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Bedeutung der Perfusions-Computertomographie

beim akuten ischämischen Insult

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Zusammenfassung

Hintergrund. Der ischämische Insult ist ein Notfall, der nach wie vor mit sehr hoher Morbidität und Mortalität verbunden ist. Intravenöse und intraarterielle Thrombolyse innerhalb eines Zeitfensters von 4,5 bzw. 6 h ist effektiv, sicher und gilt inzwischen als Standardtherapie. Vor einer Lyse muss die intrazerebrale Blutung als wichtigste Differentialdiagnose des ischämischen Insults mittels Computertomographie (CT) oder Kernspintomographie (MRT) ausgeschlossen werden.

Die CT-Agiographie und Perfusions-CT-Bildgebung (PCT) ist eine schnell verfügbare und Zusatzuntersuchung, die über den Ausschluss einer Blutung hinaus den Positivnachweis einer Ischämie erbringen kann.

Ziel. Ziel unsere retrospektive Studie war es, den prädiktiven Wert der PCT für Infarktgröße, initiales Defizit, frühe Besserung und Prognose bei lysierten und nicht lysierten Patienten zu überprüfen.

Methoden. Bei 92 Patienten (47 lysiert), die bei Aufnahme eine CT mit PCT sowie eine Kontroll-Bildgebung nach 24 Stunden erhalten hatten, wurden verschiedene PCT-Parameter gemessen und deren Vorhersagewert auf die initiale Symptomatik (gemessen mit dem NIHSS) und ihre Verbesserung, auf die Infarktgröße und der Grad der Behinderung nach der Entlassung aus der Rehabiliation (gemessen mittels modified Rankin Scale) ermittelt.

Ergebnisse. Je größer die Fläche der Perfusionsdefizits und je älter der Patient, desto schwerer war die neurologische Symptomatik bei Aufnahme (NIHSS). Die endgültige Infarktgröße wird ebenfalls von der Fläche des Perfusionsdefizits bestimmt und ist zudem größer, je verzögerter der Kontrastmittelbolus im Ischämieareal ankommt (*time-to-peak* Latenz). Während kein Parameter die frühzeitige Verbesserung der neurologischen Symptomatik vorhersagen konnte, korrelierte der Grad der Behinderung nach Entlassung aus der Rehabilitation mit der Fläche des Perfusionsdefizits – dies allerdings nur in der nicht-lysierten Gruppe.

Schlußfolgerung. Die PCT Bildgebung korreliert mit dem akuten Defizit und hat einen Vorhersagewert für die Größe der endgültigen Läsion und das funktionelle Outcome. PCT stellt eine medizinisch sinnvolle Zusatzuntersuchung beim akuten ischämischen Insult da, die in Routineprotokolle aufgenommen werden sollte, weil mit ihr der Positivnachweis einer zerebralen Ischämie mit Vorhersagewert erbracht werden kann. Diese Studie erlaubt keine Schlussfolgerungen in Bezug auf die Kernspintomographie bei akuten Schlaganfall, die im Vergleich zum CT die überlegene Methode sein könnte.

Schlüsselwörter: Ischämische Schlaganfall, Perfusions-CT, TTP, CBV, CBF, Penumbra, Entgültige Inafrktgröße, functionelle Outcome.

Abstract

Introduction. Ischemic stroke is a medical emergency that is still associated with high morbidity and mortality. Intravenous or intraarterial thrombolysis is an effective treatment to improve stroke outcomes when applied within 4.5 to 6 hours after symptom onset. Before thrombolysis an intracerebral hemorrhage has to be ruled out by computed tomography (CT) or magnetic resonance imaging (MRI).

CT angiography (CTA) and perfusion CT (PCT) are additional CT-based methods, that are readily available and allow for a direct demonstration of acute ischemia.

Aim. The aim of this retrospective study was to evaluating the predictive value of PCT for infarct volume, initial stroke-related deficit, and early improvement and mid-term outcomes after stroke in patients receiving thrombolysis and those that did not.

Methods. 92 subjects (47 received thrombolysis) with ischemic stroke who underwent non-enhanced CT and PCT on admission and a non-enhanced CT after 24 hours were included. PCT parameters were measured and their predictive value for stroke volume, initial deficit, early improvement, and outcome were evaluated.

Results. The larger the perfusion deficit and the older the patient, the graver was the stroke-related deficit upon admission (NIHSS). Likewise, final stroke volume depended on the size of the perfusion deficit. Additionally, later arrival of contrast in the ischemic area (*time-to-peak* latency) predicted stroke volume. While no parameter explained the variability in early improvement, the outcome after rehabilitation was in part explained by the size of the initial perfusion deficit – however, only in patients not receiving thrombolysis.

Conclusion. PCT imaging provides parameters that are correlated with the acute deficit and predict final lesion size and functional outcome. PCT represents a useful exam that should be added to the diagnostic CT work-up for acute

ischemic stroke, because it provides direct evidence of ischemia that can be used for the determination of prognosis. This study does not allow for conclusions about MRI in the acute setting, which may still be the superior method when compared with CT.

Key Words: Ischemic stroke, perfusion CT, TTP, CBV, CBF, Penumbra, final infarct size, functional outcome.

Introduction

Ischemic stroke is an emergency [1]. The incidence in industrialised countries is approximately 150 cases per 100,000 per year. Hence, ischemic stroke is a common disease. Stroke is more prevalent in higher age groups. Consequently, stroke is the third leading cause of death and the leading cause of disability among adults in the Western world. Two thirds of all patients with ischemic stroke are either dead or dependent after 6 months. Stroke survivors are at risk of recurrent stroke [2, 3].

In selected patients, intravenous administration of recombinant tissue-type plasminogen activator (rTPA) within 4.5 h or its intraarterial administration within 6h of symptom onset (thrombolysis), is an effective treatment option that improves outcomes [4-8]. Thrombolysis can only be given when a hemorrhagic stroke is ruled out by cranial imaging studies. These can be computed tomography (CT) or magnetic resonance imaging (MRI). While non-contrast enhanced CT (NECT) rules out hemorrhage, MRI can additionally demonstrate early ischemia. NECT is typically normal during the first hours of an ischemic stroke and even if early signs of ischemia are observed, regional definition of ischemic tissue and differentiation between viable and irreversibly damaged brain is not possible[9]. Measuring brain perfusion with contrast-enhanced CT may substantially improve the CT-based diagnosis of acute ischemic stroke.

Under normal circumstances cerebral perfusion is held constant by the autoregulation of cerebral arteries. The normal cerebral blood flow (CBF) in the grey substance varies between 50 and 60 ml/100g of brain tissue/min [10]. When a cerebral artery is occluded, tissue survival depends on the effectiveness of collateral blood supply, e.g., through the circle of Willis or leptomeningeal anastomoses. Cellular protein synthesis ceases at blood flows below 35 ml/100 g/min. At CBF levels lower than 20 ml/100 g/min synaptic transmission ceases (loss of function). Both cellular deficits are usually reversible if blood flow is reinstated (recanalisation/reperfusion). Further decrease of cerebral blood flow below 10 ml/100 g/min leads to irreversible cell damage (loss of viability) [11, 12].

The perfusion "window" in which cells are still viable, but their electrical function is lost and causes neurological symptoms, opens a window for treatments that aim at recanalization [13].

A cerebral infarct usually has a core in which perfusion is reduced below the viability threshold. In the border zone to the adjacent normal tissue, collaterals can still provide sufficient perfusion to preserve viability, but not function. This border zone is called "penumbra". It is conceptualized that recanalization through thrombolysis saves the penumbra thereby reducing final infarct size and neurological deficits [14, 6, 7].

The benefit of thrombolysis has been shown to vanish, when used later than 4.5 hours of symptom onset. With time tissue dies and the likelihood of hemorrhagic complications of thrombolysis increases. Within this time window, thrombolysis is the more effective the earlier it is administered. Therefore, patients have to be diagnosed and treated as rapidly as possible ("Time is Brain"). Acute stroke imaging protocols have to compromise between loss of time and gain of information [6, 15-18].

Perfusion CT (PCT) is a relatively new technique that measures perfusion by tracking a bolus of contrast medium passing through cerebral arteries and brain tissue. Areas of reduced perfusion can be identified and the degree of reduction can be quantified. Quantification uses deconvolution of the arterial and tissue enhancement curves, which is a mathematical operation allowing for the calculation of mean transit time (MTT) or time-to-peak (TTP) of the contrast enhancement. Regional cerebral blood volume (rCBV) can be derived as the area under the curve (AUC). Regional cerebral blood flow (rCBF) is instead derived from the central blood volume equation (CBF = CBV/MTT) [19].

PCT provides excellent information regarding the severity and extent of ischemia. The use of various perfusion maps helps to differentiate the core of infarction from the ischemic penumbra zone [20] – that is, viable tissue with reduced perfusion that potentially can be salvaged by thrombolysis [19, 21, 22].

CBF (cerebral blood flow) and CBV (cerebral blood volume) have some value in assessing the viability of ischemic brain tissue in humans[23, 24]. The reliability and

reproducibility of perfusion parameter measurements provided by CT have been validated in the literature [20, 23-26]. Sparacia et al (2007) showed that the mean transit time (MTT) is the perfusion parameter best suited for discriminating between viable and infarcted tissue.

In a CT Perfusion study combined with ASPECT score (Alberta Stroke Program Early Computed Tomography) assessing the extent of the ischemic lesion, a cerebral blood volume (CBV) ASPECT score was a good predictor of clinical outcome after intravenous thrombolysis (odds ratio, 31.43; 95% confidence interval, 3.41-289.58; p<0.002), and was superior to NIHSS, NECT and CT angiography (CTA) [27]. Examination time for the entire acute stroke imaging protocol (NECT, CTA and CTP) does not exceed 5 to 6 minutes for the CT scans and another 5 to 8 minutes for standardized analysis of the CTP and CTA studies [28].

Information on the predictive value of CTP parameters on the final stroke volume and clinical outcome in thrombolyzed and non-thrombolyzed patients is limited. In Tübingen, NECT, CTA and PCT are routinely performed in every patient with a presumed stroke or transient ischemic attack. This large collection of cases has been retrospectively analysed to evaluate the predictive value of CTP parameters.

Aim of this study

The aim of this retrospective study is to evaluate the predictive value of PCT parameters TTP, CBV and CBF on final stroke volume, early clinical improvement and mid-term clinical outcomes in thrombolysed and non-thrombolysed patients. Two specific questions are addressed:

1. Do the areas of reduced or absent (=nearly absent) perfusion predict infarct volume and outcome?

2. Does the degree of perfusion reduction (measured by MTT or reduction in CBF/CBV) predict outcome and infarct volume?

Additionally, the predictive value of parameters such as the time interval between symptom onset and CT, age, gender, anterior/posterior circulation strokes and initial deficit that were collected as part of this analysis, was assessed.

Materials & Methods

All cases of ischemic stroke confirmed by computed tomography (CT) admitted to the Stroke Unit of the University of Tübingen Hospital between January 2005 and December 2006 were retrospectively screened for inclusion into this retrospective dataset. A total of 187 patients were identified. Cases without acute-phase CT datasets in raw format that allowed postprocessing of PCT, or cases without a follow-up CT scan between 24 hours and 5 days were excluded. Ninety-two patients remained with complete datasets. Fourty-seven of those received intravenous or intraarterial thrombolysis. This high thrombolysis rate does not represent the true rate, but is the result of a selection bias because thrombolysed patients more consistently had a follow-up CT scan. Medical records and CT/PCT datasets of all patients were reviewed. Patient demographics were collected along with the National Institutes of Health Stroke Scale (NIHSS) on admission and between 2 and 5 days, the pre-admission modified Rankin Scale (mRS), the presence of atrial fibrillation (AF) and the time from symptom onset to the CT scan (time-to-CT). The functional status of the patient at the time of discharge from rehabilitation was assessed using the modified Rankin scale (discharge mRS) obtained from the discharge letters of the rehabilitation hospitals. Where unavailable, the patient was contacted by telephone to obtain the mRS based on a standardized interview [29].

Perfusion CT

CT and PCT are part of the routine diagnostic workup for ischemic stroke at our institution. Using a 16-slice CT scanner (Sensation 16, Siemens, Erlangen, Germany), a PCT protocol was acquired as previously described [9]. In brief, two slices are positioned such that they cut through the basal ganglia at the level of the internal capsule and 3-4 cm above, the angulation being adjusted perpendicular to the occipital segment of the superior sagittal sinus above the confluence of the sinuses (10 mm slice thickness). This positioning ensures that MCA, ACA and PCA vascular territories can be imaged.

A bolus of non-ionic contrast medium (Imeron 300, Altana pharma GmbH, Germany) at a concentration of 300–370 mg/ml is injected intravenously. Total injection time is five seconds. The short injection time is adjusted to the short blood transit time (approximately 3 to 5 seconds) and a relatively small fractional blood volume (approximately 2 to 5%). This requires a short bolus for optimal time resolution together with a minimum amount of contrast medium for optimal signal to noise ratio. Thirty-five to 40 ml of contrast medium are given intravenously at a flow rate of 6-8 ml/sec using a synchronised injector system (Medrad Stellant SCT 121, Siemens medical solutions, Erlangen, Germany). After injection of the contrast agent, the venous line is flushed with 35-40 ml of normal saline solution. Perfusion images are acquired for 40 s with a rate of 2 images per second with 80 kVp and 250 mAs with an effective dose of 5.3 mSv.

PCT raw data were post-processed by first computing coloured maps of time-to-peak (TTP) latency values, cerebral blood volume (CBV) and cerebral blood flow (CBF). Conventional software was used (Syngo Somaris/5, VA40c, Siemens, Erlangen, Germany). Based on contrast concentration over time curves computed for every tissue voxel as well as for voxels in a large artery, mean transit time (MTT) values are calculated using a deconvolution procedure of arterial and tissue curves. The CBV is estimated as the area under the tissue curve divided by the area under the arterial curve. CBF is derived using the central volume equation, CBF = CBV/MTT. The TTP value is the time at which the curve reaches its maximum [30].

Hence, the time-to-peak image represents the interval in which the contrast agent reaches the tissue compartment. High values indicate delayed perfusion and are the most sensitive measure of imminent ischemia [30]. The CBF image reflects the blood flow reaching the tissue, CBV its volume.

CBF and CBV are colour coded such that for the normal brain, red pixels represent vessels, green/yellow pixels gray matter, blue pixels white matter, and black pixels regions without perfusion. There, flow cannot be calculated, because no contrast reaches this region (e.g., CSF space). In the ischemic brain using the non-ischemic hemisphere as the reference for adjusting the colour codes, ischemic areas will therefore be either violet (very low flow) or black (no

blood flow). For the TTP image the colour palette is directly proportional to the latency ranging from violet (normal perfusion) → blue → green → yellow → red (delayed, abnormal perfusion). In black areas no time assessment is possible, because no contrast reached this region.

All maps were further analyzed with reference to the contralateral (intact) hemisphere (**figure 1**).
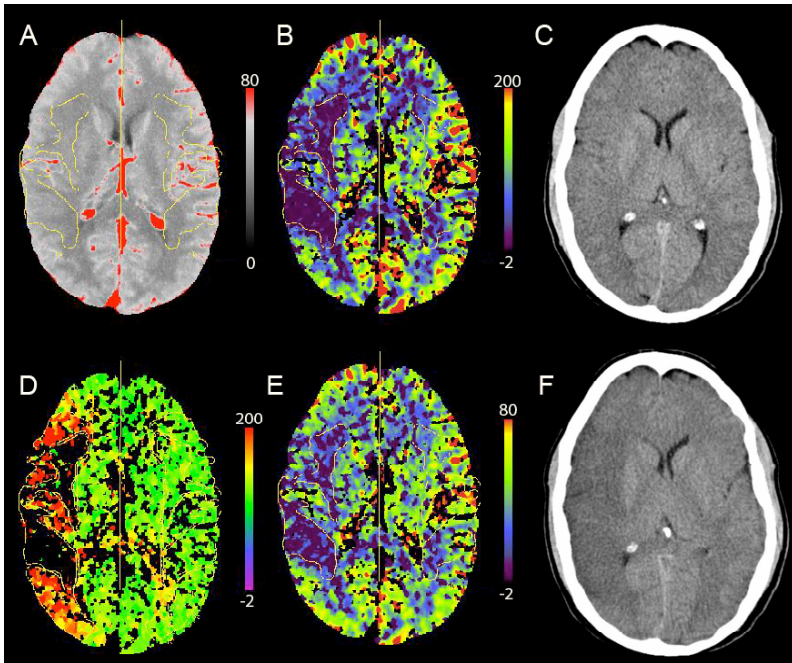

Figure 1A-F. NECT and PCT 1.5 h after the onset of symptoms: A. Selected slice of a multiscan head CT showing the occipital segment of the superior sagittal sinus, B. Colour-coded CBV map reveals an area of reduced blood volume in the left hemisphere, C. apparently normal NECT, D. Colour-coded TTP map reveals delay in perfusion (red) and extreme delay (black). E. Color-coded CBF map with superimposed area of "no perfusion" as delineated on the TTP map, F. The follow up CT after 24 hours demonstrates the area of hypodensity involving 60% of media territory excluding the basal ganglia and thalamus.

In the TTP map, two ROIs were manually delineated, (1) areas with nearly no perfusion (black regions in **figure 1**) potentially reflecting the infarct core and (2) areas of perfusion delay (red regions in **figure 1**). The sizes and the average

TTP values for both ROIs were recorded. Average TTP values were divided by the TTP values of the corresponding mirror region in the intact hemisphere.

The stroke volume was measured on follow-up CTs by manually delineating the area of hypodensity or on MRIs using the area of FLAIR hyperdensity. The section with best correspondance to PCT slice positions were selected. Follow-up imaging was available between 24 hours and 5 days.

Statistical analysis

General linear models were used to assess the predictive value of four sets of independent variables on each of the following dependent variables:

- *Time-to-CT*, as measured by the interval between symptom onset and the time of the initial CT scan,
- admission National Institutes of Health Stroke Scale (*admission NIHSS*)
- *stroke volume*, which was not a true volumetric measure but rather the size of the hypodense area on the non-contrast enhanced follow-up CT scan acquired between 24 hours and 5 days. The hypodensity was measured on the sections best corresponding to the PCT slice showing the largest perfusion abnormality.
- *early NIHSS improvement*, measured as the difference between the admission NIHSS and the NIHSS after 24 hours as documented in the records.
- and *outcome*, measured as the modified Rankin Scale (mRS) at the time of discharge to home or a nursing institution (after inpatient rehabilitation).

Separate models were computed for four sets of independent variables:

(1) demographic/history/acute management variables including *age*, *gender* [male, female], *ant./post. circulation stroke* [ant, post], *atrial fibrillation* [yes, no], *time-to-CT,*

(2) regional PCT parameters including the size of the area of PCT abnormality including the area with perfusion below the detectable threshold on the TTP map (dark pixels, for reasons of simplicity this area

will be refered to as *area_no perfusion,* although minimal perfusion may have still be present*),* and the area with reduced perfusion (red pixels, *area_low perfusion*)*.* The area was always measured on one of the two available perfusion slices, which showed the largest lesion. To assess *stroke volume* the areal size of the lesion on the corresponding non-contrast CT slice was measured.

(3) Temporal PCT parameters including

      a. the average TTP latency, CBF and CBV values in the <u>area of "no perfusion"</u>, i.e., the average pixel intensities in the respective TTP, CBF and CBV maps.

      b. the average TTP latency, CBF and CBV values in the <u>area of low perfusion</u>, i.e., the average pixel intensities in the respective TTP, CBF and CBV maps.

Separate models were computed because the number of subjects did not allow for a large combined model comprising of many independent variables. In addition, the variables of (3) were undefined for cases in which an area of "no perfusion" was not detected. Hence inclusion of these variables into a large model would have excluded many cases.

For dependent variables likely to be influenced by thrombolysis (*stroke volume, NIHSS improvement* and *outcome*) separate models were computed for each group. This was necessary because the groups differed in stroke severity – an expected disadvantage of the retrospective study design.

Where appropriate, Levene's test was applied to test for homogeneity of variances between groups. Data are reported as mean ± SEM.

Results

Subject sample

Ninty-two subjects (40 females and 52 males) who were admitted with an acute ischemic stroke to our Stroke Unit between January 2005 and December 2006 were included. Cerebral ischemia was either demonstrated by non-enhanced CT (on admission or follow-up) or by PCT. Forty-seven received thrombolysis.

Thrombolysed patients were more severely affected than non-thrombolysed subjects, reflecting a selection bias inherent to the retrospective study design. Increased severity was evident in larger stroke volume on follow-up CT, higher admission NIHSS, and worse mRS at discharge (**table 2**). Due to this difference in severity, the two subgroups were analyzed separately for all dependent variables potentially affected by thrombolysis, i.e., improvement in NIHSS, mRS at discharge and volume of hypodense tissue on follow-up CT.

Table 2: Patient sample characteristics

	Lysis	No Lysis	P
N	47	45	
Age (mean ± SEM)	68.0±2.1	69.3±1.7	0.63
Sex (f/m)	21/26	19/26	0.84
Atrial fibrillation	19 (40%)	13 (29%)	0.28
Anterior/posterior circulation	43/4	35/10	0.09
Time-to-CT	2.02±0.13	5.93±1.01	**0.0004**
Hypodensity on follow-up CT (cm^3)	15.02±2.36	5.75±1.40	**0.0012**
Admission NIHSS	11.5±0.7	6.4±0.7	**<0.0001**
NIHSS improvement	3.62±0.65	2.44±0.27	0.10
mRS before stroke	0.42±0.12	0.51±0.13	0.63
mRS at discharge	2.94±1.77	2.11±0.18	**0.0110**

Expectedly, time to CT was significantly shorter in thrombolysed as compared with non-thrombolysed patients. Overall, anterior circulation ischemia was more frequent than posterior cerebral circulation ischemia (85% versus 15 %).

Variables predicting time to initial CT scan

Female patients received their initial CT scan earlier than males (p=0.0424). Patients with anterior cerebral circulation strokes arrived earlier to CT scanning than those with posterior circulation strokes (p<0.0001). Higher NIHSS on admission was predictive of shorter onset-to-CT times (p=0.0013, **table 3**; **figures 2-4**).

Table 3. Predictive model for *time to initial CT*

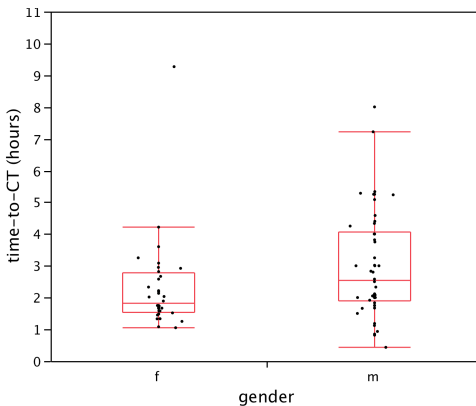| Effect	Estimate	SE	DF	F	p
Gender	-0.32	0.16	1	4.25	**0.0424**
ant_post	-1.26	0.23	1	30.27	**<.0001**
Admission NIHSS	-0.10	0.03	1	11.04	**0.0013**

Error DF 82

Figure 2. In female patients the time from symptom onset to the initial CT scan was shorter than in male patients (p=0.0424)
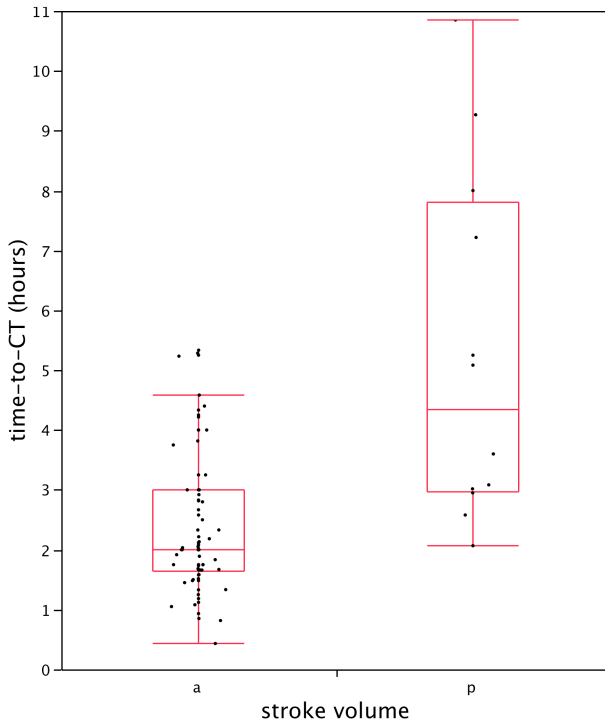
Figure 3. Patients with anterior circulation strokes (a) had shorter symptom onset-to-initial CT times than patients with posterior circulation stroke (p<0.0001).
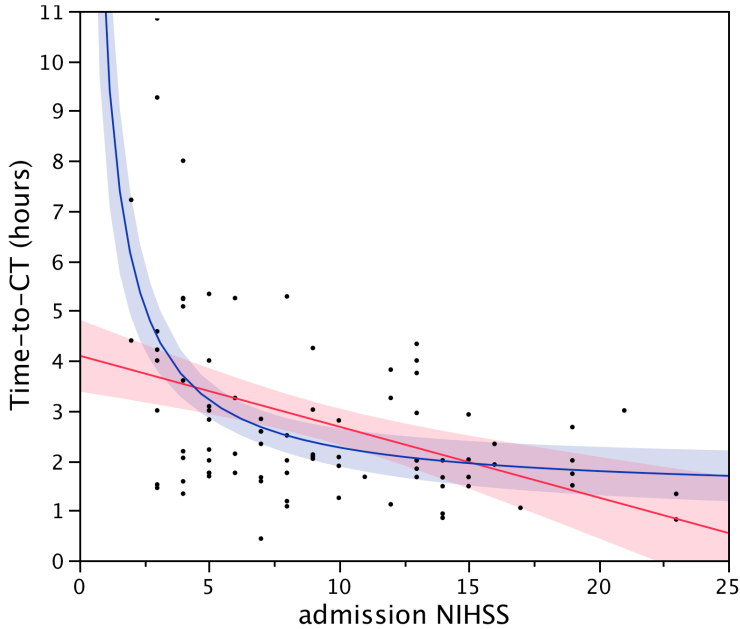
Figure 4. *Higher NIHSS on admission predicted shorter symptom onset-to-CT time (p=0.0013). The relationship was better predicted by an exponential than a linear function (light red and blue areas indicate 95% confidence intervals).*

Variables predicting the acute stroke-related deficit

Higher admission NIH Stroke Scales (NIHSS) were found in older patients (p=0.0348, **table 4, figure 5**). As mentioned above, there was a significant inverse relationship between *admission NIHSS* and *time-to-CT* (p=0.0025).

Table 4. Admission deficit predicted by *age* and *time-to-CT*.

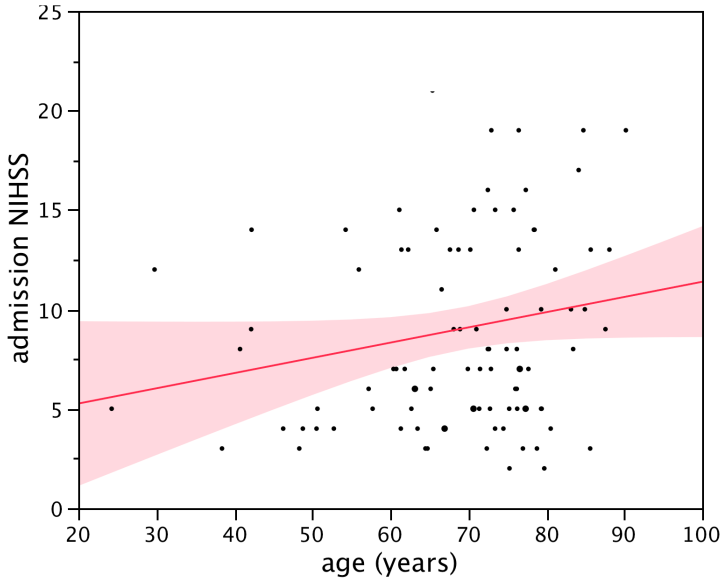| Effect	Estimate	SE	DF	F	p
Age	0.09	0.04	1	4.59	0.0348
Time-to-CT	-0.31	0.10	1	9.67	0.0025

Error DF 88

20

Figure 5. Higher age predicted higher admission NIHSS (p=0.0348, light red area indicates 95% confidence intervals).

The second model investigated the predictive value of regional PCT parameters (size of areas with low perfusion, *Area_low perfusion*, or absent perfusion, *Area_no perfusion*) on admission NIHSS; *time-to-CT* was included as a covariate because it is expected to influence PCT. Larger *area_no perfusion* regions predicted higher NIHSS (p<0.0001, **Figure 6**). This effect was independent of the effect of *time-to-CT* on *area_no perfusion* (**Table 4**). Time-to-peak latency did not predict admission NIHSS.

Table 4. Tissue hypoperfusion predicting admission deficit

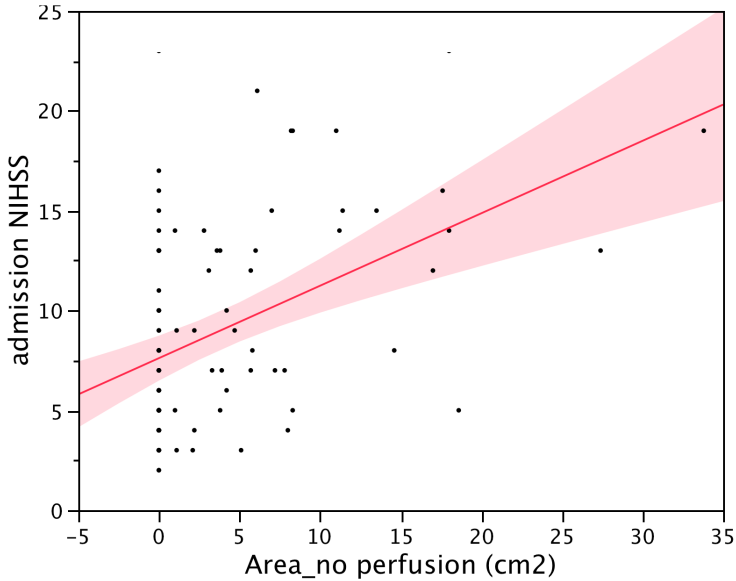| Effect	Estimate	SE	DF	F	P
Area_no perfusion	0.33	0.08	1	19.63	**<.0001**
Time-to-CT	-0.24	0.09	1	6.52	**0.0124**

Error DF 88

Figure 6. *Larger CBF tissue hypoperfusion (black area on the CBF map) predicted higher acute deficits, i.e., higher NIHSS (light red area indicates 95% confidence intervals).*

Variables predicting stroke volume

The variability in stroke volumes was not explained by any of the demographic/history/acute management variables irrespective of whether or not the patients received intravenous thrombolysis.

The tissue area with absent cerebral blood flow (*Area_no perfusion*), however, predicted stroke volume in both groups of patients, with or without thrombolysis ($p < 0.0001$, **tables 6, 7**).

Table 6. Stroke volume predicted by PCT areas in the **non-thrombolysis group**

Effect	Estimate	SE	DF	F	p
Area_no perfusion	1.88	0.25	1	54.79	<0.0001

Error DF 43

Additionally, in patients receiving thrombolysis there was a significant interaction term between *time-to-CT* and the size of the tissue with delayed time-to-peak (*Area_low perfusion*) in predicting stroke volume (**table 6**). The thrombolysis group was therefore split into those that received a CT scan (and immediately thereafter thrombolysis) in less than 3 hours versus those in whom the time-to-CT was more than 3 hours. The majority of patients were thrombolysed in less than 3 hours and demonstrated no correlation between *Area_low perfusion* and *stroke volume*. In contrast, four patients with time-to-CT greater than 3 hours showed a negative correlation (r=0.98, p=0.0222, **figure 7**).

By plotting stroke volume over the size of the tissue region with absent blood flow (*Area_no perfusion*) we explored whether all tissue with absent CBF is irreversibly lost. Most had larger stroke volumes than *Area_no perfusion* values indicating irreversibility. In six subjects *Area_no perfusion* was slightly larger than stroke volume (dots below the 45° line in **figure 8**), the difference being within the range of measurement variability.

Table 6. Stroke volume predicted by PCT areas in the **thrombolysis group**

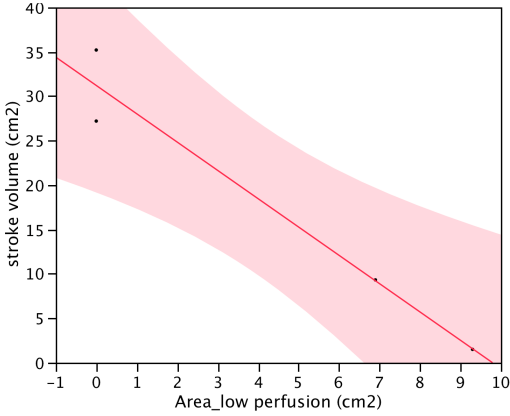| Effect	Estimate	SE	DF	F	p
Area_low perfusion	0.17	0.18	1	0.89	0.3520
Area_no perfusion	1.47	0.21	1	48.14	**<.0001**
Time-to-CT	1.11	2.07	1	0.28	0.5965
Time-to-CT x Area_low perfusion	-0.76	0.29	1	6.73	**0.0133**

Error DF 39

Figure 7*. In patients receiving thrombolysis later than 3 hours, there was a negative correlation between the tissue area with delayed time-to-peak values (r=0.98, light red area indicates 95% confidence intervals).*
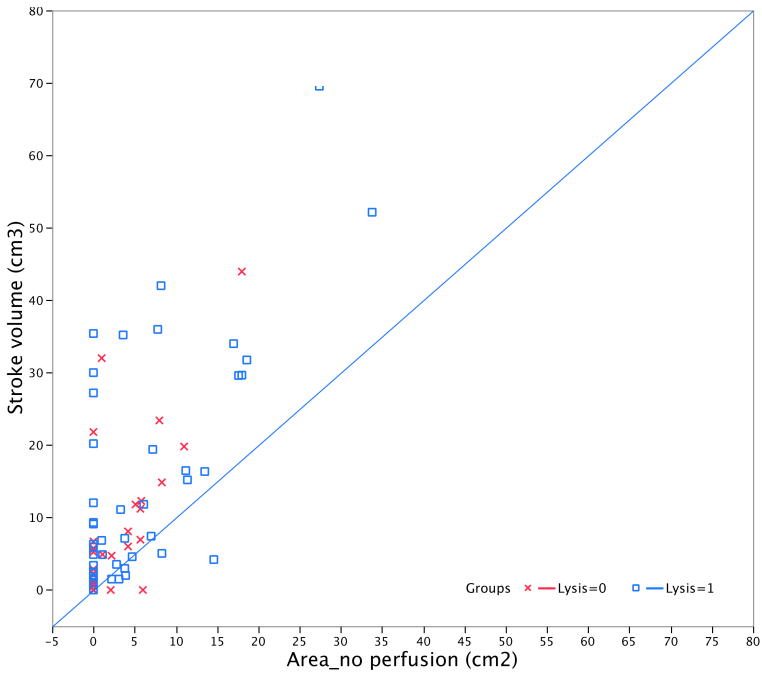
Figure 8. For the majority of patients, stroke volume was similar or larger than the area of absent perfusion determined by PCT (black CBF area). In the few cases with CBF areas larger than stroke volume (dots below the 45° line), the difference was within the measurement error, therefore, not serving as evidence that tissue with absent perfusion in the acute phase is salvagable.

Only in the non-thrombolysis group, stroke volume was predicted by the TTP latency (*TTP_low perfusion_ratio*, ratio between intact and ischemic hemisphere): higher latencies were related to greater stroke volume (**Table 7**).

Table 7: Stroke volume predicted by TTP latency in the non-thrombolysis group

Effect	Estimate	SE	DF	F	p
TTP_low perfusion_ratio	17.58	7.23	1	5.92	0.0245

Error DF 20

Variables predicting early improvement

Early improvement was quantified by the change in the NIHSS at admission and documented follow-up after 48 h (days 2 to 5). In both groups of patients with and without thrombolysis, no demographic/history/acute management or PCT variable predicted early improvement.

Variables predicting outcome

In the patients receiving thrombolysis, higher age was related to worse outcome as measured by the increase in the modified Rankin Scale (mRS) between the time before the stroke and the time of discharge to home or a nursing institution (**tables 8, figure 8**).

Table 8: mRS predicted by age in **thrombolyzed** patients

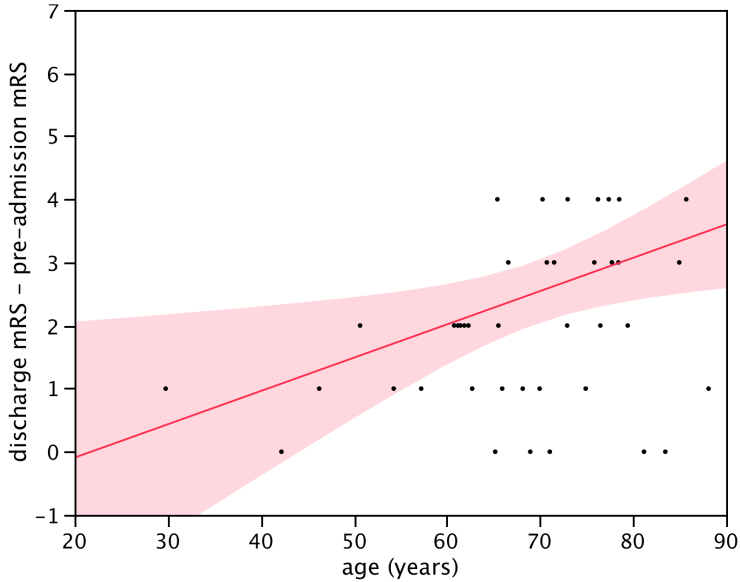| Effect	Estimate	SE	DF	F	p
age	0.05	0.02	1	6.26	**0.0160**

Error DF 45

Figure 8. In patients receiving thrombolysis, higher age was related to worse outcome (light red area indicates 95% confidence intervals).

The size of the area of nearly no perfusion on PCT (*Area_no perfusion*) predicted worse outcome in patients not receiving thrombolysis (**table 10, figure 9**). Time-to-peak latency was unrelated to outcome.

Table 10. mRS increase predicted by CBF area in **non-thombolyzed** patients

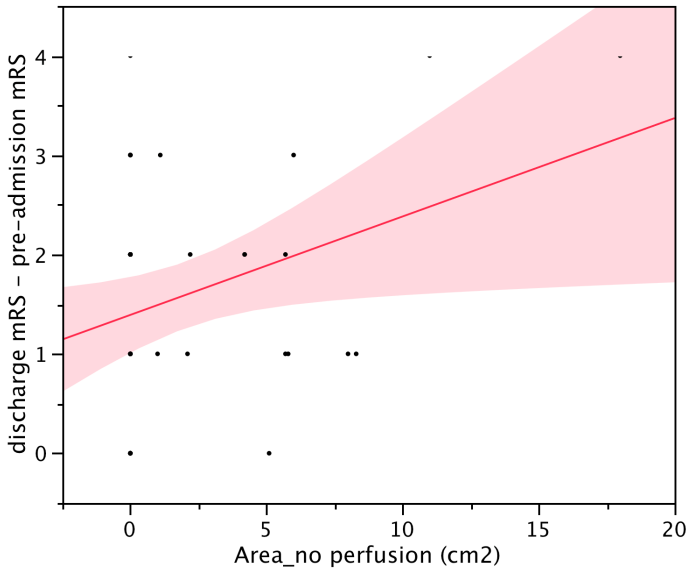| Effect	Estimate	SE	DF	F	P
Area_no perfusion	0.10	0.04	1	4.94	**0.0317**

Error DF 42

Figure 9. *Larger areas of absent CBF were related to worse outcome in non-thombolyzed patients (light red area indicates 95% confidence intervals).*

Summary of results

The following **table 11** summarizes the predictors for the different dependent variables.

Table 11. Summary of predictive models

Dependent	Population	Independent	Effect
Time-to-CT	All	*Gender*	Female < male
		Ant./post. circulation stroke	Ant. < post.
		Admission NIHSS	Inverse
Admission NIHSS	All	*Age*	Direct
		Time-to-CT	Indirect
		Area_no perfusion	Direct
Stroke volume	No thrombolysis	*Area_no perfusion*	Direct
		TTP_low perfusion_ratio	Direct
	Thrombolysis	*Area_no perfusion*	Direct
	Lysis >3h	*Area_low perfusion*	Indirect
Early NIHSS improvement	No thrombolysis	–	
	Thrombolysis	–	
Outcome (mRS at discharge – pre-admission mRS	No thrombolysis	*Area_no perfusion*	Direct
	Thrombolysis	*Age*	Direct

Discussion

Ischemic stroke is a common disease with high morbidity and mortality. In the acute phase, thrombolysis is the most beneficial treatment option, when applied intravenously within 3 hours or intraarterially within 6 hours of symptom onset. Such a short time window renders stroke a pressing emergency for which a fast and reliable diagnosis is the key to treatment success.

Perfusion CT (PCT) in addition to non-enhanced CT and CT-angiography is a reliable, easily accessible and prompt diagnostic tool for establishing the diagnosis of ischemic stroke, particularly in patients eligible for thrombolytic therapy. The goal of PCT is to identify tissue in ischaemic penumbra – that is, viable tissue with reduced perfusion that can be salvaged by thrombolytic therapy [19, 21, 22].

Here, we find that PCT parameters, especially the size of the area of tissue in which contrast arrives late (abnormal time-to-peak), are important predictors of early deficit, stroke volume and intermediate-term outcomes. Stroke volumes of the developed ischemic lesion are equal or larger than the area with nearly absent perfusion on PCT, indicating (1) that this region is not salvageable and (2) that in most patients the stroke grows between symptom onset and 24-48 hours.

The reliability and reproducibility of PCT parameters has been validated in the literature [20, 23-26]. Previous reports have demonstrated a significant correlation between perfusion and diffusion abnormalities as determined by diffusion weighted MRI (DWI) [31, 32]. It was demonstrated that a 66% reduction in CBF corresponds to a DWI lesion. Existing controversies as to which perfusion parameter is best for discriminating between viable and infarcted tissue was elucidated in a recent study, showing mean transit time, a parameter similar to TTP, to be better than CBV and CBF, with values greater than 6,05 seconds being able to identify infarcted tissue with a sensitivity of 84,6%, specificity of 100% and an accuracy of 92,3% [33]. We found a similar value of TTP latency in predicting stroke volume. However, the association was present only in patients

not receiving thrombolysis. Thrombolysis effectively improves brain perfusion by recanalising occluded vessel segments. Because it does not work in every patient, the addition of thrombolysis introduces additional variability to stroke volumes; this variability obliterates the correlation between PCT parameters and stroke volume. Only the area of nearly absent perfusion (*Area_no perfusion*) predicted stroke volume in thrombolysed patients indicating that this area is irreversibly damaged and not salvageable by thrombolysis. This finding confirms previous data [9] showing that thrombolysis has no effect on tissue blood flow less that 10ml/100 g/min. This perfusion threshold was also demonstrated in monkeys exposed to ischemia. A reduction in blood flow led to the gradual development of a neurologic deficit, progressing from mild pareses at a flow rate of 22 ml/100 g/min to complete paralysis at a rate of 8 ml/100 g/min[34]. Concurrently, the electrocorticogram and evoked potentials vanished at a flow rate of 15 to 20 ml/100 g/min[35] and the spontaneous activity of cortical neurons disappeared at approximately 18 ml/100 g/min[36]. However, individual neurons show differential vulnerability and, hence, have different perfusion thresholds [13]. In our study the mean CBF reduction was greater than 85%, which represents in absolute terms, a mean cerebral blood flow well below 10 ml/100 g/min when compared to the non-ischemic hemisphere.

Similar to stroke volume, the acute stroke deficit is predicted by *Area_no perfusion*. This area of perfusion deficit on the TTP map reflects the area of severe oligemia. Clinical deficits are related to the size of oligemic tissue explaining the correlation to admission NIHSS.

While neither demographic nor PCT parameters predicted early improvement in NIHSS, the intermediate term outcome depended on *Area_no perfusion* in non-thrombolysed patients. This finding supports and extends previous observations [27, 37]. In thrombolysed patients, only *age* had predictive value for outcome. Higher rates of comorbidities in older subjects, namely atrial fibrillation, CHD, and myocardial infarction, concomitant brain injury and brain microvascular changes, provide valid explanations. The finding supports a recent study which identified only two variables, age and NIHSS 6h after symptom onset, as predictors for functional recovery and mortality [38].

Beyond evaluating PCT we used the existing dataset to assess acute stroke management schedules at the Tübingen stroke unit. The key variable indicating a successful implementation of acute stroke protocols is the time interval between symptom onset and initiation of thrombolysis, the "door-to-needle" time. Because the time when thrombolysis was started, was not always available, the time of the CT scan was used instead. Typically, additional 15 to 20 min expires between CT and initiation of thrombolysis. Time-to-CT for patients receiving thrombolysis was 2 hours on average, which is in the range of previously published data [39]. Interestingly, patients not receiving thrombolysis did not arrive much later (5 hours on average), indicating that many more patients could receive thrombolysis within a 6 hour time window. Extending the time window requires better selection of patients potentially benefiting from thrombolysis, i.e., those with a large penumbra. Whether this selection can be achieved using PCT, remains to be evaluated prospectively.

Gender, vascular territory of ischemia and symptom severity were related to time-to-CT. Female patients and those with anterior circulation ischemia producing the "typical" stroke symptoms of hemiparesis and speech disturbance had shorter time-to-CT. Less severe deficits lead to protraction and longer time-to-CT.

Contrary to previous studies showing the proportion of atrial fibrillation in acute ischemic stroke to be around 20%, our study population showed a higher rate (35%). Subjects receiving thrombolysis also had a more severe stroke (NIHSS admission), Our data does not provide evidence for more severe strokes in patients with atrial fibrillation as suggested previously [40].

As with most retrospective studies, the effect of confounders (e.g. NIHSS on admission, atrial fibrillation, previous use of aspirin, statins etc) and bias are serious problems which we tried addressing by analysing the two subgroups separately for all dependent variables potentially affected by thrombolysis: NIHSS improvement, mRS at discharge, volume of hypodense tissue at follow-up CT etc.

Conclusion

This study evaluates the value of perfusion CT for predicting stroke volume and outcome in acute stroke with and without use of thrombolytic therapy. We were able to show that the size of the perfusion deficit is a good predictor of final stroke volume irrespective of whether or not patients received thrombolysis. Areas with nearly absent perfusion were not salvageable by thrombolysis. The degree of perfusion abnormality, i.e., how delayed the contrast bolus reaches the tissue, predicts later stroke volume but only when thrombolysis is not used to recanalise occluded vasculature. Similarly, outcome is predicted by the size of hypoperfused tissue in non-thrombolysed patients.

Hence, PCT is a fast and practical method in acute stroke diagnostic work-up protocols that can provide meaningful information contributing to early diagnosis of ischemia and the differentiation between salvageable and non-salvageable tissue. A prospective trial is necessary to evaluate its advantage over conventional non-contrast enhanced CT for identifying patients likely to benefit from thrombolysis.

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