Evaluation of perfusion CT and TIBI grade in acute stroke for predicting thrombolysis benefit and clinical outcome

Évaluation du scanner de perfusion et du score ultrasonographique TIBI dans l’accident vasculaire cérébral pour prédire le bénéfice de la thrombolyse et l’évolution clinique


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KEYWORDS
Stroke; Perfusion; Computed tomography; TIBI; Ultrasound

Summary
Objective. — To evaluate the prognostic accuracy of combining perfusion CT (PCT) and thrombolysis in brain ischemia (TIBI) ultrasonographic grade in the triage of stroke patients who will benefit from thrombolysis and in predicting the clinical outcome.

Methods. — We conducted a prospective study of all consecutive stroke patients admitted to our hospital from March 2003 to July 2007, presenting with signs of acute stroke within the therapeutic window, who had undergone either intravenous or combined intravenous and intra-arterial thrombolysis. All patients were evaluated by a complete stroke CT protocol, transcranial color-coded duplex sonographic monitoring, follow-up imaging (CT or MRI) and clinical outcome at 3 months, as assessed by the modified Rankin scale (mRS).
Background

Stroke is a leading cause of morbidity and mortality in the developed countries today. The challenge is to establish a diagnosis as early as possible to allow more patients to benefit from thrombolysis therapy. Thrombolysis was the first – and is still the only – evidence-based therapy approved for acute stroke [1]. This therapy can be administered intravenously (IV), intra-arterially (IA) [2] or in combination [3]. Imaging plays a central role in identifying patients who will benefit from thrombolysis. Indeed, the roles of imaging are manifold — to detect hemorrhage, to visualize ischemia, to show vascular occlusion and to delineate penumbra in as short a time as possible [4].

Although MRI is now establishing a role in an emergency setting [5], mainly due to the sensitivity of diffusion-weighted imaging (DWI) [6] and whole-brain perfusion [7], CT nevertheless remains the primary imaging modality in acute-stroke patients: it is considered the gold standard for ruling out hemorrhage and other alternative diagnoses; and is contraindicated for thrombolysis and allows the detection of early damage [8,9]. In addition, CT is widely accessible and can be performed without delay, which is important as the time window for treatment is narrow. Combined with perfusion CT (PCT) and CT angiography (CTA), stroke imaging is able to detect salvageable tissue and intravascular thrombi. The goal of thrombolysis is to save ischemic, yet still viable, tissue.

PCT provides an excellent assessment of tissue blood flow [10–12], but it does not reflect what is happening inside the vessel and cannot be realistically performed at many time-points within the therapeutic window for monitoring. Thus, we designed a protocol that combines PCT with Doppler ultrasound [13,14] to evaluate patients undergoing thrombolysis to evaluate both tissue perfusion and recanalization in relation to clinical outcome. We also wanted to validate a simplified approach for assessing the penumbra that uses the mean transit time (MTT) and time-to-peak (TTP) maps instead of the MTT and cerebral blood volume (CBV).

Methods

Study design

This prospective study involved patients admitted to our hospital from March 2003 to July 2007 with signs and
symptoms of acute stroke. The diagnosis of acute stroke was established on the basis of clinical status and CT findings. Only patients who fulfilled the following criteria were included:

- acute stroke (<3 h of symptom onset) of the middle cerebral artery (MCA) territory;
- complete stroke CT protocol;
- transcranial Doppler monitoring;
- IV or combined IV and IA thrombolysis;
- follow-up CT and/or MRI;
- 3 month modified Rankin scale (mRS) evaluation.

The aim of our study was to evaluate the benefits of combining PCT and thrombolysis in brain ischemia (TIBI) grade for:

- selecting patients who are likely to benefit from thrombolysis;
- predicting the clinical outcome.

The TIBI score is an ultrasound score derived from the angiographic thrombolysis in myocardial infarction (TIMI) score [13] as follows:

- grade 0 = absent flow;
- grade 1 = minimal flow;
- grade 2 = blunted flow;
- grade 3 = damped-down flow;
- grade 4 = stenotic flow;
- grade 5 = normal flow [13].

Initial clinical assessment

Informed consent was given by each participating patient, and the protocol was approved by the local ethics committee. Of a total of 65 patients, 33 (22 men and 12 women) met the inclusion criteria (median age 66.9 years; age range 33—95 years). Neurological impairment on admission was evaluated using the National Institutes of Health Stroke Scale Score (NIHSS).

Stroke CT protocol

The stroke CT standard of care at our hospital included, in succession, a non-enhanced CT (NECT), PCT, CTA and delayed imaging, using a 16-section multidetector CT scanner (Mx8000 IDT family, Philips Medical Systems). Contrast medium (Accupaque® 300) was injected through an 18-G cannula placed in the antecubital vein. NECT was performed using the following parameters: 140 kV; 250 mAs; slice thickness 3 mm; and slice acquisition interval 3 mm (from occiput to vertex). The four PCT sections were chosen by the on-duty radiologist for the NECT, the lowest one at the level of the basal ganglia. PCT parameters were: 120 kV; 100 mAs; slice thickness 4 mm × 6 mm; and 40 mL of contrast medium at a rate of 5 mL/s with no scanning delay. The color-coded maps of the CBF, CBV, TTP and MTT were then calculated using Mx View Version 5 (Philips Medical Systems) commercial software. CTA covered a scanning range that extended from the aortic arch to the vertex with a 100-mL contrast injection at a rate of 4 mL/s and a threshold of 150 HU at the aortic arch. The parameters were: 120 kV; 250 mAs; slice thickness 1.5 mm; slice acquisition interval 0.7 mm; and pitch 2.5. Finally, a 2-min delayed cerebral CT with the same acquisition parameters as the NECT was also carried out.

Transcranial color-coded duplex (TCCD) sonography

All patients were monitored by an experienced neurologist by TCCD sonography using Acuson Sequoia equipment (2—3.7 MHz). TIBI grades were assessed prior to and at the end of thrombolysis to diagnose residual MCA flow. Recanalization was considered ‘complete’ in cases of normalized or elevated values of peak systolic flow velocity, ‘partial’ when the signal improved by at least 1 TIBI grade and as ‘persistent occlusion’ in all other cases.

Thrombolysis protocol

All patients underwent IV thrombolysis with tissue plasminogen activator (tPA) (0.9 mg/kg, 90 mg maximum, 10% of total dose as a bolus over 1 min, then 90% of the infusion for 1 h) or as combined IV/IA thrombolysis. After 30 min of IV thrombolysis, either the total dose was continued intravenously in cases of partial or complete recanalization, as evaluated by TCCD sonography, or IA thrombolysis was initiated using the remaining dose of tPA in cases of persistent occlusion.

IA thrombolysis

Digital subtraction angiography (DSA) was performed using the femoral approach and the Seldinger method. The prethrombolysis angiographic protocol included bilateral internal carotid artery (ICA) and vertebral artery injection. After identification of the proximal MCA occlusion, superselective angiography was performed using a microcatheter. A bolus injection of 2000 U of heparin was given intravenously, followed by an infusion of 1000 U/h until the end of the procedure. A microcatheter (Excel 14, Target/BSC) and microguide wire (Transend 14, Target/BSC) were used to reach the occlusion site and to infuse the thrombolytic agent locally at doses ranging from 8 mg to 34 mg. Several control DSA series were performed to assess the degree of recanalization. The IA injection of tPA was stopped when either the 6-h time window was reached or complete recanalization of the occluded vessel was achieved. In all cases, the maximum dose was never greater than 34 mg.

Follow-up imaging

This was used as a gold standard to calculate the extent of infarction. Patients underwent either NECT (same parameters as for the initial CT) or MRI, using a 1.5-T scanner (Achieva, Philips Medical Systems). The standard protocol was: axial fast spin-echo (FSE) T2; coronal FLAIR; DWI; 3D angiography using time-of-flight for cerebral vessels; 3D angiography postcontrast (Omniscan, 30 cm³) for extracranial vessels; and cerebral T1 axial postcontrast.
Image analysis

The initial CT images were reviewed by an experienced neuroradiologist blinded to any clinical information—except for the diagnosis of stroke—follow-up imaging and clinical outcome. On NECT, the usual early-stage features of acute ischemia were evaluated, including the hyperdense vessel sign, the insular ribbon sign and obscuration of the lentiform nucleus. In addition, the side on which the acute ischemia was located was recorded. The color-coded perfusion maps were visually evaluated using a 1/1, 1/2, 1/3 and 3/3 classification for the infarct core, as defined by TTP, while the total ischemic tissue was defined by MTT. The MCA territory was divided into thirds, and hypoperfusion on MTT maps was considered to be 1/3, 2/3 or 3/3 (total) of the MCA territory; the same was done for infarction. The penumbra, as defined by the MTT—TTP, was also classified into three groups: 0; 1/3; and 2/3. Hemorrhagic complications as well as the extent of the final infarct, using the same classification system as for the initial CT, were identified on follow-up imaging. Initially, two neuroradiologists (S.A., K.O.L.) also compared the TTP and CBV maps.

Clinical outcome

Recovery was assessed using the modified Rankin scale (mRS) at three months after admission. A score of 0–2 was considered favorable and a score of 3–6 was unfavorable. A patient was considered to have benefited from thrombolysis if there was either no growth of the final lesion outside the boundaries of the core predicted by early PCT or if the final lesion was smaller than the early core.

Results

The mean NIHSS on admission was 14.2 [6–22]. CT imaging was performed within 103.3 min of the onset of symptoms. All stroke CT protocols and follow-up imaging were well tolerated. On the initial NECT, 24 patients had left-sided signs of ischemia and 10 patients had right-sided signs. The hyperdense vessel sign was present in 28 patients, the insular ribbon sign in 29 patients and obscuration of the lentiform nucleus in 25 patients. The total ischemic area, including the infarct core and ischemic penumbra, was determined by the MTT. Patients were separated into three groups: MTT 1/3 (two patients); 2/3 (seven patients); and 3/3 (25 patients). The infarct core, represented by the TTP, was also evaluated and patients were again assigned into three groups: 1/3 (14 patients); 2/3 (11 patients); and 3/3 (nine patients). Finally, the penumbra or salvageable tissue, represented by the MTT—TTP, was visually assessed and divided into three groups: 0 (11 patients); 1/3 (17 patients); and 2/3 (six patients).

The time lag between the onset of symptoms and thrombolysis was 150 min (range 75–195 min). Overall, 19 patients underwent IV thrombolysis and 15 underwent combined IV/IA thrombolysis, while 20 patients had no recanalization, four patients experienced complete recanalization and 11 achieved partial recanalization.

The follow-up imaging consisted of MRI in 27 patients and CT in seven patients. The delay between the two scans was 9 days (range 1–35 days). Hemorrhagic complications were identified in nine patients. The final infarct extent was divided into three groups: 1/3 (14 patients); 2/3 (nine patients); and 3/3 (11 patients).

The clinical outcome assessed by mRS was favorable in 16 patients and unfavorable in 18.

Figure 1  In this 78-year-old male patient, non-enhanced CT (NECT) shows a hyperdense arterial sign on the left, and perfusion CT (PCT) shows a penumbra of 1/3. Intravenous therapy was initiated, with an initial TIBI grade of 3 and a final TIBI grade of 5. The infarct on DWI was found to be small and cortical. The initial NIH stroke score was 6 and the final Rankin score was 0–2.

Patient âgé de 78 ans. Signe de l’artère hyperdense à gauche sur le scanner sans injection. Le scanner de perfusion montre une pénombre de 1/3. Un traitement par thrombolyse intraveineuse a été réalisé. Le TIBI initial était de 3, le TIBI final de 5. L’infarctus final était de petite taille et de siège cortical. Le score initial NIH était de 6 et le Rankin final de 0–2.
There was overall agreement regarding the presence of a mismatch between the standard MTT–CBV and the alternative MTT–TTP methods for detecting tissue at risk. However, in three of 34 cases, TTP tended to slightly overestimate the core—or it underestimated the potential penumbra—compared with the standard MTT–CBV. The MTT–TTP maps were, however, much easier to read.

On the initial PCT, 23 patients had a penumbra (MTT–TTP ≥1/3) and 11 patients did not (MTT–TTP = 0). Of these patients, we identified those who benefited from thrombolysis, defined as a final ischemic lesion smaller than the ischemic area on the initial PCT (MTT). Of the 20 such benefiting patients, 19 had a penumbra—(Figs. 1–3) and one did not—(Fig. 4). Penumbra accuracy for predicting thrombolysis benefit was statistically significant, with 95% sensitivity, 71% specificity, 82.6% positive predictive value (PPV) and 91% negative predictive value (NPV). In addition, the penumbra on the

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**Figure 2**  In this 92-year-old woman, NECT shows a hyperdense middle cerebral artery sign on the left, and PCT shows a penumbra of 2/3 with a final infarct of only 1/3. The initial TIBI score was 0 and the final TIBI score was 1. Intravenous therapy was performed. The initial NIH stroke score was 15 and the final Rankin score was 0—2.

**Figure 3**  In this 81-year-old man, NECT shows a hyperdense middle cerebral artery sign on the left, and PCT shows a penumbra of 2/3 with a final infarct of 2/3. Intravenous therapy was performed. The initial TIBI was 1, and the final TIBI was 2. The initial NIH stroke score was 20 and final Rankin score was 3–6.
initial PCT correlated significantly with the clinical outcome (75% sensitivity, 39% specificity, 52% PPV and 64% NPV).

In contrast, TIBI grade was a significant predictor of neither thrombolysis benefit nor clinical outcome. Furthermore, a statistically significant correlation was observed between MTT on the initial PCT and TIBI grade \( (p < 0.05) \).

Specifically, of 13 patients with complete occlusion (TIBI 0), 12 presented with extensive ischemic tissue on the initial PCT (MTT 3/3).

**Discussion**

The aim of stroke therapy is at least twofold: on the one hand, it should achieve recanalization while, on the other hand, reversing the potential penumbra. To achieve this goal, it is necessary to assess both flow and tissue hemodynamic parameters, which can be done by combining a brain perfusion study – in our case, PCT – with duplex ultrasonography. Our study shows that PCT was the best predictor of outcome, although the addition of TIBI grade does allow adaptation of the thrombolysis regimen.

Due to their sensitivity to hemorrhage and availability, PCT and CTA have both maintained important roles in the diagnosis and management of stroke patients. Indeed, while CT can detect early changes, this is often open to interpretation, although research has indicated its usefulness in detecting acute water accumulation as a possible means of differentiating necrotic tissue that is hypodense from penumbral tissue that is swollen [15]. This means that PCT also allows better delineation of the acutely hypoperfused area [12]. In addition, relying on a possible mismatch between data from only CT and clinical findings is less reliable [16] and, moreover, does not appear to correlate with a diffusion–perfusion mismatch [17], whereas a diffusion–clinical mismatch appears to work [18,19]. This, it may be that having some kind of information on tissue viability is indispensable — and so the need to proceed with PCT.

Having been well studied and validated, it appears that CBF and MTT variables derived from CT and MRI correspond well, whereas CT-derived CBV values may be more problematic [20]. Indeed, in our experience, CBV maps are slightly more difficult to read as the visual contrast provided by these maps is less pronounced. In addition, we have found that the MTT–TTP approach provides an estimation that is similar to that with the MTT–CBV approach, but is much more easy to read.

CT-derived protocols should also result in the same therapeutic clinical impact as MRI-based ones — which Wintermark et al. [21] found to be true in all but one case. PCT has had an impact on revealing not just hypoperfused tissue, but also in uncovering the presence of a penumbra or an infarct of the tissue core [22]. Used in addition to the ASPECTS score, it can also predict the outcome of thrombolysis better than NECT [23,24]. CT perfusion maps that demonstrate reperfusion, especially on CBV maps, suggest a better outcome and smaller infarct [25].

Grading by ultrasound using the TIBI classification allows the effect of thrombolysis on vessel patency to be followed. PCT can also, to some extent, predict the occurrence of hemorrhagic complications, based on the extent of hypoperfusion [26], but gives only one timepoint.

However, two major issues still remain to be addressed and corrected with PCT: the lack of coverage of the whole brain with most available scanners; and the lack of a clear demonstration of core infarction, as seen on diffusion MRI. Also, in patients with neurological symptoms that are probably due to small deep lacunes or cortical stroke, CT may be unhelpful as it cannot demonstrate such lesions well. Nevertheless, despite these shortcomings, PCT is of value in helping to guide therapeutic decisions in acute stroke.
patients with MCA occlusions. However, infarct volume measurements remain a problem as significant differences can occur, even when using the MR mismatch model [27].

What is also not yet clear is whether or not CT can demonstrate the potential gain of intra-arterial thrombolysis where there is little or no penumbra, and whether or not, in cases where the evolution of TIBI is not improving, there is still a rationale for resorting to intra-arterial thrombolysis. These unanswered questions need to be addressed by further data from a larger study population.

References


