Cerebral Blood Flow Threshold of Ischemic Penumbra and Infarct Core in Acute Ischemic Stroke: A Systematic Review
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Background and Purpose—Cerebral blood flow (CBF) reduction below critical thresholds discriminates between irreversible infarct core, penumbra, and benign oligemia (penumbra that recovers spontaneously). Thresholds are based on animal studies, and their diagnostic accuracy in humans has never been established. The purpose of this study was to assess the evidence available on CBF thresholds for infarct core and penumbra in adult stroke patients.

Methods—Electronic database searching using Medline, Embase and the Cochrane Library, crosschecking of references, and contact with experts and authors of primary studies was used. Studies on adult stroke patients were included if they compared CBF measurements with a diagnostic gold standard (follow-up brain CT/MRI), and reported CBF thresholds. Two reviewers independently extracted the data and assessed study quality.

Results—A meta-analysis could not be carried out because of insufficient data. The optimal reported CBF thresholds varied widely, from 14.1 to 35.0 and from 4.8 to 8.4 mL/100 g per minute for penumbra and infarct core, respectively.

Conclusions—The use of CBF thresholds in commercial software for imaging methods cannot be recommended without further evaluation. (Stroke. 2006;37:1334-1339.)

Key Words: brain ischemia • cerebral blood flow

A acute ischemic stroke is a clinical syndrome of rapid onset of focal cerebral deficit, lasting >24 hours or leading to death. A cerebral blood flow (CBF) reduction below certain values is a critical event leading to a series of functional, biochemical and structural changes culminating into irreversible neuronal death.1

The ischemic penumbra is defined as functionally impaired yet still viable tissue surrounding the ischemic core.2 The penumbra includes ischemic areas that recover spontaneously (benign oligemia; Figure 1, area a) and areas that progress to irreversible changes, unless effective treatment is used (referred to as penumbra; Figure 1, area b). The penumbra is the most clinically relevant target and is the focus of active research. Rate of progression to infarction (Figure 1, area c) depends on the degree of collateral arterial circulation, duration of insult, and functional and metabolic cellular state. The term “brain ischemia” comprises both infarct core and brain penumbra (Figure 1).

Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) is a recognized treatment in patients with acute ischemic strokes and is recommended in the guidelines of several stroke associations.3 rtPA use is associated with improved outcomes; however, in multicenter studies, only a minority of patients with ischemic stroke actually receives this treatment.4–7 One major cause for the low treatment rates is that a large proportion of patients are admitted >3 hours after symptom onset,8 the time window for which application of rtPA treatment is currently approved. But even among patients admitted within 3 hours after stroke onset, treatment rates are only moderate, ranging from 10.4%9 to 18.8%.5 In addition to a number of contraindications clearly listed in the drug approval, uncertainties about selection criteria for patients who might benefit from thrombolysis contribute to the low rates of stroke patients treated with rtPA in routine care.10

In addition to clinical criteria, discrimination between infarct core and surrounding potentially salvageable tissue is important to better identify patients suitable for treatment.11,12 In fact, the identification of the penumbra might allow restricting rtPA use to those patients with large penumbra and small infarct core even beyond the 3-hour time window. Today, several centers use MRI, including perfusion/diffusion-weighted imaging (PWI/ DWI), as diagnostic tool for hyperacute stroke before therapy decision. In fact, hyperintense areas on the DWI are generally believed to represent irreversible ischemic changes,13 whereas the PWI/DWI mismatch region, defined as the difference in
in adults with acute ischemic stroke. Therefore, systematically reviewed the medical literature to diagnostic accuracy in humans has never been established. We, /H11021

CBF thresholds might be helpful in additionally characterizing at risk tissue in terms of salvageable potential. Several imaging methods, based on CBF measurement, are available to differentiate the penumbra from infarct core at the very onset of symptoms, and they can be classified in 2 major classes of techniques: those that use a diffusible tracer (Xenon-enhanced CT, single-photon emission CT, positron emission tomography [PET]) and those that rely on a nondiffusible agent (CT perfusion, PWI). CBF thresholds of 17 and 10 mL/100 g per minute are universally reported by reference textbooks and routinely used as those values discriminating between normal tissue (including benign oligemia; CBF >17 mL/100 g per minute), penumbra (17 to 10 mL/100 g per minute) and infarct core (<10 mL/100 g per minute) (Figure 1). However, these thresholds are mainly based on experimental studies in animals, and their diagnostic accuracy in humans has never been established. We, therefore, systematically reviewed the medical literature to evaluate the evidence available and its methodological adequacy in adults with acute ischemic stroke.

Materials and Methods

Identification of Studies

Studies were identified by electronically searching Medline (January 1966 through March 2004), Embase (January 1982 through March 2004), and the Cochrane Library (January 1993 through March 2004). The following words were used both as text words and keywords: brain ischemia, cerebral ischemia, brain injury, brain blood flow, cerebral blood flow, blood flow measurement. The reference lists of all primary studies and review articles that included information on CBF were checked, and experts and authors of relevant articles were contacted directly to verify the completeness of the search. Finally, for the studies included in the review, further information was obtained on request by the authors.

Study selection was performed independently by 2 authors (E.B., M.B.), and disagreements resolved through discussion with a third reviewer (N.L.).

Study Selection

Included were studies on adults with acute ischemic stroke, in which CBF thresholds were reported and follow-up brain CT or brain MR was used as the diagnostic gold standard for diagnosing the finally infarcted area, based on currently accepted diagnostic criteria. No limits were imposed for CBF measurement techniques, nor for publication language or publication year.

Data Extraction and Evaluation of Study Quality

For each study, 2 reviewers (E.B., M.B.) independently extracted information on thresholds of the infarct core or the penumbra, number of patients studied, index and reference tests used, and clinical diagnosis. Because the development of cerebral ischemia depends on both severity and duration of the CBF disturbance, we recorded the time interval between the onset of symptoms and CBF measurement, and whether tissue reperfusion had occurred during this interval, as judged by Doppler ultrasound–related techniques.

To assess study quality, the following information was also extracted, based on the recommendations of the Standards for Reporting of Diagnostic Accuracy17,18 and the Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews19: study design (cohort or case-control study; prospective or retrospective); description of the study population (demographic characteristics, stroke severity, comorbidities); description of the reference and index tests; independent and blind comparison between reference and index tests; coregistration of the index and reference test; treatment administration during test application.

Disagreements between reviewers concerning design characteristics and data extraction were resolved through discussion with a third reviewer (N.L.).

Results

Inclusion of Studies

The whole process of inclusion and exclusion of studies is shown in Figure 2. Among the 237 articles retrieved and reviewed, only 7 fulfilled the inclusion criteria. A full list of the studies with detailed reasons for exclusion can be obtained on request by the authors.

Characteristics of the 7 studies included are summarized in Table 1. The main purpose of these studies varied: (1)

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Figure 2. Flow chart of the inclusion and exclusion of studies in the review.

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identification of penumbra in patients with stroke,\textsuperscript{20} (2) evaluation of a specific CBF measurement technique,\textsuperscript{22–24} or (3) definition of thresholds for penumbra or infarct core in patients with stroke.\textsuperscript{14,21,25}

Variability of CBF Thresholds
In the 7 studies included, CBF thresholds for penumbra and infarct core varied widely, from 14.1 to 35.0 and from 4.8 to 8.4 mL/100 g per minute, respectively (Table 2).

TABLE 2. Baseline Characteristics of Study Population and Study Results of the 7 Studies Included in the Review

<table>
<thead>
<tr>
<th>Author, y</th>
<th>No. of Patients</th>
<th>Age, Mean (SD)</th>
<th>% Male</th>
<th>Stroke Severity</th>
<th>Comorbidities</th>
<th>CBF Threshold for Penumbra (Figure 1, A)</th>
<th>CBF Threshold for Infarct (Figure 1, B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furlan, 1996</td>
<td>11</td>
<td>74</td>
<td>45.5</td>
<td>Described at patient level (MCA stroke scale and Martinez-Villa indices)</td>
<td>Described</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Marchal, 1999</td>
<td>19</td>
<td>74.6 (8.5)</td>
<td>52.6</td>
<td>Described at patient level (MCA stroke scale)</td>
<td>Described</td>
<td>NR</td>
<td>8.4</td>
</tr>
<tr>
<td>Schlaug, 1999</td>
<td>25</td>
<td>69</td>
<td>60.0</td>
<td>NR</td>
<td>NR</td>
<td>18.5* (95% CI: 11.5 to 25.5)</td>
<td>6* (95% CI: 3 to 9)</td>
</tr>
<tr>
<td>Liu, 2000</td>
<td>19</td>
<td>71 (8)</td>
<td>42.1</td>
<td>NIHSS</td>
<td>Described</td>
<td>24*</td>
<td>NR</td>
</tr>
<tr>
<td>Heiss, 2001</td>
<td>10</td>
<td>64</td>
<td>70.0</td>
<td>Little information on radiological findings and clinical symptoms of study population</td>
<td>NR</td>
<td>14.1 (SD: 1.8)</td>
<td>4.8 (SD: 0.5)</td>
</tr>
<tr>
<td>Grandin, 2001</td>
<td>66</td>
<td>69 (13)</td>
<td>62.1</td>
<td>European stroke scale: mean: 63; SD: 25</td>
<td>NR</td>
<td>35*</td>
<td>NR</td>
</tr>
<tr>
<td>Rohl, 2001</td>
<td>11</td>
<td>67</td>
<td>54.5</td>
<td>Described at patient level (clinical symptoms only)</td>
<td>NR</td>
<td>29.5*</td>
<td>NR</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale Score; NR, not reported.

*Authors of these 4 studies calculated the absolute CBF values by multiplying the PW-MRI-measured relative CBF values by 50 mL/100 g per minute (hypothesized mean CBF value).
In 3 studies\textsuperscript{20,21,23} absolute CBF values were measured by PET. In 4 studies\textsuperscript{14,22,24,25} CBF was measured by PW-MRI as the ratio between the CBF of the lesion and that of the contralateral mirror region. In these 4 studies, in order to compare the CBF values with those of other studies, the authors calculated the absolute CBF values multiplying the reported ratio by a mean CBF value of 50 mL/100 g per minute.\textsuperscript{26}

A regression analysis was performed to assess whether there was evidence of an association between CBF threshold value and time interval between the onset of symptoms and initial CBF measurement. In the 5 studies (117 patients) for which this information was available,\textsuperscript{15,17,22,24,25} there was no statistically significant relationship (regression coefficient: \(-1.66; 95\% \text{ CI: } -5.56 \text{ to } 2.25; P=0.270\)). In none of these studies was the tissue reperfusion during this time interval investigated by means of Doppler ultrasound–related techniques.

The small number of studies included in the review prevented a thorough investigation of possible reasons for the high variability in reported thresholds; however, substantial differences in measurement techniques (PET, DW-PW MRI), patients’ case-mix, and quality of the studies were evident (Tables 1 and 2).

Another possible cause of such variability, which has been investigated, is the difference in the methods used to derive the reported optimal threshold, which are reported in Table 1 and schematically presented in Figure 1. The threshold A corresponds to the cut-off value of CBF, which distinguishes between benign oligemia and penumbra, whereas the threshold B corresponds to the cut-off between penumbra and infarct core. It should be noted that in the studies which we included, the infarct core was the infarcted area identified in early scans, whereas the final infarct identified in late follow-up scans included the infarct core and the penumbra that eventually progressed to infarction. The difference between late and early scans represented the penumbra, which might have recovered if treated with thrombolysis. The benign oligemia (Figure 1, area a) was identified by the difference between the initially signal-altered area (Figure 1, area a+area b+area c) and the final infarct in follow-up scans (Figure 1, area b+area c).

In 2 studies,\textsuperscript{20,21} the threshold for penumbra (Figure 1, threshold A) was defined as the lowest CBF value measured in the area of benign oligemia, that is the noninfarcted tissue on follow-up imaging (Figure 1, area a). In the same 2 studies,\textsuperscript{20,21} the threshold for infarct core B was defined as the highest CBF value in the initially infarcted area (Figure 1, area c).\textsuperscript{20,21} In 1 study\textsuperscript{14} the thresholds A and B were defined as the mean CBF value in the corresponding areas b and c, respectively. In 2 studies\textsuperscript{22,24} the threshold A was derived from a Receiver Operating Characteristic (ROC) curve. In 1 study\textsuperscript{23} CBF thresholds A and B were defined based on cumulative probability curves: patients with a CBF value below 4.8 mL/100 g per minute (B) had at least 95\% chance of infarct; patients with a CBF value above 14.1 mL/100 g per minute (A) had at least 95\% chance of noninfarct. Finally, in 1 study, threshold A was obtained from a discriminant analysis.\textsuperscript{25} Attributable to the method used to define the threshold, the corresponding values of sensitivity and specificity were available only for 4 studies,\textsuperscript{22–25} all of which reported a CBF threshold for penumbra, whereas only 1\textsuperscript{23} also reported the CBF threshold for infarct core.

A meta-analysis, based on summary ROC curves, could not be carried out because sufficient data could not be obtained, even after contacting the authors of the studies included in this review.

Concerning the CBF threshold for penumbra, full ROC curves for 2 studies (as reported in the original article\textsuperscript{22} or obtained from the authors\textsuperscript{24}) are presented in Figure 3; 2 further threshold values (as reported in the original article\textsuperscript{25} or calculated from data obtained from the authors\textsuperscript{23}) and corresponding sensitivity and specificity are also plotted (Figure 3). Differences between the reported optimal thresholds reflected differences in sensitivity and specificity. The optimal thresholds reported by Rohl et al\textsuperscript{24} and Liu et al\textsuperscript{25} were similar (29.5 and 24 mL/100 g per minute, respectively) and showed comparable sensitivity and specificity (sensitivity of 91\% and 88\%, and specificity of 73\% and 66\%, respectively). The optimal threshold reported by Heiss et al\textsuperscript{23} was substantially lower (14.1 mL/100 g per minute) compared with the threshold reported by Rohl and Liu, but indeed it corresponded to a lower level of sensitivity (72\%) and higher specificity (90\%). Conversely, the threshold of 35 mL/100 g per minute reported by Grandin et al\textsuperscript{22} could not be interpreted in terms of differences in sensitivity and specificity (69\% and 85\%, respectively).

### Discussion

Combined use of DWI and PWI is increasingly used in hyperacute stroke in order to determine the infarct core and the penumbra (defined visually as the perfusion/diffusion mismatch) previous to rtPA treatment.\textsuperscript{11–13} This is performed even after the currently approved 3-hour time window.\textsuperscript{12,13} Therefore, defining a penumbral threshold below which the ischemic tissue will deteriorate without treatment (penumbra) is crucial. This systematic review on CBF thresholds for the diagnosis of penumbra and infarct core in patients with acute ischemic stroke explored the literature published over the last 59 years, because the first method for measuring CBF in humans became available in 1945.\textsuperscript{27} Only 7 studies were identified in which CT or MR were used as a gold standard to diagnose the finally infarcted area,\textsuperscript{14,20–25} and the results showed that the optimal reported CBF thresholds varied considerably for both penumbra and infarct.

### Investigation of Variability in Threshold Values

Although the investigation of methodological and clinical sources of variability in threshold values was limited by the small number of studies included, this review did identify the definition of “threshold” as an important source of variability. Only the 4 most recent studies\textsuperscript{22–25} obtained their optimal threshold from a ROC curve, cumulative probability curves, or discriminant analysis, which provide sensitivity and specificity for each threshold value. Interpretation of a single threshold value cannot be separated from the interpretation of its associated sensitivity and specificity, because different values of sensitivity and specificity can be required for clinical decision making, and the use of a ROC curve allows
the identification of the optimal threshold in terms of sensitivity and specificity.28

Time Dependence of CBF Thresholds
CBF thresholds associated with cerebral ischemia are highly influenced by the time of measurement in the course of acute ischemia because the development of brain damage depends on both severity and duration of the CBF disturbance.2 We did not find a correlation between CBF thresholds and the time interval between the onset of symptoms and CBF measurement. However, the power of our analysis to detect such a relationship, if one existed, is low attributable to the small number of studies available. Other reasons20,29,30 can be related to the fact that the reported onset time of ischemic symptoms may not always correspond to the onset of ischemia, and that brain tissue reperfusion, spontaneous or otherwise, may occur in the interval between the onset of symptoms and the initial CBF measurement. This latter hypothesis could not be investigated because no studies reported a measure of reperfusion by means of Doppler ultrasound-related techniques.

Need for Improved Quality of Primary Studies
Among the 73 studies evaluating the performance of CBF measurements in the diagnosis of brain ischemia in patients with ischemic stroke, only 1114,20–25,31–34 investigated CBF threshold values for penumbra and infarct core, and only 714,20–25 fulfilled the basic methodological requirement of comparing the test under evaluation with a gold standard. The sample size of these 7 studies was small, with only 1 having >25 patients,22 and none of them satisfied all the suggested criteria for the optimal design of diagnostic test evaluation: a prospective, blind comparison of the index diagnostic test with an accepted gold standard in a consecutive series of patients from a relevant clinical population.17

Summary
At present, differentiation between benign oligemia and penumbra based on a predetermined CBF threshold is not an imaging prerequisite for thrombolytic treatment;3,35; however, many stroke experts advocate it as a way to improve and extend indications for thrombolysis.11,12 This systematic review demonstrates that the currently proposed viability thresholds are based on weak evidence; therefore, their use in commercial software for imaging methods cannot be recommended without further evaluation. Adoption of standardized CBF measurement techniques and measures of arterial reperfusion should be important considerations in future studies. From a methodological point of view, prospective studies on larger patient samples with blind comparison between index and reference test are necessary to validate CBF thresholds, and reporting of results should be based on ROC curves.

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approved the final version of the manuscript. N.L. is guarantor of the article.

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