Postcontrast CT Extravasation Is Associated With Hematoma Expansion in CTA Spot Negative Patients

Ashraf Ederies, MBChB; Andrew Demchuk, MD, FRCP; Tze Chia, BSc; David J. Gladstone, MD, PhD, FRCP; Dar Dowlatshahi, MD, PhD; Gabriel BenDavit, MD; Kelly Wong; Sean P. Symons, MD; Richard I. Aviv, MBChB

Background and Purpose—The purpose of this study was to assess the effect of postcontrast CT (PCCT) leakage (PCL) on hematoma growth in CTA spot negative patients.

Methods—A retrospective study of 61 patients presenting within 6 hours of primary ICH onset imaged with CT angiography (CTA) and PCCT. Presence of CTA spot sign and PCL were documented. PCL was defined as the presence of contrast extravasation on the PCCT study at a location remote from the CTA spot sign if present. Hematoma expansion was defined as >6 mL or 30% hematoma enlargement. Patients were dichotomized by CTA spot sign presence and PCL and compared for baseline demographic data, hematoma size, and growth using the unpaired t test and Mann–Whitney test for continuous and categorical data, respectively. A probability value <0.05 was considered significant.

Results—PCL was present in 11/61 patients (18%), occurring in 5 without a spot sign (45%). Spot negative PCL patients demonstrated larger absolute ($P=0.02$) and percentage hematoma growth ($P=0.02$) compared to those without PCL. The mean volume and percent increase was 6.7 mL and 26%, respectively. Inclusion of PCL together with CTA spot sign as risk factor for hematoma expansion increased sensitivity from 0.78 (95% CI; 0.52 to 0.94) to 0.94 (95% CI; 0.72 to 1.00) and NPV from 0.90 (95% CI; 0.76 to 0.97) to 0.97 (95% CI; 0.85 to 1.00).

Conclusion—Inclusion of PCCT in the investigation of ICH patients allows detection of PCL which, together with the CTA spot sign, increases sensitivity and negative predictive value for predicting hematoma expansion. This finding should be validated in larger studies. (Stroke. 2009;40:1672-1676.)

Key Words: computed tomography angiography ■ contrast extravasation ■ CTA spot sign ■ spot sign mimic ■ hematoma expansion

Early hematoma growth is associated with neurological deterioration and increased mortality. Hematoma growth usually implies ongoing active bleeding and occurs in approximately 18% to 38% of ICH patients scanned within 3 hours of onset.1–3 Contrast extravasation seen on CT, CT angiography (CTA), MRI, and DSA has been correlated with hematoma growth.4–15 The incidence of radiographic contrast extravasation is estimated to be around 40% to 50%.6,14 ICH enlargement during the first few hours presents a potential opportunity for intervention using hemostatic agents. The CTA spot sign has recently been reported as a promising marker for hematoma expansion.16–18 However, a small number of hematomas continue to enlarge in the absence of the spot sign, reducing the diagnostic performance of this sign for predicting hematoma expansion. Recently, we have observed contrast accumulation within a hematoma on postcontrast CT studies (PCCT) performed after initial CTA either remote from a CTA Spot sign or more importantly in CTA spot negative patients. The accumulation of contrast between CTA and PCCT indicates interval interstitial contrast leakage from the intravascular space. The findings led us to hypothesize that contrast extravasation remote from or in the absence of a CTA spot sign represents secondary vascular injury and that the demonstration of PCCT leakage (PCL) could reasonably be expected to confer a higher risk of hematoma expansion and may be the reason for expansion in CTA spot negative hematomas.

Patients and Methods

Study Group
A retrospective review was performed of consecutive patients presenting with ICH within 6 hours of ictus presenting between January 2004 and June 2008 who underwent a CT stroke protocol including CTA and PCCT. Eighty-five cases were reviewed.

Received October 28, 2008; accepted November 12, 2008.

From the Division of Neuroradiology and Department of Medical Imaging (A.E., G.B., K.W., S.P.S., R.I.A.), the Department of Neurology and North and East GTA Regional Stroke Centre (D.J.G.), Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada; and Seaman Family MR Research Centre and Departments of Clinical Neurosciences (D.D., A.M.D.), Foothills Medical Centre, Calgary Health Region, Canada.

Correspondence to Dr R. Aviv, Diagnostic Imaging, Division of Neuroradiology, Room AG 31, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5, Canada. E-mail richard.aviv@sunnybrook.ca

© 2009 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.108.541201
Twenty-four patients were excluded; 14 patients presented beyond the 6-hour cut-off (mean presentation 2029±1811 minutes), 7 patients underwent decompressive surgery or craniectomy, and 3 patients did not get follow-up 24-hour unenhanced CT studies. Sixty-one patients constituted the final study cohort. Thirty-nine patients from this cohort are previously published.16 The study was approved by the institutional review board approved.

Materials/Image Acquisition
CT imaging was performed on a 4-slice (2004–2005) or a 64-slice (2005–2008) CT (GE Lightspeed plus and VCT; GE) scanner. All patients presenting with stroke symptoms to our institution are investigated with a stroke protocol which includes a noncontrast CT (NCCT) head followed by a CTA and postcontrast study. Pre- and postcontrast head imaging is acquired from the skull base to vertex with parameters: 120 kVp; 340 mA; 4x5 mm collimation; 1 second/rotation; and a table speed of 15 mm/rotation. CTA studies are acquired from C6 to the vertex in the helical HS mode with parameters: 0.7 mL/kg contrast (to a maximum of 90 mL through an antecubital vein via at least an 18- or 20-gauge angiocatheter); 5 to 10 second delay; 120 kVp; 270 mA; 1 second/rotation; and a table speed of 1.25 mm slice thickness (reconstructed to 0.625 mm), table speed 3.75 mm/rotation. Postprocessing including all multiplanar reformats is performed by the CT technologists at the CT operator’s console. Coronal and sagittal multiplanar reformat images are created as 10.0-mm-thick images, spaced by 3 mm. Axial reformats were 4 mm thick with a 2-mm gap and aligned to match the NCCT and PCCT angle. Rotational multiplanar reformat images are created at each carotid terminus with 7-mm thickness and 3-mm spacing. All images were viewed on AGFA Impax 4.5 PACS workstation.

Imaging Analysis/Interpretation
All studies were evaluated by a single neuroradiologist blinded to clinical and radiological outcome for the presence or absence of PCL by simultaneously visualizing NCCT and PCCT studies cross-linked with axial CTA reformats (Figures 1 and 2). An identical window was applied to all studies that best visualized vessel density (Approximately WW 177/WL 77). PCL (Figures 1 and 2) was defined as an increased volume of contrast from a CTA spot sign are not mutually exclusive. Hematoma volume at presentation and follow-up study was calculated by a separate study neuroradiologist blinded to CTA spot or PCL status by measuring baseline and follow-up NCCT hematoma volume using the previously validated ABC/2 method.19 Hematoma expansion was defined as an increased volume of >6 mL or 30% or more. The rationale for these thresholds are based on a study in posttraumatic ICH showing that expansion of at least 5 mL predicted the need for late surgical evacuation.20 Mayer et al also showed significantly worse outcomes in patients who did not receive factor VII with an absolute mean increase of only 5.8 mL in the highest recombinant factor VIIa dose group.21 Intraventricular hemorrhage was not considered for the purposes of hematoma expansion. Study time is automatically inserted as a time stamp onto each image and is displayed within the patient data window on PACS. Smart prep trigger time was defined as the final smart prep image time at the moment when the CTA was triggered. CTA and PCCT start time was the time stamp on the initial CTA/PCCT image and mid hematoma time is the time stamp at the mid point of the hematoma.

Statistical Methods
For each patient baseline data including time from presentation to CTA, time between smart prep scan and CTA at the level of the mid point of the hematoma, time between smart prep scan and PCCT, the presence of the PCL/ CTA spot sign, age, gender, NIHSS, anticoagulant/antiplatelet use, mean arterial pressure pressure, clotting profile, and glucose were collected. Presentation and follow-up hematoma size, presence of hyperglycemia (glucose >8.3 mmol/L) and hypertension (mean arterial pressure [MAP] >120 mm Hg)14,19

Figure 1. 62-year-old male patient presenting within 130 minutes of ICH onset. Axial unenhanced CT (A), CT angiogram (B), postcontrast CT (PCCT; C) and 24-hour follow-up noncontrast CT study (D) demonstrates a lobar hemorrhage with local mass effect. Postcontrast CT leakage (PCL) is demonstrated on PCCT (C, white arrows) in the absence of a CTA spot sign (B). Follow-up NCCT at 24 hours was degraded by patient motion but showed hematoma enlargement of 24 cm³ or 21%.

Figure 2. 44-year-old male patient presenting within 75 minutes of ICH onset. Axial unenhanced CT (A), CT angiogram (B), postcontrast CT (PCCT; C) and 24-hour follow-up noncontrast CT study (D). Four foci of PCL are present at the periphery of the hematoma (white arrows). Expansion of 10 cm³ or 9% occurred at 24 hours (D).
were documented. Ninety-day modified Rankin scores were recorded. Patients groups were divided by spot sign and PCL presence. Groups were compared for age, gender, MAP, glucose, time to CTA/PCCT scan, hematoma volume at presentation and follow-up, absolute and percentage hematoma growth, NIHSS, and clinical outcome. The unpaired *t* test and Mann–Whitney tests were used for group comparisons for continuous and categorical data comparisons respectively. A probability value \( P < 0.05 \) is considered significant.

### Results

There were 61 patients (41 male; 67%) with mean age 64 ± 15 years. Baseline demographic data are indicated in the Table. CTA demonstrated 21 CTA spot sign–positive or group A patients (21/61; 34%) and 40 patients (group B) without the spot sign (40/61; 66%). Median time to presentation was 120 minutes (33 to 312 minutes). Eleven (11/61; 18%) patients demonstrated PCL (Figure 1) with 5 (5/11; 45.5%) occurring in group B patients. All patients had a solitary focus of PCL, except 1 patient with 4 foci (Figure 2).

CTA was present in 6/21 (28.6%) group A patients and was associated with larger initial hematoma size \( (P=0.04) \). The remaining baseline demographic data and outcome were similar. The final volume \( (P=0.07) \) and absolute volume change \( (P=0.07) \) tended to be higher with PCL but the percentage volume change \( (P=0.9) \) was similar. Four patients (4/6; 66.7%) with PCL underwent hematoma expansion.

Among group B subjects, 5/40 (12.5%) had PCL. The presence of PCL was associated with larger absolute \( (P=0.02) \) and percentage hematoma volume expansion \( (P=0.02) \). Although the range of hematoma expansion volume was wide (0.5 and 14.2 cm\(^3\)), the mean volume and percent increase relative to group B patients without PCL was 6.7 mL and 26%, respectively. Three (3/5; 60%) PCL group B patients underwent hematoma expansion. Median mRS was higher in PCL patients at follow-up than those without, but the difference was not significant \( (P=0.21) \).

Comparing patients with PCL, group A patients demonstrated larger initial \( (P=0.02) \) and follow-up hematoma size \( (P=0.03) \) and larger absolute hematoma volume expansion \( (P=0.03) \). The inclusion of PCL together with CTA spot sign for predicting hematoma resulted in 2 PCL cases (all group B patients) being reclassified as false positives and 3 as true positives. PCL inclusion increased sensitivity from 0.78 (95% CI; 0.52 to 0.94) to 0.94 (95% CI; 0.72 to 1.00) and NPV from 0.90 (95% CI; 0.76 to 0.97) to 0.97 (95% CI; 0.85 to 1.00). Reductions in specificity from 0.84 (95% CI; 0.69 to 0.93) to 0.79 (95% CI; 0.64 to 0.90) and PPV from 0.67 (95% CI; 0.43 to 0.85) to 0.65 (95% CI; 0.44 to 0.83) were observed. There were 7 group A patients who did not fulfill criteria for expansion. One of these patients, CTA spot and PCL-positive, narrowly missed the definition for expansion, demonstrating a 5.4 mL and 16% hematoma increase.

There was no time difference from presentation to CTA for group A and B patients (110 ± 35 versus 125 ± 76 minutes; \( P=0.99) \). Patients with PCL were imaged earlier than those without for both groups, however this only achieved significance for CTA-negative PCL patients \( (P=0.02) \). No difference in scan time from CTA smart prep trigger time to CTA nid hematoma level between PCL and non-PCL groups (27 ± 13 seconds and 32 ± 11 seconds, respectively; \( P=0.2) \) nor for time from smart prep trigger to the beginning of the PCCT acquisition (2 ± 0.5 minutes and 2.4 ± 1.4 minutes; \( P=0.5) \). The overall median time to scan in all PCL cases irrespective of CTA status was 59.5 minutes (range 33 to 75 minutes) compared to 131 minutes (range 44 to 312 minutes) without PCL \( (P=0.008) \).

### Discussion

Group B ICH patients with PCL demonstrated a larger volume and percentage of hematoma expansion compared to those without PCL. Significant hematoma expansion was
seen in 60% of these cases in the absence of a spot sign. Group A patients with PCL tended to have larger absolute hematoma expansion and demonstrated larger initial hematoma volumes compared to Group A PCL negative patients. The larger initial hematoma size in Group A PCL patients and larger initial and follow-up hematoma sizes and absolute volume changes in group A PCL patients compared to group B PCL patients suggests that hematoma growth secondary to the CTA spot sign overshadows PCL-attributed growth but also implies a cumulative effect of the spot sign and PCL on hematoma formation and growth.

Fisher implicated a number of potential histopathologic findings in ICH formation and growth including microaneurysms and fibrin globes. Fibrin globes occur in vessels 100 to 200 µm in size and comprise red cells delimited by concentric fibrin rings adjacent to an arteriolar defect. These lesions are thought to be traumatic in origin induced by secondary vessel disruption by expanding hematoma. Fibrin globes vary from 0.3 to 1 cm, well within PCCT resolution (0.5 mm). Fisher did not preclude a primary role but proposed a “domino” effect whereby a single vascular lesion may rupture, contributing to most of the hematoma growth, followed by secondary vessel disruption. Irrespective of the primary initiating event we propose that PCL represents secondary vessel damage, manifest by early but slow parenchymal leakage. Whether hematoma expansion from these lesions is a result of persistent early ongoing bleeding or represents delayed rebleeding is unknown.

The CTA spot sign was first described as a predictor of hematoma expansion in ICH patients presenting within 3 hours by Wada et al. Active extravasation beyond the 3-hour window had been reported in 2 prior studies and one abstract. An ongoing prospective study (PREDICT; Predicting hEmatoma growth and outcome in Intracerebral hemorrhage using contrast bolus CT study) has reported lower sensitivity and negative predictive values within the 3-hour window because of expansion of spot-negative patients. Addition of PCCT in the investigation of ICH provides an explanation for hematoma expansion in this patient group. Two possibilities for expansion of CTA spot-negative patients have been suggested. Firstly, the CTA acquisition may be too quick relative to bolus injection and not permit sufficient time for spot opacification. Supporting this hypothesis is the higher frequency of extravasation demonstrated on PCCT than CTA. Alternatively, there may be a reason other than the CTA spot sign for hematoma expansion. To address the first possibility we found no contrast-to-scan time difference between group A and B patients for CTA or PCCT that could account for disparity in CTA spot sign prevalence. Patients exhibiting PCL were imaged earlier than those without PCL for both groups in agreement with a prior study, although only reached significance in group B patients. The earlier time to scan in the group B PCL subgroup may explain the smaller presentation ICH volumes compared to non-PCL patients.

Despite the mixed results of recombinant factor VIIa (rFVIIa) in phase 2 and 3 studies, there is growing interest in the CTA spot sign and other markers of extravasation as potential targets for drug intervention to reduce hematoma expansion. The effect of rFVIIa on the CTA spot sign is the subject of the currently funded NINDS/SPOTRIAS STOP-IT study (The SpoT sign fOr Predicting and treating ICH growth study). A high sensitivity and negative predictive value is required for patient screening to avoid unnecessary adverse effects of rFVIIa in patients at least risk of hematoma expansion. The addition of PCL to CTA spot sign improves sensitivity and negative predictive value with little effect on specificity and positive predictive value. Inclusion of PCL is justified by existing literature where contrast extravasation on delayed CTA or PCCT was associated with increased hematoma growth, poorer clinical outcome, and increased mortality.

The study is limited by a small sample size, which is further exacerbated by subgroup analysis precluding a multivariate assessment of whether PCL independently predicts hematoma enlargement in group B patients. We encourage other investigators to add a PCCT into their ICH protocols to further evaluate the significance of this finding. Further small sample size likely explains the absence of clinical outcome differences reported. Although the presence of hematoma expansion is strongly linked to worse outcomes in several previous studies, it remains to be determined whether PCL is an independent predictor of worse clinical outcome. We can only hope that larger studies such as PREDICT may answer this question. The indications for CTA in ICH remain controversial, and therefore not all patients at our institution underwent CTA angiographic imaging. This is especially true for patients included in the study before May 2006. However, because this date the majority of patients admitted with ICH have undergone CTA. We cannot entirely exclude unknown referral biases in our early patient dataset, although we believe the presented dataset is representative of the spontaneous ICH population.

**Summary**

In conclusion, we describe the contribution of PCL to hematoma growth in a CTA spot negative patient group imaged within 6 hours of stroke onset. Inclusion of PCCT in the investigation of ICH patients will allow detection of PCL and increases sensitivity and negative predictive value for predicting patients at high risk of hematoma expansion. The findings should be validated in larger series.

**Acknowledgments**

We acknowledge the dedicated service of our CT techs without whom this work would not be possible.

**Disclosures**

None.

**References**


Postcontrast CT Extravasation Is Associated With Hematoma Expansion in CTA Spot Negative Patients
Ashraf Ederies, Andrew Demchuk, Tze Chia, David J. Gladstone, Dar Dowlatshahi, Gabriel BenDavit, Kelly Wong, Sean P. Symons and Richard I. Aviv

*Stroke*. 2009;40:1672-1676; originally published online March 12, 2009;
doi: 10.1161/STROKEAHA.108.541201

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/40/5/1672

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/