Whole-Brain Perfusion CT Using a Toggling Table - Technique to Predict Final Infarct Volume in Acute Ischemic Stroke

CT-Ganzhirnperfusionsmessung durch „Toggling-Table-Technik" zur Infarktvolumenvorhersage beim akuten ischämischen Schlaganfall

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Abstract

Purpose: To evaluate how accurately final infarct volume in acute ischemic stroke can be predicted with perfusion CT (PCT) using a 64-MDCT unit and the toggling table technique.

Materials and Methods: Retrospective analysis of 89 patients with acute ischemic stroke who underwent CCT, CT angiography (CTA) and PCT using the "toggling table" technique within the first three hours after symptom onset. In patients with successful thrombolytic therapy (n = 48) and in those without effective thrombolytic therapy (n = 41), the infarct volume and the volume of the penumbra on PCT were compared to the infarct size on follow-up images (CT or MRI) performed within 8 days. The feasibility of complete infarct volume prediction by 8 cm cranio-caudal coverage was evaluated.

Results: The correlation between the volume of hypoperfusion on PCT defined by cerebral blood volume reduction and final infarct volume was strongest in patients with successful thrombolytic therapy with underestimation of the definite infarct volume by 8.5 ml on average. The CBV map had the greatest prognostic value. In patients without successful thrombolytic therapy, the final infarct volume was overestimated by 12.1 ml compared to the MTT map on PCT. All infarcts were detected completely. There were no false-positive or false-negative results.

Conclusion: Using PCT and the "toggling table" technique in acute stroke patients is helpful for the rapid and accurate quantification of the minimal final infarct and is therefore a prognostic parameter which has to be evaluated in further studies to assess its impact on therapeutic decision.

Key Points:
- Using PCT and the "toggling table technique" allows accurate quantification of the infarct core and penumbra.
- It is possible to record dynamic perfusion parameters quickly and easily of almost the entire supratentorial brain volume on a 64-slice MDCT unit.
- The technique allows identification of those patients who could profit from thrombolytic therapy outside the established time intervals.

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Zusammenfassung

Ziel: Quantitative Untersuchung der Vorhersagegenauigkeit des maximalen endgültigen Infarktvolumens bei der zerebralen Ischämie unter Anwendung der Perfusions-CT (PCT) mittels „Toggling-Table-Technik".

Material und Methoden: Retrospektive Auswertung der Perfusionsdatensätze von 89 Patienten mit einem akuten Schlaganfall. Die PCT erfolgte an einem 64-Zeilen-CT unter Anwendung der sog. „Toggling-Table-Technik". Die Patienten wurden innerhalb der ersten 3 Stunden nach Infarktereignis mittels nativer CT (nCCT), PCT und CT-Angiografie (CTA) untersucht. Die Kontrolluntersuchungen führten wir mittels CT oder MRT nach 1 – 8 Tagen durch. Bei Patienten mit erfolgreicher Lysetherapie (n = 48) und bei Patienten ohne erfolgreiche Lysetherapie (n = 41) verglichen wir die Volumina von Infarktkern und Penumbra in der PCT mit den tatsächlichen Infarktvolu-

mina. Zudem untersuchten wir, ob die Infarkte innerhalb eines 8 cm langen kranio-kaudalen Scanbereichs vollständig abgebildet werden konnten.
Ergebnisse: Die Übereinstimmung zwischen den Volumina mit reduziertem Cerebral Blood Volume (CBV) in der PCT und den definitiven Infarktvolumina war bei Patienten nach erfolgreicher Rekanalisation am größten. Dabei wurde das finale Infarktvolumen im Mittel um 8,5 ml unterschätzt. In der Patientengruppe ohne Rekanalisation wurde das endgültige Infarktvolumen im Vergleich zu den Volumina mit verlängerter MTT in der PCT im Mittel um 12,1 ml überschätzt. Alle Infarkte wurden fast vollständig mittels der PCT erfasst. Es gab keine falsch positiven oder falsch negativen Befunde.
Schlussfolgerung: Der Einsatz der „Toggling-Table-Technik“ bei der Perfusions-CT ermöglicht beim akuten Schlaganfall eine schnelle und genaue Quantifizierbarkeit des Mindestvolumens des irreversibel geschädigten Hirnparenchyms und liefert somit einen prognostischen Parameter, der innerhalb zukünftiger Studien in Bezug auf die Therapieentscheidung evaluiert werden sollte.

Introduction

In clinical stroke centers, acute ischemic stroke is currently primarily diagnosed via non-contrast cerebral computed tomography (nCCT), CT angiography (CTA), and perfusion CT (PCT). nCCT makes it possible to rule out bleeding, detect early signs of infarct, and visualize thrombi. Occlusions of the intracranial arteries can be reliably detected with CTA. The greater imaging volume of MSCT makes it possible to additionally evaluate the branches of the three cerebral arteries as well as the carotid arteries, given a sufficiently large scanning area [1]. With perfusion CT (PCT) ischemia can be diagnosed early, even before a morphological correlate is visible in nCCT [2]. PCT provides precise information about the volume of the infarct core and penumbra [3 – 5]. This makes it possible to quickly and reliably differentiate between patients who could profit from thrombolytic therapy outside of the established time intervals and patients for whom such treatment is contraindicated due to the extent of irreversible brain parenchymal damage. Patients can undergo thrombolytic therapy within a time window of up to 4.5 hours after an infarct [6]. Thanks to new mechanical thrombectomy methods, patients can now be treated up to 8 hours after infarct onset [7].
One of the main disadvantages of conventional PCT using a 4-slice or 16-slice multidetector CT (MDCT) unit is the narrow detector width and the consequently small imaging area of the brain which has been limited to approximately 4 cm [8 – 11]. The method of covering the largest possible area via multiple successive examinations of different brain sections resulted in high effective doses and contrast agent quantities. In a current study the entire brain was able to be examined with a dose of only 1.67 mSv using a 256-row CT unit [12]. To allow examination on MDCT units with a smaller detector width, e. g. 64-slice CT units, as used in many hospitals and to satisfy the demand for a large imaging area at the lowest possible dose, the so-called toggling table technique has recently been used. After a single contrast agent administration, two adjacent sections of the brain are alternately scanned by repeatedly moving the table back and forth, thus making it possible to record exact dynamic perfusion parameters of almost the entire supratentorial brain volume [13, 14].
The goal of our study was to determine whether physiological cerebral blood volumes (CBV), cerebral blood flows (CBF), and the mean transit time (MTT) of the contrast agent in brain areas not affected by the stroke can be determined using the toggling table technique. For the first time quantitative (volumetric) analysis was to be used to determine whether the estimation of the volume of the penumbra and infarct core via PCT is a good predictor of the final infarct volume to be expected.

Materials and Methods

Patients

Patients with an acute stroke who were examined at our institute with non-contrast CCT and PCT within the first three hours after the onset of the first symptoms in the period from April 2007 and June 2009 were included in this retrospective study. All patients included in the study received intravenous thrombolytic therapy. The initial vascular occlusion was typically detected via CTA while transcranial Doppler sonography (TCD) was used in some of the patients. All patients with intracerebral bleeding (ICB) and patients with a significantly prolonged blood circulation time, e. g. in the case of cardiac insufficiency, were excluded. Another exclusion criterion was limited image quality due to artifacts. The final infarct volume had to be documented in all patients on the basis of a follow-up CCT or MRI performed within a period of 24 hours to 8 days after the stroke. The success or failure of the recanalization therapy had to be checked via TCD within 48 hours of the onset of symptoms at the latest. In exceptional cases, typically due to poor imaging conditions as a result of the skullcap, MR angiography (MRA) or CTA was performed.

Computed tomography

nCCT and PCT were performed on a 64-slice CT unit with a detector width of 40 mm (Brilliance 64 CT, Philips Medizin Systeme, Hamburg). PCT was performed using the toggling table technique in which two adjacent sections of the brain are scanned in succession by moving the CT table back and forth along the longitudinal axis of the patient's body and the attenuation curves after contrast agent injection are measured at different time points at a specific scanning interval which is used to calculate the CBV, CBF, and MTT via suitable software (Extended Brilliance Workspace, Philips Medical Systems, Best, The Netherlands). The selected imaging protocols listed in **Table 1** for CCT and CTA correspond to standard protocols. 60 ml of the iodine-containing contrast agent iopamidol (Imeron 350, Bracco Imaging, Constance, Germany) were injected intravenously with a speed of 5 ml/s for PCT and CTA. The contrast agent bolus was followed by a 30-ml water bolus injected with the same speed. In the selected PCT protocol, the scanning interval was 4 seconds. The scans were repeated 15 times resulting in a total data acquisition time of 1 minute. The mean effective dose of a PCT examination was 8.4 mSv. **Fig. 1** schematically shows the toggling table technique principle.

	nCCT	PCT	CTA
tube voltage	120 kV	80 kV	80 kV
current-time product	320 mAs	150 mAs	280 mAs
slice thickness	2.5 mm	10 mm	0.9 mm
collimation	16 × 0.625 mm	32 × 1.25 mm	64 × 0.625 mm
mode	sequential	sequential	spiral
contrast agent	–	Imeron 350	Imeron 350
injection speed	–	5 ml/s	5 ml/s
contrast agent quantity	–	60 ml	60 ml

Table 1 Imaging protocol for non-contrast CCT, perfusion CT and CT angiography.

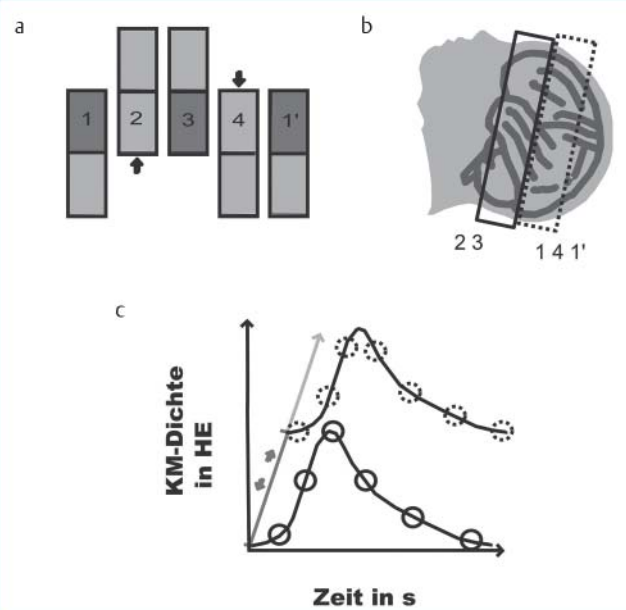


Fig. 1 Toggling table technique (according to Youn et al. 2008). **a, b** axial scanning was repeated at two table locations in a to-and-fro fashion (phases 1 – 4). **c** Time-density curves for each slice in **b** with tissue enhancement in Hounsfield units (HE) over time in s. The points of the curve undersampled (circle) are detected alternately. The temporal sampling interval was 4 s.

Follow-up MRI

The examinations were performed on a 1.5 Tesla MRI unit (Achieva, Philips Medical Systems) using a protocol consisting of a diffusion-weighted sequence, T1 and T2-weighted TSE sequences, T2-weighted flair scans, and a 3 D time-of-flight (TOF) MRA of the intracranial arteries.

Analysis of the CT perfusion data sets

A venous sinus with the greatest density integral was marked for determining the venous output function. Analogously, the further analysis for the basilar artery, the middle cerebral artery, and the anterior cerebral artery of each hemisphere was performed separately. By comparing the flow dynamics, it was ensured that there was no significant delay in the arterial inflow in any of the arteries available for additional analysis. For the further analysis, the reference vein and reference artery with the greatest density integral of the vessel cross-section were selected. With the help of evaluation software, color-coded cards showing the MTT, CBV, CBF, and the time-to-peak (TTP) were created using the principle of deconvolution [15] for every pixel (see **Fig. 2**). For the determination of the physiological CBF and CBV values, all brain perfusion values of the unaffected brain hemisphere for every included patient were shown in a histogram and an analysis of the two maxima of the bimodal distribution (one maximum for the gray matter and one for the white matter) was performed. Standard deviations and average values were calculated via the maxima and a group comparison was performed via t-test.

The calculation of the percentage of the infarct area in the maximally cranial slice and the maximally caudal slice in the imaging area made it possible to make a statement about the scanned portion of the infarct area.

CT and MRI analysis

In the CT or MRI follow-up examinations, the definitive infarct volumes were determined on the basis of the hypodense areas in CCT or the areas with a diffusion restriction in MRI. The corresponding regions were manually encircled in all slices in consensus by two experienced neuroradiologists on an imaging workstation (Impax, Agfa-Gaevert, Mortsel, Belgium), whereby the enclosed surface was determined directly. A typical evaluation result is shown in **Fig. 3**. The volume could then be calculated via the particular slice thickness of the sectional images and the determined total surface of the infarct areas. The infarct volume calculated on the basis of the follow-up examinations was then compared to the infarct volume predicted on the basis of PCT.

Statistical evaluation

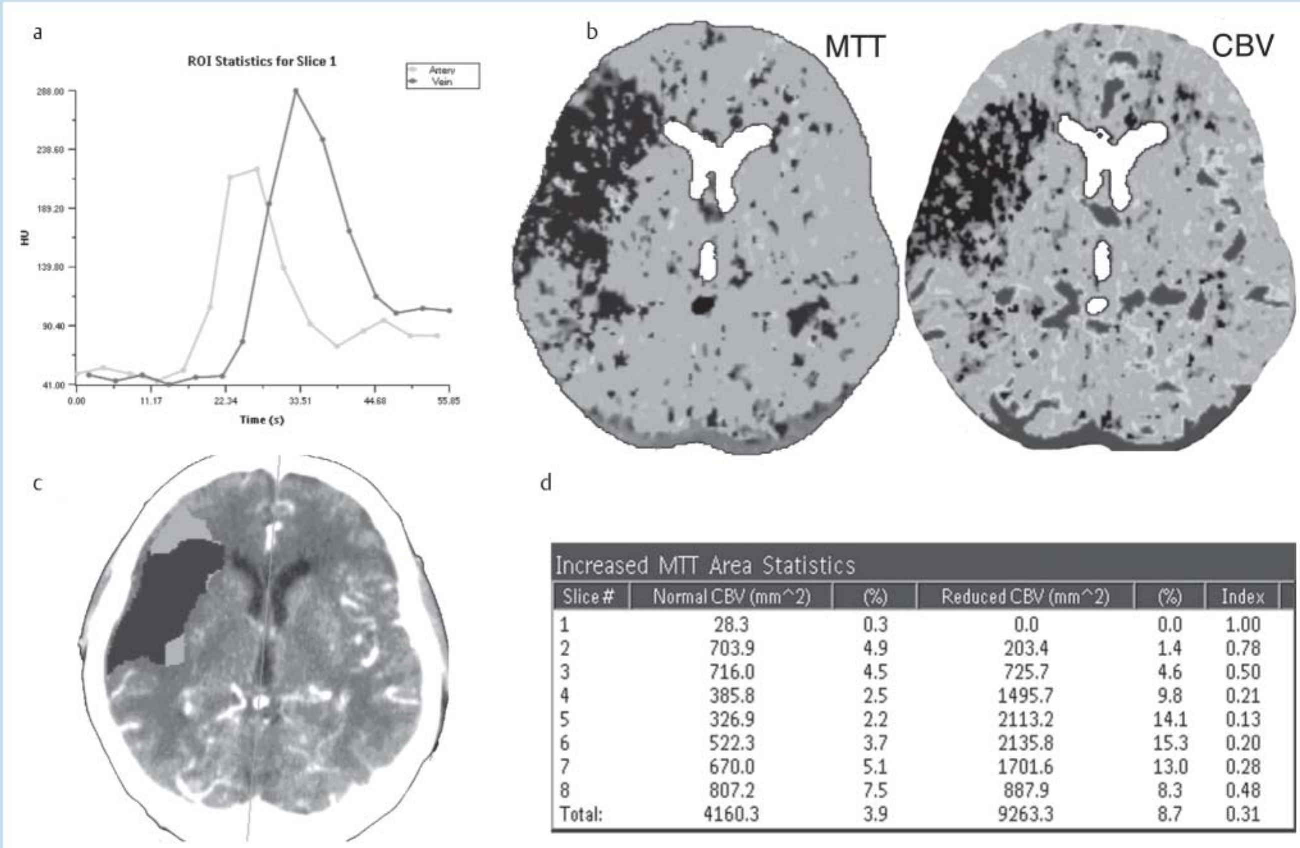
Statistical analysis was performed with Aabel 3.05 (Gigawiz Ltd. Co.).

If not otherwise specified, the calculated numbers are noted as mean +/- standard deviation. The maximum brain perfusion values for the gray and white matter in the hemisphere not affected by stroke were analyzed for significant differences via t-test for the patient group with recanalization and the patient group without recanalization. A p-value of < 0.05 was defined as the significance level.

Results

Patients

Of a total of 189 patients who underwent a CT perfusion examination in the study period, this examination was indicated in 152 patients on the basis of an acute ischemic stroke. In 35 patients the PCT examination was performed due to a suspicion of cerebral vasospasms after subarach-



Slice #	Normal CBV (mm^2)	(%)	Reduced CBV (mm^2)	(%)	Index
1	28.3	0.3	0.0	0.0	1.00
2	703.9	4.9	203.4	1.4	0.78
3	716.0	4.5	725.7	4.6	0.50
4	385.8	2.5	1495.7	9.8	0.21
5	326.9	2.2	2113.2	14.1	0.13
6	522.3	3.7	2135.8	15.3	0.20
7	670.0	5.1	1701.6	13.0	0.28
8	807.2	7.5	887.9	8.3	0.48
Total:	4160.3	3.9	9263.3	8.7	0.31

Fig. 2 Sample PCT dataset. **a** Reference arterial input and venous output function measured in the left middle cerebral artery and the superior sagittal sinus. **b** From the area under the time-enhancement curves, maps, e. g. for the mean transit time (MTT) and the cerebral blood volume (CBV), are calculated. **c** Tissue at risk of infarction (light gray and dark in **b** is described by the region with prolonged MTT, the infarct core (dark region in **b** and **c**) is described by the region with decreased CBV. **d** Automatically generated PCT parameters for the prediction of the penumbra and infarct core.

Fig. 3 Diffusion-weighted imaging (DWI) shows focal diffusion restriction on left MCA territory corresponding to cerebral ischemic lesion.

noidal bleeding. PCT was performed to differentiate between Todd's palsy and stroke in the two remaining patients.
The following exclusion criteria reduced the number from 152 to n = 89 patients included in this study: 23 patients had ICB, 16 patients had substantially delayed contrast wash-in so that the arterial inflow function and the venous outflow function could not be fully visualized, the contrast agent bolus was insufficient in another 10 patients due to the low cardiac output, the remaining 14 patients had scans with significant overlapping primarily due to motion artifacts as well as foreign material artifacts. More precise details regarding the epidemiology of the included patients are provided in **Table 2**. The distribution of male and female patients is not significantly different ($p = 0.39$).

CBF and CBV values of the unaffected brain hemisphere

Non-physiological cerebral blood flow and blood volume values in the gray and white matter of the sections of the brain not affected by stroke were not detected in any of the included patients.
In the group of successfully recanalized patients, the CBF and CBV values were 62.3 ± 5.4 ml/min/100 g and 6.8 ± 0.5 ml/100 g, respectively, in the gray matter and 23.8 ± 4.7 ml/min/100 g and 1.9 ± 0.4 ml/100 g, respectively, in the white matter. In the group of patients who could not be recanalized, the CBF and CBV values were 66.8 ± 6.5 ml/min/100 g and 6.9 ± 0.4 ml/100 g, respectively, in the gray matter and 21.6 ± 4.9 ml/min/100 g and 2.1 ± 0.5 ml/100 g, respectively, in the white matter. The t-test for the group comparison does not result in a significant difference ($p = 0.32$).

Predictability of the infarct area on the basis of PCT

The prediction of the size of the infarct area on the basis of PCT depends on the success of the thrombolytic therapy:
In the case of successful recanalization, the volume of the area with a decreased CBV should be used as a prognostic value for the volume of the infarct, while the infarct can ex-

Table 2 Epidemiology of the patients.

Patients	Total	Recanalized	Not recanalized
all (n)	89	48	41
gender			
female (n)	45	22	23
male (n)	44	26	18
age (years)	67,9 ± 12,8	66,8 ± 14,2	68,5 ± 11,1
recanalization follow-up group			
TCD (n)	62	34	28
MRA (n)	12	5	7
CTA (n)	15	11	4

The patients with and without successful recanalization are listed according to gender and age, and according to the selected imaging methods.

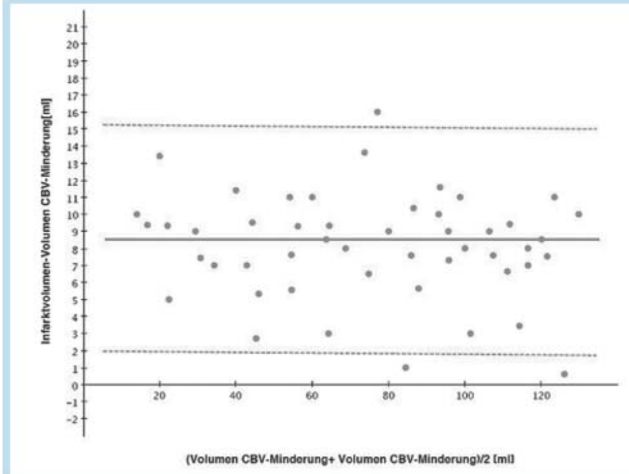


Fig. 4 Bland-Altman diagram for the comparison of the extent of the infarct volume predicted by decreased CBV and final infarct volume in case of arterial recanalization.

tend to the entire hypoperfused area, i. e., the region with a significantly prolonged MTT, in the case of failed recanalization [16]. The volume of the infarct regions (CBV decreased in the initial perfusion measurement) of all patients with successful recanalization is compared to the volume of the infarct area in the follow-up examination in a Bland-Altman diagram in ▶ **Fig. 4**. This shows that the value predicted on the basis of PCT underestimates the infarct volume by 8.5 ml on average. For the deviation from this mean value, a 95 % confidence interval of 6.7 ml is calculated.

The Bland-Altman diagram (▶ **Fig. 5**) with respect to the unsuccessfully recanalized stroke patients shows that the MTT measurement provides a significantly less accurate prediction of the final infarct volume compared to the CBV measurement in the recanalized patients. Therefore, the volume measurement of the prolonged MTT overestimates the final infarct volume by an average value of 12.1 ml. The 95 % confidence interval is also greater with ± 15.2 ml.

The final infarct volumes only exceed the volume of the areas with MTT extension determined in the PCT data in the case of significant hypoperfusion above a hypoperfused volume of approximately 80 ml as was the case in 4 patients. These patients developed malignant infarcts.

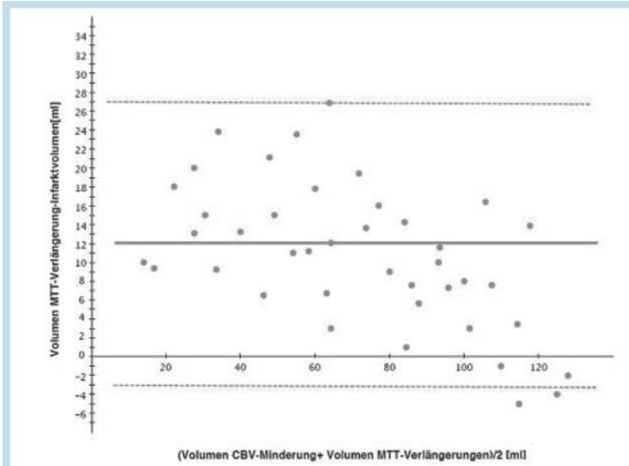


Fig. 5 Bland-Altman diagram for the comparison of the extent of infarct volume predicted by decreased MTT and final infarct volume described by decreased CBV in case of persistent arterial occlusion.

Location of the infarct in the scanning area

The above-described PCT measurement covers a scanning area of 8 cm (consisting of 8 individual slices). ▶ **Fig. 6** shows the percentage distribution of hypoperfused brain volume for the 8 sectional images.

Only approximately 3 % of the total hypoperfused volume is located in the maximally cranial slice and 5 % in the maximally caudal slice so that the total hypoperfused brain tissue was almost fully visualized in our collective.

Discussion

PCT provides prognostic information regarding the volume of the infarct core and penumbra so that it is possible to quickly and reliably select patients presenting outside of the established time interval but who would still profit from recanalization treatment [8, 17 – 19]. At the same time patients with a high risk for a malignant infarct can be identified [20].

Due to the ready availability and quick and uncomplicated implementation of PCT compared to MRI, PCT is currently being used in numerous hospitals [19, 21]. Compared to examination via MRI perfusion, the main disadvantage of PCT using 4 and 16-slice MDCT units is the small scanning area due to the narrow detector width so that complete scanning of hypoperfused areas and infarcts in cranial sections of the cerebrum is not reliably ensured [11, 22, 23]. The attempt to resolve this issue by increasing the examination area by scanning different sections of the brain in succession resulted in increased radiation exposure for the patient and the use of a greater contrast agent quantity due to the repeated applications [3, 24, 25]. PCT using a 256-slice or 320-slice MCDT unit recently made it possible to record hemodynamic data for the entire brain after only one contrast agent application and with a relatively low radiation dose [12, 23]. However, most hospitals use MDCT units with significantly

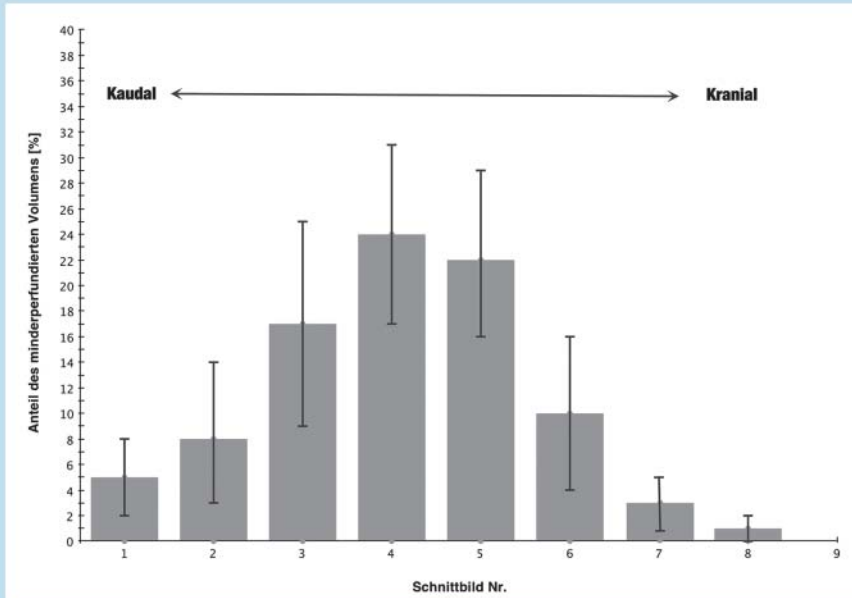


Fig. 6 Share of the volume of perfusion abnormality of the total volume. Volume with prolonged MTT in PCT slices 1 – 8 in percent with the corresponding standard deviations.

fewer slices and thus a narrower detector width. To be able to scan the entire brain volume with a 64-slice MDCT unit, the toggling table technique is now used for PCT in numerous hospitals [14, 26]. In this process two adjacent sections of the brain are scanned in a specific sequence and an imaging field with a width of approximately 8 cm is examined. Almost the complete volume of the infarct area in all patients was scanned in our study. All infarct areas were large since PCT was only performed in patients with suspicion of a larger (territorial) ischemia and thus who were potential candidates for thrombolytic therapy. Accordingly, the lower sensitivity of PCT compared to MRI with regard to the detection of smaller or infratentorial infarcts as shown in the studies of other authors [14, 25, 27] does not play a role in our collective.

Data of other authors describing a relatively high sensitivity and specificity of PCT in connection with the toggling table technique is currently available. However, these studies either include study populations with disease entities other than cerebral ischemia [14] or examine ischemia in infratentorial sections of the brain [28]. In other cases, the technique applied by other workgroups differed in that a combination of CTA and PCT was used in one examination procedure [13]. Moreover, the precision of PCT was checked primarily visually and thus subjectively by comparison to follow-up MRI examinations [14, 28]. Although quantitative evaluations of the comparison of PCT to MRI perfusion are currently available [8, 17, 18], there are none for the perfusion data generated using the toggling table technique in the case of supratentorial ischemia. We examined this in our study on the basis of the comparability of the expected and definitive infarct volumes in PCT and in follow-up examinations. The results showed high predictability of PCT for patients both with and without successful thrombolytic therapy but we found greater agreement between the predicted and actual infarct volumes in patients with successful recanalization than in those without recanalization. This is probably related to the fact that the infarcted area extends beyond the initially calculated infarct core into the penumbra in the case of a lack of recanalization [29]. In the recanalized patients, the final infarct volume having the greatest concordance with the volume with decreased CBV [11, 16] is underestimated by 8.5 ml on average (95 % confidence interval of 6.7 ml). Using the volume with prolonged MTT as the most suitable predictor for the final infarct volume in patients without successful thrombolytic therapy [3, 16] results in an underestimation of the final infarct volume by 12.1 ml on average (95 % confidence interval ± 15.2 ml).

The toggling table technique used in our study has decreased temporal resolution. However, this is not a disadvantage since it was able to be shown in numerous studies that an extension of the scanning interval to up to 4 s does not result in any significant quantitative imprecision of the hemodynamic parameters (with simultaneous dose reduction) [10, 30].

A disadvantage of this necessary extension of the sampling interval is that individual images can no longer be excluded (e. g. due to motion artifacts) without invalidating the entire data set. This may be why the exclusion rate for technical/patient-related reasons in our study is extremely high (40 of 129 patients with acute cerebral ischemia). Other studies consistently report exclusion rates of < 10 % for PCT [12, 24]. Other possible criticisms of our study are that both the follow-up examinations and the check for recanalization were not performed at a standardized time point so that the exact recanalization instant was not known. Moreover, two different methods (MRI and CT) were used in the follow-up examinations. The recanalization success was also verified via different methods (TCD, MRA, and CTA) since the intracranial basal arteries could not be visualized through the transtemporal bone window in approx. 15 % of the stroke patients due to thickening of the skullcap [31]. Since the follow-up examination was not performed in any patient within the first 24 hours after the onset of symptoms, the infarct areas could be equally reliably visualized on the basis of the distinctive features in DWI MRI and the typical hypodense areas in CT.

The exact effect of the selection of the inflow function on the obtained perfusion data could not be examined in our study. Selecting inflow and outflow functions with a high integral value, i. e., only arterial and venous blood vessels with a large cross-sectional area were taken into consideration, made it possible to standardize the measurement method. The range of variation of blood flow was not fully taken into consideration since arterial vessels of both cerebral hemispheres were not compared. However, the cerebral volume principle used in our study to calculate the dynamic perfusion parameters which is based on the mathematic principle of deconvolution yields quantitative CBV, CBF, and MTT values at low injection speeds and thus independently of a delay of the contrast agent passage [15, 32] in contrast to the so-called maximum slope model, which is based on the assumption that no contrast agent exits the compartment via a venous path up to a certain point in time after arrival of the bolus in the tissue [33].

The average effective dose of our PCT protocol was 8.4 mSv and therefore differs only minimally from the dose of 7.6 mSv applied for PCT with a 320-slice MDCT unit [23]. As a result of the relatively high total dose of 4.7 – 9.5 mSv for an imaging protocol typically consisting of numerous CT examinations on a 64-slice MDCT unit [23, 34], possibly followed by catheter angiography, the indication for the individual examination and the selection of the follow-up examination method must be reviewed in each case. The benefit of the examination with respect to the survival and the least possible subsequent impairment of the stroke patient must be taken into consideration here.

It was already able to be shown in multiple studies that the use of the toggling table technique in perfusion CT makes it possible to quickly and easily record dynamic perfusion parameters of almost the entire supratentorial brain volume [13, 14]. On the basis of our quantitative analysis of the predicted and final infarct area, we were able to prove that the parameters acquired using the toggling table technique are precise. The technique allows accurate quantification of the infarct core and penumbra as the foundation for a safe and quick treatment decision.

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