

**Acute CBF Versus Infarct Area**

The extent of infarction was measured in patients 1 through 12 from CT scans obtained between 2 and 41 days after initial presentation (Figure 2). In these patients, significant correlations were found between the extent of severe cerebral ischemia of $\leq 6$ or $10$ cm$^3 \cdot 100$ g$^{-1} \cdot \text{min}^{-1}$ and the final area of infarction, with Pearson correlation coefficients of 0.866.
and 0.901, respectively ($P<0.01$). The area of infarction was not measured in patients 13 through 15, who developed post-IATL hemorrhages, and no follow-up CT scans were available for patients 16 through 20. However, the distribution of severe ischemia and surrounding moderate CBF reductions did not differ between these groups.

The ischemic core ($6 \text{ cm}^3 \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$) most closely correlated to the area of final infarction and never overestimated the infarct by $>10\%$ (Figure 3). In patient 4, the final infarct was significantly more extensive than the initial CBF measurements would have predicted, which may have resulted from secondary ischemic insults after the initial XeCT. Initial CT scans free of early lucency or swelling did not correspond to the duration of symptoms or extent of final infarction. The extent of final infarction was also not appreciably influenced by the IATL interventions (Figure 3).

**Discussion**

Development of cerebral infarction depends primarily on the duration and severity of ischemia.\textsuperscript{1} Although there are few data on the acute quantitative CBF in human stroke, experimental studies have shown that severe ischemia produces infarction within 1 hour. Yonas et al\textsuperscript{41,42} demonstrated that selective occlusion of the lenticulostriate arteries in baboons reduced CBF to $8 \text{ cm}^3 \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, which consistently produced infarction of the involved territory after 60 minutes. Others have also demonstrated that a CBF threshold in the first hour of cerebral ischemia is predictive of infarction.\textsuperscript{1,33,34} A threshold for cerebral viability has also been suggested by the results of PET studies that demonstrate infarction of all tissue with cerebral metabolic rate $<1.5 \text{ cm}^3 \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$.\textsuperscript{34,43,44} Recently, Touho and Karasawa\textsuperscript{30} showed with XeCT in humans that CBF $<9 \text{ cm}^3 \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ at 2 hours
after stroke onset was associated with infarction. However, the extent of severe ischemia was not compared with follow-up CT scan–defined infarction. Our findings indicated that the extent of severe ischemia corresponds to the final infarct. The present study has some limitations, including the retrospective nature, variable intervals between follow-up CT scans, and analysis at a single level. However, the statistically significant correlations between areas with CBF ≤6 cm$^3$·min$^{-1}$ measured between 140 and 360 minutes and the final infarct suggest that quantitative XeCT may be a powerful tool to delineate the ischemic core in acute human stroke.

Astrup et al.$^{15,16}$ described the ischemic penumbra as an area of moderate cerebral ischemia with reduced electrical activity that still maintained a membrane function and therefore was potentially viable. Neurological deficits may be reversed in penumbral tissue when normal CBF is reestablished within 6 to 8 hours.$^1$ Although medical diagrams often depict a substantial rim of penumbral cerebral tissue surrounding the ischemic core, the extent of such potentially reversible cerebral ischemia has not been well characterized in human stroke. Our quantitative CBF measurements between 60 and 360 minutes demonstrated no widened rim of moderate ischemia (7 to 20 cm$^3$·mg$^{-1}$·min$^{-1}$) around the well-delineated ischemic core at risk for infarction. These observations were consistent at 60 and 360 minutes, suggesting that the core of irreversible ischemic injury may be determined very early in the course of acute stroke.

It is not surprising that attempted IATL did not beneficially influence the relationship between the acute ischemic core and final infarct (Figure 3). Although these interventions were usually initiated >2 hours after stroke onset, the acute CBF measurement results suggest that the early extent of severe ischemia defines the final extent of infarction. Therefore, the actual therapeutic window probably is <1 to 2 hours, and hyperacute interventions are needed to reduce infarct volume. Such treatments may include agents to facilitate reperfusion and increase cerebral tolerance to ische-

Figure 2. Continued.
mia (ie, neural protection). Whereas late treatments may not affect infarct size, efficacy can be assessed only if the therapeutic target is defined with pretreatment CBF measurements.

XeCT may also be useful in differentiation between transient ischemic attacks and impending infarction, which may present with similar clinical deficits. For example, patient 1 had no significant area of critically low CBF, despite a clinical MCA stroke syndrome and angiographic demonstration of proximal MCA occlusion. IATL was not initiated because the guide wire punctured the MCA and produced a subarachnoid hemorrhage. Nevertheless, the patient recovered with no MCA infarction, in keeping with the acute CBF measurements (Figure 2). This case illustrates the potential value of categorizing the extent of severe ischemia with XeCT CBF measurements at the time of presentation to assess the effects of therapeutic interventions.

Inspection of the color-coded XeCT images and follow-up CT scans in Figure 2 indicates that confluent areas of mixed cortical gray and white matter with CBF $\leq 6 \text{ cm}^3 \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ were destined to infarction, as was the immediately associated deep white matter. Whereas similar areas of nearly zero flow seen in the lateral ventricles represent imaging artifacts, additional highlighted areas of low flow are seen sporadically in deep white matter bilaterally. These areas did not develop infarcts, indicating the greater tolerance of white matter for low flow. Our analyses were limited to a single XeCT scan level that demonstrated the largest proportion of the MCA territory, including watershed zones with the anterior and posterior cerebral arteries, as well as deep and cortical circulations. Although no efforts were made in the present study to distinguish CBF measurements in white and gray matter, such assessments are within the capabilities of the XeCT technology. Future studies should include CBF analyses throughout the cerebral hemispheres to define the ischemic threshold for the various cerebral tissues.

Conclusions

Acute measurements of CBF are necessary to delineate the extent and severity of cerebral ischemia in human stroke patients. Quantitative techniques such as XeCT have the capacity to accurately predict the area of irreversible ischemic injury at risk for infarction and facilitate the evaluation of stroke interventions. The preliminary results provided in this report suggest that the severely ischemic core established in the first hours after acute MCA occlusion in humans is destined to infarct. Furthermore, the surrounding ischemic penumbra is narrow. Therefore, hyperacute interventions to facilitate reperfusion or neural protection are necessary to limit the extent of infarction.

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References

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