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Perfusion computed tomography in prediction of functional outcome in patients with acute ischaemic stroke

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Abstract

PURPOSE: To determine the value of perfusion computed tomography (CT) in prediction of the clinical course and late functional outcome in patients with acute ischaemic stroke who had unremarkable initial brain CT examination.

MATERIAL AND METHODS: Single slice perfusion CT was performed in 55 consecutive patients (27 women, mean age 67 ± ± 11 years) with acute ischaemic stroke within 6 hours (median 2.26 hours) from onset of symptoms. Values of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) obtained from affected hemisphere were compared to respective values in non-affected hemisphere (relative parameters). Initial neurological deficits were estimated using NIH Stroke Scale (NIHSS) score and correlated with perfusion CT values, employing Spearman rank correlation coefficient (r). Values of perfusion CT parameters in prediction of functional outcome were determined by comparing against scores on modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS) after three months of onset of stroke.

RESULTS: All perfusion CT parameters significantly correlated with initial neurological deficit. The highest correlation with the NIHSS was found for relative CBF, which correlated better than absolute CBF (rCBF r = 0.69; CBF r = 0.50, P < 0.001). In prediction of favourable outcome (mRS ≤ 2) the commonly employed thresholds (in parentheses) and associated sensitivity, specificity, positive and negative predictive values were: 87%, 44%, 79%, and 58% for CBF (10 ml/min/100 g), 59%, 81%, 88%, and 49% for rCBF (48%), 49%, 56%, 73%, and 31% for CBV (2 ml/100 g), 87%, 44%, 79% and 58% for rCBV (60%), 41%, 81%, 84% and 36% for MTT (6 s) and 54%, 81%, 87% and 49% for rMTT (145%), respectively, while for prediction of excellent outcome (mRS ≤ 1), the only statistically significant respective accuracy measures were for rCBV, 90%, 35%, 60%, 75%, and for rCBF, 62%, 69%, 69% and 62%.

CONCLUSIONS: In patients within the first 6 hours from stroke onset, and without a hypodensity sign on initial routine CT examination, perfusion CT provides quantitative parameters that correlate well with initial neurological status and late functional outcome.

Key words: acute ischaemic stroke, computed tomography, perfusion, outcome assessment, neurological deficit

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Introduction

Neurological deficits associated with regional cerebral ischaemia occur when perfusion decreases below 25 mL/100 g per minute. In the range of 12–25 mL/100 g per minute, the neuronal tissue preserves its biological integrity, thus restoring perfusion may allow the tissue to return to normal function [1, 2]. In acute brain ischaemia, the water content in the tissue increases rapidly causing regional oedema that can be detected based on low density using routine computed tomography (CT) [2, 3]. Early brain tissue hypodensity observed in CT is associated with more severe neurological symptoms, larger infarct volume, and higher risk of secondary cerebral haemorrhage [4–6]. Development of the CT-detectable oedema, however, may be delayed well beyond the first 6 hours [4, 5].

The information on whether the ischaemic neuronal tissue is viable and potentially salvageable is crucial for patient management and prediction of outcome. Perfusion-CT (PCT) is able to

Table 1. Principal acronyms of Perfusion-CT and clinical scales used in text

Acronym	Term	Units or values
CBF	Cerebral Blood Flow — the blood supply to the brain in a given time, in PCT measured in millilitres of blood per 100 grams of brain tissue per minute	ml $100g^{-1}$ min^{-1}
CBV	Cerebral Blood Volume — the blood amount in a given brain area, in PCT measured in millilitres of blood per 100 grams of brain tissue	ml $100g^{-1}$
MTT	Mean Transit Time — the time in which venous contrast bolus passes through brain vasculature during PCT examination	S
GOS	Glasgow Outcome Scale — a descriptive scale of gross outcome in acute illness, consists of five categories: dead, vegetative state, severely disabled, moderately disabled, and good recovery	1–5 pts
mRS	Modified Rankin Scale — a scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke	0–6 pts
NIHSS	National Institutes of Health Stroke Scale — an assessment tool providing a quantitative measure of stroke-related neurologic deficit, most often used in the acute phase of stroke	0–42 pts

differentiate cerebral ischaemia from infracted tissue [7]. The coverage of imaged brain hypoperfusion with or without correlation to observed infarction core was shown to be prognostic for final infarct size and clinical outcome, even when recanalisation therapy was utilized [7–9]. Although brain PCT thresholds of tissue at risk are well defined, the accuracy of cerebral blood flow measurements using PCT in prediction of clinical outcomes is still poorly determined.

The purpose of this study was to explore the relationship between clinical state and PCT parameters in the acute phase (< 6 hours) of ischaemic stroke in patients whose routine emergency CT did not show signs of hypodensity. We also compared the value of established prognostic perfusion thresholds with ours as determined with PCT for delayed functional outcome.

The principal acronyms of Perfusion-CT and clinical scales used in the following text are shown on Table 1.

Material and methods

Patients

We included patients who were consecutively referred to our Stroke Unit over a period of 3 years (2003–2005). The inclusion criteria were: (1) clinical diagnosis of acute stroke, with (2) stroke onset less than 6 hours previously, and (3) absence of early hypodense changes in routine initial non-contrast CT. Patients with evidence of intracranial haemorrhage, contraindications to PCT or to contrast media, acute respiratory or circulatory insufficiency, neoplasm in case history, or qualified for thrombolytic treatment were excluded.

Clinical assessment on admission and during 3-month follow-up was carried out prospectively and included: demographic data, risk factors, current stroke and imaging timing, neurological presentation on admission, day 1 and day 7 measured on the National Institute of Health Stroke Scale (NIHSS),and functional outcome on day 90 measured using modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS).

The research protocol was approved by the local Ethical Committee. Each patient or designated decision-maker gave informed consent.

Perfusion computed tomography

Perfusion computed tomography (PCT) examinations were performed on a GE HiSpeed (GE Medical Systems, Milwaukee, USA) scanner immediately after routine non-contrast CT, in one 10 mm layer, according to accepted protocol. The level of the examination was chosen in relation to the clinical symptoms, and was positioned parallel to the orbitomeatal plane and above the orbital roof to protect eye lenses from radiation. A detailed PCT protocol is given in Table 2.

Collected imaging data were transferred to a diagnostic workstation where calculations for selected PCT modalities — mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV) — were populated automatically using a Central Volume Principle deconvolution algorithm with commercial software delivered by the scanner manufacturer (GE Medical Systems, Milwaukee, USA).

Imaging review

Imaging data were elaborated using routine protocol by the neruoradiologist on duty, who was experienced in PCT, was not blinded to information about the side of the ischaemic incident, but was blinded to other clinical data. Pre-prepared, manually drawn template of regions of interest (ROIs), discriminating all territories of supratentorial vascularisation of the main cerebral arteries (anterior, middle, and posterior), was placed primarily in the affected hemisphere, and, in an automated way, mirrored ROIs were generated in the contralateral hemisphere as a reference. The measurements concerned whole imaged brain sections, not only visually selected regions of hypoperfusion. Averaged within particular ROIs, values of perfusion parameters in both hemispheres were calculated in all ROIs, direct values on the affected side, and relative to the contralateral hemisphere values of each PCT parameter (given with initial r) were used in further analysis.

Statistical analysis

Measurements from both hemispheres were compared using a paired 2-sided t test after checking for normality of distributions. Spearman's R rank correlation test with t test of significance was used to analyze the relationship between early brain perfusion dis-

Table 2. Perfusion CT imaging protocol performed immediately after routine non-contrast CT

Scanner	GE HiSpeed (GE Medical Systems, Milwaukee, USA)
Rows of detectors	2 n
Layer thickness	10 mm
Number of lamp rotations	45
Number of scans	45 (1 scan per 1 lamp rotation — 1 s)
Time of examination	50 s
Acquisition parameters	80 kVp, 190 mAs
Matrix	512 × 512
Contrast media	Iodine, noionic, 350 mg/ml (Omnipaque®, Amersham Health, USA)
Contrast volume	50 ml
Speed of infusion	4–5 ml/s
Time of infusion	10–12 s
Contrast route	Intravenous
Time delay to scanning start	5 s (from contrast infusion start)

turbances in PCT and early neurological deficit measured by NIHSS, as well as with 3-month outcome measured by mRS and GOS scales. This was analyzed for each PCT parameter and was treated as a continuous variable.

To assess sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PCT imaging in relation to 3-month outcome measured in mRS, each PCT parameter was dichotomized with arbitrary accepted thresholds adopted from current literature, differentiating infarction from non-infarction: CBV $<$ 2.0 ml/100 g, rCBV $<$ 60%, CBF $<$ 10 ml/min/100 g, rCBF $<$ 48%, and expressing significant and nonsignificant regional brain ischaemia: MTT $>$ 6 s, rMTT $>$ 145% [7, 10, 11]. Analyses concerned stroke outcome measured by mRS in two functional conditions: an excellent outcome with no disability (90-day mRS dichotomized to score $\leq$ 1 and $>$ 1) and independent functional outcome with slight disability (90-day mRS dichotomized to score $\leq$ 2 — as favourable, and $>$ 2 — as unfavourable outcome), using Fisher's exact test.

A P value $<$ 0.05 indicated statistical significance (SYSTAT for Windows [Microsoft®]; SYSTAT Software Inc. Chicago, IL, USA).

Results

Based on emergency CT examination, ischaemic stroke was diagnosed in 879 patients out of 1107 consecutive patients referred to our Stroke Unit in the period 2003–2005 with initial suspicion of acute stroke. In the ischaemic stroke group, PCT examination was performed in 86 patients admitted within six hours of onset of symptoms. We excluded from further analysis three patients with neoplasmatic illness diagnosed following observation, four with different diagnoses than stroke, seven with TIA, four in whom the time of onset of symptoms was uncertain, four because of treatment with rt-PA, and two patients because they were transferred to another hospital and were lost to follow-up. A further seven patients were excluded because hypodense areas of brain parenchyma were detected on emergency CT.

Finally, we analyzed data from 55 patients (27 women), with mean age 67 $\pm$ 11 years (range, 36 to 82 years). Median time from symptoms onset to PCT was 2.26 hours (interquartile range 1.53 to 4.91 hours), median NIHSS on admission was 8.0 (interquartile range 5.5 to 11.5), and at 7 days (or earlier discharge) was 5.0 (interquartile range 2.0 to 9.0). Arterial hypertension was reported in 76.4% of patients, ischaemic heart disease in 63.6%, previous stroke in 10.9%, TIA in 7.3%, previous myocardial infarction in 14.5%, atrial fibrillation in 30.9%, diabetes mellitus in 23.6%, and hyperlipidaemia in 21.8%.

Significant differences of mean registered values between both hemispheres in all analyzed PCT parameters were observed (Table 3). No significant statistical difference between sex subgroups was found in age, known risk factors of ischaemic stroke, registered values of cerebral blood flow in affected and non-affected hemispheres, initial and follow-up clinical state, or mean values of circulation parameters (blood pressure and heart rate; Student's t-test, $P > 0.05$). Additionally, time from onset of symptoms to PCT study, and circulation parameters in time of imaging examination, such as blood pressure and heart rate, did not influence the PCT results in any observed parameters (Spearman's rank correlation, $P > 0.05$).

Table 4 presents the result of analysis of the correlation between initial cerebral flow disturbances observed in all selected PCT parameters and neurological deficit on admission, on days 1 and 7 measured by NIHSS, and with degree of disability at day 90 measured by mRS and GOS. Neurological deficit severity on admission and during hospital observation significantly correlated with all direct and relative PCT parameters, although at day 90 functional outcome significantly correlated only with initial CBF and all relative PCT parameters. Relative values (r) of selected PCT parameters, calculated as percentages of the values registered in the contralateral hemisphere, demonstrated notably higher correlation with the degree of initial neurological deficit and final disability intensity than absolute values, with rCBF showing the strongest correlation denoted by the highest R statistic.

Table 3. Mean cerebral perfusion values in affected and non-affected hemispheres observed in PCT in patients with acute ischaemic stroke at time < 6 hours from onset of symptoms and without parenchymal hypodensity in routine initial non-contrast CT

PCT parameter	Affected hemisphere Mean (–95% CI – +95% CI; SD)	Non-affected hemisphere
CBV [ml/100g]*	2.35 (1.80–2.90; 2.03)	2.88 (2.42–3.34; 1.70)
CBF [ml/100g/min]**	25.92 (20.45–31.39; 20.23)	54.88 (44.54–65.22; 38.25)
MTT [s]**	10.58 (8.81–12.35; 6.55)	4.61 (3.50–5.72; 4.10)

CBV — cerebral blood volume; CBF — cerebral blood flow; MTT — mean transit time; CI — confidence interval; SD — standard deviation; *$P < 0.05$; **$P < 0.001$ (n = 55; paired 2-sided t test)

Table 4. Relationship between brain perfusion disturbances in PCT (<6 hours from onset) and observed neurological early deficit and functional outcome in patients with acute ischaemic stroke and without parenchymal hypodensity in initial non-contrast CT

PCT	NIHSS Day 0	NIHSS Day 1	NIHSS Day 7 or discharge	mRS Day 90	GOS Day 90
CBV	–0.32*	–0.37*	–0.36*	–0.24	0.27*
rCBV	–0.37*	–0.38*	–0.45*	–0.37*	0.41*
CBF	–0.50†	–0.50†	–0.50†	–0.34*	0.39*
rCBF	–0.69†	–0.62†	–0.64†	–0.47†	0.52†
MTT	0.40*	0.37*	0.39*	0.25	–0.28*
rMTT	0.49†	0.39*	0.43*	0.28*	–0.34*

CBV — cerebral blood volume; CBF — cerebral blood flow; MTT — mean transit time; mRS — modified Rankin Scale; NIHSS — National Institute of Health Stroke Scale; GOS — Glasgow Outcome Scale. Parameters with (r) indicate relative to contralateral hemisphere values respectively. Negative correlation is marked with minus (–) sign; *$P < 0.05$; †$P < 0.001$. (n = 55; Spearman's rank correlation with *t* test of significance; *R* statistic)

Table 5. Prognostic value of observed PCT parameters for 3-month functional outcome

Outcome	PCT	Sensitivity	Specificity	PPV	NPV
Excellent mRS ≤ 1	CBV	51.7%	57.7%	57.7%	51.7%
	rCBV *	89.7%	34.6%	60.5%	75.0%
	CBF	86.2%	30.8%	58.1%	66.7%
	rCBF *	62.1%	69.2%	69.2%	62.1%
	MTT	37.9%	69.2%	57.9%	50.0%
	rMTT	51.7%	65.4%	62.5%	54.8%
Favourable mRS ≤ 2	CBV	48.7%	56.3%	73.1%	31.0%
	rCBV *	87.2%	43.8%	79.1%	58.3%
	CBF *	87.2%	43.8%	79.1%	58.3%
	rCBF *	59.0%	81.3%	88.5%	44.8%
	MTT	41.0%	81.3%	84.2%	36.1%
	rMTT *	53.8%	81.3%	87.5%	41.9%

PPV — positive predictive value; NPV — negative predictive value; CBV — cerebral blood volume; CBF — cerebral blood flow; MTT — mean transit time; mRS — modified Rankin Scale. Parameters with (r) indicate relative to contralateral hemisphere values respectively [n = 55; Fisher's exact test (two-tail); *$P < 0.05$]

The prognostic value of initial PCT for 3-month functional outcome measured with mRS in ischaemic stroke patients is presented in Table 5. Accepted brain perfusion thresholds observed in PCT were better predictors for favourable than for excellent outcome, with high sensitivity and positive predictive value. Relative values of observed PCT parameters were clearly better predictors than absolute values, with statistically significant differences for favourable outcome in all relative parameters, and for excellent outcome in rCBV and rCBF.

Discussion

This study demonstrates the significant clinical usefulness of local cerebral perfusion measurements performed with PCT in acute ischaemic stroke patients, in which routine emergency CT does not detect hypodensity. It was reported that the extent of initial brain hypointensity in routine CT significantly correlates with NIHSS and mRS [4, 6]; however, in many cases, adequate local brain infarction oedema is not observed in first CT and hypointense areas arise later than in the first 6 hours after artery occlusion [4]. Initial NIHSS evaluation is an important prognostic factor for clinical change [12] and for further outcome [13], but in clinical practice, in cases with normal initial CT results, prognosis may be based solely on baseline clinical presentation, or have to be supplemented by other studies. We have determined that the relationship between initial clinical presentation and observed in PCT early cerebral ischaemic deficit may enhance the prediction of clinical course and functional outcome in patients not treated with thrombolysis. Widely used measures of disability after stroke are mRS or Barthel Indexes [14]; nevertheless, we observed significantly better correlation with GOS than with mRS, which was probably associated with better distinction of exact degree of disability in this rating tool. We have shown that in patients without early hypodense changes in CT imaging, clinical evaluation may be supplemented by measurement of actual cerebral perfusion deficit, and presumably can help with judgment of forthcoming changes in unclear cases like progressive stroke or in case of transient ischaemic attack (TIA).

High sensitivity and specificity of PCT in the diagnostics of cerebral ischaemia have been reported, mainly in differentiation of infarction cores from tissue at risk [7]. An evaluation of the extent of local cerebral blood flow disturbances with PCT is useful in the prognosis of final infarction size, and the proportion of penumbral and ischaemic core coverage may be prognostic to clinical outcome [15]. An association between PCT parameters and clinical state has been reported previously; however, there are still a small number of studies exploring the direct relationship between initial blood flow reduction and remote functional outcome, and they are based only on small groups of patients, and usually in a longer time window [8, 16]. For the delayed prognosis, the thresholds of perfusion that we adopted from literature were better predictors of independent (mRS 0–2) than of excel-

lent (mRS 0–1) outcome. The sensitivity and positive predictive value of direct measurements were high and statistically significant for favourable outcome only in CBF (87.2% and 79.1%, respectively). However, in relation to the contralateral hemisphere, all the parameters reached statistical significance. The specificity and negative predictive value were only satisfactory, probably due to the small sample size and limited brain amount imaged. Moreover, most authors underline that absolute values of cerebral perfusion in PCT do not illustrate exact cerebral blood flow; only Positron Emission Tomography (PET) is the accepted method of correct ischaemic threshold estimation [17, 18]. Direct values of CBF and CBV may substantially differ depending on various factors, e.g. they show near 20% individual variability, and gradual reduction with age [19, 20], and because of this, the relative evaluation of registered values with the contralateral (non-affected) hemisphere is of higher significance in every available parameter [8, 10]. In our study relative (r) parameters also demonstrated stronger correlation with clinical state, and the dependence of external factors or age was not confirmed.

The method we used in PCT analysis may raise a few technical issues, although we designed it from a clinical, not radiological perspective and aimed to shorten the time of analysis. In routine clinical practice, volumetric assessment of the ischaemic core and penumbra involves time-consuming calculations and may be difficult in an emergency setting. Furthermore, depending on the software used, the results of the PCT may be presented in various colourful maps, with different colours indicating different blood flows [21], and the decision of whether an exact part of the brain tissue is still viable or irreversibly infracted is based on the subjective visual judgment of a radiologist using software-presupposed thresholds. To simplify the procedure we have prepared a template of ROIs covering a whole imaged brain section, discriminating all territories of vascularisation of the main cerebral arteries in both hemispheres, delivering exact values of perfusion parameters, averaged within particular ROIs, and compared between hemispheres. This procedure was quick and easy to use, even by a technician. Additionally, in our analysis we adopted perfusion thresholds from current literature, because we were unable to reliably establish our own thresholds due to the fact that we only had initial PCT results without the following imaging control verifying localization of measurements. According to the WHO definition of stroke [22], the final diagnosis of ischaemic stroke is not radiological but clinical, and, following the guidelines, this was a matter of routine pragmatics, where, in the majority of patients, after initial CT excluding haemorrhage, the subsequent examinations are not performed if it is not definitely necessary.

Application of cerebral perfusion studies have been proposed as a useful additional tool in the thrombolytic treatment qualification process [23, 24]. The results of rt-PA therapy in acute stroke are not only dependent on time from artery occlusion to recanalisation, but first of all on the proportion of the extent of penumbra and infarction size [25–27]. We did not observe patients treated with thrombolysis because our study started before this treatment was approved in the EU and Poland, but the protocol assumed the inclusion patients potentially eligible for thrombolysis. On the other hand, even if the treatment window for thrombolysis in acute ischaemic stroke is widening [28, 29], there is still, proportionally, a tremendous number of patients excluded from rt-PA therapy, requiring appropriate monitoring and control of clinical changes and effects of conservative treatment.

PCT is a well-tolerated study that is not time-consuming, and it can easily be integrated with routine CT in standard imaging processes in the acute stroke setting in all patients; however, a few disadvantages of this technique should be noted. Examination of PCT, depending on the scanner, may be performed only in a limited region of the brain (1–4 cm thick layer), and due to this, the exact localization of the ischaemic process can be omitted. In our study this was a 1 cm thick layer, and localization of the performed measurements (ROIs) was not controlled by follow-up imaging evaluation. Furthermore, PCT technique favours supratentorial strokes, and therefore patients with circulation deficits in the vertebro-basilar region are under-represented in most studies.

Conclusions

In acute stroke patients with normal CT results within the first 6 hours, direct values of local cerebral perfusion derived from brain PCT show good correlation with initial neurological status and may help in the prognosis of late functional outcome. Acute ischaemic stroke patients with normal routine initial CT results and PCT values lower than accepted, perfusion thresholds for brain ischaemia have a less favourable clinical course.

Disclosures

Nothing to disclose.

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