Added diagnostic utility of CT perfusion and CT angiography in acute ischemic stroke.
Evaluation of three different patient categories

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Summary
Patients with a clinical picture of acute ischemic stroke are a heterogeneous group. The aim of this study was to evaluate the added utility of CT perfusion (CTP) and CT angiography (CTA) in the workup of three different categories of acute ischemic stroke patients. Fifty patients (61±15 years old) were included in this retrospective analysis. Twenty-nine patients had transient ischemic attacks (TIAs) (Group I), 15 were not eligible for treatment with thrombolysis (Group II) and six showed no improvement after thrombolysis (Group III). CTP and CTA provided additional information, not revealed by plain CT, in all the Group II patients and in one third of the patients belonging to the other groups. The final diagnoses were TIA (n=23), thromboembolic cerebral infarctions (n=22), carotid artery dissection (n=4) and metastases (n=1). Of the 29 patients admitted with TIA, only 22 patients still had this diagnosis on discharge from the stroke unit. Given the risk of impending stroke, it would be important to include these modalities in the initial workup of TIA.

KEY WORDS: CT angiography, CT perfusion, oligemia, penumbra, TIA.

Introduction
Non-enhanced computed tomography (CT) is the method of choice in the initial workup of acute ischemic stroke (1). However, modern CT techniques offer new possibilities: CT perfusion (CTP) allows hemodynamic evaluation of cerebral circulation, and CT angiography (CTA) morphological assessment of cerebral blood vessels. A combination of non-enhanced CT, CTP and CTA fulfills all the requirements of hyperacute stroke imaging (2). CTP may help to delineate the infarct core and the ischemic penumbra, whereas CTA can define the occlusion site, determine the degree of occlusion, rule out the presence of arterial dissection and display the collateral circulation. Multimodal CT evaluation has been shown to improve detection rate and prediction of the final size of infarction when compared with unenhanced CT, CTA, and CTP, each used alone (3). Thrombolytic therapy is an evidence-based treatment for patients with acute ischemic stroke admitted within 3 hours of stroke onset (4). The ECASS trial has recently provided data that extend this therapeutic window to 4.5 hours (5). However, acute ischemic stroke covers a wide range of patient categories in addition to those admitted to stroke units within 4.5 hours of onset of stroke symptoms and treated with tissue plasminogen activator (tPA). An important category of patients are those who present with transient ischemic attacks (TIAs), as they are at risk of an impending major stroke. A TIA is classically defined as a sudden, focal neurologic deficit that lasts for less than 24 hours, is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery (6). However, Albers et al. have proposed a new definition of TIA, omitting the 24-hour time limit and defining TIA as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour and without objective evidence of acute infarction (6). Unfortunately, there exist no established, evidence-based strategies or guidelines for the radiological workup of TIAs.

We here present our experience with CTP and CTA in 50 patients belonging to three different categories of acute ischemic stroke, all admitted beyond 3 hours of onset of stroke symptoms and submitted to radiological investigation with CT, CTP and CTA. This study was conducted with the particular aim of evaluating the added utility of CTP and CTA in the workup of patients with acute ischemic stroke.

Materials and methods
Fifty patients (25 males, 25 females; age 61±15 years, mean±SD) with acute ischemic stroke consecutively admitted to the acute stroke unit were included in this retrospective analysis. Patients with acute ischemic stroke who met the criteria for treatment with tPA were not included. All the patients included in this retrospective analysis were thoroughly examined by a stroke neurologist.

Patients
Three categories were identified in this sample of patients, who were thus grouped as follows:
Group I: patients with repeated TIAs. The patients included were those who had suffered at least two TIAs in the previous few days. Twenty-nine patients (age: 61±16 years, mean±SD; 17 males, 59%) were admitted with a diagnosis of TIA. Fourteen of them were submitted to CT, CTP and CTA during a TIA episode. The remaining 15 patients were examined within 24 hours of the last TIA.

Group II: patients not eligible for thrombolytic treatment. This group included 15 patients (mean age: 60±15 years, 6 males, 67%): seven who had been admitted to the acute stroke unit beyond the therapeutic window for treatment with tPA (Group IIA), five in whom the time of onset of stroke symptoms could not be established with certainty (Group IIB), and three who presented contraindications to treatment with tPA (Group IIC), namely, oral anticoagulant therapy, malignancy and a history of trauma.

Two Group IIA patients were examined within 4 hours of the onset of symptoms (the time window for thrombolysis therapy was 3 hours at the time these examinations were performed, four patients within 9 hours, and the seventh patient was examined >12 hours after the onset of symptoms. All the Group IIC patients were examined within 3 hours of the onset of symptoms.

Group III: non-responders. These were patients who received tPA but showed no clinical improvement or presented recurrent stroke symptoms within a day of the onset of the initial stroke. Six patients (4 females; 67%) with a mean age of 58±18 years were included in this group. These patients were admitted to the stroke unit after receiving treatment with tPA; five patients were examined 2-3 hours after the treatment and the sixth patient was examined one day after the treatment.

CT examinations

All examinations were performed using a 16-slice CT scanner (SOMATOM Sensation 16, Siemens AG, Forchheim, Germany). All the patients were submitted to both non-enhanced brain CT and CTP, while 49 patients were also examined with CTA.

The scan parameters for non-enhanced CT scanning were: tube voltage 120 kV, image quality reference for tube current-time product 320 mAs, cycle time 3 sec, scan time per cycle 1 sec, and slice collimation 0.75 mm. A soft tissue algorithm (e.g. Head20) was used. Two axial sections with slice thickness of 1.2 cm were obtained from CTP with the lower cut placed at the level of the aortic arch or in the common carotid artery (depending on the cranio-caudal scan length). The scan start delay was 15 seconds with a triggering threshold of 120 Hounsfield units (HU). After image acquisition, reformat ted axial images with thickness of 3 mm were obtained. Multiplanar reconstruction with maximum intensity projection was performed to obtain coronal and sagittal reconstructions with 3 mm thickness and 3 mm distance between images. 3D-imaging was available as a post-processing option.

All images were evaluated by two neuroradiologists in consensus pattern. Each patient’s non-enhanced CT was reassessed in the light of CTP and CTA results, to establish whether abnormalities had been missed or gone unrecognized in the initial assessment. The CTP and/or CTA examinations were considered to have added utility whenever one or both modalities provided additional, symptom-related information not revealed by the non-enhanced CT. Since patients with TIAs (Group I) are potentially important targets for therapy, the added utility of CTP and CTA in this group was compared with the added utility of these modalities in Groups II and III. For this comparison, SPSS automatically computed Fisher’s exact test in addition to the chi-square test. Differences with a p value ≤ 0.05 were considered statistically significant.
Results

Clinical outcome and diagnosis at discharge

Group I: The stroke symptoms, CT, CTP and CTA findings in patients admitted with repeated TIAs (Group I) are detailed in Table I. Twenty-two (76%) patients with a diagnosis of TIA on admission had the same diagnosis at discharge. These patients showed complete regression of the neurological deficit and no radiological evidence of ischemic injury. The remaining patients admitted with a diagnosis of TIA (n=7) had the following diagnoses at discharge: four showed thromboembolic cerebral infarction, one was found to have cerebral metastases and two had carotid artery dissection with subsequent development of embolic cerebral infarctions (blue bar, Fig. 1, over).

Group II: The patients belonging to this group showed the following final outcomes: 12 patients developed thromboembolic cerebral infarctions (2 watershed infarctions, 2 lacunar infarctions and 8 infarctions in a large vessel territory). One patient showed venous infarction secondary to extensive sinus thrombosis and two had internal carotid artery (ICA) dissection with sub-

Table I - Clinical features, radiological findings and final diagnoses in patients with TIA (Group 1).

<table>
<thead>
<tr>
<th>PN</th>
<th>Symptoms</th>
<th>CT</th>
<th>CTP</th>
<th>CTA</th>
<th>Diagnosis at discharge</th>
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<td>2</td>
<td>Rt HP and dysphasia</td>
<td>Parasagittal parietal infarct, Lt</td>
<td>Penumbra, frontal, Lt</td>
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<td>CI</td>
</tr>
<tr>
<td>3</td>
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<tr>
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<td>Oligemia, temporal, Rt</td>
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<td>TIA</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>CI</td>
</tr>
<tr>
<td>7</td>
<td>FP and Lt arm weakness</td>
<td>Infarct, watershed area, Rt</td>
<td>Severe ischemia, temporal and parietal, Rt*</td>
<td>Dissection suprachinal ICA, Rt</td>
<td>ICAD</td>
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<tr>
<td>9</td>
<td>Dysphasia</td>
<td>Infarct, parietal Lt</td>
<td>Severe ischemia, parietal, Lt*</td>
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<td>CI</td>
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<tr>
<td>11</td>
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<td>0</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>ICA stenosis, Lt</td>
<td>TIA</td>
</tr>
<tr>
<td>17</td>
<td>Aphasia</td>
<td>0</td>
<td>Old frontal infarct, Lt*</td>
<td>0</td>
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</tr>
<tr>
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<td>TIA</td>
</tr>
<tr>
<td>26</td>
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<td>0</td>
<td>0</td>
<td>TIA</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>28</td>
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<td>2 metastases</td>
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<td>Penumbra, Rt</td>
<td>0</td>
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<tr>
<td>33</td>
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<td>0</td>
<td>0</td>
<td>ICA stenosis, bilat.</td>
<td>TIA</td>
</tr>
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<td>34</td>
<td>Rt amaurosis fugax</td>
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<td>0</td>
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<td>TIA</td>
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<td>Old brainstem infarct, Lt</td>
<td>0</td>
<td>ICA stenosis, Rt*</td>
<td>TIA</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>TIA</td>
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<tr>
<td>37</td>
<td>Lt HP, paresthesia and dysarthria</td>
<td>Old infarct, watershed area, Rt</td>
<td>Oligemia, Rt</td>
<td>ICA occlusion, Rt</td>
<td>TIA</td>
</tr>
<tr>
<td>38</td>
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<td>0</td>
<td>0</td>
<td>TIA</td>
</tr>
<tr>
<td>39</td>
<td>Rt HP, FP and dysarthria</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>TIA</td>
</tr>
<tr>
<td>42</td>
<td>Rt paraesthesia</td>
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<td>0</td>
<td>0</td>
<td>TIA</td>
</tr>
<tr>
<td>43</td>
<td>Rt arm weakness</td>
<td>Infarct internal capsule, Lt</td>
<td>Oligemia, Lt</td>
<td>0</td>
<td>CI</td>
</tr>
<tr>
<td>45</td>
<td>Lt HP, hemianopia and neglect</td>
<td>Cortical infarct, parietal, Rt</td>
<td>Established MCA ischemia, Rt</td>
<td>ICA dissection, Rt</td>
<td>ICAD</td>
</tr>
<tr>
<td>48</td>
<td>Rt arm weakness, paresthesia, visual disturbance</td>
<td>0</td>
<td>0</td>
<td>ICA stenosis, Rt*</td>
<td>TIA</td>
</tr>
<tr>
<td>49</td>
<td>Rt HP and paresthesia</td>
<td>0</td>
<td>Oligemia, Lt</td>
<td>ICA stenosis Lt, Occlusion, Rt</td>
<td>TIA</td>
</tr>
</tbody>
</table>

Abbreviations and symbols: *No added utility despite detection of significant pathology; PN=patient number; CT=computed tomography; CTP=CT perfusion; CTA=CT angiography; Rt=right; Lt=left; Bilat=bilateral; 0=no pathological finding; HP=hemiparesis; FP=facial palsy; ICA=internal carotid artery; MCA=middle cerebral artery; TIA=transient ischemic attack; CI=cerebral infarction; ICAD=internal carotid artery dissection.
sequent development of embolic infarctions in the MCA territory and in the watershed areas between the MCA, ACA and PCA (violet bar, Fig. 1).

Group III: This group included five patients who did not show significant improvement after treatment with tPA and one patient who recovered completely after thrombolysis but developed TIA the following day. The latter patient did not sustain any ischemic injury (and thus still had a TIA diagnosis at discharge) whereas the other five developed infarcts in the MCA territory (yellow bar, Fig. 1).

**Added utility of CTP and CTA**

CTP and CTA provided additional information not revealed by non-enhanced CT in all the Group II patients compared with 10 and 2 of the Group I and III patients, respectively (Table II). This difference was statistically significant (Fisher’s exact test; p<0.001). The difference in the added utility of CTP and CTA in the Group I versus the Group III patients was not statistically significant (Fisher’s exact test; p<0.957).

Of the 23 patients with TIA as the final diagnosis (22 belonging to Group I plus the one Group III patient with TIA after thrombolysis), six patients benefited from examination with CTP, CTA or both (figure 2 shows an example of a patient with TIA who benefited from CTP). Seventeen of the 22 patients who sustained thromboembolic...
Discussion

In this study, CTP and CTA were shown to provide clinically significant findings in patients with TIA. CTP, along with TIA, is used to establish the final diagnosis in patients with TIA. The added utility of CTP in patients with TIA was 33% (Table II). The added utility of CTP+CTA in patients with TIA was 93%, 80% and 100% respectively. These findings were clinically significant, but were not deemed to be a clinically significant finding, and suggests that TIA should be regarded as a serious entity with the potential to develop into a major stroke (13,14).

Furthermore, CTP and CTA showed several changes compatible with established ischemic injury in one patient already treated with an-15. Group II provided additional information in 14 of the 15 Group II patients (Table III), showing the oligemic phase of ischemia in one patient already treated with anticoagulant therapy. Penumbra in four patients and CTP changes compatible with leukomalacia in nine patients. CTA provided the following additional information: 12 of the 15 patients (80%) showed partial regression of the CTA changes. CTA showed focal regressive changes in one patient whose CTP scan only showed scattered ischemic changes in the right temporal lobe within the MCA territory. The CTP scan highlighted a larger area of penumbra in the MCA territory. This patient responded to treatment with tPA. CT=computed tomography; CTP=CT perfusion; CTA=CT angiography; (+)=positive finding.

Abbreviations and symbols: I=patients with repeated transient ischemic attacks; II=patients not eligible for treatment with tPA (IIa=admitted beyond the therapeutic time window; IIb=uncertain time of symptom onset; IIc=contraindications to treatment with tPA); III=patients who did not respond to treatment with tPA; Cr=computed tomography; CTP=CT perfusion; CTA=CT angiography; (+)=positive finding; CT=(three and four respectively, marked with * in Table 1).

Summary

CTP and CTA were shown to provide clinically significant findings in patients with TIA. The added utility of CTP in patients with TIA was 33% (Table II). The added utility of CTP+CTA in patients with TIA was 93%, 80% and 100% respectively. These findings were clinically significant, but were not deemed to be a clinically significant finding, and suggests that TIA should be regarded as a serious entity with the potential to develop into a major stroke (13,14).
contribute to increasing the utility of these modalities, either because they were not correlated with the patients' present symptoms or because they were abnormalities already known to be present. One of the major issues in TIA patients with normal radiological investigations is the difficulty confirming that the cause of the symptoms is cerebrovascular. It is especially important to rule out migraine and epilepsy. Hence the need to involve stroke neurologists in the workup of all patients with suspected stroke.

Literature data on the hemodynamic changes in TIA are scarce. In one report of 20 patients, 13 showed perfusion abnormalities in the form of increased TTP with no significant changes on CBF map (15). In our study, seven patients showed perfusion abnormalities more severe than simply increased TTP, namely one case of increased TTP and severely decreased CBF and CBV (established ischemia), four cases with oligemia and two patients with penumbra. Of these 7 patients, four recovered completely and had a diagnosis of TIA at discharge, whereas the other three sustained cerebral infarctions and were no longer considered to have TIA. Another report (16) on the usefulness of CT, CTP and CTA in acute stroke investigated 24 patients admitted within 24 hours of onset. In this study, CTP revealed ischemic changes of various degrees in 10 out of 11 patients who had had negative CT scans. In accordance with us, these authors showed that CTP and CTA do have added utility in acute stroke even after the therapeutic window of 3-4.5 hours. Guidelines need to be established for patients with TIA in order to regulate hospital admissions, investigation algorithms, risk stratification and treatment alternatives in this group.

Patients with acute stroke who fulfilled the criteria for treatment with tPA were not included in the analysis because we believe that addition of further diagnostic modalities should not be allowed to delay the initiation of an evidence-based therapy in this category of patients. From a prognostic point of view, the non-responders to tPA (Group III) constitute a particularly difficult group. Whereas in Group II (patients not eligible for tPA), the added utility of CTP and CTA was 100% and the results of the hemodynamic studies provided important prognostic information, in Group III the results of these studies had the least impact on treatment planning, given that these patients had already received thrombolytic therapy. Nevertheless, CTP and CTA provided additional information that helped to direct the treatment strategy in one Group III case, and to rule out ischemic injury in another. Therefore, these modalities have to be considered beneficial in this group as well.

One of the drawbacks of this study is its retrospective nature. However the study population nevertheless included different categories of patients with ischemic stroke, reflecting the situation encountered in daily clinical practice. The role of CTP and CTA in the workup of patients with acute ischemic stroke eligible for treatment was not the focus of this paper.

The other drawback of this study is that only 14 out of 29 patients with TIA were examined during a TIA episode and the remaining 15 patients were examined within 24 hours. Theoretically this could have contributed to some underestimation of the beneficial role of CTP at least in the workup of TIA.

In conclusion, CTP and CTA were shown to have added diagnostic utility in the radiological workup of patients with acute stroke admitted to the stroke unit after the therapeutic window for treatment with tPA. Although the added utility of these modalities was lower in patients with TIA compared with the abovementioned patient category, the potentially high risk of development of cerebral infarction in patients with TIA should encourage the use of CTP and CTA in these patients. CTP and CTA helped the physicians to make the final diagnosis in one third of patients with TIA. Thus these modalities should be regarded as valuable tools in the management of acute ischemic stroke even in patient categories other than those submitted to thrombolysis therapy. In patients with a primary diagnosis of TIA, adding CTP and CTA to the acute radiological workup not only helps identify possible persistent cerebral ischemia but also provides important information for rapid instigation of prophylactic strategies.

References