Quantitative Assessment of the Ischemic Brain by Means of Perfusion-Related Parameters Derived From Perfusion CT

Matthias Koenig, MD; Michael Kraus; Carmen Theek, MSc; Ernst Klotz, DPhys; Walter Gahlen, MD; Lothar Heuser, MD

Background and Purpose—Besides the delineation of hypoperfused brain tissue, the characterization of ischemia with respect to severity is of major clinical relevance, because the degree of hypoperfusion is the most critical factor in determining whether an ischemic lesion becomes an infarct or represents viable brain tissue. CT perfusion imaging yields a set of perfusion related parameters which might be useful to describe the hemodynamic status of the ischemic brain. Our objective was to determine whether measurements of the relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), and relative time to peak (rTP) can be used to differentiate areas undergoing infarction from reversible ischemic tissue.

Methods—In 34 patients with acute hemispheric ischemic stroke <6 hours after onset, perfusion CT was used to calculate rCBF, rCBV, and rTP values from areas of ischemic cortical and subcortical gray matter. Results were obtained separately from areas of infarction and noninfarction, according to the findings on follow-up imaging studies. The efficiency of each parameter to predict tissue outcome was tested.

Results—There was a significant difference between infarct and peri-infarct tissue for both rCBF and rCBV but not for rTP. Threshold values of 0.48 and 0.60 for rCBF and rCBV, respectively, were found to discriminate best between areas of infarction and noninfarction, with the efficiency of the rCBV being slightly superior to that of rCBF. The prediction of tissue outcome could not be increased by using a combination of various perfusion parameters.

Conclusions—The assessment of cerebral ischemia by means of perfusion parameters derived from perfusion CT provides valuable information to predict tissue outcome. Quantitative analyses of the severity of ischemic lesions should be implemented into the diagnostic management of stroke patients. (Stroke. 2001;32:431-437.)

Key Words: cerebral infarction ■ cerebral ischemia ■ perfusion ■ tomography, x-ray computed
routine for the diagnostic workup of stroke patients. Based on the indicator dilution principle, it provides various functional maps of the cerebral perfusion status, which may be used for the detection and characterization of the ischemic brain. The aim of our study was to describe typical changes of the perfusion-related parameters CBF, CBV, and TP in areas undergoing infarction and in tissue compartments of reversible ischemia. We also intended to define threshold values of ischemia for various parameters derived from perfusion CT studies and to evaluate the quality of classification of hypoperfused tissue as infarction or as reversible ischemia. Finally, we analyzed whether the potential of predicting the tissue outcome could be increased by using a combination of functional perfusion parameters.

Subjects and Methods

Patients

Thirty-four patients with acute nonlacunar ischemic stroke of the supratentorial brain were enrolled in the study. There were 14 men and 20 women (mean±SD age 65.4±13.5 years). A conventional CT study, obtained within 6 hours of symptom onset to rule out intracranial hemorrhage, was followed immediately by perfusion CT that showed areas of cerebral hypoperfusion in all cases.

The study was approved by an institutional review committee, and informed consent was obtained from all patients or from their close relatives. Intravenous heparin was given to 20 patients in whom stroke was suspected to be caused by cardiac emboli but who did not fulfill the inclusion criteria for fibrinolytic therapy according to the guidelines at our stroke center. One patient received intravenous rtPA according to the NINDS Stroke Study protocol,14 and 11 patients were treated with local intra-arterial fibrinolysis (LIF). In an additional 2 patients in whom LIF was initiated shortly after surgery, treatment had to be stopped after injection of a small dose of rtPA (8 mg and 10 mg, respectively) because of bleeding complications. For the remaining patients in the fibrinolysis group, the dosage and duration of treatment ranged from 10 to 80 mg rtPA and from 30 to 180 minutes, respectively. For local intra-arterial fibrinolysis, rtPA was superselectively administered into the thrombus by a microcatheter after demonstration of an embolic occlusion within the carotid distribution. A bolus of 5000 IU heparin was given intravenously at the beginning of the procedure in each patient. Arterial recanalization was rated by way of repeated angiography at the end of intra-arterial fibrinolysis by using the classification of the Thrombolysis In Myocardial Infarction (TIMI) Trial,15 with scoring from 0 (persisting occlusion) to 3 (full recanalization). Follow-up CT or MRI scans for the depiction of definite infarction were obtained at 2 to 10 days.

CT Perfusion Imaging

Our perfusion CT technique has been previously described in detail.16,17 Briefly, axial, single-section dynamic CT at the level of the basal ganglia was performed to encompass areas of the anterior, posterior, and middle cerebral artery territory. The slice thickness was 10 mm, and the matrix size for data acquisition was 512×512. For each study, a bolus of 50 mL iodinated contrast agent was injected into an antecubital vein with a power injector. A sequence of 32 to 40 images was then collected at a rate of 1 image/s to measure the signal intensity change during the first passage of the bolus through the vasculature of the brain. To achieve quantitative cerebral perfusion data, we used the Perfusion CT software (Siemens) which allows the calculation of CBF, CBV, and TP maps based on the CT time attenuation curves for each pixel. Our previous investigations indicated these parameters to be useful for the delineation of hypoperfused brain tissue in acute stroke.18 Thus, in this study we also focused on quantitative values of CBF, CBV, and TP to assess the degree of ischemia, although other parameters (eg, time to bolus start and maximum enhancement) are routinely provided by the software. The calculation of CBF is based on the maximum slope model, whereas for the CBV the normalized maximum enhancement was used as an estimate. The TP is defined as the time lag between the first arrival of the contrast agent within major arterial vessels included in the section and the local bolus peak in the brain tissue. Thus, while in the normally perfused brain the TP is expected to be in the range of a few seconds because of the unimpaired antegrade flow, in the ischemic hemisphere the TP may be prolonged, reflecting the delayed perfusion caused by leptomeningeal pathways.

Image Analysis

For the quantitative assessment of reversible and irreversible ischemia, we compared the perfusion impairment shown on the CBF, CBV, and TP maps with the findings on follow-up imaging studies. The section of the follow-up CT or MRI study that best fit the chosen scan level of perfusion CT was used to define those areas of hypoperfusion that eventually became infarcted and those that did not (Figure 1). In our experience, the results of these 2 imaging techniques are generally quite similar as long as the phase of the “fogging effect” is avoided for CT evaluation. Regions of interest (ROIs) were manually drawn in the CBF map to outline areas of infarction of the cortical and subcortical gray matter as shown on the follow-up images. ROIs were also defined for those ischemic compartments that did not undergo infarction. To reduce potential errors from the differences of the physiological perfusion values within the gray and white matter, care was taken not to involve substantial parts of the cerebral white matter within a given ROI. This was facilitated by an overlay of the ROI mask to a high-resolution anatomic image provided by the software. To evaluate all functional images, the ROI mask was then applied to the CBV and TP maps in a similar manner. One to 4 ROIs were obtained in each patient, yielding a total of 83 ROIs. From each ROI the mean values of the CBF, CBV, and TP were calculated.

Previous investigations16,17 have shown that absolute measurements of the CBF and CBV do not provide accurate results because of limitations of the underlying model. Similarly, the TP values within the intracranial vascular system may be influenced by the dispersion of the contrast bolus caused by the cardiovascular status of the patient and the contrast injection protocol. Thus, absolute values of these parameters do not correctly reflect the perfusion status of the ischemic tissue. To compensate for that, the perfusion...
parameters were assessed semiquantitatively by using the results from mirrored regions within the contralateral hemisphere as reference. For the CBF and CBV, the ratio of the affected brain tissue to the normally perfused contralateral hemisphere was calculated; for the TP, the difference was used, thus yielding a relative perfusion score for each functional parameter. Areas of local hyperperfusion (both rCBF and rCBV >1) suggestive of early postischemic hyperemia were excluded from the study.

**Statistical Analysis**

Standard descriptive statistics such as mean±SD values of rCBF, rCBV, and rTP derived from the infarcted and noninfarcted brain were calculated. Differences between the 2 outcome groups were examined by the Student *t* test or the Wilcoxon test. The functional data from all regions of interest were also correlated by using linear regression analysis and the Spearman rank correlation coefficient, including test of significance. Statistical significance was set at *P*<0.05. Univariate discriminant analysis was used to obtain a threshold value of each perfusion parameter to discriminate between areas of reversible ischemia and brain tissue that underwent infarction. We also examined a combination of 2 or 3 perfusion parameters by calculating a multivariate discriminant function. To test the contribution of fibrinolytic therapy on tissue outcome, the treatment modality used in our study (fibrinolysis versus heparin) was introduced into a stepwise multivariable discriminant analysis that also included all perfusion parameters. Patients treated with rtPA were assigned to the fibrinolysis group regardless of the degree of recanalization that had been achieved. Finally, reclassification of our data were performed on the basis of the best threshold values and cutoff functions derived from the discriminant analyses to compare the sensitivity (true positive prediction of infarction), specificity (true positive prediction of reversible ischemia), and efficiency to predict tissue outcome (χ² test).

**Results**

Five of 13 patients who received LIF had complete recanalization (TIMI grade 3) on posttreatment angiogram, whereas partial recanalization (TIMI grade 2) was achieved in 4 patients. No reperfusion (TIMI grade 0) was observed in 4 patients, including the 2 patients in whom treatment had to be stopped at an early stage because of bleeding complications. The patient who had received intravenous thrombolysis recovered well immediately after treatment and showed no persisting neurological deficit on follow-up examinations. Although the clinical benefit may be indicative for a successful recanalization, there was no information available regarding the arterial patency in this case.

There were 46 ROIs classified as gray matter infarction and 37 ROIs derived from noninfarcted ischemic brain areas. The mean values of the relative perfusion scores from areas of infarction and noninfarction are shown in Table 1. Although in infarcted regions the mean rCBF and mean rCBV were both significantly lower than in the ischemic but noninfarcted regions (all *P*<0.001), no differences were found with respect to the rTP. Data analysis of all 83 ROIs revealed a close relationship between the rCBF and rCBV. Depending on the severity of hypoperfusion, a decrease of rCBF was regularly accompanied by a reduction of rCBV, thus leading to a strong correlation of both parameters (*r*=0.96, *P*<0.001; Figure 2). Because of the algorithm used in our study, an increase of rCBV >1 was not commonly seen in areas of moderate ischemia. There was a roughly linear increase of rTP with falling rCBF, but the correlation was weak (*r*=-0.496, *P*<0.001; Figure 3).

From discriminant analysis, the thresholds for the discrimination of infarcted and noninfarcted tissue were estimated to be approximately 0.48 for rCBF and 0.60 for rCBV if both parameters were used as a single discriminator (Figures 4 and 5). The lowest rCBF and rCBV values among areas not developing infarcts were 0.29 and 0.40, respectively. rCBV was superior to rCBF regarding the sensitivity, specificity, and efficiency to predict tissue outcome, although the differences did not reach statistical significance. However, the influence of this parameter was confirmed by multivariate

<table>
<thead>
<tr>
<th>Tissue Outcome</th>
<th>rCBF</th>
<th>rCBV</th>
<th>rTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarction</td>
<td>0.34±0.20</td>
<td>0.43±0.22</td>
<td>4.8±3.0 s</td>
</tr>
<tr>
<td>Noninfarction</td>
<td>0.62±0.17</td>
<td>0.78±0.18</td>
<td>4.3±1.9 s</td>
</tr>
</tbody>
</table>

*The relative perfusion score for CBF and CBV indicates the side-to-side ratio; for the calculation of rTP, the difference was used.*
discriminant analysis of all variables included, yielding a significance level of $P=0.002$ for the inclusion of rCBV and $P=0.21$ for rCBF. The predominant value of rCBV was additionally reflected by the magnitude (absolute values) of the weighting coefficients of the best linear discriminant function for both rCBF and rCBV: $D = -2.979 - 4.084 \times rCBF + 8.29 \times rCBV$.

As Table 2 illustrates, the rTP by itself was not a suitable measure. Compared with the rCBV, the overall performance of classifying areas of acute ischemia could not be increased by any combination of the functional parameters. Moreover, stepwise variable selection analysis did not demonstrate a significant impact of the treatment modality on the preservation of brain tissue in our study group. Thus, no separate analysis was performed for heparin-treated patients and for the LIF group.

### Discussion

In the past, various perfusion imaging techniques have been reported to be efficient for the clinical investigation of acute stroke patients. Apart from the delineation of cerebral hypoperfusion, much experimental and clinical work has focused on the discrimination of areas of infarction and reversible ischemia because of its considerable clinical impact.\textsuperscript{5,12,13,19--23} Although there is no doubt that impaired blood flow below a certain critical level is the primary cause for functional and structural neuronal damage, a variety of perfusion-related parameters have been proposed to describe cerebral ischemia with respect to the extent and severity of the perfusion deficit. We have shown recently\textsuperscript{24} that perfusion CT is a reliable measure for the depiction of cerebral hypoperfusion in acute stroke. Among others, this technique has the advantage of providing functional information from several parameters derived from a single, routine examination. Results from a recent CT perfusion study have demonstrated that within the affected vascular territory, the ischemic findings as shown on the CBF, CBV, and TP maps may differ in terms of the extent and severity, thus making the significance of each parameter still a matter of debate.\textsuperscript{18} This was also reported by other groups using MR perfusion maps.\textsuperscript{22,23} Thus, for a more reliable assessment of different states of hypoperfusion, quantitative analyses of perfusion data must be added to the qualitative aspects of functional images.

In addition to current radionuclide imaging modalities, dynamic contrast-based MR and CT techniques have become increasingly popular for the assessment of cerebral perfusion-related parameters. However, only PET has been considered a reliable method to define absolute viability thresholds of ischemia.\textsuperscript{7,8,10,25} It is well known that absolute normal values of CBF and CBV may vary widely, depending on technical factors such as the imaging modality, the algorithm used for calculation, and the evaluation technique. In addition, measurements of both CBF and CBV have shown an interindividual variability of >20% and a decrease with age in healthy volunteers.\textsuperscript{26} Hence, in the setting of acute stroke, the calculation of accurate absolute values becomes impractical, and the use of absolute thresholds for therapeutic decision making is questionable.

Intrasubject normalization of the data is a measure frequently used to deal with these problems. To meet the clinical

![Figure 4](image_url)

**Figure 4.** rCBF (a) and rCBV (b) in infarcted and noninfarcted ischemic gray matter areas. From univariate discriminant analysis, the threshold levels for the best discrimination of infarcted and noninfarcted tissue were 0.48 and 0.60 for rCBF and rCBV, respectively.

![Figure 5](image_url)

**Figure 5.** Maps of CBF (a), CBV (b), and TP (c) in a patients with left middle cerebral artery occlusion. The extent of the ischemic territory is clearly depicted on the CBF and TP images. Infarction of the frontotemporal and insular cortex (arrow) was indicated by low values of both rCBF and rCBV (0.18 and 0.28, respectively). Despite a low rCBF (0.40), reversible ischemia was predicted for the posterior temporal cortex (arrowhead) because of an rCBV value of 0.68. This was confirmed by the CT scan at day 2 (d).
TABLE 2. Sensitivity, Specificity, and Efficiency of Perfusion-Related Parameters and Therapeutic Regimen to Predict Tissue Outcome

<table>
<thead>
<tr>
<th>Discriminant Analysis (Variables to be Included)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)†</th>
<th>Efficiency (%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTP</td>
<td>52.2</td>
<td>45.9</td>
<td>49.4</td>
</tr>
<tr>
<td>rCBF</td>
<td>76.1</td>
<td>73.0</td>
<td>74.7</td>
</tr>
<tr>
<td>rCBV</td>
<td>80.4</td>
<td>86.5</td>
<td>83.1</td>
</tr>
<tr>
<td>rCBF, rCBV</td>
<td>76.1</td>
<td>89.2</td>
<td>81.9</td>
</tr>
<tr>
<td>rCBF, rCBV, rTP, therapy†</td>
<td>76.1</td>
<td>89.2</td>
<td>81.9</td>
</tr>
</tbody>
</table>

*Sensitivity indicates true positive prediction of infarction.
†Specificity indicates true positive prediction of reversible ischemia.
‡Therapy indicates treatment with thrombolytics versus heparin.

need for prompt and detailed informations concerning the hemodynamic state of an ischemic tissue compartment, we calculated a relative perfusion score for CBF, CBV, and TP by using the contralateral hemisphere as reference. This was done on a routine basis without any need for time-consuming postprocessing.

With this approach we were able to demonstrate significant lower values of rCBF for areas of infarction compared with those suffering from reversible ischemia (0.34 ± 0.2 and 0.62 ± 0.17, respectively). Similar results (0.39 ± 0.12 and 0.69 ± 0.15, respectively) were reported by Hatazawa et al.13 using the side-to-side ratio of radioactivity derived from HMPAO SPECT; in other SPECT studies,27,28 mean values for both infarcted and noninfarcted tissue were found to be slightly higher. MR perfusion maps have also been used for the quantitative assessment of ischemic tissue compartments, but mean values of relative CBF have shown to be substantially lower than those mentioned above.23 The differences might mainly be due to the different imaging modalities and evaluation procedure, because for the perfusion MRI study the ischemic penumbra was operationally defined to those ischemic regions that developed an infarct as shown on follow-up diffusion-weighted MR images. Thus the penumbra area was not compatible with those regions that had been referred to as “reversible ischemia” in our study.

As demonstrated by PET and perfusion MR imaging studies, an increase of CBV is a common finding in ischemic areas affected by moderate hypoperfusion.13,23,29,30 Unlike others who use the area under the concentration–time curve for the calculation of CBV, we prefer the ratio of the maximum enhancement values obtained from the parenchyma and from an intravascular voxel not affected from partial volume averaging. We may reasonably assume that our approach leads to an underestimation of CBV for areas perfused mainly by collateral flow. In the present study, brain tissue undergoing infarction showed a significant reduction of mean rCBV compared with the surrounding ischemic area (0.43 ± 0.22 versus 0.62 ± 0.17), but, as expected theoretically, we did not observe an elevation of CBV in regions with moderate hypoperfusion. Schlaug and coworkers23 have demonstrated that various indexes of relative CBV derived from a dynamic bolus-contrast study may be valid for the discrimination of the infarct core and the peri-infarct ischemic tissue.

However, quantitative comparison did show significant differences between the results of these functional estimates of CBV. This study and ours support the view that for different states of hypoperfusion the results of CBV measurements may strongly depend on the algorithm used making a comparison of the data obtained with different techniques a challenge.

Despite these limitations, our results add to the notion that in hyperacute stroke the perfusion impairment is associated with changes of both CBF and CBV. In our patient group a severe reduction of rCBF was always followed by a marked decrease of rCBV indicating the core of infarction, while in the borderzone with only moderate hypoperfusion the rCBV was maintained to nearly normal or only slightly decreased levels. The high correlation of both perfusion parameters is in agreement with the study of Sorensen et al.22

Temporal changes of the local contrast bolus dynamic have been well documented for hypoperfused tissue compartments and among those parameters characterizing the bolus transit the TP may be easily derived from the concentration-time curves. Our observations confirm that the prolongation of the TP obviously reflects flow via collateral pathways or sluggish flow. Comparing the TP values from the affected and nonaffected hemisphere, we found bolus delays up to a maximum of 10 seconds. Unlike observations from an animal study,21 we did not see areas with a lack of a bolus peak indicating no flow, which is probably due to some residual vascular enhancement that could always be noted within large-sized ROIs even in infarct lesions.

Although in previous studies TP maps have been shown to provide excellent information in terms of the extent of the perfusion impairment,18,31 this parameter may not serve as a good quantitative estimate of flow because of the weak correlation to the corresponding rCBF values. Areas of reversible and irreversible ischemia did not significantly differ with respect to their bolus delay; in contrast to Neumann-Haefelin et al.12 we therefore suggest that the TP cannot reliably be used to discriminate between infarcted and noninfarcted ischemic tissue.

A value of 0.48 for rCBF was found as a best estimate for the discrimination of the infarct and peri-infarct regions, yielding an efficiency of 74.7% for the prediction of tissue outcome. rCBV tended to be more efficient in predicting the fate of the ischemic tissue (83.1%) if a cutoff value of 0.6 was used. It is, however, important to recognize that because of the overlap of the data from the infarcted and noninfarcted regions, these best cutoff values do not reflect the lowest level (ie, the real threshold for a given tissue compartment to survive an ischemic injury). In addition, the data presented here were obtained from regions that had been treated with heparin or thrombolytic therapy, and no distinction was made between whether an area was successfully reperfused or not. Only a small number of patients had complete arterial patency (TIMI 3) after LIF, and in those cases with partial restoration of flow no definite evaluation of the ROIs could be performed in relation to the reperfused and nonreperfused arterial branches. We therefore suggest that the cutoff values would have been even lower if a sufficient number of patients with full posttreatment recanalization had been recruited.
This would also have allowed dealing with the true viable tissue, i.e., the "potentially salvageable brain," instead of "reversible ischemia," as defined in our study. Taking into account that in noninfarcted regions the lowest perfusion values (rCBF 0.29 and rCBV 0.4) were obtained from the fibrinolysis group, these levels can be used as a rough estimate to separate viable from nonviable tissue. Assuming normal values of CBF for cerebral gray matter to be in the range of 55 to 70 mL/100 mL·min⁻¹ as derived from PET and xenon CT studies, a CBF value of 0.29 corresponds to an absolute value of about 15 to 20 mL/100 mL·min⁻¹, which is in agreement with the widely accepted critical threshold of ischemia.²⁻³⁻⁵⁻³³⁻³²

In a recent comparative MR perfusion study, Sorensen et al.²² have shown that although not perfect, CBV is a better predictor of the final infarct size than CBF. No quantitative analysis of the perfusion parameters was performed in this study; rather, it was based on the assessment of the lesion size as shown on the perfusion maps. The authors hypothesized that the distinction of already-infarcted tissue and tissue at risk would possibly be improved if a combination of various perfusion-related parameters and the apparent diffusion coefficient were used. Our results from multivariate discriminant analysis also confirmed the thesis that rCBV is superior to rCBF to separate areas of infarction and noninfarction. Regarding the slightly better sensitivity and specificity of rCBV, we speculate that within a critically perfused area structural damage may be prohibited by maintenance of a certain level of CBV. This vascular volume has also been referred to as perfused CBV, indicating the fraction of the vascular compartment that still receives some residual blood supply.³⁴ It probably points the way for the outcome of the ischemic tissue. Unlike considerations from Sorensen et al., the combination of rCBF and rCBV did not offer any benefit in predicting the fate of the hyperperfused brain. Also, inclusion of rTP did not improve the overall efficiency level reached by the use of the blood flow and blood volume parameters derived from perfusion CT.

We were not able to demonstrate an additional benefit of the therapeutic regimen on the prediction of tissue outcome, which is apparently due to the small number of patients in whom full arterial patency was achieved after thrombolytic therapy. To avoid erroneous conclusions from the slightly limited predictability of noncritical (i.e., reversible) ischemia, it must be considered that during the days after the perfusion study there might have been various unknown events that led to further deterioration of blood flow and subsequent metabolic damage in certain cases. This limitation, however, holds true for all functional modalities commonly used for the assessment of acute stroke. Nevertheless, results from diffusion-weighted MR imaging may add further information to a certain number of regions (e.g., areas of postischemic hyperemia) that may be already definitely infarcted although their perfusion values cannot be categorized as critical at the time of the initial perfusion study.

Regarding the 3D capability of MRI, it might be criticized that the information obtained with perfusion CT is still restricted to a single section that has to be carefully set to cover the level suspected to be ischemic; however, in the near future the problem may partly be overcome by using modern multislice CT technology. Furthermore, we suggest that the expertise gained with perfusion CT may easily be translated to MR perfusion techniques as far as comparable algorithms are implemented.

In conclusion, within a certain time window patients suffering from symptoms of acute stroke may be candidates for thrombolytic therapy if further criteria of an adequate selection are fulfilled. In the present study, we quantitatively described the hemodynamic state of the ischemic brain by means of perfusion-related parameters derived from perfusion CT.

Although rCBV was shown to be superior to rCBF, both parameters proved to be efficient for the prediction of whether an ischemic area survived or to become infarcted. Quantitative analyses may be restricted to these parameters, because the rTP values did not allow to discriminate between infarcts and reversible ischemia. It may be assumed that the recruitment of a larger number of successfully recanalized patients will make the results of CT perfusion measurements even more conclusive in terms of defining thresholds of tissue viability. With this future outlook, quantitative assessment of the ischemic brain by means of perfusion CT may play an increasing role for the selection of a subset of patients who may be successfully treated with potentially harmful therapeutic regimens such as thrombolyisis.

References


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Stroke. 2001;32:431-437
doi: 10.1161/01.STR.32.2.431

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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