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Original Article

Dose reduction in perfusion CT in stroke patients by lowering scan frequency does not affect automatically calculated infarct core volumes

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ABSTRACT

Background and purpose. – CT Perfusion technique (CTP) is a quantitative, easily performed, accepted and reliable method for detection of ischemic brain changes. Based on calculated parameters, the size of ischemic penumbra and irreversibly damaged infarct core can be determined which helps guide treatment decisions. However, due to the dynamic nature of the CTP study, it is dose intensive. This study determines the consequences of retrospectively reducing the number of scans in the dynamic acquisition by half on the volume of the automatically calculated infarct core (non-viable tissue) and penumbra (tissue at risk) volumes. Our hypothesis was that equivalent volumetric information could be obtained at a substantial dose savings.

Materials and methods. – Fifty one consecutive patients with occlusion of M1 and/or M2 segment of the middle cerebral artery and ischemic stroke proven by follow-up MRI were included. CTP scans were first analyzed in a standard fashion and automatically generated volumes measured in milliliters were recorded in a database. A second analysis was conducted after removing every second data acquisition from the sequential CTP scans. Automatic volume measurements were repeated, recorded and compared to the initial values obtained using the full dataset.

Results. – The two CTP protocols were statistically equivalent pertaining to automatic infarct core volume calculation but a case-by-case analysis revealed substantial overestimation in some cases.

Conclusion. – Reduction of radiation exposure in CTP without objective loss of accuracy of automatically calculated infarct core volume is feasible but might lead to clinically relevant infarct core overestimation in individual cases.

Introduction

In recent years CT-perfusion (CTP) has become a mainstay in the assessment of acute stroke despite MR imaging being a more sensitive modality for the infarct core. CTP is fast and readily available and provides clinically acceptable estimations of the infarct core and penumbra, aiding in subsequent therapeutic decisions.

With current CTP acquisition, coverage of almost the whole brain can be achieved. Brain tissue is scanned in cine mode during the first pass of intravenously administered iodinated contrast medium. Color parameter maps depicting cerebral blood volume (CBV), cerebral blood flow (CBF) and time to peak (TTP), mean transit time (MTT) and time to drain (TTD), among others, can be calculated. These allow for identification of infarct core and penumbra based on parameter and threshold recommendations based on established data provided by software suppliers. In addition, an automated calculation of volumes of infarct and penumbra is possible. Certain volume thresholds have been used as a basis for decision making concerning thrombectomy or best medical treatment in multiple research papers [1–5]. Particularly, publication of positive wake-up stroke trials using CTP for patient selection for endovascular treatment (DAWN and DEFUSE 3) show a reliance on standard and automatic volume calculation of infarct and penumbra [6,7]. However, due to the repetitive scanning nature of the dynamic acquisition, CTP is a dose-intensive imaging method which has led to health concerns not only in professional but also lay publications [8]. Several publications have described methods of reducing radiation dose in CTP, such as adjusting tube current, voltage and different means of image reconstruction as well as the consequences of those adjustments (i.e. image quality and the effects on the mathematically derived parameters) [9–12]. Lowering the acquisition frequency is one method which can potentially

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CTP	CT perfusion
CBV	cerebral blood volume
CBF	cerebral blood flow
TTP	time to peak
MTT	mean transit time
rMTT	relative mean transit time
TTD	time to drain
NECT	non-enhanced CT
PACS	picture archiving and communicating system
ED	emergency department
ROI	region of interest
NVT	non-viable tissue (infarct core)
TAR	tissue at risk (penumbra)
TDLP	total dose length product
ALARA	as low as reasonably achievable
DWI	diffusion weighted imaging
TOST	two one-sided test

significantly reduce radiation exposure [11]. In our study we investigated whether the increasing of time between individual scans affects the automatically calculated infarct core and penumbra volumes and, thus, if dose reduction in this manner affects crucial treatment-relevant parameters.

Materials and methods

We have searched our institutional Picture Archiving and Communicating System (PACS) for patients fulfilling the following inclusion criteria: admission to emergency department (ED) with a suspected diagnosis of ischemic stroke in the time period from 27.07.2015 to 31.03.2016, having undergone our standard CT imaging stroke protocol, diagnostic CTP (proven occlusion of M1-/M2-segment of MCA (on CTA), and an available follow-up MRI examination to prove the suspected diagnosis of ischemia. Exclusion criteria included a stroke mimics (e.g., intracranial hemorrhage, epileptic seizure), no follow-up MRI examination or a non-diagnostic CTP due to excessive motion artifacts or bolus timing inaccuracies resulting in inadequate time attenuation curves. A total of 474 patients from our emergency department in that time period received a CTP scan for suspicion of ischemic stroke and from that group 51 patients (20 males, 31 females; mean age 76,4 y. SD 12,5 y.) fulfilled inclusion criteria and created the study group (Fig. 1).

Examinations were conducted on a 128 detector row CT (Somatom Definition AS+, Siemens, Germany). After cerebral non-enhanced CT (NECT) for intracranial hemorrhage exclusion, the radiologist manually selected the lowest slice for CTP (base of stack) which contained cerebral arteries used for determining of arterial inflow. The following scan parameters for CTP were used: coverage of 100 mm; tube voltage, 80 kV (peak); tube current, 100 mAs; scan time, 54 seconds; variable temporal resolution (first 20 scans every 1.5 seconds, last 8 scans every 3 seconds) amount of administered contrast medium, 50 mL with 370 mg iodine per ml, flow of 5 mL/s, followed by a saline bolus of 30 mL. The contrast agent was injected via 18 g or 20 g cannula in the antecubital vein with a power injector. After CTP data acquisition, images were reconstructed with 5 mm slice thickness and stored in PACS as well as transferred to Syngo.Via software suite (Siemens, Forchheim, Germany) where a CT Neuroperfusion workflow (using deconvolution calculation method) was used to calculate CTP maps. For defining infarct core and penumbra we used established values of CBV lower than 2 mL/100 g brain tissue and relative MTT (rMTT) higher than 145% [13]. rMTT calculation was determined by manually drawing a circular region of interest (ROI) in the contralateral (unaffected) hemisphere at the level of the biggest cross section of ischemic stroke in transverse plane (Fig. 2). Using those parameters, an automated volume evaluation of infarct core and penumbra was performed. Calculated values in milliliters were recorded in a database (Fig. 3).

In the next step, all of the CTP examinations were reloaded into Syngo.Via and every second time point of the acquisition was excluded (Fig. 4), resulting in total of 14 scans (first 10 scans every 3 seconds, last 4 scans every 6 seconds) and automated infarct core and penumbra volume calculations were performed again and results were recorded in a database.

Schuirmann's two one-sided test (TOST) for paired samples was used to show equivalence of volume means between standard CTP and low frequency CTP. The sample size allows for testing of equivalence with a power of 90% (alpha = 0.05).

The data analysis for this paper was generated using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). This study received approval from the regional ethics committee.

Results

The mean volume of penumbra calculated based on standard CTP protocol was 122.8 mL (SD 44.36 mL, Min. 24 mL, Max. 213.7 mL). The mean volume of infarct core in this group was 103.7 mL (SD 39.01 mL, Min. 22.5 mL, Max. 208.3 mL)

After reducing the number of CTP scans, an automated volume calculation resulted in a mean value of penumbra of 105.3 mL (SD 47.83 mL, Min. 31.8 mL, Max. 231.3 mL) and infarct core of 113.9 mL (SD 39.56 mL, Min. 30.7 mL, Max. 223.5 mL). TOST calculations were conducted using the equivalence margins set to −15 mL and + 15 mL (based on calculated mean infarct core and penumbra volumes of standard CTP protocol). For infarct core, the 90% confidence interval (7.33 mL, 13.16 mL) is completely contained within the equivalence interval (Fig. 5). Equivalence of volume measurement in infarct core between standard CTP and reduced frequency CTP can be declared ($P < 0.05$). Manual analysis of individual cases revealed that in 10 patients the infarct core in low frequency CTP group was overestimated by ≥ 25%.

For penumbra, the 90% confidence interval (−23.85 mL, −11.24 mL) is not contained within the equivalence interval. Equivalence of volume measurement in penumbra between standard CTP and reduced frequency CTP cannot be declared ($P > 0.05$). Further analysis of individual cases revealed that in 17 patients the percentage difference between base values and those calculated after reduction of CTP scans were higher than 25% and even ≥ 50% in 10 subjects.

Total dose length product (TDLP) values for standard CTP and the group with low frequency were 1437 mGy/cm and 718.5 mGy/cm respectively.

Discussion

The last decade's developments in endovascular treatment of stroke and, in particular, positive trial results are currently in the spotlight. Recent publication of the DAWN trial will potentially increase the number of thrombectomies performed more than 6 hours after initial stroke onset [6]. But to apply DAWN's results by adhering to the inclusion criteria, a method of infarct core evaluation for patient stratification is needed. Hospitals which do not rely on magnetic resonance imaging could use CTP for infarct core volume calculation and therapeutic decision making. Simultaneously, the well-known ALARA (As Low As Reasonably Achievable) principle applies and thus methods for robust infarct

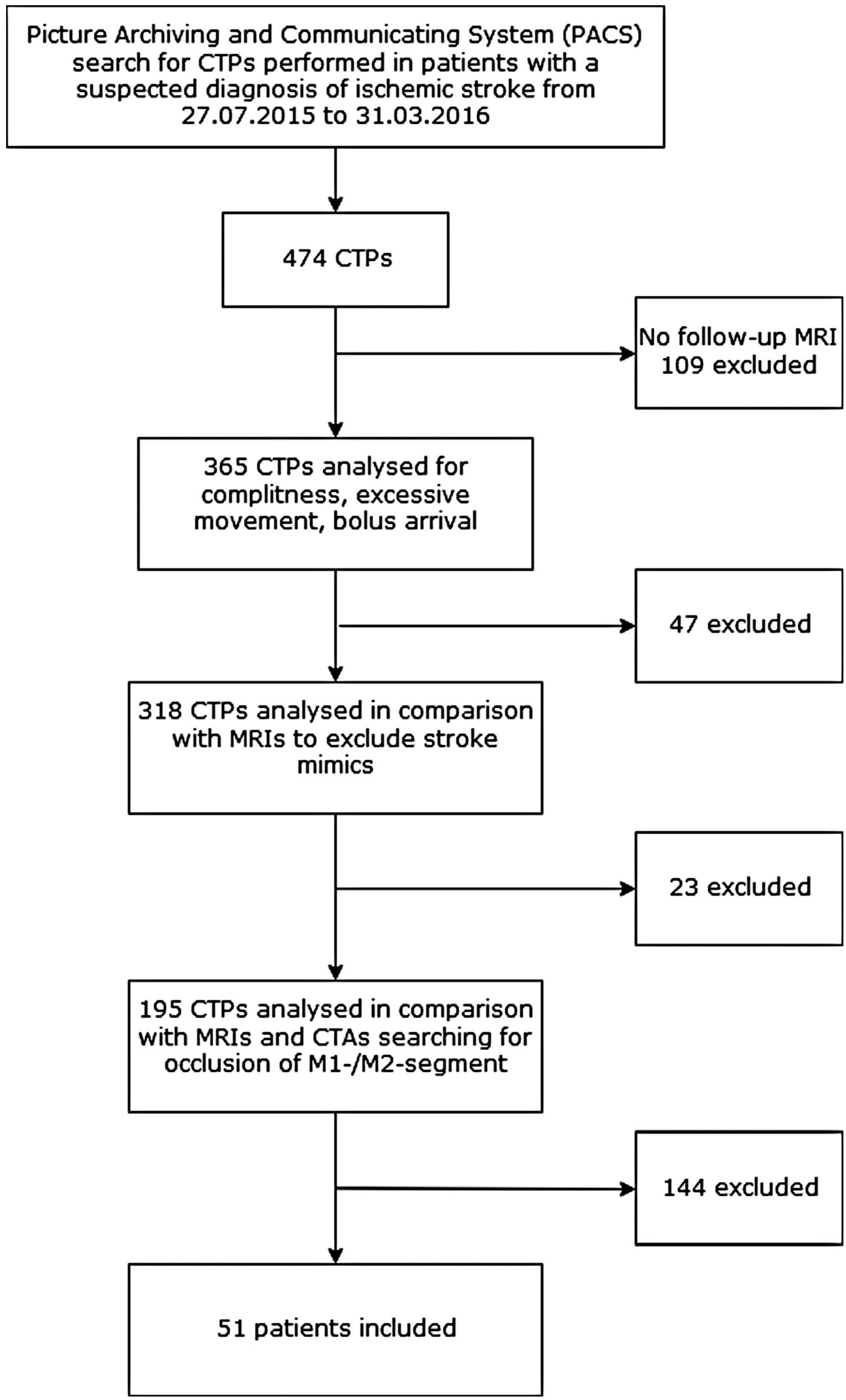

Fig. 1. Flowchart of inclusion criteria.

core volume calculation while reducing radiation exposition of the patients should be explored. As part of our in-house CTP optimization, we have been using a protocol with a variable sampling rate since 2013 but we elected to further optimize by exploring additional methods of dose reduction. Perfusion values of brain tissue acquired with dynamic CT perfusion are affected by various parameters and thus their accuracy depends upon multiple factors. On the other hand, there are multiple possibilities to reduce radiation exposure of the patient undergoing CTP. Many publications have addressed both dose reduction through tube current

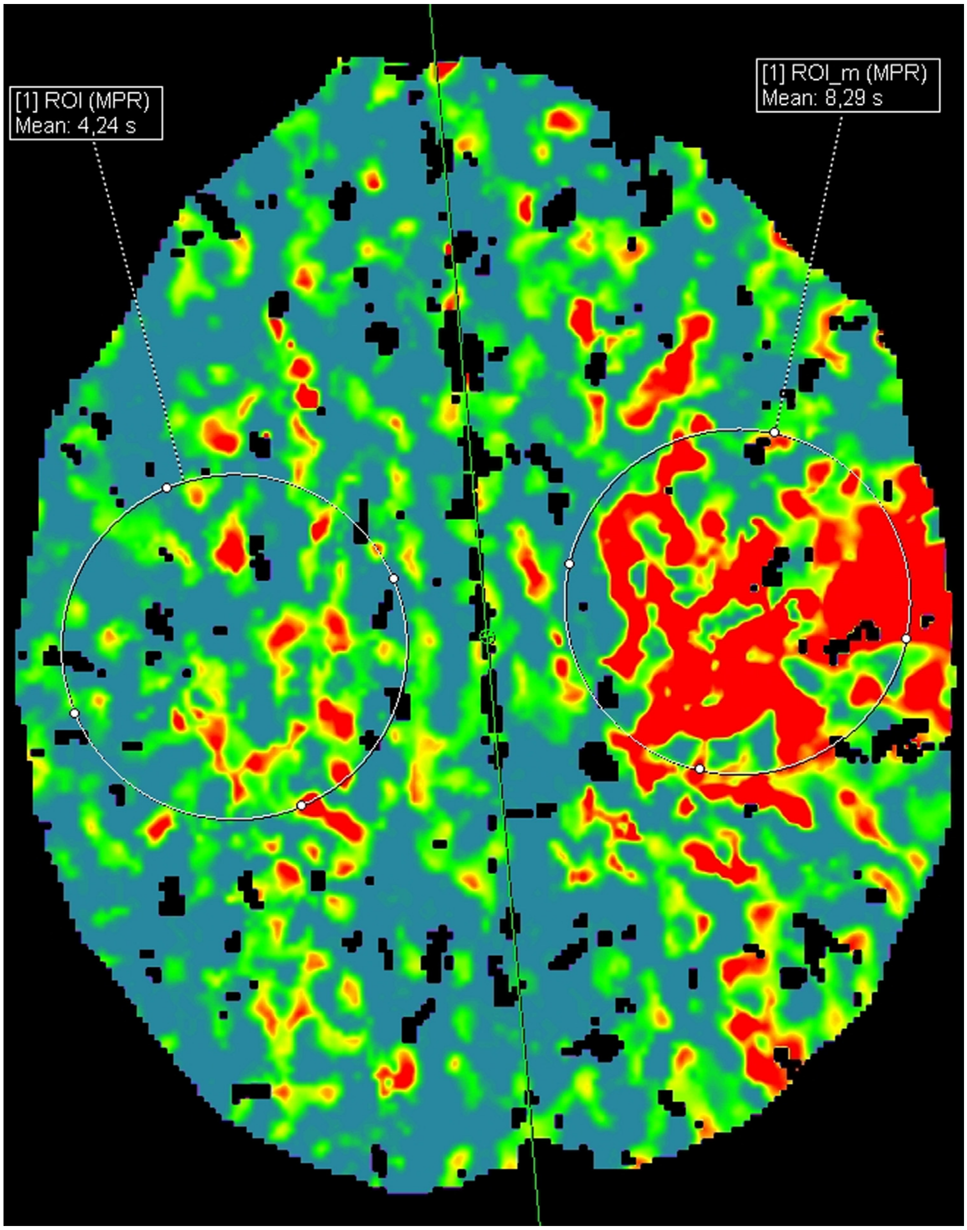

Fig. 2. MTT map shows a delay in the middle part of the left hemisphere as quantified by average value obtained by drawing a ROI.

adjustment, total CTP scan duration, temporal resolution adjustment and contrast volume and chaser bolus volume modification to obtain optimal results for ischemic stroke assessment but none of them has investigated influence of those changes on automatic volume calculations of ischemic lesions [10,11,14,15]. We assessed the influence of the temporal sampling reduction in CTP on automatic volume calculation of infarct core and penumbra as well as on delivered radiation dose. We have chosen the well-established values of CBV < 2 mL/100 g and rMTT > 145% defined by Wintermark et al to identify infarct core and penumbra respectively and we observed whether sparser sampling rate leads to significantly different volumes of stroke affected brain tissue [13].

There is currently no consensus on the optimal sampling rate of CTP. Some authors recommend a temporal scan resolution of 1–2 scans per second, advocating the need of precise depiction of time-attenuation curves, however, this approach results in a substantial radiation exposure [15,16]. A different recommendation was made by Wintermark et al.: his group found that the volume of injected contrast bolus influences temporal resolution and certain combinations of those parameters allow for a sparser sampling rate [17]. Based on those results, we use a 50 ml bolus of Ultravist 370 followed by a saline chaser of 30 ml administrated with a flow of 5 mL/s. According to Wintermark and Wiesman these parameters could theoretically allow for lowering of temporal resolution to 1 scan every 3 seconds without affecting significantly quantitative CTP parameters [10,17]. It should be mentioned that different scan protocols, patient groups, software packages, calculation algorithms, pre- and post-processing settings, and CTP thresholds (if applicable) used in the above mentioned publications contribute to difficulty in comparing the results and could potentially explain different recommendations. The software used in our study calculates CTP values using a deconvolution algorithm. Although this computing approach is supposed to be more robust while using sparser sampling it is known that resulting quantitative CTP parameters (such as CBV and MTT) are dependent on scan frequency, i.e. lower CTP sampling affects CBV. Some authors suggest that lower sam-

Fig. 3. An example of results showing the volumes of penumbra (TAR – tissue at risk) and infarct core (NVT – non-viable tissue).

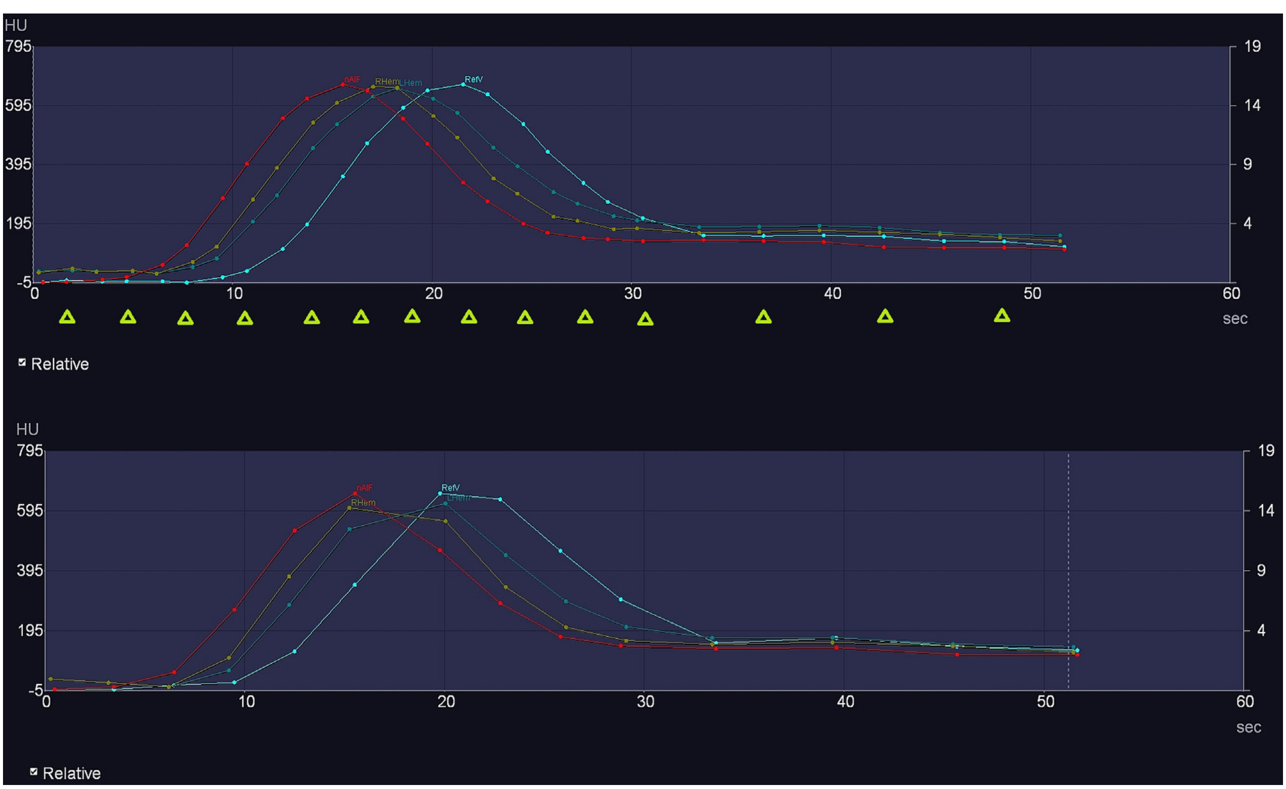

Fig. 4. Comparison of two curves depicting the arterial inflow (red), venous outflow (cyan) and attenuation changes in hemispheres (remaining two curves). The graph in the upper part derives from an examination with 28 scans/time points. The lower graph is a result of manual deletion of every second time point.

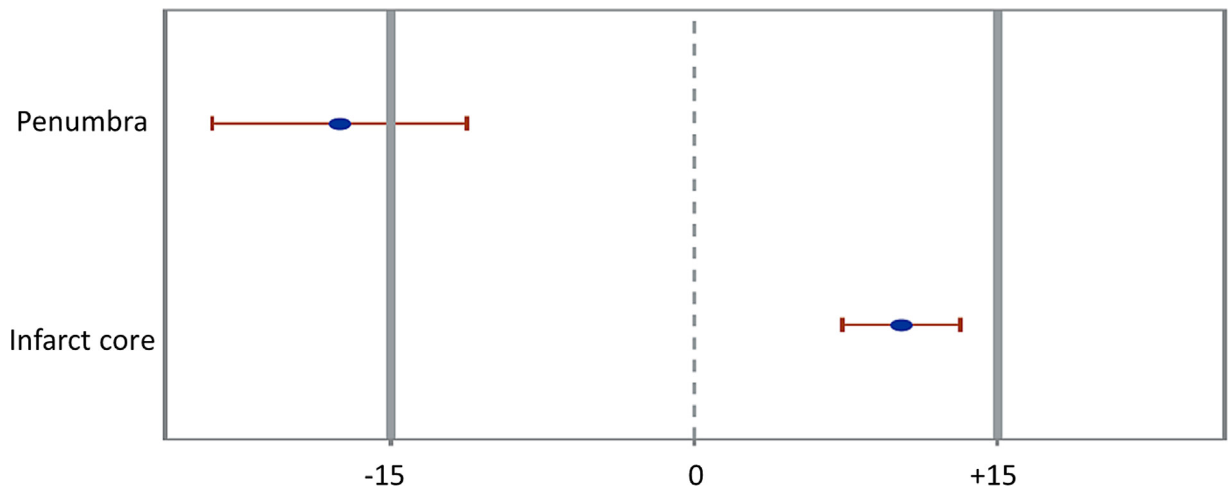

Fig. 5. Results of two-sided and two one-sided test (TOST) (δ = 15) procedures to compare volume calculations obtained with low frequency CTP to reference values of standard CTP.

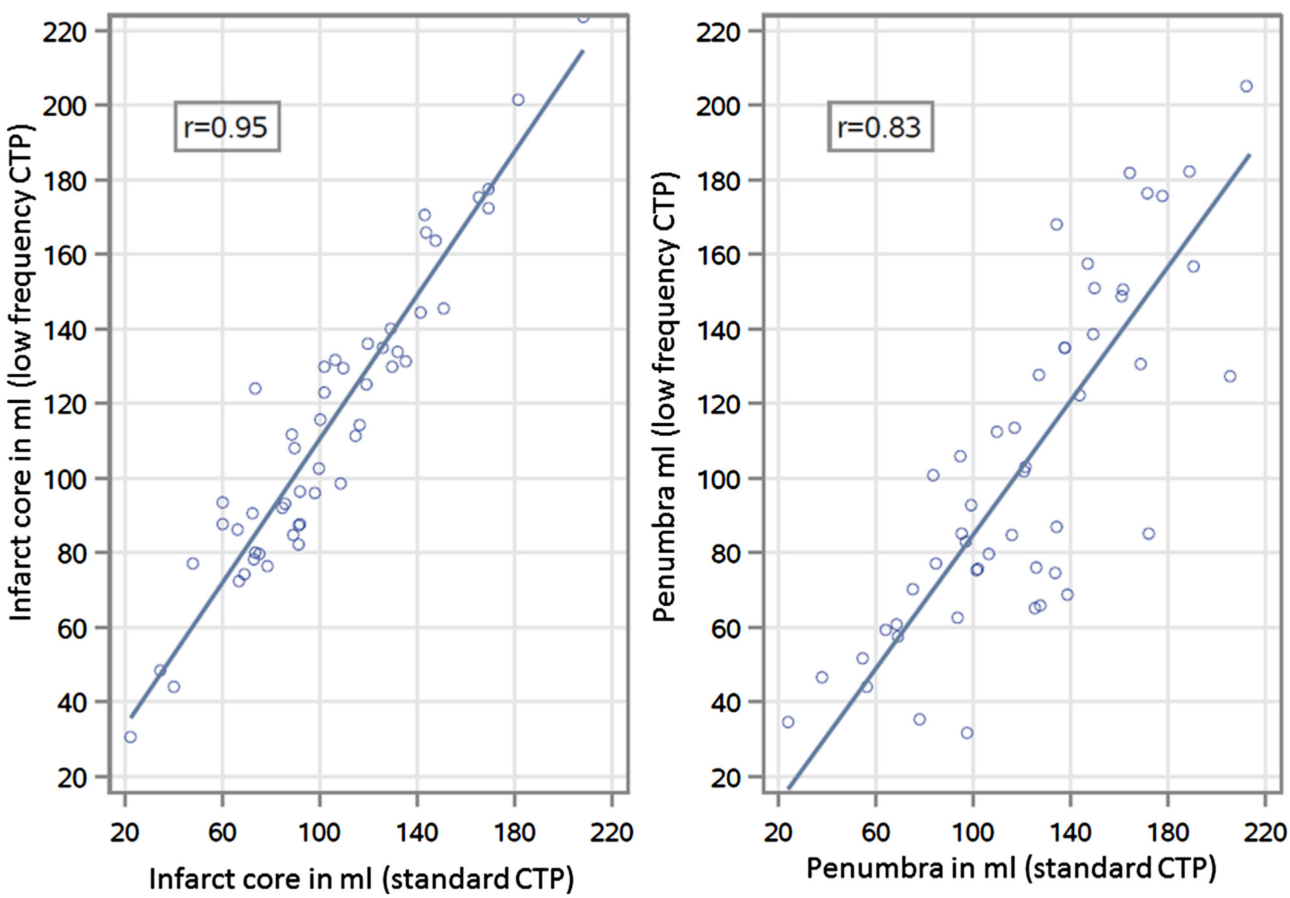

Fig. 6. Scatter plots depicting relation between penumbra and infarct core volumes calculated with standard and low frequency CTP protocols.

pling rate could lead to truncation of the peak of attenuation curve and thus lead to an underestimation of volume of blood in examined brain tissue [15]. Abels et al presented contradicting results. In their publications, lowering temporal resolution (from scanning every 1 second to every 2 seconds) lead to higher infarct core estimations, although this effect was not as pronounced in areas suspected for infarct as in areas not suspected for stroke [16]. We have observed similar results, as reducing CTP scan frequency lead to a trend for overestimation of infarct core volume (in our study those calculations were based on CBV values) (Fig. 6). In 10 patients, the volume of infarct core in the group with lower sampling rate was ≥ 25% in comparison to the calculations based on our standard CTP protocol. This effect could potentially prevent qualifying those cases from endovascular treatment if infarct core volume is used as a strict exclusion criterion (Fig. 7).

Mean transit time is also affected by temporal resolution of CTP. MTT is an intrinsic, patient specific value and, as such, should be assessed by appropriate, high sampling rate in order to be precisely measured [10]. Shorter MTTs require a higher sampling rate (with resulting increased radiation exposure). It has been reported that

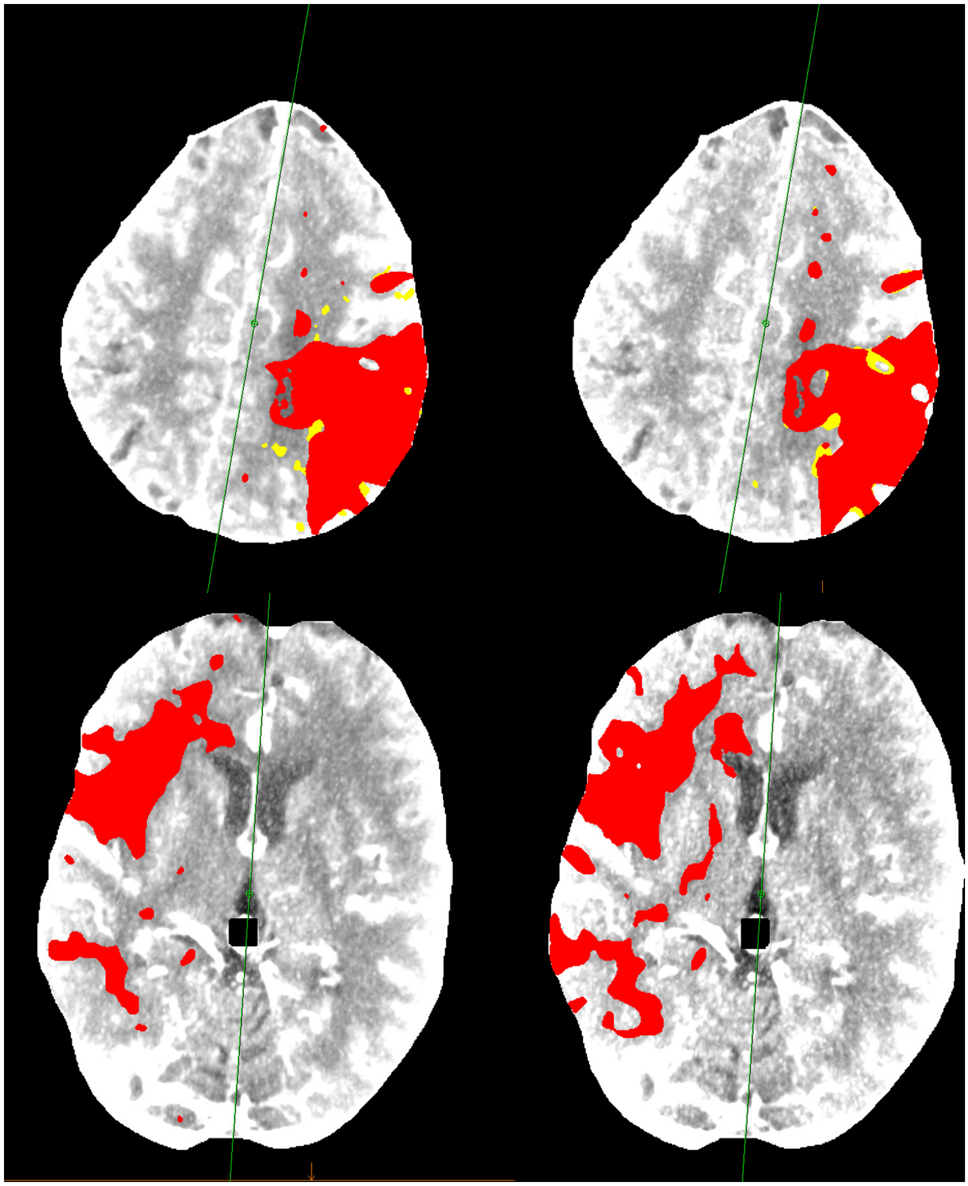

Fig. 7. Upper row shows virtually no difference in infarct core size (left column uses original CTP source images, right column is based on the reduced dataset). Lower row shows a scan of a different patient, depicting a difference in automatically calculated infarct core between the two protocols, with overestimation in the results based on CTP source images with low frequency sampling.

increasing intervals between individual scans leads to underestimation of MTT [16]. In different publications, changes of MTT with different temporal resolutions did not show a clear trend and, additionally, seemed to be affected in a different manner in ischemic and healthy brain tissue [15]. In our study, we have observed that reducing CTP scan frequency lead to underestimation of the penumbra which was calculated based on MTT values. It is noteworthy to mention that in 17 patients in our cohort deviations from penumbra volumes calculated with a sparser sampling differed more than 25% from values obtained using the standard protocol. This, analogous to infarct core overestimation in low frequency CTP group, could have direct influence on therapy choices by affecting the core infarct-penumbra mismatch calculation and thereby disqualify patients that would have otherwise been eligible for endovascular treatment. Although we have not seen a statistically significant difference between automatically calculated infarct core and penumbra volumes between our two protocols, we cannot advocate a sparser sampling in CTP while using CBV and rMTT for calculation of infarct core and penumbra sizes due to the potential disadvantage in decision making in individual, but not isolated cases. Due to our software's method of determining infarct core volume (based on CBV) our results are not comparable to results generated by other programs which use different parameters to define infarct core (i.E. iSchemaView RAPID) [6,7].

The second objective of our research was dose reduction in CTP. In 2008, the FDA started an investigation into the safety of CTP. Although it was caused by overexposure at a single center it affected about 40% of 200 patients scanned over a period of 1.5 years and highlighted the need for quality assurance and efforts to reduce radiation exposure in CTP [18]. In our institution, we record total dose length product (TDLP) for every CT examination. TDLP is a product of a CT dose index (CTDIvol) derived from a phantom (value provided by the manufacturer) and of the imaged object‘s length and a well-established quantification method of radiation exposure. In our study, lowering the temporal resolution of our standard protocol lead to a reduction of number of individual scans in CTP from 28 to 14. This in turn resulted in a 50% reduction of the TDLP from 1437 mGy/cm to 718.5 mGy/cm. The advantage of dose reduction in perfusion examinations performed with CT becomes more apparent considering a steadily growing number of these examinations performed in our institution (almost 700 examinations in 2015) and the fact that a number of those patients will undergo additional X-ray examinations such as digital subtraction angiography for endovascular thrombectomy as well as follow-up CT – increasing the overall individual radiation exposure.

Conclusion

We have shown that lowering temporal resolution of CTP, as we described above, does not significantly affect automated volume calculations of infarct core when using CBV. As a consequence, halving of the radiation exposure without disrupting crucial CTP results could be achieved for the majority of patients. However, the results obtained from the low frequency CTP could be potentially significantly misleading in individual cases when calculating infarct core and, additionally, were found to not be equivalent for penumbra volume calculation based on rMTT. Therefore, it is not recommended to use those parameters for this purpose in low frequency CTP protocols.

Disclosure of interest

The authors declare that they have no competing interest.

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