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Low dose CT perfusion in acute ischemic stroke

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Abstract
Introduction The purpose of this investigation is to determine if CT perfusion (CTP) measurements at low doses (LD=20 or 50 mAs) are similar to those obtained at regular doses (RD=100 mAs), with and without the addition of adaptive statistical iterative reconstruction (ASIR).
Methods A single-center, prospective study was performed in patients with acute ischemic stroke (n=37; 54 % male; age=74±15 years). Two CTP scans were performed on each subject: one at 100 mAs (RD) and one at either 50 or 20 mAs (LD). CTP parameters were compared between the RD and LD scans in regions of ischemia, infarction, and normal tissue. Differences were determined using a within-subjects ANOVA ($p<0.05$) followed by a paired t test post hoc analysis ($p<0.01$).
Results At 50 mAs, there was no significant difference between cerebral blood flow (CBF), cerebral blood volume (CBV), or time to maximum enhancement (Tmax) values for the RD and LD scans in the ischemic, infarcted, or normal contralateral regions ($p<0.05$). At 20 mAs, there were significant differences between the RD and LD scans for all parameters in the ischemic and normal tissue regions ($p>0.05$).
Conclusion CTP-derived CBF and CBV are not different at 50 mAs compared to 100 mAs, even without the addition of ASIR. Current CTP protocols can be modified to reduce the effective dose by 50 % without altering CTP measurements.

Keywords CT perfusion · Effective dose · Radiation · Acute ischemic stroke

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Introduction

CT is a major source of radiation dose and contributes to an overall increased cancer risk [1–3]. The addition of CT perfusion (CTP) to stroke imaging protocols increases radiation dose up to twice that of an unenhanced head CT [4]. Nonetheless, an imaging protocol that includes unenhanced CT, CT angiography (CTA) from the aortic arch to vertex, and CTP has been shown to be sensitive for identifying infarcted and penumbral tissue and thus may play a major role in treatment decisions [5].

Recommended stroke imaging protocols suggest that CTP imaging is performed at 80 kV and 100 mAs [6]. On current 64-slice CT scanners using these parameters, the approximate effective dose for unenhanced head CT is 2 mSv, 6 mSv for CTA, and 5 mSv for CTP [4, 7]. Imaging protocol alterations to reduce dose include, but are not limited to, lowering the tube current (mAs), causing proportional noise increase, and lowering the kV, which does not produce optimal CTP images below 80 kV [8]. Iterative reconstructive techniques have been available for over 30 years as a way to reduce noise in images obtained at low mAs. In the past, they have been limited by the need for considerable computing power and lengthy image reconstruction times, which is no longer a considerable limitation.

Adaptive statistical iterative reconstruction (ASIR) has been used in abdominal and thoracic CT [9, 10]. Initial reports have demonstrated up to 40 % dose reduction without compromising the signal-to-noise ratio (SNR) in unenhanced head CT [11, 12]. Despite these reported benefits, the utility of iterative reconstruction in CTP imaging is less clear. A recent report on an iterative reconstruction algorithm, iDose (Philips Healthcare), showed no difference in absolute perfusion values obtained at 80 mAs with and without the iterative reconstruction algorithm [13]. These results suggest that it may be possible to obtain accurate CTP information at lower

doses than are currently employed in standard practice, even without the application of additional iterative reconstruction software.

In this investigation, we compare regular dose (RD) to low dose (LD) CTP reconstructed with filtered back projection (FBP) and ASIR in patients with acute ischemic stroke. The purpose of this investigation is to determine if CTP measurements at low doses (20 or 50 mAs) are similar to those obtained at regular doses (100 mAs), with and without the addition of ASIR.

Methods

Study design

A single-center, prospective study was performed in patients with acute anterior circulation ischemic stroke (n=37) presenting to a regional stroke center from Jan 2010–Dec 2012. Each case was screened by one of two neuroradiologists (XX, XX). All subjects or their substitute decision makers provided informed consent. Regular dose (RD) CTP was performed at admission and 24 h following presentation as per institutional standards. At 24 h, two CTP scans were performed on each patient: one at a RD (100 mAs) and one at a low dose (LD; 20 or 50 mAs). The protocol was approved for use due to the overall unchanged radiation dose to the patient achieved by removing a routine post-contrast CT study normally performed at 24 h. Cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to maximum arterial concentration (Tmax) were compared between RD and LD 24-h CTP scans.

Clinical data collection

Clinical data collected included baseline and 24-h NIHSS and mRS. ASPECTS from admission non-contrasts CT (NCCT), clot burden score (CBS), and collateral score (CS) from CTA images.

CT and MR imaging

All admission and 24-h CT scans were performed on a 64-slice CT scanner (VCT, GE Healthcare) as per the institutional standard stroke protocol. Non-contrast CT (NCCT): 120 kV; 300 mAs; 1-s rotation, 5-mm-thick slice, 5-mm spacing. Baseline and 24-h CTA: 0.7 mL/kg iodinated contrast agent up to a maximum of 90 mL (Omnipaque 300 mg iodine/mL); 5–10-s delay, 120 kV; 270 mA; 1 s/rotation; 1.25-mm-thick slices; table speed 20.62 mm/rotation. RD biphasic CTP protocol was performed at baseline and 24 h: 80 kV, 100 mAs, 1-s rotation time, 25-cm FOV, and 8×5-mm slice thickness (4 cm of coverage centered at the basal ganglia). The first phase was a 45-s cine (continuous) scan while the following second phase was another 7 scans at 15-s intervals. Immediately following the RD CTP scan, all subjects received a LD CTP using 50 mAs (n=10) or 20 mAs (n=27) at the same scanning parameters and table position selected for the RD study.

RD scans were reconstructed using filtered back projection (FBP). LD scans were reconstructed using either FBP or a combination of 20 % FBP and 80 % adaptive statistical iterative reconstruction (ASIR; GE Healthcare). Eighty percent ASIR was chosen in order to optimize the accuracy of perfusion modeling. A third set of LD CTP maps were generated with the addition of SmartSmooth (SS), a spatial smoothing post-processing technique available on CT perfusion 5 (prototype version of CT Perfusion 4D, GE Healthcare). Therefore, four sets of CTP maps were generated for each subject: RD, LD, LD+ASIR, and LD+ASIR+SS. Follow-up MRI was performed on days 5–7 that minimally included DWI (8125 ms/min (TR/TE), FOV 26 cm, matrix 128*128 image matrix, section thickness 5 mm) and fluid attenuation inversion recovery (FLAIR) (8000/120/200 (TR/TE/TI (inversion time)), FOV 22 cm, matrix 320*224, section thickness 5 mm with a 1-mm gap).

Imaging analysis

CBF, CBV, MTT, and Tmax maps generated from the 24-h CTP scans were analyzed offline. Regions of interest were visually drawn around the baseline CBV and MTT abnormality and designated the *ischemic region*. Infarct was delineated on FLAIR MRI using Medical Image Processing, Analysis and Visualization (MIPAV; Center for Information Technology, National Institutes of Health, version: 4.4.1). FLAIR MRI, follow-up and baseline CTP studies, and their associated regions of interest (ROIs) were co-registered with baseline NCCT using Statistical Parametric Mapping (SPM8, Welcome Trust, London, UK). The ROIs were reflected across the axis of symmetry to derive mirror ROIs. Final *infarct region* was defined as the intersection between the MTT perfusion abnormality identified on the baseline CTP and MRI-derived ROI. Non-infarct regions or benign oligemia comprised MTT perfusion abnormality outside of the final infarct region within the ischemic region. To minimize the contribution of blood vessels, pixels with CBF >100 mL (100 g^{-1} min^{-1}) or CBV >8 mL (100 g^{-1}) were excluded.

Effective radiation dose calculation

The dose-length product (DLP) for each CTP scan performed was obtained from the dose reports provided by the software at the time of image acquisition. The effective doses for each RD and LD scan were calculated using estimated conversion factors for the head [14].

Statistical analysis

The mean and standard deviation for CBF, CBV, MTT, and Tmax parameters were calculated for the ipsilateral *ischemic* and *infarct regions* and contralateral *ischemic region* for each of the four CT perfusion maps (RD, LD, LD+ASIR, LD+ASIR+SS) from each subject. Differences between CBF, CBV, MTT, and Tmax parameters calculated from the RD and LD maps were determined using a within-subjects ANOVA omnibus test followed by post hoc paired *t* tests corrected for multiple comparisons. The between-subjects factors included in the omnibus tests were the tube current value for the LD scans (20 or 50 mAs).

All statistical analysis was performed using the SPSS software package. Differences were considered significant for within-subjects omnibus tests at the level of $p<0.05$ with Bonferroni corrections for multiple comparisons.

Results

Study group characteristics

There were 37 subjects (54 % (20/37) male; age=74± 15 years) included in the study group (Table 1). All patients demonstrated an occlusion in the anterior cerebral circulation on the baseline CTA. IV recombinant tissue plasminogen activator (rtPA) was given in 28/37 (76 %).

CT perfusion—ischemic and contralateral regions

At 20 mAs, there were significant differences between the RD and LD scans for all CTP parameters in both the contralateral and ipsilateral regions except for Tmax ($p<0.05$; Figs. 1a and 2). The addition of ASIR and ASIR+SS to the LD scans did not eliminate the differences in CBF and CBV between RD and LD scans.

At 50 mAs, there was no significant difference between RD and LD CBF, CBV, or Tmax values in the ipsilateral or contralateral regions (Figs. 1b and 2). MTT was significantly higher on the RD scan than the LD scan for both the ipsilateral ($p=0.001$) and contralateral ($p=0.003$) regions. There were no significant differences in the MTT values between the LD+ASIR or the LD+ASIR+SS and the RD scan for either the ipsilateral or contralateral hemisphere. Standard deviations for all CTP parameters were not significantly different between the RD and LD scans at 50 mAs.

Table 1 Study group characteristics

NIHSS—baseline	12.3 (8.8)[a]
NIHSS—24 h	9.8 (8.8)
mRS—24 h	3.5 (1.0)
ASPECTS	7.4 (2.1)
Clot burden score	6.7 (3.2)
Collateral score	2.2 (0.7)

[a] Mean (SD) for the study population

CT perfusion—infarct region

At 20 mAs, there was no difference in CBV or Tmax ($p>0.05$; Figs. 1a and 2) but CBF and MTT were significantly different between LD and RD scans in the infarcted region ($p<0.01$). There was no difference in MTT between RD and LD+ASIR and LD+ASIR+SS scans or in CBF between RD and LD+ASIR+SS scans.

At 50 mAs, mean and standard deviation for all CTP parameters in the infarcted regions were not significantly different between the RD and LD scans ($p<0.05$; Figs. 1b and 2).

Effective radiation dose

The DLPs for the CTP portion of the examination (4 cm of coverage) performed at 100, 50, and 20 mA were 1205, 602, and 241 mGy cm, respectively. The effective dose was calculated to be 2.5 mSv for the 100-mA CTP scans, 1.3 mSv for the 50-mA CTP scans, and 0.51 mSv for the 20-mA CTP scans.

Discussion

CT perfusion performed at 50 mAs provides quantitative perfusion information comparable to images acquired at 100 mAs in the setting of acute ischemic stroke. These findings are consistent irrespective of recanalization status, and are reproducible in regions of ischemia or infarction, and in the contralateral hemisphere with normal perfusion.

CT is the largest source of radiation dose in medical imaging [3]. Substantial increases in its use over the past decade have raised concerns regarding the potential risks of dose exposure. These concerns with CTP were highlighted by a 2009 investigation by the US Food and Drug Administration into excess radiation doses produced by CTP scans at a single center. Although this was an isolated incident resulting from incorrect scan protocols, it raised broader issues surrounding radiation dose, including its potential risks, the need for quality control, and avenues for dose reduction [15, 16].

CTP is part of the standard imaging protocol for acute stroke in many tertiary centers. The information it provides regarding tissue viability may be an important prognostic indicator of outcome and thus helps to guide treatment decisions in acute stroke [5, 16]. The benefits of CTP come at a

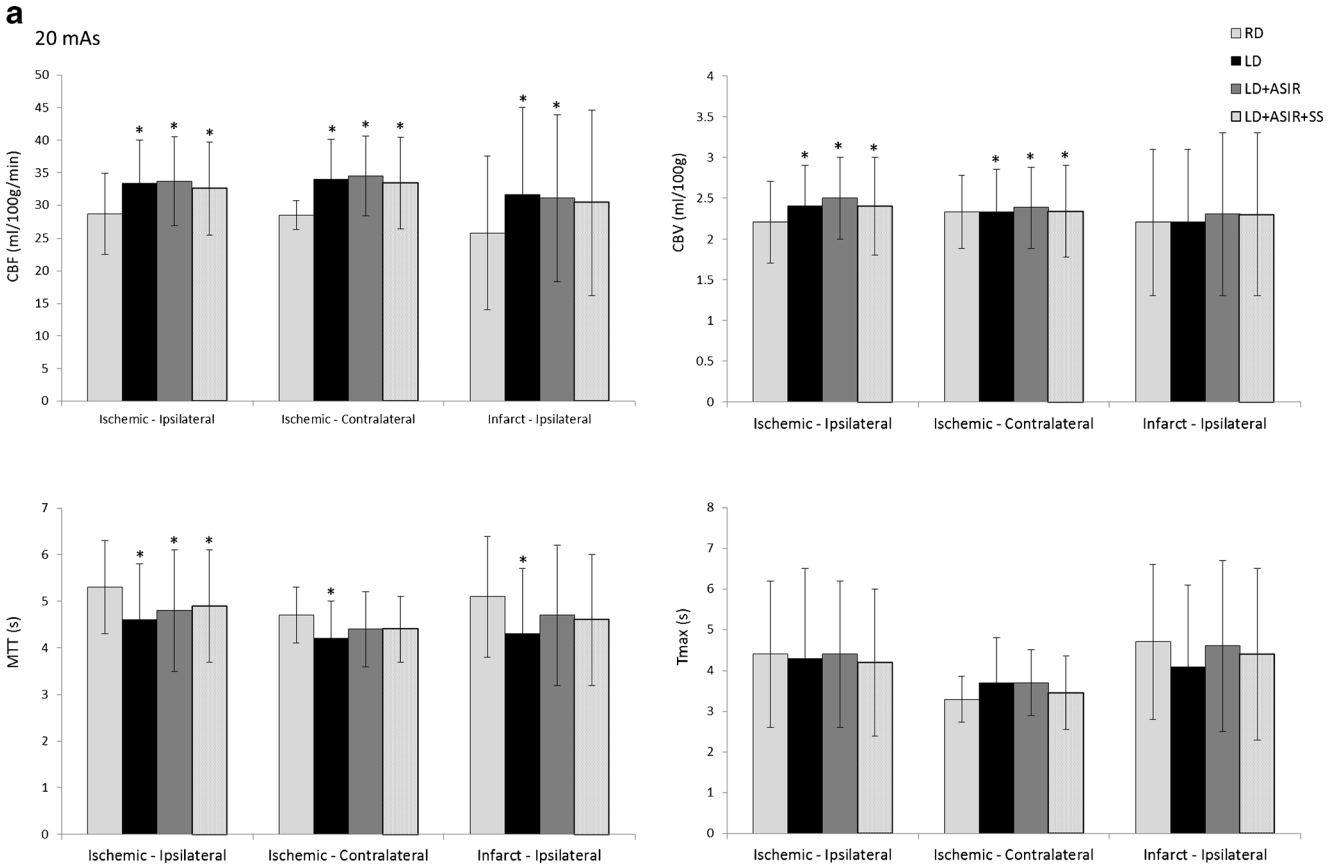

Fig. 1 CT perfusion data at 20 mAs (**a**) and 50 mAs (**b**) in regions of ischemia, infarction, and contralateral normal tissue including mean± standard deviation for cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to maximum arterial concentration (Tmax). *$p<0.05$ significant difference

cost of increased radiation dose, in large part due to the cine (continuous) nature of scanning [4]. Recommended protocols for CTP include image acquisition parameters of 100 mAs and 80 kV [6]. Clinical and simulation studies using these parameters have demonstrated estimated effective doses from the CTP in the range of 3–5 mSv [4, 7]. Simulation studies that have performed CTP at 50 mAs have demonstrated effective doses as low as 2 mSv for the CTP portion and 7.5 mSv for an entire stroke protocol including NCCT, CTA, and CTP [17]. In our investigation, the mean effective dose for RD scans at 100 mAs was 2.5 mSv. Scanning at 50 mAs resulted in 50 % reduction in mean effective doses to 1.3 mSv. This was achieved without variation in the quantitative perfusion information provided by CTP in regions of normally perfused brain or in regions of ischemia and infarction.

There are several proposed methods of reducing dose in CTP by adjusting scan parameters. Narrow beam width decreases the overall effective dose, but limited coverage runs the risk of jeopardizing the diagnostic accuracy of the images [7]. Current protocols advocate for a tube voltage of 80 kV, resulting in substantially lower effective doses than compared to earlier protocols with 120 kV [6, 18]. Further alterations in tube voltage are not desirable given that optimal image quality is obtained at 80 kV [8]. Increasing temporal sampling above 1 s can also reduce radiation dose, however at the expense of lowering the quantitative accuracy of CTP measurements [19–22].

We chose to alter the tube current as a means of reducing radiation dose because it is linearly related to effective dose; a 50 % reduction in mAs, if all other parameters are constant, corresponds to half of the effective dose [7]. Reductions in tube current, however, lead to increasing image noise. Several reconstruction algorithms aimed at reducing image noise have been proposed [23, 24]. ASIR (GE Healthcare) is an iterative reconstruction technique that uses forward projection and compares it to predicted statistical photon fluctuations to create an image [9]. Initial limitations of computing power and processing capabilities have become less concerning with technological advances and are now feasible in a clinical setting. ASIR is increasingly being used in abdominal and thoracic CT and has been shown to reduce dose up to 40 % in unenhanced head CT [11, 12].

In this investigation, CBF and CBV acquired at 50 mAs were no different from 100 mAs, with no difference in the standard deviations, at 50 % of the effective dose. There was a small, significant elevation in MTT at 50 mAs that was

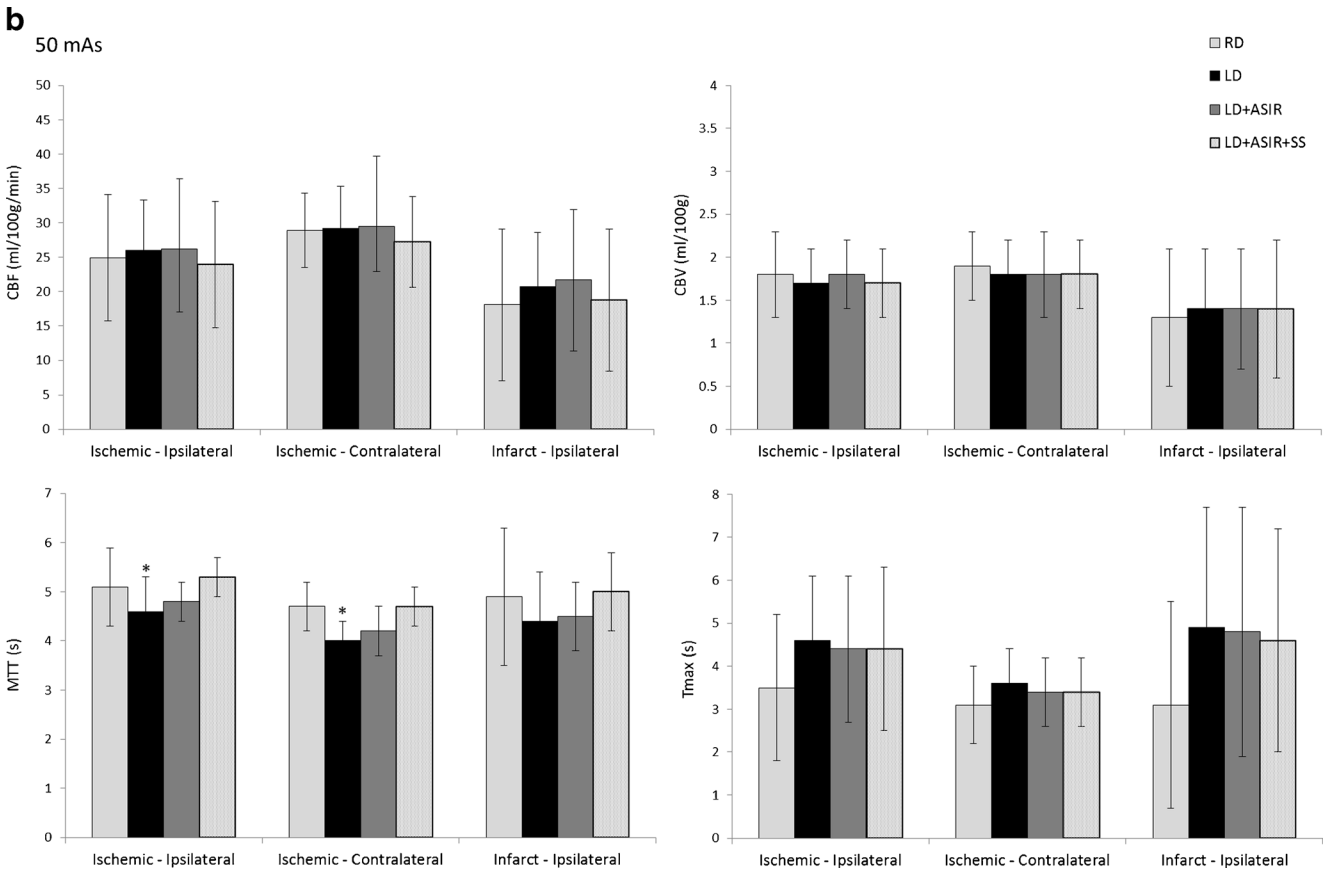

Fig. 1 (continued)

eliminated with ASIR; this can be explained by combined influence of CBF and CBV on MTT demonstrated by the central volume principle (MTT=CBV/CBF). Tmax, however, is not directly dependent on this ratio and is not different between 100 and 50 mAs. The similarity between CBF and CBV at 50 and 100 mAs is likely because SNR is already optimized at 50 mAs; Fig. 2a, b shows little variability between the enhancement curves at 100 and 50 mAs. It is also possible that the deconvolution algorithm is relatively insensitive to noise [25]. Further reductions to 20 mAs introduced differences in CBF for ischemic, infarcted, and normal tissue that were not improved by the addition of ASIR alone. Additional spatial smoothing with SS at 20 mAs in the regions of infarction may have provided some benefit, eliminating differences between images at 100 mAs and those at 20 mAs. Additional spatial smoothing of CBF maps with SS was not relevant at 50 mAs, given that there were no differences even without ASIR between images at 100 and 50 mAs.

CBF is the most sensitive parameter for the diagnosis of infarct core and a key factor in the decision to proceed with thrombolytic therapy in acute stroke management [26]. Our results demonstrate that there are no differences in CBF measured at 100 and 50 mAs and were reproducible in areas of ischemia (regions of low CBF identified on initial stroke examinations), infarcted tissue, and normal brain. Although the diagnostic accuracy of baseline CTP at 50 mA was not examined in this study, this data suggests the hypothesis that CBF/CBV mismatch on baseline CTP images obtained at 50 mAs has similar accuracy as at 100 mA, which has been shown to be approximately 80 % for the detection of acute infarction compared to DWI [27]. At 20 mAs, differences in CBF are introduced that could limit the detection of acute infarction, especially in small cortical strokes where the diagnostic accuracy of CTP is already limited [27].

Previous studies have suggested that CTP be performed at lower doses than current protocols. An investigation of stroke imaging protocols at different hospitals in Japan demonstrated considerable variation in effective dose, all of which were lower than obtained with current recommendations for CTP imaging [6, 7]. The authors suggest that decreasing scan length and narrow beam widths are significant factors contributing to this difference. However, both of these recommendations have been shown to jeopardize the diagnostic accuracy of CTP images [22]. Our approach to dose reduction (reducing mAs) is supported by results from a recent investigation of iScan, an interative reconstruction algorithm generated by Philips [13]. They demonstrated no difference in quantitative CTP parameters at 80 mAs compared to 100 mAs (20 % dose

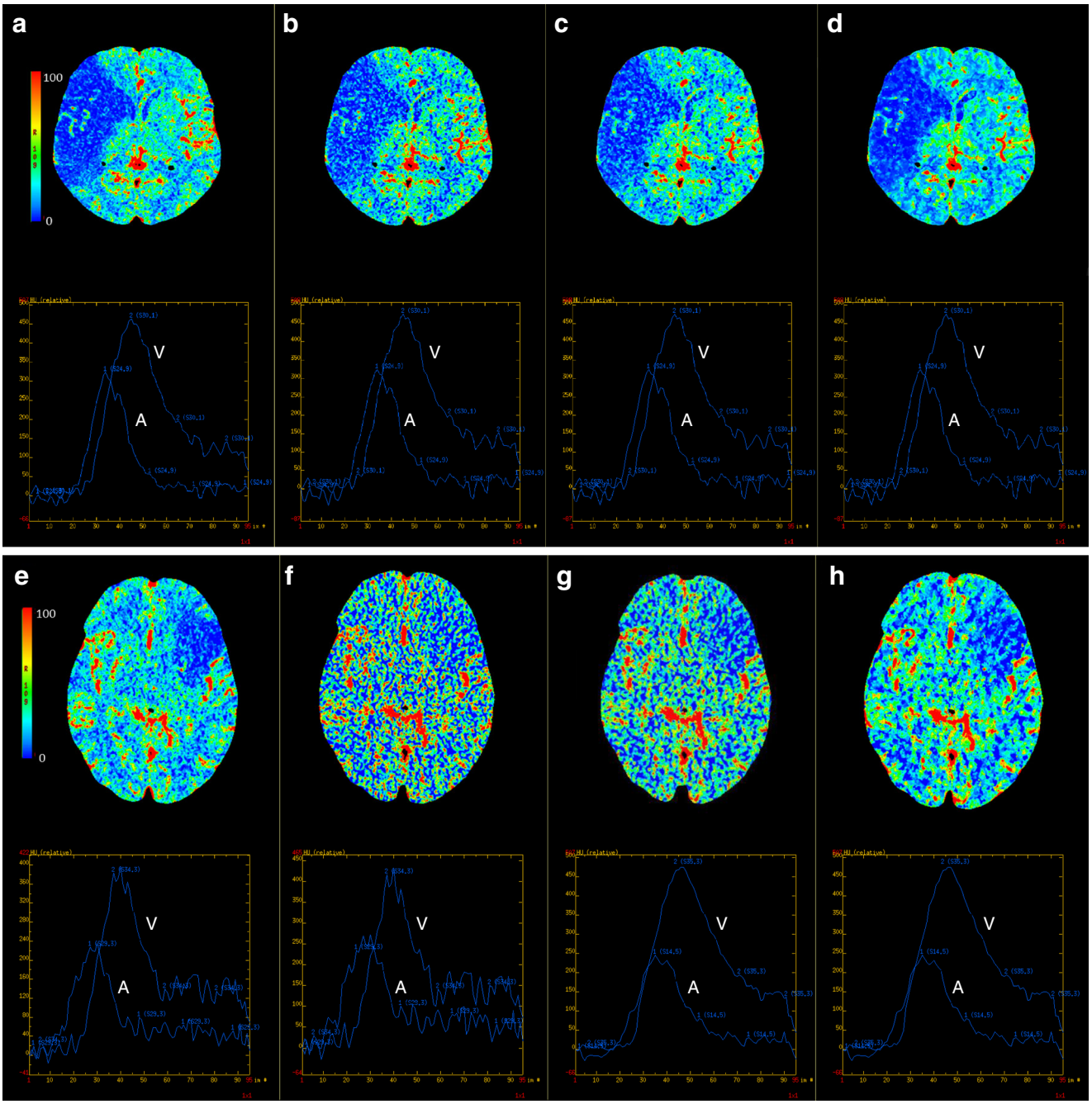

Fig. 2 Cerebral blood flow CTP maps with corresponding arterial (**a**) and venous (V) time density curves. *Top* **a**–**d** 76-year-old male with right middle cerebral artery occlusion at **a** 100 mAs, **b** 50 mAs, **c** 50 mAs+ASIR, and **d** 50 mAs+ASIR+SS. *Bottom* **e**–**h** 40-year-old male with left middle cerebral artery occlusion at **e** 100 mAs, **f** 20 mAs, **g** 20 mAs+ASIR, and **h** 20 mAs+ASIR+SS

reduction), even without the use of iScan. In this study, we reduce the effective dose even further, by 50 % from 100 to 50 mAs, while continuing to maintain accurate CTP images.

We achieved a 50 % reduction in effective dose without affecting CTP parameters. Although the benefit of this dose reduction with regards to limiting the stochastic effects of radiation may not be significant in our subject population with an average age of 74 years, it is relevant in younger populations. CTP is increasingly being used in subarachnoid hemorrhage and brain tumor imaging, both of which have patient populations that are much younger than the ischemic stroke population. In these settings, the ability to achieve 50 % dose reduction while obtaining the same CTP information is significant. Our study has the advantage of consecutive CTP studies that were acquired at different tube currents in the same individual with minimal delay between the two

acquisitions. This reduces the variability from any changes in physiological status and tissue perfusion and also allows for high-powered within subject statistical analysis.

There are limitations to this investigation which must be acknowledged. The comparison between RD and LD scans was on the 24-h scan rather than the presentation scan, which was necessary to allow for sufficient time to obtain consent. Coverage was limited to 4 cm centered at the basal ganglia; thus, the application of these results is limited to anterior circulation strokes. A lower SNR may be expected in the posterior fossa and at the vertex secondary to beam hardening artifact. ASIR could provide additional benefit in posterior circulation strokes or whole-brain CTP that we were unable to assess in this investigation. Finally, a qualitative analysis of the CT perfusion maps was not included in the study design. This would be an important addition in future investigations of low dose CT perfusion protocols in clinical practice.

Conclusion

We demonstrated that CTP imaging at 50 mAs produces CBF and CBV values that are similar to those obtained at 100 mAs. We propose that this change be instituted in current CTP protocols allowing optimal image quality with 50 % lower effective dose.

Ethical standards and patient consent We declare that all human and animal studies have been approved by the St. Michael's Hospital Research Ethics Board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest T-YL licenses CT Perfusion software to, and receives research funding from, GE Healthcare.

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