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Phantom-Based Standardization of CT Angiography Images for Spot Sign Detection

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COMPLIANCE WITH ETHICAL STANDARDS

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Abstract

Purpose—The CT angiography (CTA) spot sign is a strong predictor of hematoma expansion in intracerebral hemorrhage (ICH). However, CTA parameters vary widely across centers and may negatively impact spot sign accuracy in predicting ICH expansion. We developed a CT iodine calibration phantom that was scanned at different institutions in a large multicenter ICH clinical trial to determine the effect of image standardization on spot sign detection and performance.

Methods—A custom phantom containing known concentrations of iodine was designed and scanned using the stroke CT protocol at each institution. Custom software was developed to read the CT volume datasets and calculate the Hounsfield Unit as a function of iodine concentration for each phantom scan. CTA images obtained within 8 h from symptom onset were analyzed by two trained readers comparing the calibrated vs. uncalibrated density cutoffs for spot sign identification. ICH expansion was defined as hematoma volume growth >33%.

Results—A total of 90 subjects qualified for the study, of whom 17/83 (20.5%) experienced ICH expansion. The number of spot sign positive scans was higher in the calibrated analysis (67.8% vs 38.9% $p<0.001$). All spot signs identified in the non-calibrated analysis remained positive after calibration. Calibrated CTA images had higher sensitivity for ICH expansion (76% vs 52%) but inferior specificity (35% vs 63%) compared with uncalibrated images.

Conclusion—Normalization of CTA images using phantom data is a feasible strategy to obtain consistent image quantification for spot sign analysis across different sites and may improve sensitivity for identification of ICH expansion.

Keywords

intracerebral hemorrhage; spot sign; CT angiography; phantom standardization

INTRODUCTION

The CT angiography (CTA) spot sign is a validated predictor of hematoma expansion and unfavorable outcome in patients with acute intracerebral hemorrhage (ICH) [1–3]. Spot sign positive patients with cerebellar hemorrhages are also at higher risk of intraoperative active bleeding during surgery [4]. This imaging marker is associated with intraprocedural aneurysm rupture in patients with acute subarachnoid hemorrhage as well [5, 6]. There is great variability in CTA acquisition parameters across different centers, without a consensus about the optimal CTA protocol for spot sign detection [7–9]. Acquisition parameters including scan timing, tube potential, and tube current can influence image quantification and spot sign performance in predicting ICH expansion [10, 11]. This highlights a need for harmonization of spot sign diagnosis across different institutions. The Spot Sign score in restricting ICH growth (SCORE-IT) study study [12] examined the ability of spot sign to stratify clinical benefit from BP reduction in the international clinical trial Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-II) [13]. As part of this study, we aimed to standardize CTA image quantification and therefore spot sign detection across clinical trial sites. To control for heterogeneity in CTA acquisition protocols across different sites, we created a phantom to scan at different institutions using their local CTA protocol. Phantom generated calibration parameters were used to investigate whether the phantom-based calibration of CTA images can standardize spot sign analysis across different institutions and improve the diagnostic accuracy of this marker.

METHODS

Participants

SCORE-IT is a prospective observational study nested within the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-II)trial [12]. Patients with acute ICH enrolled in ATACH-II were randomly assigned to intensive (systolic BP target: 110–139 mmHg) versus standard (systolic BP target: 140–179 mmHg) BP treatment within 4.5 h from stroke onset. Demographic and clinical data were collected upon enrollment in the clinical trial, as previously described in detail [13, 14]. Subjects enrolled in SCORE-IT were eligible for the present analysis if they underwent a CTA within 8 h from stroke onset [15].

Image Acquisition

Axial non-contrast CT (NCCT) and CTA images were obtained at each participant's institution using standard local protocols. We retrospectively collected the following CTA acquisition parameters: tube current (mA) and tube potential (kV).

A custom phantom for iodine calibration was designed by our team, and was produced under contract by a commercial phantom company (CIRS, Tissue Simulation and Phantom Technology, http://www.cirsinc.com) for this application. The phantom consisted of a 13

mm diameter rod that was 160 mm in length. The rod contained six specific sections which correspond to a range of known physiological concentrations of iodine (0, 2, 5, 10, 15, and 20 mg Iodine / cm^3), encased in a thin plastic housing. The iodine calibration phantom was placed in a widely-available head CT dosimetry index (CTDI) phantom as shown in Figure 1A. The CTDI phantom is a cylinder composed of polymethyl methacrylate with a 160 mm diameter and 150 mm in length.

The iodine calibration phantom embedded in the CTDI phantom was scanned and reconstructed using the stroke CT protocol at each individual institution. An example of a reconstructed coronal image through the iodine calibration phantom is shown in Figure 1B. Custom software was developed to read in the CT image data produced from each phantom scan. Six regions-of-interest (ROIs) of equal area containing the six known concentrations of iodine were identified manually in the coronal plane, and the corresponding Hounsfield units (HU) for each concentration was measured and recorded. Using the measured HU values and the known iodine concentration of each section in the phantom, linear regression was used to determine the fit coefficients for each data set, corresponding to each CT scanner used in this study. All the images were analyzed to determine the mean HU value corresponding to each known iodine concentration. For a linear fit corresponding to $I = a \times HU + b$, a unique set of coefficients a and b were calculated and recorded for each scanner (Figure 1C). These coefficients were then used to convert the HU values for each CTA image to absolute concentrations of iodine. The linear relationship between iodine concentration and HU values was different for every scanner and therefore the standardization procedure provided a calibrated HU threshold for spot sign identification that was specific for every scanner.

Image Analysis

Baseline and follow-up hematoma volumes at 24 h were calculated on NCCT images with semi-automated computer-assisted volumetric analysis (Analyze Direct version 11.0). ICH expansion was defined as hematoma growth > 33% from baseline volume [13].

First pass CTA images were initially reviewed by trained readers using the conventional 120 Hounsfield Units cutoff for all the scanners [9]. Following the phantom-based standardization, all the scans were reanalyzed by the same readers using the calibrated HU cutoff for spot sign identification. Spot signs were defined as presence of at least one focus of contrast extravasation within the hematoma, with any size or morphology and density above the conventional or phantom-calibrated density threshold. An illustrative example of the comparison between uncalibrated versus calibrated density cutoff for spot sign detection is provided in figure 2.

Statistical Analyses

Continuous variables with normal and non-normal distribution were expressed as mean (standard deviation [SD]) and median (range) respectively, while categorical variables were expressed as count (percentage). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the two spot sign definitions in predicting ICH expansion. Categorical variables were compared with the Bowker's test of symmetry.

Statistical significance was set at p values < 0.05 and all the analyses were performed using the statistical package SAS 9.4.

RESULTS

A total of 90 patients enrolled in the ATACH-II trial were eligible for the present analysis and the characteristics of the study population are summarized in table 1. We observed great heterogeneity in CTA acquisition protocols, especially regarding the tube current levels, with values ranging from 85 to 765 mA. After calibration, the mean density cutoff for spot sign identification was 109.0 ± 10.6 HU. The calibrated threshold was decreased in 78 (86,7%) scanners and remained 120 HU in 12 (13,3%) scanners. The diagnostic performance of the conventional 120 HU cutoff versus calibrated cutoff is reported in table 2. The number of spot sign positive scans was significantly higher in the calibrated analysis (67.8% vs 38.9%, p < 0.001). All spot signs identified in the uncalibrated analysis remained positive after phantom-based calibration of CTA images. Using a calibrated threshold, the sensitivity of spot sign for ICH expansion improved from 52% to 76% whereas the uncalibrated threshold showed higher specificity (63% vs 35%).

DISCUSSION

In this multi-center international prospective pilot study we showed that phantom-based iodine calibration of CTA images for spot sign detection is feasible and increases the sensitivity of the spot sign for ICH expansion. Hematoma expansion is a common event in the early natural history of ICH and given its influence on outcome represents an appealing target for acute ICH treatment [16]. Rapid and efficient prediction of ICH expansion is therefore crucial in order to select those patients most likely to benefit from anti-expansion therapies. In this regard the CTA spot sign is the strongest validated biomarker of ICH expansion [1, 2, 17]. However, there is great variability in the reported diagnostic accuracy of this imaging marker [18, 19]. The heterogeneity in CTA acquisition protocols [8] with lack of consensus on the optimal CTA setting for spot sign detection may account for this inconsistency. Multiple studies show that scan parameters influence CTA quality and spot sign accuracy in predicting hematoma growth [10, 11, 20–22] suggesting the need to harmonize CTA analysis across different centers. The results of our study confirmed the presence of great variability in CTA protocols, and showed that phantom-based iodine calibration may help in standardizing image analysis across multiple sites. Our results may have relevant implications for future clinical trials using the CTA spot sign to identify patients with parenchymal or subarachnoid hemorrhages at high risk of active bleeding. The calibration procedure may indeed represent the optimal technique to standardize CTA images analyses across different international sites. This technique may also improve spot sign detection and prediction of intraoperative aneurysm rupture in patients with acute subarachnoid hemorrhage [5, 6]. In addition, the “leakage sign” has been recently described as a promising imaging marker of ICH expansion [23] and the calibration procedure may improve the diagnostic performance of this CTA based marker as well.

We observed a superior sensitivity in the calibrated analysis whereas specificity and overall accuracy for ICH expansion were higher using a non-standardized spot sign cutoff. All the

spot signs detected in the analysis of uncalibrated CTA images remained positive after calibration and the proportion of spot sign positive scans was significantly higher using a calibrated threshold. This suggests that phantom based iodine calibration improves sensitivity for ICH expansion allowing the detection of a higher number of spot signs. A more inclusive spot sign analysis, using calibrated image analysis, may be preferred when using anti-expansion treatments with a good safety profile. On the other hand, when selecting for therapies with potential harm such as pro-hemostatic drugs, it may be that higher specificity is needed, in which case a simple HU cutoff may be best [24]. Another way to standardize CTA images across different scanners could be the use of a spot sign definition with a relative density threshold that is based on the surrounding hematoma density, as previously described [1].

Some limitations should be considered in the interpretation of our findings. The main limitation of our study is the relatively small sample size. Less than 20% of the subjects enrolled in ATACH-2 received a CTA as part of their diagnostic workup. Furthermore, a total of 27 patients were excluded from the present analysis because CTA was performed after 8h from stroke onset. Several parameters of CTA acquisition including contrast volume, injection rate and scan triggering method may influence image quality and spot sign identification and we were not able to control for these potential confounders. Acquisition of 90-second delayed CTA images may improve the spot sign accuracy in predicting ICH expansion and these sequences were not systematically acquired [25]. In addition, other CT techniques including post contrast CT and dual energy CT may further improve the ability to detect the presence of contrast extravasation in patients with acute ICH [26–28]. We did not compare the diagnostic performance of the calibrated threshold with an arbitrarily lower cutoff. Therefore we cannot exclude that an increase in sensitivity for ICH expansion prediction with the spot sign may also be obtained with an arbitrary reduction of the absolute density cutoff for spot sign detection. This approach would probably be limited by a significant reduction in specificity and further studies are warranted to explore this possibility. Finally, our findings are best interpreted as hypothesis generating and require confirmation in future studies.

CONCLUSION

There is great heterogeneity in the CTA acquisition protocol for spot sign detection, suggesting the need to harmonize CTA analysis across different institutions. Phantom-based iodine calibration of CTA images is feasible and may improve sensitivity for early identification of ICH patients at risk of hematoma expansion.

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Conflict of interest

JR receives research funding from the NIH. JG receives research funding from the NIH, Boehringer Ingelheim, Pfizer and Portola, and consults for Bristol Myers Squibb. TAB receives funding from the NIH, the Minnesota State

and Spinal Cord Injury and Traumatic Brain Injury Grant and Vertex Pharmaceuticals. CL receives research funding from the NIH.

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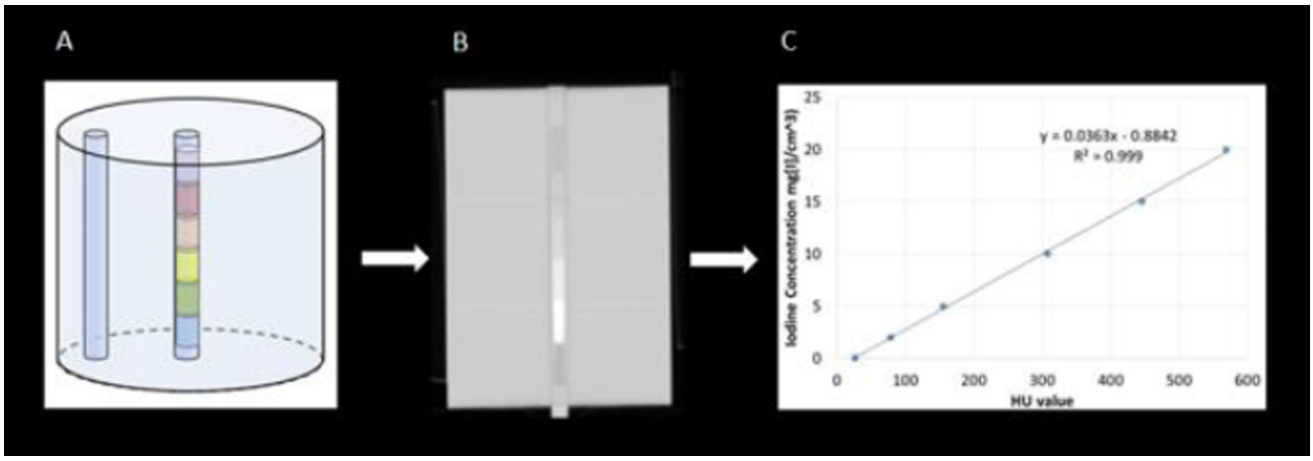

Figure 1. Custom Phantom for CTA calibration

A) Phantom containing a rod with six specific sections with different iodine concentrations; B) CT coronal images of the phantom; C) Calibration curve (linear relationship between iodine concentration and HU values).

CTA indicates CT angiography; HU, Hounsfield Units.

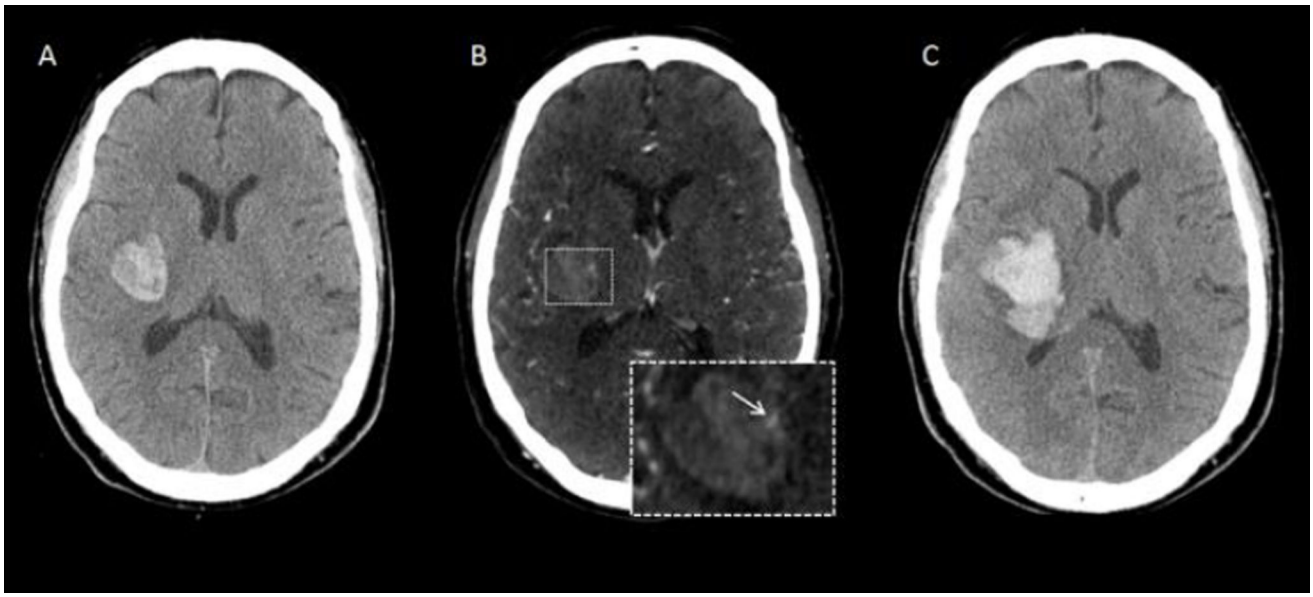

Figure 2. Comparison between calibrated vs non-calibrated spot sign analysis

A) Baseline NCCT scan, ICH volume = 11 mL; B) CTA with 114 HU spot sign (negative with standard 120 HU threshold – positive with calibrated 100 HU threshold); C) Follow-up NCCT scan showing hematoma expansion, ICH volume = 36 mL.

NCCT indicates non-contrast CT; CTA, CT angiography; HU, Hounsfield Units.

Table 1

Baseline characteristics (n = 90).

Characteristic	
Age – yr [1]	60.2 ± 11.0
Male sex – no. (%)	63 (70.0)
Hypertension – no./total no. (%)	66/82 (80.5)
Admission SBP – mmHG	206.6 ± 27.9
Diabetes – no./total no. (%)	13/86 (15.1)
Randomized to SBP<140 – no. (%)	50 (55.6)
Initial GCS score – no. (%)	
3–11	7 (7.8)
12–14	23 (25.6)
15	60 (66.7)
Median ICH volume (range) – mL [2]	10.2 (0.8, 65.5)
IVH present – no./total no. (%)	35 (38.9)
Hematoma Expansion – no./total no. (%)	17/83 (20.5)
Median CTA tube –voltage (range) –kVp	120 (100, 120)
Median CTA tube – current (range) – mA [3]	362 (85, 765)
Time from onset to CTA – min	167.0 ± 105.3
Mortality at 90 days – no. (%)	7 (7.8)
mRS > 3 at 90 days – no./total no. (%)	37/81 (45.7)

[1] Plus-minus values are means ± SD.

[2] Hematoma volume was measured by a central reader. The rapid assessment of the hematoma volume by the site investigator was used to determine eligibility.

[3] CTA tube current missing for 1 subject.

Table 2

Comparison between different density thresholds for spot sign detection

	Non Standardized Threshold (120 HU)	Phantom-Calibrated Threshold	p-value
Number of Spot Signs			<0.001
Negative, n (%)	55 (61.1)	29 (32.2)	
Single Spot Sign, n (%)	16 (17.8)	33 (36.7)	
Multiple Spot signs, n (%)	19 (21.1)	28 (31.1)	
ICH Expansion			
Sensitivity (95% CI)	0.52 (0.29 – 0.77)	0.76 (0.56 – 0.97)	
Specificity (95% CI)	0.63 (0.52 – 0.75)	0.35 (0.23 – 0.46)	
Positive Predictive Value (95% CI)	0.27 (0.12 – 0.42)	0.23 (0.12 – 0.34)	
Negative Predictive Value (95% CI)	0.84 (0.74 – 0.94)	0.85 (0.72 – 0.99)	
Accuracy	0.61	0.43	

HU indicates Hounsfield Units; CI indicates confidence interval.