Observational Study

Medicine®

OPEN

Prevalence and the predictive performance of the dynamic CT-angiography spot sign in an observational cohort with intracerebral hemorrhage

Dar Dowlatshahi, MD, PhD[a,b,*], Hee Sahng Chung, MD[a], Michael Reaume, MSc[a], Matthew J. Hogan, MD, PhD[a], Dylan Blacquiere, MD[a], Grant Stotts, MD[a], Michel Shamy, MA, MD[a], Franco Momoli, PhD[b], Richard Aviv, MD[c], Andrew M. Demchuk, MD[d], Santanu Chakraborty, MD[e]

Abstract

The CT-angiography (CTA) spot sign is a predictor of hematoma expansion (HE). We have previously reported on the use of dynamic CTA (dCTA) to detect spot sign, and to study its formation over the acquisition period. In this study, we report the frequency of dCTA spot sign in acute intracerebral hemorrhage, its sensitivity and specificity to predict HE, and explore the rate of contrast extravasation in relation to hematoma growth.

We enrolled consecutive patients presenting with primary intracerebral hemorrhage within 4.5 hours. All patients underwent a dCTA protocol acquired over 60 seconds following contrast injection. We calculated frequency of the dCTA spot sign, predictive performance, and rate of contrast extravasation. We compared extravasation rates to the dichotomous definition of significant HE (defined as 6 mL or 33% growth).

In 78 eligible patients, dCTA spot sign frequency was 44.9%. In 61 patients available for expansion analysis, sensitivity and specificity of dCTA spot sign was 65.4% and 62.9%, respectively. Contrast extravasation rate did not significantly predict HE (Odds Ratio 15.6 for each mL/min [95% confidence interval 0.30–820.25], $P = .17$). Correlation between extravasation rate and HE was low ($r = 0.297$, $P = .11$). Patients with significant HE had a higher rate of extravasation as compared to those without (0.12 mL/min vs 0.04 mL/min, $P = .03$).

Dynamic CTA results in a higher frequency of spot sign positivity, but with modest sensitivity and specificity to predict expansion. Extravasation rate is likely related to HE, but a single measurement may be insufficient to predict the magnitude of expansion.

Abbreviations: CI = confidence interval, CTA = CT-angiography, dCTA = dynamic CT-angiography, HE = hematoma expansion, ICH = intracerebral hemorrhage.

Keywords: computerized tomography, hematoma expansion, hemorrhagic stroke, intracerebral hemorrhage

1. Introduction

Hematoma expansion (HE)after acute intracerebral hemorrhage (ICH) is a major determinant of outcome.[1] The CT-angiography (CTA) spot sign was initially proposed as a promising predictor for HE, but subsequent studies suggest its prevalence and predictive performance are modest at best.[2–4] Recent innovations in multi-phase CTA have suggested a higher prevalence of spot signs with improved sensitivity, and a potential to provide better insight into the physiology of contrast extravasation and spot sign formation.[5–7]

Editor: Bernhard Schaller.

DD was supported by a Heart and Stroke Foundation of Canada Grant in Aid and Clinician-Scientist Award. DD and MJH have a patent for "Computerized Automatic Detection of Leakage (CARL): method and system for identifying bleeding." Patent No. PAT 80049P-2 US.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Medicine, [b] School of Epidemiology and Public Health, University of Ottawa and Ottawa Hospital Research Institute, Ottawa, [c] Division of Neuroradiology and Department of Medical Imaging, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada, [d] Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, [e] Department of Medical Imaging, University of Ottawa and Ottawa Hospital Research Institute, Ottawa, Canada.

[*] Correspondence: Dar Dowlatshahi, C 2182b Ottawa Hospital Civic Campus, 1053 Carling ave, Ottawa, ON, K1Y 4E3 Canada (e-mail: ddowlat@toh.ca).

How to cite this article: Dowlatshahi D, Chung HS, Reaume M, Hogan MJ, Blacquiere D, Stotts G, Shamy M, Momoli F, Aviv R, Demchuk AM, Chakraborty S. Prevalence and the predictive performance of the dynamic CT-angiography spot sign in an observational cohort with intracerebral hemorrhage. Medicine 2020;99:47 (e23278).

Received: 16 April 2020 / Received in final form: 15 September 2020 / Accepted: 21 October 2020

http://dx.doi.org/10.1097/MD.0000000000023278

We have previously reported on the use of dynamic CTA (dCTA) to detect and measure the spot sign, and to study its formation over the acquisition period.[5,6] We now report on the predictive performance of dCTA and our observations on the rate of formation of the spot sign. Our primary objective was to determine the frequency, sensitivity and specificity of the dCTA spot sign in a prospective cohort of patients presenting with acute ICH. Our exploratory objective was to measure the rate of contrast extravasation over 60 seconds, and to determine whether it correlates with HE.

2. Methods

We enrolled consecutive patients presenting with ICH who underwent dCTA within 4.5 hours from symptom onset at a tertiary care academic hospital (the Ottawa Hospital, Ottawa, Canada) as part of an ongoing prospective imaging registry.[5] Patients were enrolled with Ottawa Health Science Network Research Ethics Board approval, including a waiver of consent to ensure consecutive enrollment. We excluded patients presenting with known secondary causes of ICH such as trauma, malignancy, aneurysms, or arteriovenous malformations.

The dCTA acquisition protocol has been previously described.[6] Briefly, non-contrast CT head images followed by dCTA acquisition were performed using a 320-row volume CT scanner (Toshiba Aquilion ONE^{TM}). We acquired whole-brain angiographic images over a 60 second period: once at 7 seconds (used as a mask for subtraction) from the start of injection of contrast; then every 2 seconds from 10 to 35 seconds, followed every 5 seconds to 60 seconds. We calculated hematoma volumes and dCTA spot sign volumes using a computer-assisted planimetric platform previously validated for ICH.[8]

For our primary outcome, we defined "significant hematoma expansion" as either an absolute growth of 6 mL or relative growth of 33%,[9] and total HE as combined intraparenchymal and intraventricular hematoma growth. We calculated frequency of the dCTA spot sign in the full cohort, and calculated sensitivity and specificity of the dCTA spot sign in patients with follow-up CT imaging. Based on our prior work,[5] we estimated the rate of contrast extravasation as a measure of dCTA spot sign growth by calculating the slope of a time-density plot using two techniques: the first from the earliest point of terminal internal carotid artery contrast arrival to the maximal volume of the dCTA spot sign ("early arterial extravasation rate"), the second from the earliest point of spot sign appearance to the maximal spot volume of the dCTA spot sign ("local vessel extravasation rate"). We compared extravasation rates to the dichotomous definition of significant HE using logistic regression and Mann-Whitney U, and to absolute HE using Pearson or Spearman Rank correlation, as appropriate. All statistics were performed using SPSS v25 and vassarstats.net.

3. Results

We enrolled 83 consecutive patients, 5 of whom were excluded due to secondary causes of ICH (Fig. 1). There were 35 dCTA spot positive patients, for a spot frequency of 44.9%. Demographic information for dCTA spot positive vs negative patients is shown in Table 1. Dynamic CTA spot positive patients were more likely to be older, have higher National Institutes of Health Stroke Scale scores at presentation, and have higher baseline ICH volumes (median 34.4 mL vs 11.2 mL in spot negative; $P < .001$).

Of the 78 eligible patients, 17 did not have follow-up CT scans, therefore 61 patients were available for HE analysis. In this sample, significant HE occurred in 17/30 (56.7%) of spot positive patients and 9/31 (29.0%) of spot negative patients (p = 0.040). The dCTA spot sign sensitivity and specificity to predict significant HE were 65.4% (95% confidence interval [CI] 0.44–0.82) and 62.9% (95% CI 0.45–0.78) respectively.

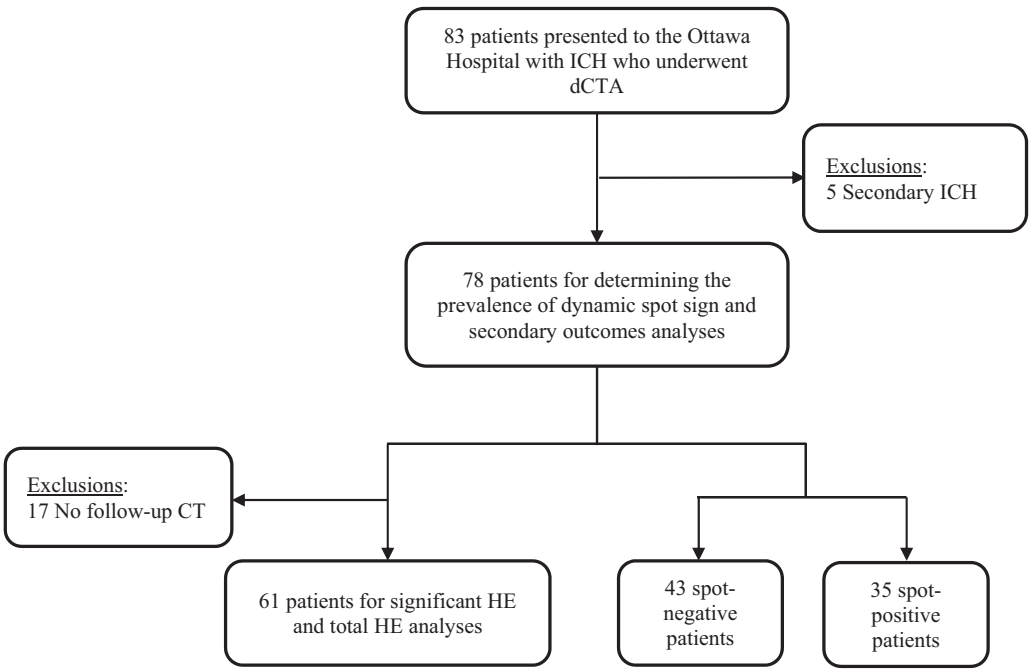

Figure 1. Flow diagram of enrolled subjects. dCTA = Dynamic CT angiography, HE = hematoma expansion, ICH = intracerebral hemorrhage.

Table 1

Baseline demography. Data are n/N (%) or median (25th, 75th percentile). NIHSS = National Institutes of Health Stroke Scale (21 missing values).

	Spot Negative	Spot Positive	*P* Value
Total N	43	35	
Demographics			
Age (yr)	72 (64, 80.5)	80 (70, 86.5)	.016*
Male sex	20/43 (46.5)	15/35 (42.9)	.747
Past Medical History			
Ischemic Stroke or TIA	6/43 (14.0)	7/35 (20.0)	.549
Coronary Artery Disease	2/43 (4.6)	2/35 (5.7)	1
Intracerebral Hemorrhage	6/43 (14.0)	3/35 (8.6)	.504
Hypertension	25/43 (58.1)	18/35 (51.4)	.649
Diabetes Mellitus	3/43 (7.0)	6/35 (17.1)	.285
Atrial Fibrillation	4/43 (9.3)	6/35 (17.1)	.330
Baseline Medications			
Aspirin	10/43 (23.3)	10/35 (28.6)	.613
Plavix	2/43 (4.6)	4/35 (11.4)	.400
Aggrenox	2/43 (4.6)	0/35 (0)	.499
Warfarin	3/43 (7.0)	5/35 (14.3)	.456
Heparin	1/43 (2.3)	2/35 (5.7)	.585
Baseline Presentation			
ICH Volume Baseline mL	11.23 (4.5, 29.9)	34.54 (15.3, 58.2)	.001*
IVH Volume Baseline mL	0 (0, 0)	0 (0, 2.24)	.241
Total Volume Baseline mL	13.15 (4.6, 33.3)	35.53 (19.8, 63.5)	.001*
NIHSS**	11 (6, 14.8)	14 (10, 19)	.038*

NIHSS = National Institutes of Health Stroke Scale.
* $P < .05$.

Both technique 1 (early arterial extravasation) and technique 2 (local vessel extravasation) yielded rates that were highly correlated ($r = 0.967$, $P < .0001$). Using technique 1, rate of contrast extravasation predicted HE with an odds ratio of 15.6 for each mL/min of extravasation, but this was not statistically significant (95% CI 0.30–820.25; $P = .17$). Similarly, the rate derived using technique 2 non-significantly predicted significant HE with an odds ratio of 7.2 (95% CI 0.33–160.7; $P = .21$). Neither rate technique revealed a statistically significant correlation between extravasation rate and absolute HE (technique 1: $r = 0.297$, $P = .11$; technique 2: $r = 0.243$, $P = .20$). Patients with significant HE had a higher rate of extravasation as compared to those without (median [IQR]: 0.12 [0.33] mL/min vs 0.04 [0.13] mL/min, $P = .03$).

4. Discussion

We report that dCTA performed acutely in patients with ICH reveals a spot sign approximately 45% of the time, which is higher than previously reported with single phase CTA, but consistent with triple-phase CTA.[7] However, the sensitivity and specificity for the dCTA spot sign to predict HE was modest. Our findings do not suggest dCTA has any additional advantage over routine CTA for predicting HE.

Using dCTA, our study provides additional insight into contrast extravasation during acute ICH. We were able to quantify and compare the rate of contrast extravasation using two different approaches: first by measuring the rate of spot sign formation once contrast arrives into the cerebral arterial system, and then by measuring its formation from the point at which the spot sign begins to form at the affected vessel. Both approaches were highly correlated, suggesting there is minimal difference between the two; either approach can be used in future studies seeking to explore contrast extravasation. Our second technique to calculate rate of extravasation using dCTA is analogous to a technique used in a recent dual-phase CTA study,[10] where spot volumes from a first and second pass CTA was used to estimate rate. Our technique has the advantage of having better temporal resolution with multiple time points, which theoretically increases the accuracy of our rate estimates.

Patients with significant HE were more likely to have higher extravasation rates, though extravasation rate and absolute HE were poorly correlated. It is possible this is simply the result of small sample size and lack of statistical power. However, the lack of correlation may also highlight the inherent limitation of assessing extravasation at a single time point in a highly dynamic process: it is entirely possible a low rate of extravasation may still lead to significant HE due to a secondary vessel rupture sometime after imaging is acquired. Conversely, a high rate of extravasation may be in the process of slowing down, to ultimately undergo tamponade and hemostasis before significant expansion occurs. These possibilities are supported by a recent animal model of contrast extravasation depicting three distinct patterns of accelerating and decelerating rates within a 5-minute measurement period[11] and suggest serial dynamic imaging may be required to fully appreciate the physiology of acute extravasation.

Our study has important limitations. The sample size was geared towards exploring the frequency, sensitivity and specificity of dCTA spot sign, and may have been underpowered to correlate rate of extravasation with HE or to perform multivariate modelling. Furthermore, our objective was to predict early HE, therefore our sample was restricted to ICH presenting under 4.5 hours. The frequency and predictive values of the dCTA spot sign may vary in later time points. Finally, our measurement of rate assumes a constant linear relationship over the course of 60 seconds. It is possible emerging automated machine learning measurement techniques may be better able to model extravasation rate.

5. Conclusion

Our study reveals that dCTA done within 4.5 hours of ICH onset results in a higher frequency of spot sign detection, but with modest sensitivity and specificity to predict HE, and therefore offers no clear advantage over traditional CTA. Furthermore, our exploration of extravasation rate suggests a single measurement in time may be insufficient to predict the magnitude of subsequent HE. This highlights the need for further study into the dynamics of extravasation in acute ICH.

Author contributions

Conceptualization: Dar Dowlatshahi, Matthew J. Hogan, Grant Stotts, Franco Momoli, Richard Aviv, Andrew M. Demchuk, Santanu Chakraborty.

Data curation: Dar Dowlatshahi, Hee Sahng Chung, Michael Reaume, Dylan Blacquiere, Michel Shamy.

Formal analysis: Dar Dowlatshahi, Hee Sahng Chung, Michael Reaume, Dylan Blacquiere, Franco Momoli, Santanu Chakraborty.

Funding acquisition: Dar Dowlatshahi, Grant Stotts, Franco Momoli, Richard Aviv, Andrew M. Demchuk, Santanu Chakraborty.

Investigation: Dar Dowlatshahi.

Methodology: Dar Dowlatshahi, Matthew J. Hogan, Franco Momoli.

Project administration: Dar Dowlatshahi, Grant Stotts, Michel Shamy.
Resources: Dar Dowlatshahi, Michel Shamy.
Supervision: Dar Dowlatshahi, Santanu Chakraborty.
Visualization: Santanu Chakraborty.
Writing – original draft: Dar Dowlatshahi.
Writing – review & editing: Dar Dowlatshahi, Hee Sahng Chung, Michael Reaume, Matthew J. Hogan, Dylan Blacquiere, Grant Stotts, Michel Shamy, Franco Momoli, Richard Aviv, Andrew M. Demchuk, Santanu Chakraborty.

References

[1] Davis SM, Broderick J, Hennerici M, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology 2006;66:1175–81.
[2] Wada R, Aviv RI, Fox AJ, et al. Ct angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. Stroke 2007;38: 1257–62.
[3] Goldstein JN, Fazen LE, Snider R, et al. Contrast extravasation on ct angiography predicts hematoma expansion in intracerebral hemorrhage. Neurology 2007;68:889–94.
[4] Dowlatshahi D, Brouwers HB, Demchuk AM, et al. Predicting intracerebral hemorrhage growth with the spot sign: the effect of onset-to-scan time. Stroke 2016;47:695–700.
[5] Dowlatshahi D, Wasserman JK, Momoli F, et al. Evolution of computed tomography angiography spot sign is consistent with a site of active hemorrhage in acute intracerebral hemorrhage. Stroke 2014;45:277–80.
[6] Chakraborty S, Alhazzaa M, Wasserman JK, et al. Dynamic characterization of the ct angiographic 'spot sign'. PloS One 2014;9:e90431.
[7] Rodriguez-Luna D, Coscojuela P, Rodriguez-Villatoro N, et al. Multiphase ct angiography improves prediction of intracerebral hemorrhage expansion. Radiology 2017;285:932–40.
[8] Kosior JC, Idris S, Dowlatshahi D, et al. Quantomo: validation of a computer-assisted methodology for the volumetric analysis of intracerebral haemorrhage. Int J Stroke 2011;6:302–5.
[9] Dowlatshahi D, Demchuk AM, Flaherty ML, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. Neurology 2011;76:1238–44.
[10] Brouwers HB, Battey TW, Musial HH, et al. Rate of contrast extravasation on computed tomographic angiography predicts hematoma expansion and mortality in primary intracerebral hemorrhage. Stroke 2015;46:2498–503.
[11] Liu R, Huynh TJ, Huang Y, et al. Modeling the pattern of contrast extravasation in acute intracerebral hemorrhage using dynamic contrast-enhanced mr. Neurocritical Care 2015;22:320–4.