Characteristics of Misclassified CT Perfusion Ischemic Core in Patients with Acute Ischemic Stroke

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Abstract

Background

CT perfusion (CTP) is used to estimate the extent of ischemic core and penumbra in patients with acute ischemic stroke. CTP reliability, however, is limited. This study aims to identify regions misclassified as ischemic core on CTP, using infarct on follow-up noncontrast CT. We aim to assess differences in volumetric and perfusion characteristics in these regions compared to areas that ended up as infarct on follow-up.

Materials and Methods

This study included 35 patients with >100 mm brain coverage CTP. CTP processing was performed using Philips software (IntelliSpace 7.0). Final infarct was automatically segmented on follow-up noncontrast CT and used as reference. CTP and follow-up noncontrast CT image data were registered. This allowed classification of ischemic lesion agreement (core on CTP: $rMTT \geq 145\%$, $aCBV < 2.0$ ml/100g and infarct on follow-up noncontrast CT) and misclassified ischemic core (core on CTP, not identified on follow-up noncontrast CT) regions. False discovery ratio (FDR), defined as misclassified ischemic core volume divided by total CTP ischemic core volume, was calculated. Absolute and relative CTP parameters (CBV, CBF, and MTT) were calculated for both misclassified CTP ischemic core and ischemic lesion agreement regions and compared using paired rank-sum tests.

Results

Median total CTP ischemic core volume was 49.7ml (IQR:29.9ml-132ml); median misclassified ischemic core volume was 30.4ml (IQR:20.9ml-77.0ml). Median FDR between patients

was 62% (IQR:49%-80%). Median relative mean transit time was 243% (IQR:198%-289%) and 342% (IQR:249%-432%) for misclassified and ischemic lesion agreement regions, respectively. Median absolute cerebral blood volume was 1.59 (IQR:1.43–1.79) ml/100g (P<0.01) and 1.38 (IQR:1.15–1.49) ml/100g (P<0.01) for misclassified ischemic core and ischemic lesion agreement, respectively. All CTP parameter values differed significantly.

Conclusion

For all patients a considerable region of the CTP ischemic core is misclassified. CTP parameters significantly differed between ischemic lesion agreement and misclassified CTP ischemic core, suggesting that CTP analysis may benefit from revisions.

Introduction

Acute ischemic stroke is the third most common cause of death and the leading cause of permanent invalidity in industrialized countries [1]. Early recanalization of arteries to restore perfusion of regions at risk but still viable (penumbra) is vital [2]. Recanalization can be achieved by intravenous administration of recombinant tissue plasminogen activator (rtPA) or intra-arterial treatment (IAT) [3]. Intravenous rtPA is proven to be a beneficial treatment for ischemic stroke patients, but due to haemorrhage risk, has a limited time-window of four and a half hours after onset of symptoms [4]. Recent multi-center randomized control trials, like MR CLEAN, EXTEND-IA, SWIFT PRIME, ESCAPE and REVASCAT, showed that intra-arterial treatment after intravenous rtPA is beneficial in restoring reperfusion within 6 hours after onset of symptoms and significantly improved patient outcome after 90 days [5–9]. However, a successful early recanalization by IAT does not guarantee a good outcome at 90 days. CT perfusion (CTP) has the potential to limit the number of futile recanalizations by improving critical patient selection for treatment [10,11].

CTP software distinguishes ischemic core from penumbra and unaffected regions by measuring blood perfusion in cerebral regions, based on venous contrast agent injection. Cerebral Blood Flow (CBF), Cerebral Blood Volume (CBV), and Mean Transit Time (MTT) are parameters determined by CTP analysis, which are used for assessment of ischemic core and penumbra [12–14]. CTP has certain advantages [15–18]. It is widely available at almost all emergency units, rapid and easily performed, and has a high spatial resolution [12]. Therefore this technique has the potential to become a useful diagnostic tool in acute settings.

Despite the potential of CTP there are some issues which may cause inaccurate results and hamper its acceptance in clinical practice [16]. Different processing software packages, based on different underlying algorithms, have been proven to produce different results [19,20]. Other causes can be incorrect manual selection of arterial or venous input or too short acquisition times causing truncation of time attenuation curves [21–23]. Head-movement or biological (certain vascular- or neurodiseases or cardiac output) or anatomical (lesions, variations in Circle of Willis or vascular system) causes can also influence data analysis [22–24].

CTP software creates summary maps to visualize ischemic core and tissue "at-risk" (penumbra). Classification of this ischemic core and penumbra is based on parametric thresholds. Suboptimal thresholds may influence CTP results. Thresholds used for classification of ischemic core are derived from large samples and can agree in large-scale studies. However, these thresholds can produce large errors when applied to individual patients [22,25]. Studies have shown that strict threshold values can lead to over- or underestimation of ischemic core volume and

penumbra, as they may not be specific for individual cases [23,26]. A previous study showed the appearance of false ischemic penumbra, caused by upstream flow restriction, old infarction, vascular anatomy variations and dysregulation, and patient misplacement in scanner [27].

Currently CTP still misclassifies a large area as ischemic core [28]. For CTP to be more reliable in clinical settings, accuracy has to be improved [1,17]. MR-DWI is considered the most accurate modality to assess cerebral infarct and has been used as a gold standard in various studies [29,30]. However, MR-DWI is not commonly available in the acute setting of treatment of ischemic stroke patients [1]. Alternatively, it is proposed to use follow-up noncontrast CT as reference standard. Follow-up noncontrast CT is accurate in quantification of final infarct [31]. However, it is known that in the period between baseline and follow-up scanning, the infarct may grow [32,33]. Nevertheless, because it is not possible to have an ischemic core on baseline that has disappeared on follow-up imaging, follow-up noncontrast CT can be used as reference standard to identify regions misclassified as ischemic core on CTP. In this study we aim to identify misclassified CTP ischemic core using follow-up noncontrast CT and determine perfusion characteristics of ischemic core that can be used to improve CTP analysis.

Materials and Methods

Population

This study included patients from the MR CLEAN trial (www.mrclean-trial.org) [5]. Patients were eligible for inclusion in the MR CLEAN trial, if they had a clinical diagnosis of acute ischemic stroke, with a deficit on the National Institutes of Health Stroke Scale (NIHSS) of 2 points or more, CT or MRI ruling out haemorrhage, and intracranial artery occlusion of the distal intracranial carotid artery or middle (M1/M2) or anterior (A1/A2) cerebral artery. All patients or relatives signed an informed consent.

Seventy-one patients from MR CLEAN trial received >100 mm brain coverage baseline CTP. Final infarct volume was determined on 5–7 day follow-up noncontrast CT. For two patients, 5–7 day CT was not available and 24-hours follow-up noncontrast CT was used for determining final infarct volume. Patients were excluded for the following reasons: CTP available, but no follow-up CT (N = 18); excessive movement (N = 2); poor quality of the scans (N = 4); midline shift over 5 mm on follow-up CT (N = 7); craniectomy on follow-up CT (N = 3); no ischemic core on baseline CTP (penumbra only) (N = 2). After exclusion, final sample size of this study was 35 patients.

CT imaging

Baseline CTP imaging. Scanner, scanning protocol and acquisition time differed per center; detailed information can be found in Table 1. If necessary, multiple 0.5 mm slices were averaged to 5 mm slices using MATLAB (The MathWorks, Massachussets, USA) to enable processing by the perfusion analysis software. CTP series were post-processed using commercially available Philips IntelliSpace Portal 7.0, Brain Perfusion application software (Royal Philips Healthcare, Best, The Netherlands). 3D motion correction and filtering was applied on all scans, using the built-in features. To ensure standard protocol, arterial input function (AIF) and venous output function (VOF) were always placed in the internal carotid artery and sagittal sinus. Ischemic core, defined as a relative MTT $\geq$ 145% and an absolute CBV < 2.0 ml/100g, was automatically classified and presented in a summary map [25]. All quantitative (absolute) parameter maps (aCBF, aCBV, aMTT) and summary maps were exported for further analysis. Relative parameter values were calculated in respect to their contralateral value resulting in relative MTT (rMTT), CBF (rCBF), and CBV (rCBV) in MATLAB.

Table 1. Scanners, brain coverage, acquisition time and contrast agent for CT perfusion amongst hospitals included in this study.

Center	1	2	3	4
Scanner	Toshiba Aquilion ONE[a]	Toshiba Aquilion ONE[a]	Siemens Somatom Definition Flash[b]	Siemens Somatom Definition Edge[b]
Kernel	FC26	FC26	H31s	H31s
Nr. of patients	13	6	14	2
Brain coverage	160 mm	160 mm (except 1: 140 mm)	100 mm	125 mm or 155 mm
Acquisition time	53 sec. (N = 13)	53 sec. (N = 6) or 50 sec. (N = 1)	44 sec. (N = 5) or 60 sec. (N = 9)	53 sec. (N = 1) or 60 sec. (N = 1)
Contrast agent	Ultravist 370	Iomeprol 300	Ultravist 300	Iomeprol 400
Contrast volume	50 ml followed by 50 ml saline	50 ml followed by 40 ml saline	50 ml followed by 40 ml saline	40 ml followed by 45 ml saline
Injection rate	5 ml/sec.	5 ml/sec.	7 ml/sec.	6 ml/sec.
Start of acquisition	5 sec. after start of injection	5 sec. after start of injection	2 sec. after start of injection	With start of injection

[a] Toshiba Medical Systems, Tokyo, Japan
[b] Siemens, Erlangen, Germany

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It has been shown that truncation may cause inaccuracies in CTP results [21]. AIF, VOF and tissue time-attenuation curves (TAC) were visually classified as truncated or complete. Attenuation curves were classified as complete when the attenuation values returned close to their baseline values

Follow-up noncontrast CT imaging. Patients received follow-up noncontrast CT at 24 hours and 5–7 days after hospitalization. Final infarct size was determined on 5–7 day follow-up noncontrast CT scanning if possible. When these were not available, infarct was determined on 24 hours follow-up noncontrast CT (N = 2). Follow-up noncontrast CT images were registered with motion corrected CTP images using Elastix [34]. Infarct on follow-up noncontrast CT was determined using a semi-automated method by in-house developed software (MATLAB) [35].

Ethics statement. The CTP protocol has been approved by the institutional review board (Medisch Ethische Toetsings Commissie) from the Academic Medical Center, Amsterdam, The Netherlands. Patients or legal representatives signed informed consent.

Selection of misclassified ischemic core

Registration of follow-up noncontrast CT with baseline CTP allowed direct comparison of CTP derived ischemic core and follow-up noncontrast CT derived infarct (Fig 1) CTP ischemic core, follow-up noncontrast CT infarct and CTP derived parameter maps registration was performed in MATLAB.

Voxel-based comparison of CTP ischemic core with follow-up noncontrast CT infarct resulted in two areas of interest. The first is "misclassified ischemic core", which is defined as the area classified as ischemic core on CTP and not as infarct on follow-up noncontrast CT. The second area of interest is the area in which CTP ischemic core and follow-up noncontrast CT infarct agree, which is referred to as "ischemic lesion agreement" in the following.

Misclassified ischemic core and ischemic lesion agreement were used as regions of interest (ROIs) for further analysis. ROIs were projected on follow-up noncontrast CT for visual assessment (Fig 1) and on quantitative parameter maps of the MTT, CBF, and CBV.
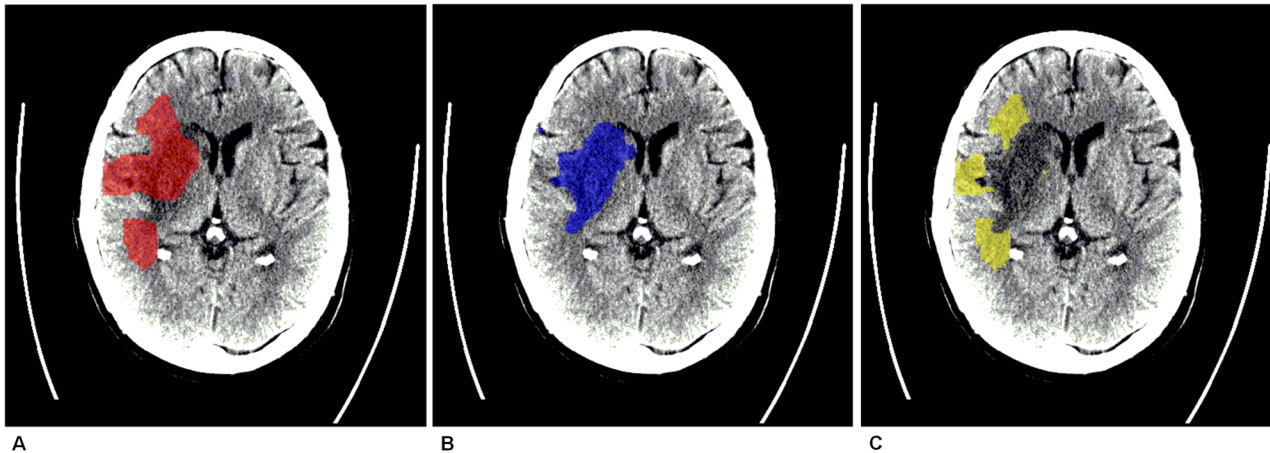
Fig 1. Example of a misclassified ischemic core. A. Ischemic core as selected by CT perfusion software on baseline CTP (projected on follow-up noncontrast CT). B. Final infarct as determined on follow-up noncontrast CT. C. Misclassified ischemic core region projected on follow-up noncontrast CT.

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Statistical Analysis

Median and IQR of the total ischemic core, misclassified ischemic core and ischemic agreement lesion volume were determined. The false discovery ratio (FDR), defined as the misclassified ischemic core volume divided by the total ischemic core volume, was calculated. Median values of voxel-based CTP parameter values (rMTT, aCBF, rCBF, aCBV, and rCBV) were calculated per patient. Median of these median parameter values for misclassified ischemic core and ischemic lesion agreement amongst all patients were combined and analyzed separately with a rank-sum test. All analyses and visualization were performed in IBM SPSS 22.0 (IBM Corporation, Armonk, New York, USA).

Results

Core volumes, false discovery ratio & identification of truncation

Median total CTP ischemic core volume was 49.7ml (IQR: 29.9–131.8ml, min.-max.: 12.2–197.4ml). Median misclassified ischemic core volume was 30.4ml (IQR: 20.9–77.0ml, min.-max.: 5.1–159.7ml). Median ischemic lesion agreement volume was 18.6ml (IQR: 6.5–56.9ml, min.-max.: 1.9–98.0ml). Median FDR was 62% (IQR: 49%-80%, min.-max.: 23%-97%). These values are schematically presented in Fig 2.

Truncation of AIF or VOF was observed in 12 out of 35 patients. Truncation of tissue TAC only was observed in 20 out of 35 patients.

Perfusion parameter value analysis

All perfusion parameter values were statistically significant different between misclassified ischemic core and ischemic lesion agreement areas($P < 0.01$). Median parameter values for all patients are shown in Table 2 and Figs 3–7.

Discussion

Comparison of baseline CTP ischemic core with follow-up noncontrast CT infarct showed that a large part of the ischemic CTP core volume was misclassified. For all perfusion parameters a significant difference was observed between misclassified ischemic core and ischemic lesion
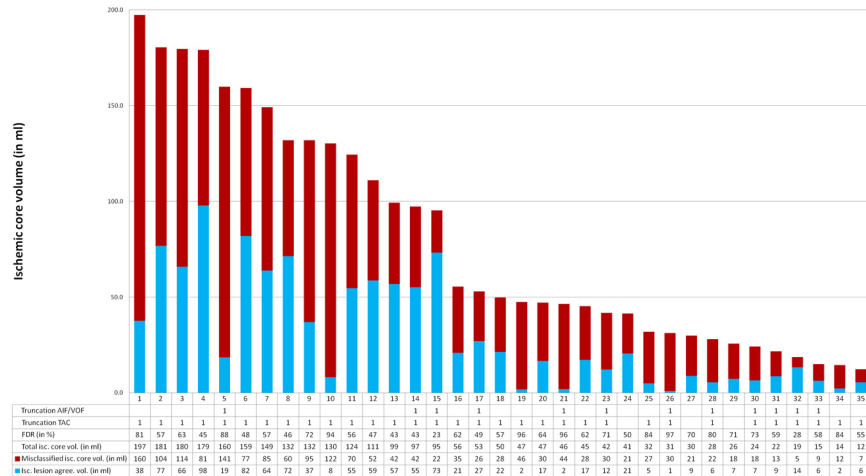
Fig 2. Total ischemic core volume (isc. core vol.), ischemic lesion agreement (light blue) and misclassified ischemic core (dark blue) volume (ml) and FDR (%) for all patients. If truncation was observed in time-attenuation curves (AIF/ VOF or tissue TAC), this is denoted as 1.

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agreement. This suggests that currently used thresholds and software used in this study cannot reliably identify ischemic core and may benefit from revisions.

To our knowledge, misclassification of CTP ischemic core volume has not been compared with follow-up noncontrast CT infarct volume to this extent. Several studies have compared CTP ischemic core volume with MR-DWI ischemic core volume obtained at baseline. A high measurement variability in ischemic core volumes was shown between both modalities, with large differences for CTP derived ischemic volumes compared to MR-DWI ischemic core volumes [36,37]. Our study agrees with the limited accuracy of CTP ischemic core volume estimations and shows that ischemic core misclassifications are large. Underlying parameter values differed significantly between misclassified ischemic core and ischemic lesion agreement regions, suggesting room for improvement in threshold definition for ischemic core.

We acknowledge this study comprises a number of limitations. Infarct growth in the time between obtaining baseline CTP and follow-up noncontrast CT can impede accurate comparison between baseline CTP ischemic core volume and follow-up infarct volume. This can lead to underestimation of the FDR of ischemic core on CTP. While misclassified ischemic core can only be caused by flaws in the CTP analysis, agreement between CTP and follow-up noncontrast CT may be partly caused by infarct core growth. The infarcted lesion may grow in the time between baseline and follow-up imaging, therefore it is possible that tissue classified as

Table 2. Median perfusion parameter values for misclassified and ischemic lesion agreement of all 35 patient specific values.

Parameter	Misclassified ischemic core median (IQR)	Ischemic lesion agreement median (IQR)
rMTT*	243% (198%-289%)	342% (249%-432%)
aCBF*	8 ml/100g/min (7–11 ml/100g/min)	6 ml/100g/min (5–8 ml/100g/min)
rCBF*	21.5% (17.3%-29.5%)	13.6% (9.7%-18.0%)
aCBV*	1.59 ml/100g (1.43–1.79 ml/100g)	1.38 ml/100g (1.15–1.49 ml/100g)
rCBV*	51.4% (39.3%-62.0%)	41.6% (31.6%-52.3%)

* Significantly different for misclassified and ischemic lesion agreement region (rank-sum, P<0.01).
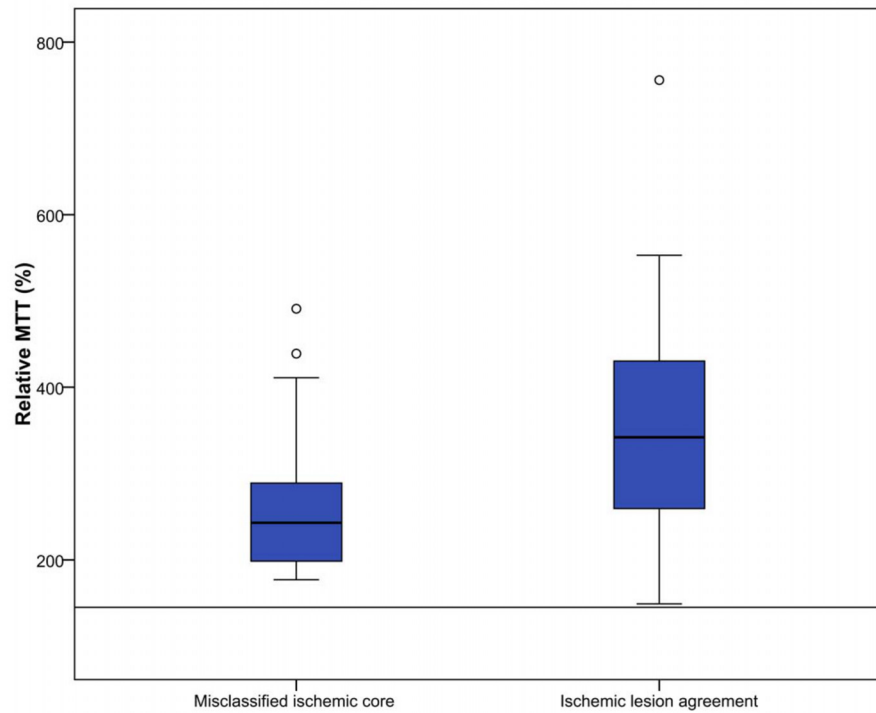
doi:10.1371/journal.pone.0141571.t002

Fig 3. Relative MTT (%) for misclassified ischemic core and ischemic lesion agreement. Threshold value for defining ischemic core is 145%, which is visualized in this figure by the horizontal line.
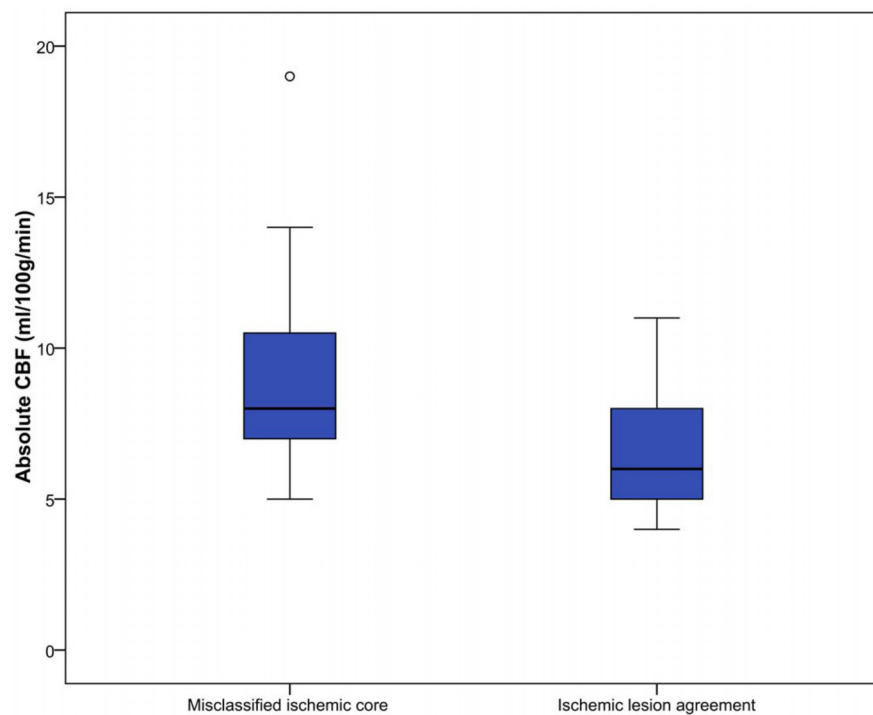
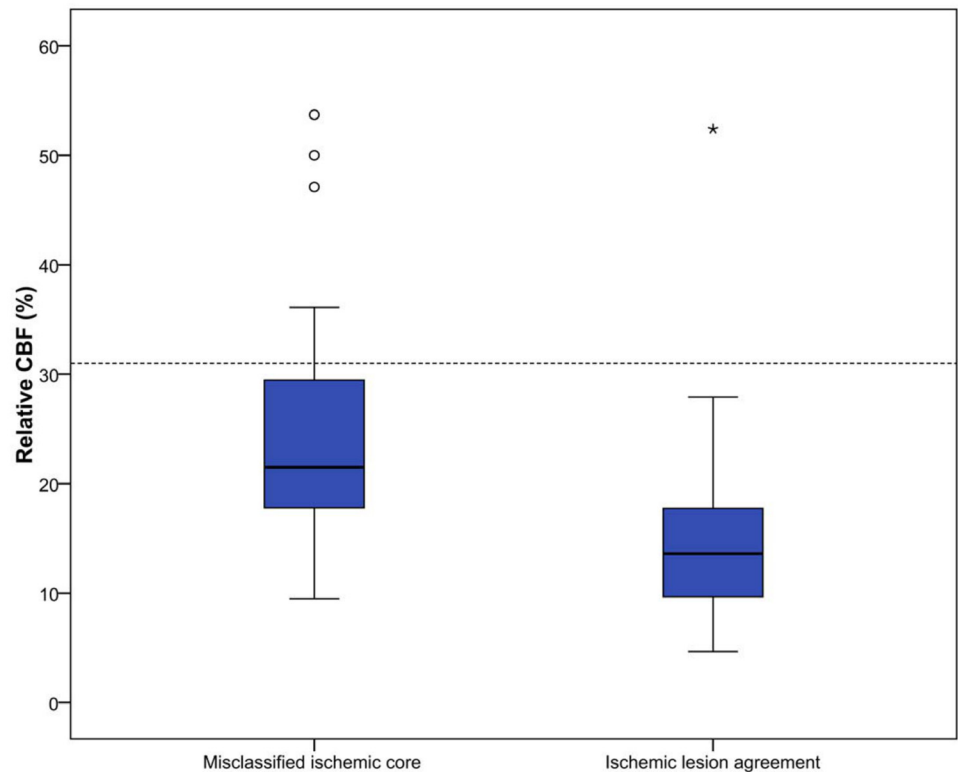**Fig 4. Absolute CBF (ml/100g/min) for misclassified ischemic core and ischemic lesion agreement.**

Fig 5. Relative CBF (%) for misclassified ischemic core and ischemic lesion agreement. Proposed hypothetical threshold value for defining ischemic core is 31%, visualized by a dotted line [42].

ischemic core on baseline CTP was actually misclassified at baseline but this misclassification was covered up due to infarct core growth [2,32,33,38].

Strict inclusion criteria were applied, excluding many patients, so results may not be generally applicable. A large number of patients were excluded because of missing follow-up imaging. This may have resulted in a bias of our results since, for example, patients who did not survive the first days could not be included.

The level of misclassification may also be influenced by various baseline and imaging factors and may be correlated with patient outcome. However, with the relative low number of patients included in this study, the statistical power was not sufficient to correctly perform statistical tests to address this relation.

Though our sample size is relatively small, all perfusion parameters showed a significant difference between the two groups. CT imaging was obtained from two manufacturers which could provide a limitation. It is possible that imaging data derived from different scanners produce different results and may not co-operate optimally with the software. However, we observed similar FDR for both scanners. Furthermore, it has been suggested that delay-insensitive methods might produce more accurate ischemic core classifications compared to delay-sensitive methods we used in this study [39]. This however, has recently been disputed. Delay-sensitive methods produce similar ischemic core volumes as delay-insensitive methods if validated thresholds are used [40]. Thresholds used in this study have been validated in previous studies and are currently used by this software in clinical practice. Several other studies found that usage of (sets of) other thresholds for the definition of infarct core used in other software packages might result in more accurate CTP assessments [18,41–44]. Due to limitations of the
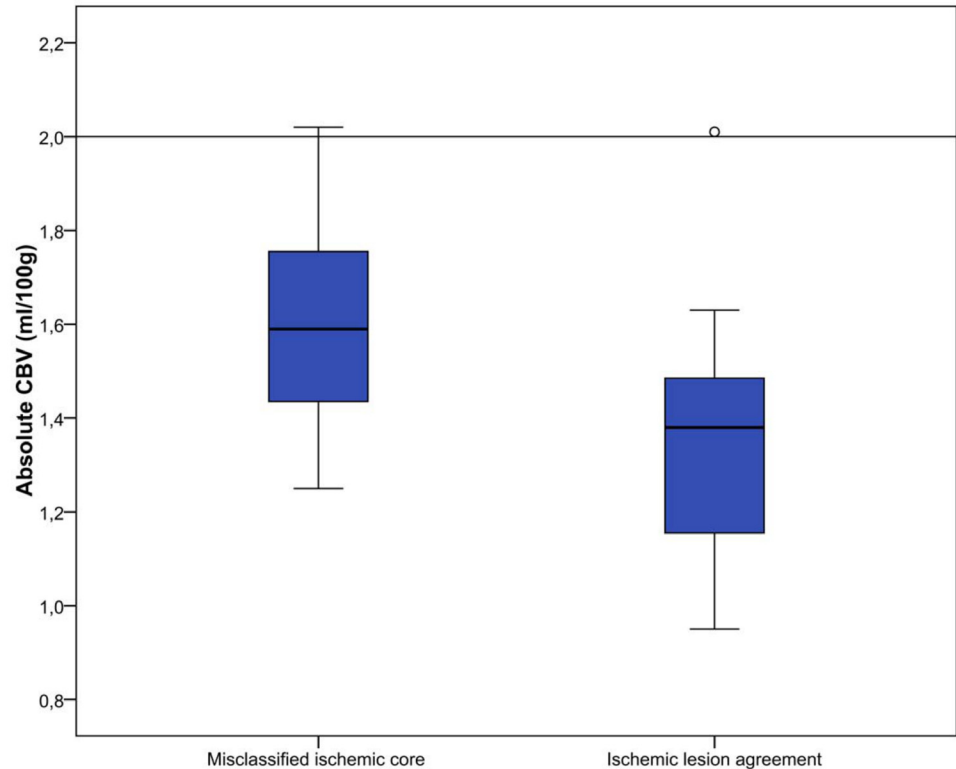
Fig 6. Absolute CBV (ml/100g) for misclassified ischemic core and ischemic lesion agreement.
Current threshold value for defining ischemic core is 2.0 ml/100g, and visualized by a horizontal line.

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software we were not able to evaluate the accuracy of using these alternative thresholds to define ischemic core.

Low signal to noise ratio contributes largely to limitation of CTP accuracy [45]. When quantified, CTP showed a relative low contrast-to-noise ratio (CNR), making it problematic to accurately analyze data [36]. Besides that, it has been shown that truncation of time-attenuation curves can cause inaccuracies in CTP-derived hemodynamic measurements [21,46]. We observed truncation in almost all patients. This was largely due to the applied scan protocol of 60 seconds of scanning, as a result of restricted acquisition times. However, we did not find a clear correlation between truncation and FDR, and could thus not relate truncation to inaccuracies in CTP analysis.

Potential causes of the presented errors in CTP analysis could include biological and anatomical causes that can lead false perfusion results and either mimic or hamper (in-)correct diagnosis of acute ischemic stroke. This could be due to certain vascular or neurological diseases, variations in vascular anatomy and dysregulation, upstream flow restriction, cardiac output or lesions and old infarctions [22,23,27,46]. Misplacement of the patient and motion within the scanner, which is likely to occur in emergency settings, can further impede ideal CT imaging [24,27].

CTP software used in this study calculates ischemic core based on pre-set thresholds (rMTT $\geq$ 145%, aCBV < 2.0 ml/100g) [25]. Median values for both rMTT and aCBV for misclassified ischemic core regions were closer to their threshold values than for ischemic lesion agreement regions, suggesting that some misclassification of ischemic core could be avoided if thresholds would be redefined. Thresholds currently used in CTP analysis are optimized for
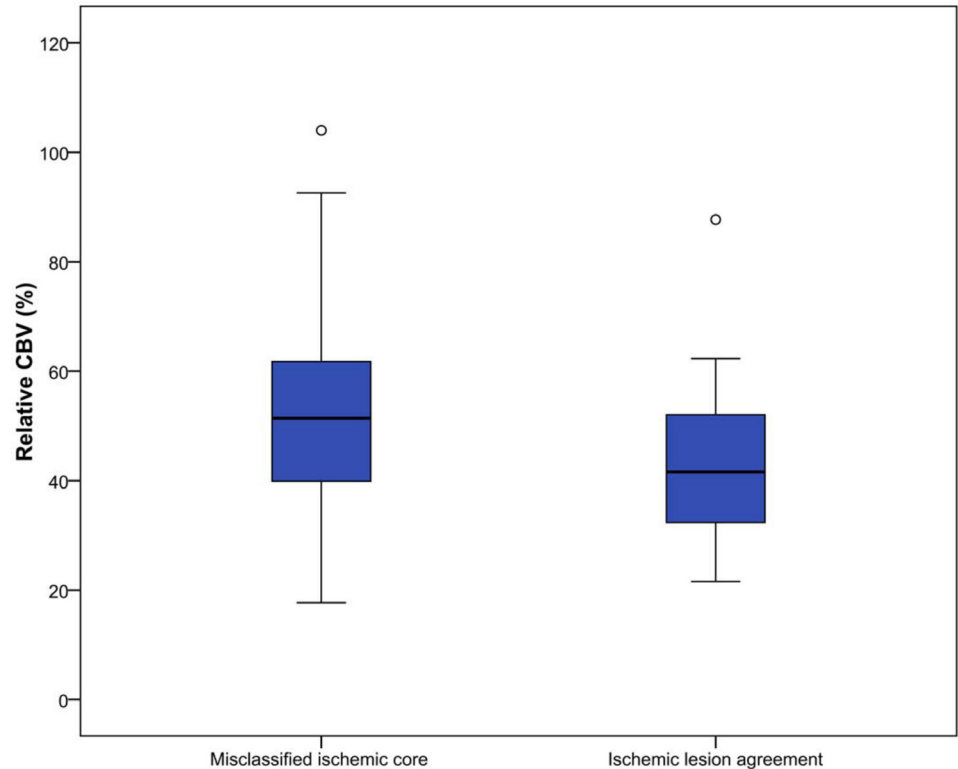
Fig 7. Relative CBV (%) for misclassified ischemic core and ischemic lesion agreement.

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standard acquisition time (<60 sec). It is shown that extension of acquisition time could produce more accurate results, which is increasingly performed [21,25,46]. Therefore, thresholds used currently could be suboptimal in individual cases. It has been suggested to abandon absolute thresholds and use rCBF as a possible optimal perfusion parameter for assessing ischemic core [42–44]. Our results for the rCBF parameter agree with this novel definition for ischemic core. In some cases usage of rCBF as threshold for ischemic core definition would have excluded some misclassified ischemic core regions.

The approach in which CTP parameters are associated with infarct core can be used to improve the current CTP analysis methods as it gives direct measures of these parameters at locations that end up as final infarct volume. Our study indeed shows that on a group level there are large differences between CTP parameters in CTP ischemic core volumes that end up as infarct and the volumes that ended up as healthy tissue on follow-up imaging. However, on a patient-specific level, current CTP analysis methods are insufficient. Approaches that use thresholding of voxel-based values to determine summary maps of ischemic core and penumbra are limited since CTP only reflects the current state of hemodynamics in brain tissue. Brain tissue's accumulation of ischemic injury is gradual, and becomes irreversible only if reperfusion is not achieved and after a given time has elapsed. Treatment and time to reperfusion is not included in current CTP analysis packages, which is a conceptual limitation of the method currently used.

CTP can provide a valuable tool for ischemic core volume estimations in acute ischemic stroke patients, if causes for misclassification can be identified. Novel methods to define ischemic core, improved CT scanners, and more accurate postprocessing may improve CTP analysis and may eventually provide a powerful diagnostic method in acute ischemic stroke management.

Conclusion

This study has shown that perfusion analysis results in a large absolute and relative misclassified ischemic core volume. There was a statistically significant difference for all perfusion parameter values between misclassified ischemic core and ischemic lesion agreement. This suggests that currently used thresholds and software used in this study cannot reliably identify ischemic core and may benefit from revisions.

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