The Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT (PREDICT) study validated the computed tomography angiography (CTA) spot sign, reported in prior single-center studies, for predicting significant intracerebral hemorrhage (ICH) expansion in a prospective multicenter study. However, the sensitivity of the spot sign for predicting significant hematoma expansion was only 51% in the PREDICT study. While positive predictive values from single-center studies compared favorably with that from PREDICT study (24%–79.3% versus 61%), negative predictive values were higher in single-center studies (91.7%–98% versus 78%).

**Background and Purpose**—Variability in computed tomography angiography (CTA) acquisitions may be one explanation for the modest accuracy of the spot sign for predicting intracerebral hemorrhage expansion detected in the multicenter Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT (PREDICT) study. This study aimed to determine the frequency of the spot sign in intracerebral hemorrhage and its relationship with hematoma expansion depending on the phase of image acquisition.

**Methods**—PREDICT study was a prospective observational cohort study of patients with intracerebral hemorrhage presenting within 6 hours from onset. A post hoc analysis of the Hounsfield units of an artery and venous structure were measured on CTA source images of the entire PREDICT cohort in a core laboratory. Each CTA study was classified into arterial or venous phase and into 1 of 5 specific image acquisition phases. Significant hematoma expansion and total hematoma enlargement were recorded at 24 hours.

**Results**—Overall (n=371), 77.9% of CTA were acquired in arterial phase. The spot sign, present in 29.9% of patients, was more frequently seen in venous phase as compared with arterial phase (39% versus 27.3%; \(P=0.041\)) and the later the phase of image acquisition (\(P=0.095\)). Significant hematoma expansion (\(P=0.253\)) and higher total hematoma enlargement (\(P=0.019\)) were observed more frequently among spot sign–positive patients with earlier phases of image acquisition.

**Conclusions**—Later image acquisition of CTA improves the frequency of spot sign detection. However, spot signs identified in earlier phases may be associated with greater absolute enlargement. A multiphase CTA including arterial and venous acquisitions could be optimal in patients with intracerebral hemorrhage. (Stroke. 2014;45:00-00.)

**Key Words:** hematoma • intracerebral hemorrhage
Variations in image acquisition after the administration of the contrast bolus at the different institutions of PREDICT study may have resulted in failure to detect some spot signs producing many false negatives. Recent studies suggest that second-pass imaging, which introduces a delay after contrast bolus, can increase the yield of the CTA spot sign for predicting hematoma expansion.\textsuperscript{9,10} Time-resolved dynamic CTA can detect late spot signs absent in earlier phases of CTA.\textsuperscript{11,12}

Because hemostatic therapy with recombinant factor VIIa demonstrated reductions in hematoma expansion\textsuperscript{13} without improvement in clinical outcomes in a heterogeneous population,\textsuperscript{14} 2 clinical trials have begun recruitment stratifying patients according to the CTA spot sign presence to avoid treating patients in whom expansion is unlikely (Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy [SPOTLIGHT], NCT00810888; and The Spot Sign for Predicting and Treating ICH Growth Study [STOP-IT], NCT01359202). Similarly, another ongoing clinical trial aims to prevent hematoma expansion in patients treated with tranexamic acid selected by the presence of the CTA spot sign (The Spot Sign and Tranexamic Acid on Preventing ICH Growth-Australasia Trial [STOP-AUST]).\textsuperscript{15} Therefore, it would be important to determine the optimal CTA image acquisition phase for spot sign detection to select patients optimally for emerging treatments such as recombinant factor VIIa and tranexamic acid.

The objectives of the present study were to determine the frequency of the CTA spot sign depending on the phase of image acquisition, to determine whether the inter-rater reliability for detecting the spot sign depends on the phase of image acquisition, and to evaluate whether the relationship between the spot sign and hematoma expansion varies depending on the phase of CTA acquisition.

Subjects and Methods

Study Population and Data Acquisition

The design of the PREDICT study has been previously published.\textsuperscript{1} Briefly, PREDICT study was a multicenter, prospective, observational cohort study of consecutive patients aged \( \geq 18 \) years with a symptomatic and radiologically confirmed ICH of <100 mL presented within 6 hours from symptom onset. Exclusion criteria included secondary cause of ICH, Glasgow coma scale score <6, known renal impairment, modified Rankin scale score >3, or major comorbid or terminal illness. The enrollment of patients continued after PREDICT study main results publication\textsuperscript{1} until February 27, 2012. All patients from the entire PREDICT cohort were eligible for the present study.

The PREDICT study protocol was approved by the research ethics board of the University of Calgary, Calgary, Alberta, Canada. The requirement for additional local ethics approval differed among participating countries, and additional consent was obtained if required by the local ethics board. All patients gave written informed consent according to the requirements established by each site ethics board. When a patient was incapacitated by the stroke and unable to give consent, the next of kin or legal guardian gave surrogate consent.

Patients underwent noncontrast CT scans at baseline and at 24 hours and a CTA immediately after baseline CT scan. The details of image acquisition and processing have been described before.\textsuperscript{1} Relevant demographic and clinical characteristics were recorded.

CTA and CT Image Analysis

A stroke neurologist (D.R.-L.) masked to follow up CT scans measured the maximum Hounsfield units (HU) of a specific artery and venous structure at 3 levels of each CTA scan (Table 1). The side contralateral to ICH was chosen to measure the HU to avoid the potential impact of ICH mass effect on the vascular structures. According to the location of the ICH, 1 of the 3 levels of HU measurement was chosen to classify each study into the phase of acquisition (Table 1). Each CTA study was classified into 1 of 2 phases: arterial, when HU in the artery were higher than in venous structure, or venous, when HU were equal or higher in venous structure. Finer classification of CTA studies into 1 of 5 specific image acquisition phases (early arterial, peak arterial, equilibrium, peak venous, and late venous) was done by using both the arterial and venous contrast density measurements as shown in Table 2.

To assess CTA acquisition phase reliability, 2 stroke neurologists (D.R.-L., D.D.) independently measured the maximum HU from 30 randomly selected CTA scans. Each of these 30 CTA studies were classified into arterial or venous phases as well as into 1 of the 5 specific phases following the same methodology described above. The CTA source image data were independently interpreted for the presence and the number of spot signs by a neuroradiologist (R.L.A.) masked to follow up CT scans. The spot sign was defined according to previously established criteria.\textsuperscript{16} Volumetric analysis of ICH and total hematoma (ICH and intraventricular hemorrhage) was completed by a stroke neurologist (A.M.D.) masked to CTA scans and spot sign status using validated computerized planimetry software.\textsuperscript{17}

Outcome Parameters

The primary outcome parameter was significant hematoma expansion at follow-up CT defined as an ICH absolute growth \( >6 \) mL or relative enlargement of \( >33\% \) from baseline CT.\textsuperscript{18} Total hematoma enlargement was evaluated as a secondary outcome parameter.

Definition of hematoma expansion \( \geq 12.5 \) mL was also explored as a secondary analysis because no consensus exists on the preferred cutoff for clinically significant hematoma expansion and it correlated best to clinical outcome in a previous study.\textsuperscript{19}

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 software. The categorical variables are presented as absolute values and percentages and the continuous variables as means and SD or medians and interquartile intervals. Statistical significance for intergroup differences was assessed by Pearson \( \chi^2 \) or the Fisher exact test for categorical variables and by Student t or Mann–Whitney U test for continuous variables. The inter-rater reliability for the CTA classification phases between the 2 stroke neurologists as well as for the

<table>
<thead>
<tr>
<th>ICH Location</th>
<th>Level</th>
<th>Artery</th>
<th>Venous Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infratentorial</td>
<td>Skull base</td>
<td>Distal V4 segment of vertebral artery</td>
<td>Sigmoid sinus</td>
</tr>
<tr>
<td>Deep: temporal or occipital lobes</td>
<td>Circle of Willis</td>
<td>Proximal M1 segment of MCA</td>
<td>Confluence of sinuses</td>
</tr>
<tr>
<td>Frontal or parietal lobes</td>
<td>High convexity</td>
<td>Distal A2 segment of ACA</td>
<td>Superior sagittal sinus</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; CTA, computed tomography angiography; ICH, intracerebral hemorrhage; and MCA, middle cerebral artery.
determination of the spot sign by the site investigators and by the core laboratory neuroradiologist stratified by CTA acquisition phases was calculated with the multirater unweighted κ statistic. A 2-way analysis of variance was used to assess the interaction of CTA acquisition phases and spot sign status on total hematoma enlargement. A 2-sided P value of <0.05 was considered significant for all tests. All analyses are considered as secondary analyses of the primary PREDICT study and therefore exploratory and hypothesis generating. Thus, no correction was made for multiple tests.

Results
From June 24, 2006, to February 27, 2012, 392 patients were enrolled in 12 centers in 6 countries. After the exclusion of 4 subjects who did not fulfill the inclusion criteria and 2 who withdrew consent, 386 patients constituted the entire PREDICT cohort. From the entire cohort, 15 subjects were excluded from the present study for the following reasons: 7 did not have available baseline CT images, 3 did not have available CTA source images, and 5 did not have an independent determination of the spot sign. Therefore, 371 patients were included in the primary analysis.

Two hundred eighty-nine (77.9%) CTA scans were acquired in arterial phase and 82 (22.1%) in venous phase. The frequency of CTA studies according to the 5 specific phases is shown in Table 2. The inter-rater reliability for the CTA image acquisition classification between the 2 raters was excellent for combined arterial and venous phases classification (κ=0.839; 95% confidence interval [CI], 0.675–1.000) and for the combined 5 specific phases classification (κ=0.820; 95% CI, 0.657–0.983) in the 30 randomly selected CTA scans.

The CTA spot sign was present in 111 (29.9%) patients. The frequency of the spot sign was higher in subjects whose CTA were acquired in venous phase compared with those whose CTA were acquired in arterial phase (39% versus 27.3%; P=0.041). Similarly, the frequency of the spot sign was higher in later phases of image acquisition (Figure, P=0.095).

Multiple spot signs were observed in 46 (41.4%) of the 111 spot sign–positive patients. No differences were found when comparing the presence of multiple spot signs in venous and in arterial phase (37.5% versus 43%; P=0.592) or across the 5 specific phases (P=0.594). The median spot sign number was 1 (interquartile interval, 1–2) in both arterial and venous phases (P=0.877).

The median contrast density of the spot sign was 271 (181–328) HU and was higher in those CTA acquired in venous phase as compared with arterial phase (303 [260–395] versus 235 [163–309] HU; P=0.003). Similarly, the median spot sign density was 201 (150–312) HU in early and peak arterial phases, 276 (231–348) HU in equilibrium phase, and 291 (241–380) HU in peak and late venous phases (P=0.009).

Site investigator interpretations for the presence of the spot sign were prospectively collected for 229 patients. In this subgroup, the spot sign was observed in 63 (27.5%) patients by the site investigators and in 64 (27.9%) patients by the core laboratory neuroradiologist. While the presence of the spot sign was determined in 12 patients by the core laboratory neuroradiologist and not by site investigators, presence of the spot sign was interpreted in 11 patients by site investigators and not by the core laboratory neuroradiologist. The inter-rater reliability for the determination of the spot sign by the site investigators and by the core laboratory neuroradiologist was good (κ=0.749; 95% CI, 0.653–0.845). Inter-rater agreement differed slightly among images acquired in equilibrium phase (κ=0.938; 95% CI, 0.818–1.000), in peak and late venous phases (κ=0.793; 95% CI, 0.621–0.965), and in early and peak arterial phases (κ=0.661; 95% CI, 0.512–0.810).

Apart from a higher frequency of the CTA spot sign, subjects with CTA acquired in venous phase showed a higher frequency of lobar ICH location (65.9% versus 17%; P<0.001), higher ICH (25.5 [12–44.8] versus 11.8 [6.2–24.1] mL; P<0.001) and total hematoma (30.9 [14–48.3] versus 16.2 [7.2–32] mL; P<0.001) volumes, and lower systolic (167±30.5 versus 176.9±34.8 mm Hg; P=0.022) and diastolic (90.5±19.7 versus 95.9±21.5 mm Hg; P=0.045) blood pressure than those with CTA acquired in arterial phase. Lobar hematomas showed higher frequency of CTA acquired in venous phase (52.4%,
10.7%, and 6.3%; \(P < 0.001\)), higher frequency of the spot sign (40.8%, 26.6%, and 12.5%; \(P = 0.003\)), and higher median ICH volume at baseline (34.9 [16.7–52.2], 11.5 [6.1–20.2], and 3.2 [2.1–8.5] mL; \(P = 0.011\)) than deep and infratentorial hematomas, respectively.

Hematoma expansion analysis was limited to 320 patients after the exclusion of 51 patients for the following reasons: 14 were treated with off-label recombinant factor VIIa, 16 underwent a neurosurgical procedure, and 21 did not have a follow-up CT (10 of them because of death within first 24 hours). In this subgroup, the spot sign was present in 87 (27.2%) subjects, significant hematoma expansion (ICH absolute growth >6 mL or relative enlargement of >33% from baseline CT) occurred in 89 (27.8%) patients, and median total hematoma enlargement was 1 (−0.2 to 8.5) mL. Patients with the spot sign had more frequent significant hematoma expansion (50.6% versus 19.3%; \(P < 0.001\)) and higher total hematoma enlargement (10 [1.6–29.9] versus 0.4 [−0.3 to 2.9] mL; \(P < 0.001\)) than those without the spot sign.

Hematoma expansion occurred nonsignificantly more frequently in patients with a spot sign identified on CTA acquired in arterial phase as compared with those identified in venous phase (54.1% versus 42.3%; \(P = 0.314\)) and in earlier phases of image acquisition (Figure, \(P = 0.253\)). Total hematoma enlargement was greater among patients who showed a spot sign in a CTA acquired in earlier phases of image acquisition (Figure, \(P = 0.019\)). The number of patients in each CTA acquisition phase who experienced or not hematoma expansion by spot sign status, as well as the total hematoma enlargement in each phase, are shown in Table 3.

The presence of the CTA spot sign predicted significant hematoma expansion with positive predictive value of 50.6%, negative predictive value of 80.7%, sensitivity of 49.4%, and specificity of 81.4%. Predictive values varied depending on the phase of image acquisition. Images acquired in venous phase showed positive predictive value of 42.3%, negative predictive value of 90.7%, sensitivity of 73.3%, and specificity of 72.2%. Conversely, those CTA acquired in arterial phase showed positive predictive value of 54.1%, negative predictive value of 78.4%, sensitivity of 44.6%, and specificity of 84.2%.

Hematoma expansion >12.5 mL was present in 54 (16.9%) patients and occurred more frequently in subjects with the spot sign than those without (41.4% versus 7.7%; \(P < 0.001\)). Similar to that observed with >6 mL or >33% cutoff, in spot sign–positive patients, hematoma enlargement >12.5 mL was more frequent in earlier phases of image acquisition: 48.1% in early arterial, 50% in peak arterial, 36.8% in equilibrium, 36.8% in peak venous, and 16.7% in late venous (\(P = 0.214\)).

### Discussion

This study provides evidence that the frequency of the CTA spot sign in patients with acute ICH varies with the phase of image acquisition. Later image acquisition phases are associated with higher frequency of spot sign detection, but lower severity of hematoma expansion.

Previous single-center studies have shown wide variations in the frequency of the CTA spot sign (17.3%–55.8%).2–8 Although these differences may have occurred, at least in part, attributable to the variability in the time from ICH onset to imaging (3–48 hours) and to the different criteria used to define the spot sign in these studies, variations in image acquisition after the administration of the contrast bolus were likely influential. Several studies have shown a higher frequency of the spot sign in both delayed CTA and postcontrast CT images, detecting cases not seen in earlier images,4,7,8,10 whereas single case reports have identified the presence of the spot sign in later phases of acquisition but not in earlier phases by the use of dynamic CTA.11,12 In our study, the spot sign was more frequent in those CTA acquired in venous phase than those acquired in arterial phase.

The higher frequency and density of the CTA spot sign observed in later phases as compared with earlier phases of image acquisition in this study may reflect that arterial phase of image acquisition is too early in some cases to allow contrast accumulation within the hematoma, especially in those patients with a lower cardiac output or higher peripheral vascular resistance. This fact might explain both the higher frequency of spot sign observed in later phases in our study as well as in delayed images in previous studies4,7,9,10 and the slightly higher interrater reliability for the interpretation of the spot sign in peak and late venous phases as compared with early and peak arterial phases. However, although CTA acquisition in venous phase increases the probability of spot sign detection, some cases have been reported in which the spot sign is seen in earlier images but not in delayed acquisitions.7,20–22 Therefore, a multiphase CTA including image acquisition in arterial and venous phases could be optimal for the detection of the spot sign because each one could demonstrate cases not seen on the other.

Interestingly, CTA spot signs observed on arterial compared with venous phase of image acquisition may discriminate between 2 populations of patients with ICH. Those with venous phase spot signs had a greater tendency to a lobar

### Table 3. Patients in Each CTA Acquisition Phase Who Experienced or Not Hematoma Expansion by Spot Sign Status

<table>
<thead>
<tr>
<th>Phases</th>
<th>Hematoma Expansion</th>
<th>Total Hematoma Enlargement, mLYes (n=87)</th>
<th>No Spot Sign (n=233)</th>
<th>Total Hematoma Enlargement, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=44)</td>
<td>No (n=43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early arterial</td>
<td>15 (55.6)</td>
<td>12 (44.4)</td>
<td>17.1 (−1.5 to 35.8)</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 (20.2)</td>
</tr>
<tr>
<td>Peak arterial</td>
<td>11 (68.8)</td>
<td>5 (31.3)</td>
<td>17.8 (3.5 to 48.2)</td>
<td>49</td>
</tr>
<tr>
<td>Equilibrium</td>
<td>8 (42.1)</td>
<td>11 (57.9)</td>
<td>6.6 (2 to 22.6)</td>
<td>57</td>
</tr>
<tr>
<td>Peak venous</td>
<td>8 (42.1)</td>
<td>11 (57.9)</td>
<td>5.9 (0.3 to 40.8)</td>
<td>38</td>
</tr>
<tr>
<td>Late venous</td>
<td>2 (33.3)</td>
<td>4 (66.7)</td>
<td>5.2 (3.6 to 32.5)</td>
<td>5</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or median (interquartile intervals) as appropriate. CTA indicates computed tomography angiography.
location, larger baseline ICH volume, and lower blood pressure. This suggests that the underlying pathophysiology of the spot sign may differ between patients with typical lobar hemorrhage and typical deep hypertensive hemorrhage.

In the present study, the CTA spot sign was closely associated with total hematoma enlargement and significant hematoma expansion. While several studies have shown that patients with the CTA spot sign present hematoma expansion more frequently and faster than those without, supporting the role of the spot sign as a surrogate marker of active bleeding, others have reported that its presence in postcontrast CT images may improve the sensitivity of the spot sign in the prediction of hematoma expansion, as we have observed in venous phase of CTA acquisition. Moreover, a recent study has shown by the use of perfusion CT a higher rate of contrast leakage when the spot sign is observed in CTA images than when is found in delayed images. The observation that a spot sign identified on earlier phases of image acquisition implies a greater hematoma expansion is concordant with these observations, and we think it implies an arterial, rather than venous, bleeding source.

These findings have potential implications for clinical trials design in patients with acute ICH because the success of future treatments, including hemostatic therapies, may depend on accurate determination of patients at risk of hematoma expansion. If the phase of CTA acquisition could stratify spot sign–positive patients into higher and lower risk patient groups, a multiphase acquisition CTA could allow, apart from more robust spot sign detection, better stratification of patients at risk of hematoma expansion. Therefore, stratified randomization or minimally post hoc adjustment for acquisition phase may be important.

This study has some limitations. Most of the CTA studies were acquired in arterial phase, which may have limited the statistical power to detect other differences between venous and arterial acquisition phases. Only 1 image acquisition per patient was performed for the detection of the CTA spot sign in this study. Therefore, spot signs identified in venous phase could have been also present in arterial phase. It remains to be determined whether the spot sign frequency and its accuracy for predicting hematoma expansion varies within patient when performing both arterial and venous CTA acquisition phases. Because analyses were considered exploratory and therefore hypothesis generating, no correction was made for multiple tests. However, models including variables such as hematoma volume, clinical stroke severity, and blood pressure are unstable because of multicollinearity of variables. Therefore, it was inappropriate to present multivariable models attributable to the nature of the disease under study. Because our results represent a secondary analysis of an existing data set, they should be replicated.

Conclusions

Venous phase of image acquisition improves the yield of the CTA for the detection of the spot sign. In addition, earlier acquisition phases may be associated with greater absolute enlargement, reaffirming the value of arterial phase image acquisition with CTA in ICH. An automated multiphase acquisition CTA which includes both arterial and venous weighted images should be tested to determine whether it could better detect a spot sign and stratify risk of hematoma expansion.

Sources of Funding

External support from the Canadian Stroke Consortium and from NovoNordisk Canada was received to cover costs of study enrollment.

Disclosures

Dr Rodriguez-Luna received a Rio Hortega research training contract (CM11/00087) from the Carlos III Health Institute (Spanish Ministry of Science and Innovation) and the Vall d’Hebron Research Institute.

Dr Hill was supported by the Heart and Stroke Foundation of Alberta, the Hotchkiss Brain Institute, and by Alberta Innovates Health Solutions.

The other authors have no conflicts to report.

References


Venous Phase of Computed Tomography Angiography Increases Spot Sign Detection, but Intracerebral Hemorrhage Expansion Is Greater in Spot Signs Detected in Arterial Phase


Stroke. published online January 30, 2014;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 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/early/2014/01/30/STROKEAHA.113.003007

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/