Inter-rater Agreement in Three Perfusion-Computed Tomography Evaluation Methods before Endovascular Therapy for Acute Ischemic Stroke

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Purpose: There is ongoing debate on which method of perfusion computed tomography (PCT) evaluation in ischemic stroke is the most appropriate for improved selection of patients for endovascular treatment. We sought to test different assessment methods for inter-rater reliability. *Methods:* Twenty-six patients were enrolled prospectively before endovascular therapy for acute anterior circulation ischemic stroke. Three raters experienced in stroke imaging and blinded to other imaging and clinical information independently analyzed 22 technically successful PCT scans according to 3 prespecified assessment methods applied to cerebral blood flow (CBF)/cerebral blood volume (CBV) and time-to-peak (TTP) maps: (1) visual mismatch estimate (VME), (2) Alberta Stroke Program Early CT Score perfusion method (ASPECTS-PCT), and (3) quantitative perfusion ratios (qPRs): R_{CBF}, R_{CBV}, R_{TTP}. Inter-rater agreement was assessed with Cohen's kappa, intraclass correlation coefficients (ICC), Bland–Altman plots, and global and descriptive statistics. *Results:* Significant differences between raters were found with VME and ASPECTS-PCT ($P < .001$) but with qPRs only for CBV ($P = .03$). Inter-rater agreement for VME was at best moderate by kappa statistics (.51); moderate by ICC for all parametric maps of ASPECTS-PCT (.56-.62), strong for R_{TTP} (.76), and excellent for R_{CBF} (.92) and R_{CBV} (.86). Pairwise comparisons revealed less scattering of individual values with qPRs and less deviation of mean differences from 0, suggesting minor systematic deviation by any 1 rater as compared with VME or ASPECTS-PCT. *Conclusion:* PCT evaluation methods used before endovascular therapy for acute anterior circulation stroke are subject to substantial inter-rater disagreement. QPRs in PCT evaluation had better inter-rater reliability than the often used VME and ASPECTS-PCT assessment.
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Introduction

As evidence for the efficacy of intravenously or intra-arterially administered thrombolytics has become available,[1,2] and with the increasing advent of mechanical clot manipulation procedures,[3-5] the main treatment goal in acute ischemic stroke remains reperfusion achieved by recanalization. Reperfusion is particularly efficient if it occurs in viable but functionally impaired brain areas ("ischemic penumbra") to prevent their evolution to irreversible infarction.[6] Modern cerebral imaging techniques can differentiate areas of hemodynamically impaired but still salvageable brain "tissue at risk" from the irreversibly damaged infarct core with increasing accuracy.[7-11]

Computed tomography (CT)-based perfusion studies (perfusion computed tomography [PCT]) have gained increasing attention for this purpose because of its availability and well-characterized properties. Several important studies have been published analyzing appropriate criteria and thresholds for distinction of a viable tissue at risk versus an irreversibly damaged tissue.[12-15] Furthermore, PCT-based randomized clinical trials for intravenous[16] and endovascular revascularization[17] have shown its potential as a selection tool for patients with high likelihood of benefitting from therapy. Yet, nonstandardization of nomenclature, of thresholds, and inter-rater variability have hindered its widespread implementation in routine clinical use.[18,19]

With the technical advances in endovascular approach to achieve recanalization of occluded brain arteries, a more refined selection of patients presenting with acute ischemic stroke requires rapid noninvasive diagnostic tools. Such new techniques must show reproducible performance and must be time-saving, reliable, and valid for use by clinicians in the emergency care setting.

The aim of this study was to analyze different PCT assessment methods for inter-rater variability in the setting of endovascular treatment (eT) of acute ischemic stroke.

Methods

We prospectively enrolled patients admitted to our stroke center for acute ischemic stroke. Eligible patients had clinical symptoms consistent with acute stroke, had a moderate or severe neurological deficit (defined as National Institutes of Health Stroke Scale score ≥5), aged between 18 years or older and 85 years or younger, and underwent the full imaging protocol with the aim to initiate eT within 6 hours after symptom onset. If initial non–contrast-enhanced cranial CT had ruled out intracranial hemorrhage and early signs of infarction[20] larger than one third of the middle cerebral artery (MCA) territory. PCT and computed tomography angiography (CTA) were routinely performed in the absence of contraindications such as known renal failure or documented allergy to iodine contrast material. If CTA revealed an occlusion of the distal internal carotid artery, the carotid "T," or the proximal MCA, patients underwent eT as described previously.[21]

All examinations were carried out on a 16-row multislice CT scanner (Somatom Sensation 16; Siemens Medical Systems, Erlangen, Germany). Scanning parameters for the initial non–contrast-enhanced cranial CT were 4.5-mm section thickness, 120-kV tube voltage, 360-mAs tube current, and a pitch of 1. Next, the CTA result of the cervicocranial arteries was acquired from the level of the sixth cervical vertebra up to the vertex as described previously.[21] Thereafter, PCT was performed by acquisition of 2 slices with a slice thickness of 12 mm at the level of the basal ganglia according to previously described criteria.[22,23] Image acquisition was performed for 60 seconds with 1 image per second after administration of an intravenous bolus of 60 mL of iodinated contrast agent (Visipaque 270; GE Healthcare Buchler GmbH & Co. KG, Braunschweig, Germany) followed by a saline flush of 40 mL, both at 6 mL/second. PCT datasets were analyzed using the vendor's software (NeuroPCT, SyngoCT 2007S; Siemens Medical Systems). The arterial input function was placed in the anterior cerebral artery contralateral to the presumed stroke.[24]

PCT datasets were processed in a standardized fashion by 3 independent raters blinded to all clinical, demographic patient information, CTA and eT datasets and results, and outcome. The rating panel consisted of 2 board certified neuroradiologists and 1 experienced stroke neurologist. Each rater independently created color-coded maps from both 12-mm slices for regional cerebral blood flow (CBF), cerebral blood volume (CBV), and time to peak (TTP), from the raw acquisition data. The perfusion parameter maps were used for 3 different independent assessments:

(A) Visual Mismatch Estimate (VME)
Color-coded PCT maps for CBF and CBV were used for this algorithm. The size of the areas of CBF and CBV perfusion disturbance (with reference to the contralateral hemisphere) were assessed visually for any difference (Fig 1), termed "mismatch." First, the raters were required to provide a categorical estimate whether there was any mismatch at all. If so, the raters were to "eyeball" a ratio of the estimated difference in relation to the area of CBF impairment as denominator ($(A_{CBF} - A_{CBV})/A_{CBF}$), with values in 10% increments ranging from 0% to 100%, indicating no apparent difference and no lesion visually detectable in the CBV map, respectively.[25-27]

(B) Alberta Stroke Program Early CT Score (ASPECTS) Perfusion
The two 12-mm slices were scored for each perfusion parameter (CBF, CBV, and TTP) according to the modified ASPECTS method, assigning 1 of 10 possible points for each section of the MCA territory not affected by perfusion disturbance as compared with the contralateral hemisphere (Fig 1).[23,28]

(C) Quantitative Perfusion Ratios (qPRs)
This approach is based on the color-coded maps for all 3 parameters CBF, CBV, and TTP. A region of interest (ROI) was manually outlined around the area of perfusion disturbance in the affected hemisphere for each perfusion parameter and slice. As ipsilateral reference, an ROI was placed around the entire hemisphere on the affected side; as contralateral reference, an ROI corresponding to the manually placed ROI of perfusion disturbance was mirrored to the unaffected hemisphere with the vendor's perfusion software tool (Fig 1). The software automatically calculated the average CBF, CBV,

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