

Admission CT Perfusion Is an Independent Predictor of Hemorrhagic Transformation in Acute Stroke with Similar Accuracy to DWI

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Key Words

Stroke · Hemorrhagic transformation · CT scan · Perfusion

Abstract

Background: The utility of admission CT perfusion (CTP) to that of diffusion-weighted imaging (DWI) as a predictor of hemorrhagic transformation (HT) in acute stroke was compared. **Methods:** We analyzed the admission CTP and DWI scans of 96 consecutive stroke patients. HT was present in 22 patients (23%). Infarct core was manually segmented on the admission DWI. We determined the: (1) hypoperfused tissue volume in the ischemic hemisphere using a range of thresholds applied to multiple different CTP parameter maps, and (2) mean relative CTP (rCTP) voxel values within both the DWI-segmented lesions and the thresholded CTP parameter maps. Receiver operating characteristic area under curve (AUC) analysis and multivariate regression were used to evaluate the test characteristics of each set of volumes and mean rCTP parameter values as predictors of HT. **Results:** The hypoperfused tissue volumes with either relative cerebral blood flow (rCBF) <0.48 (AUC = 0.73), or relative mean transit time (rMTT) >1.3 (AUC = 0.70), had similar accuracy to the DWI-segmented core volume (AUC = 0.68, p = 0.2 and p = 0.1, respectively) as predictors of HT. The mean rMTT voxel

values within the rMTT >1.3 segmented lesion (AUC = 0.71) had similar accuracy to the mean rMTT voxel values (AUC = 0.65, p = 0.24) and mean rCBF voxel values (AUC = 0.64, p = 0.22) within the DWI-segmented lesion. The only independent predictors of HT were: (1) mean rMTT with rMTT >1.3, and (2) mechanical thrombectomy. **Conclusion:** Admission CTP-based hypoperfused tissue volumes and thresholded mean voxel values are markers of HT in acute stroke, with similar accuracy to DWI. This could be of value when MRI cannot be obtained.

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Introduction

Hemorrhagic transformation (HT) is an unwanted complication of ischemic stroke that may severely worsen prognosis. Many studies have tried to determine clinical and imaging parameters associated with HT so as to identify patients at highest risk for thrombolytic or endovascular therapies. These studies have found infarct-core volume on admission diffusion-weighted imaging (DWI) scans to be an independent predictor of HT [1]. Other variables that have been correlated with HT include low mean apparent diffusion coefficient (ADC) [1], large ves-

Table 1. Demographics of patients not included in the study

Patients not in the study (n = 57)	Hemor-rhage (%)	No hemor-rhage (%)
Number of cases	16 (25)	41 (68)
Patients demographics		
Mean age	70	71
Female	11 (69)	19 (46)
Male	5 (30)	22 (53)
Clinical characteristics		
Mean admission NIHSS	14	15.13
Imaging findings		
DWI lesion volume	53.0	34.2
Large vessel occlusion (BASIS)	9 (69)	31 (75)
Treatment modalities		
tPA	8 (61)	6 (14)

There was a similar incidence of HT and similar demographics in those patients excluded from our study due to incomplete datasets.

sel circle of Willis occlusion [2], low attenuation [3] or poor collateral vessels [4] on CT angiography (CTA) source images, and signs of blood-brain barrier disruption such as increased CT perfusion (CTP) and MR perfusion permeability values [3–5], MRI hyperintense acute injury marker sign [6], and reduced cerebral blood volume (CBV) or flow (CBF) [7, 8].

Multiple studies have suggested that HT results from reperfusion into a large volume of severely ischemic tissue [9]. Flow measures might therefore be useful to identify ischemic tissue at risk of HT. Indeed, Ueda et al. [10] demonstrated an increased likelihood of HT in ischemic brain with more than 65% CBF reduction. In patients with middle cerebral artery (MCA) occlusion, ischemic tissue with a mean CBF ratio <0.18 is more likely to hemorrhage [9]. Low or completely absent contrast arrival in cerebral perfusion scans has been reported to reflect tissue at risk for HT [11].

The aim of our study was therefore to compare the utility of admission CTP to that of DWI as a predictor of HT of acute stroke. CTP-based risk markers have the potential to substitute for DWI when the latter is not available. Imaging variables we studied included CTA-defined arterial occlusion, recanalization following endovascular treatment, DWI lesion volumes, and CTP parameter map volumes and thresholded voxel values. Clinical variables included admission NIH stroke scale (NIHSS) score, time elapsed from ictus to hospital admission, and the use of thrombolytic or mechanical endovascular therapies.

Methods

Patients

We retrospectively reviewed the medical records and imaging data of 153 consecutive patients with acute ischemic stroke who were admitted to our emergency department between April 2008 and May 2009. All patients had admission NIHSS scores recorded and underwent our routine stroke imaging protocol. Inclusion criteria for imaging evaluation consisted of a non-contrast CT (NCCT) of the head, CTA of the head, neck, and arch, CTP with 8-cm anterior circulation coverage (shuttle mode), MRI-DWI within 9 h of symptom onset, and a follow-up scan (NCCT or MRI) within the following 5 days for HT evaluation. Ninety-six patients had a complete set of images and were included in our study. The 57 excluded patients had a similar incidence of HT and demographics compared to the study cohort (table 1). Patients were treated according to standard institutional protocols, including intravenous (IV) thrombolysis or intra-arterial (IA) therapy as clinically indicated [12].

Our institutional review board approved our retrospective review of all medical and imaging data.

Image Acquisition

CT imaging was performed using a helical scanner (Light-Speed 64; GE Medical Systems, Milwaukee, Wisc., USA) in the emergency department. NCCT scans were performed in helical mode (1.25 mm thickness, 120 kV, 250 mA). CTA was performed during the administration of 80 ml of non-ionic contrast agent (Omnipaque 370; Nycomed Inc., Roskilde, Denmark) followed by 40 ml of saline, both at a rate of 4 ml/s, from the aortic arch to vertex (1.25 mm thickness, 120 kV, 350–800 mA, 0.5–0.7 s/rotation). CTP was acquired using shuttle perfusion mode during administration of 35 ml of non-ionic contrast (7 ml/s) followed by 40 ml of saline (4 ml/s) (time of acquisition 91 s, 80 kV, 500 mA), providing 16 slices with 5 mm thickness (8 cm coverage); total radiation exposure was <500 mGy. Perfusion images were post-processed using GE's software CTP3. Using the protocol described above, the total estimated effective radiation dose was approximately 14.2 mSv (NCCT 2.0 mSv, CTA 4.3 mSv, and CTP 7.9 mSv).

MR scans were performed on a 1.5 T Signa whole-body scanner (GE Medical Systems). TR was 5,000 ms; TE was minimum (typically 85–110 ms). Isotropic admission DWI and ADC maps were reviewed, as well as follow-up GRE T2* susceptibility sequences.

Image Analysis

All images were analyzed by a radiologist with 5 years of general and 1 year of dedicated neuroradiology experience (L.C.S.S.), blinded to the patients' clinical histories, and follow-up imaging. Admission images were assessed for stroke laterality and the presence of target large vessel occlusion (LVO) on CTA, according to the Boston Acute Stroke Imaging Scale (BASIS) criteria [13]. LVO was defined as occlusion of the terminal internal carotid artery, proximal MCA (M1 or M2), and/or the basilar artery. Follow-up scans were assessed for the presence of HT. The follow-up scans included NCCT in 70% (67/96) of cases and MR in the remaining 30% (29/96). Of those patients with HT, 40% (8/22) had MRI and 60% (14/22) had NCCT as their follow-up. Any new hemorrhage on follow-up was considered HT, collapsing the European Coop-

erative Acute Stroke Study I (ECASS I) classification system [14] into a single category.

Recanalization was determined in the subset of patients who received IA therapy, and in those who had a follow-up CTA or MRA, for vascular patency assessment. In those who underwent IA therapy, a TIC1 score of 2a or higher was considered recanalization. On non-invasive imaging, recanalization was defined as complete luminal opacification of previously occluded vessels.

For each patient, the volume of infarction was manually segmented on the admission DWI based on visual qualitative assessment of both the DWI and ADC images, using a commercial image analysis software (L.S.) (Analyze 8.1, AnalyzeDirect; Mayo Clinic, Rochester, Minn., USA). All MRI-DWI, CTP scans, and the DWI outlined lesions were automatically co-registered to the MNI-152 template using the Linear Image Registration Tool (FLIRT5.5; Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford, UK). On a voxel-by-voxel basis, relative CBF (rCBF), CBV (rCBV), mean transit time (rMTT), and permeability surface (rPS) values were calculated as the ratio of absolute voxel values in the ischemic hemisphere to corresponding, contralateral mirror voxels, using a custom-made software program (Y.W.) (MatLab7.8; The MathWorks, Natick, Mass., USA). First, we used the resulting CTP parameter maps (consisting of relative voxel values on the ischemic hemisphere) to examine the performance of the hypoperfused CTP lesion volumes in determining HT. Specifically, we determined the volume of the ischemic lesions with rCBF and rCBV voxel values below thresholds ranging from 0.1 to 0.7 at 0.02 intervals, as well as those with rMTT and rPS above thresholds ranging from 1.3 to 2.8 at 0.05 intervals. Next, the mean rCTP parameter voxel values within the hypoperfused lesion volumes were calculated for the thresholds that optimally determined HT. The mean rCTP voxel values within the infarct core – segmented admission DWI lesions – were also determined.

Statistical Analysis

Patients were stratified into two groups based on the follow-up scan: those with HT versus those without HT ('HT' vs. 'non-HT').

Receiver operator characteristic (ROC) curves were generated for the DWI and thresholded CTP lesion volumes to determine and compare their individual test characteristics in distinguishing HT from non-HT patients, including area under curve (AUC), sensitivity and specificity. The CTP threshold with the highest AUC was selected for each parameter map (CBF, BCV, MTT and rPS).

We performed univariate analyses to compare the imaging and clinical variables between these two groups. We used Student's t test (variables with normal distribution), Mann-Whitney rank test (variables without a normal distribution), and χ^2 (categorical variables).

Using those clinical and CT-based imaging variables that were significant in the univariate analyses, we determined the independent predictors of HT using multivariate binary logistic regression modeling (thresholds for inclusion/exclusion of variables were $p \leq 0.05$ and $p \geq 0.1$, respectively). We have additionally performed univariate and multivariate analyses after stratification according to time elapsed from ictus to scanning (≤ 4.5 vs. >4.5 h). ROC curves were generated to evaluate each significant variable's test characteristics in distinguishing HT from non-HT.

STATA 10 (Stata Corp., College Station, Tex., USA) and SPSS 17.0 (SPSS Inc., Chicago, Ill., USA) software were used to perform the statistical analyses. All values are expressed as either mean \pm SE, median (interquartile, IQ), or number (percentage), to the $p < 0.05$ level of significance.

Results

Ninety-six patients were included in our analysis. Of these, 22 (23%) had HT on follow-up scan. Of the 22 hemorrhage cases, 3 were classified as parenchymal hematomas (PH) and 19 as hemorrhagic infarctions (HI); there were insufficient PH cases to stratify for subgroup analysis. A detailed list of the characteristics of the patients with hemorrhage is shown in table 2.

The median ictus to CTP interval was 3.9 h (IQ 2–5), and the median CTP to DWI interval was 57 min (IQ 41–78).

CTP versus DWI

In the ROC curve analysis, DWI-based infarct volume had an AUC of 0.68 ($p < 0.01$) for determining HT. At an admission infarct volume of 100 ml (the operating point of the ROC curve), there was 51% specificity and 91% sensitivity. The Mann-Whitney test showed a significant difference between the median infarct volumes of the two groups (33 ml (IQ 15–74) for HT and 10 ml (IQ 4–48) for non-HT, $p = 0.01$).

For CTP, the hypoperfused volumes in the ischemic hemisphere that optimally determined HT were obtained at thresholds of $rCBF \leq 0.48$ and $rMTT \geq 1.3$, with AUCs of 0.73 ($p = 0.03$) and 0.70 ($p = 0.04$), respectively. There was no significant difference between the DWI and the CTP-based volumes in distinguishing HT from non-HT ($p = 0.21$ vs. rCBF, and $p = 0.10$ vs. rMTT). For $rCBF \leq 0.48$, at an optimal operating point threshold volume of 43 ml, there was 86% sensitivity and 53% specificity. For $rMTT \geq 1.3$, at an optimal operating point threshold volume of 87 ml, there was 82% sensitivity and 60% specificity. The AUCs for both rCBV and rPS ROC curves were < 0.6 for determining HT, therefore these CTP parameters were excluded from further multivariate analysis. The average volumes of hypoperfused brain based on the $rCBF \leq 0.48$ and $rMTT \geq 1.3$ thresholds were significantly higher in patients with HT versus those without (75.2 ± 6.9 vs. 53.6 ± 5.0 ml, $p = 0.03$, and 120.4 ± 10.0 vs. 89.5 ± 6.9 ml, $p = 0.04$, respectively).

The mean rCBF and rMTT values within the DWI-segmented infarct core were significantly different be-

Table 2. Hemorrhagic transformation cases characteristics

HT	Age	Sex	DWI vol, ml	0.48 CBF vol, ml	1.3 MTT vol, ml	Mean rMTT of 1.3 MTT lesion	IV t-PA	Mechanical thrombectomy	Recanalization	Symptomatic	Ictus – CTP interval	CTP – DWI interval	Ictus – IV t-PA interval	Ictus – intervention interval	Intervention – HT interval	Ictus-recanalization interval
HI1	51	F	67.7	102.4	132.8	4.1	Yes	Yes	Yes	No	5:30	0:36	1:30	8:52	14:55	10:20
HI1	43	M	20.7	67.1	113.3	3.4	No	No	No	No	5:50	4:01	N/A	N/A	N/A	N/A
HI1	79	F	7.8	26.2	59.5	3.2	No	No	Yes	No	5:00	0:37	N/A	N/A	N/A	–
HI1	84	M	50.0	66.7	113.6	3.8	Yes	No	No	No	4:28	1:10	2:45	N/A	N/A	N/A
HI1	37	F	11.2	43.4	28.4	5.4	No	Yes	Yes	No	8:13	0:27	N/A	10:35	17:30	8:39
HI1	37	F	11.2	30.1	66.4	4.4	No	Yes	Yes	No	8:10	0:25	N/A	10:20	17:20	8:30
HI1	58	M	92.7	93.3	152.3	3.8	No	No	No	No	3:58	0:50	N/A	N/A	N/A	N/A
HI1	62	M	31.9	139.3	221.1	3.1	No	No	–	No	1:09	1:11	N/A	N/A	N/A	–
HI1	60	M	24.7	83.8	131.1	4.0	Yes	Yes	No	No	3:15	0:54	1:50	7:29	17:36	N/A
HI2	54	M	75.0	106.7	168.0	3.0	No	Yes	Yes	No	4:57	0:23	N/A	7:58	4:09	9:09
HI2	59	M	34.8	85.5	164.2	3.5	No	No	–	No	1:00	4:26	N/A	N/A	N/A	–
HI2	77	F	128.8	118.7	196.6	4.3	Yes	No	No	Yes	4:50	0:55	2:00	N/A	N/A	N/A
HI2	70	M	73.6	62.1	160.8	5.4	No	No	No	Yes	7:00	1:04	N/A	N/A	N/A	N/A
HI2	48	M	10.4	57.4	99.6	3.1	Yes	Yes	Yes	No	0:27	0:27	1:05	3:18	0:36	4:52
HI2	85	F	135.1	44.6	106.0	3.7	Yes	No	Yes	No	3:50	2:01	1:44	N/A	N/A	–
HI2	52	M	20.2	115.4	100.5	3.8	No	Yes	Yes	No	3:38	0:44	N/A	6:20	1:06	8:30
HI2	74	M	49.1	65.4	99.8	2.7	Yes	No	–	No	2:00	1:10	1:35	N/A	N/A	–
HI2	82	F	2.6	36.6	72.0	3.1	Yes	Yes	No	Yes	4:50	0:50	1:51	6:50	12:46	N/A
HI2	77	M	107.3	128.6	151.2	4.2	Yes	No	–	Yes	4:20	0:45	0:33	N/A	N/A	–
PH1	79	F	26.1	63.5	123.1	3.7	No	No	–	Yes	3:38	0:47	N/A	N/A	N/A	–
PH1	81	F	38.5	52.6	99.6	3.7	No	No	No	No	1:50	0:53	N/A	N/A	N/A	N/A
PH2	55	M	16.0	65.0	89.4	3.9	No	Yes	Yes	Yes	4:50	5:49	N/A	7:20	1:37	9:33

tween the HT and non-HT groups (0.44 ± 0.03 vs. 0.57 ± 0.03 , $p = 0.02$ for rCBF, and 3.08 ± 0.22 vs. 2.48 ± 0.10 , $p = 0.01$ for rMTT, respectively). Likewise, the mean rMTT within the MTT-segmented lesion (rMTT >1.3) was significantly different between the HT and non-HT groups (2.78 ± 0.61 vs. 2.30 ± 0.57 , $p = 0.001$). There was no significant difference between the AUCs of these parameters (rMTT within the MTT-segmented lesion AUC = 0.71 vs. rMTT within the DWI-segmented lesion, AUC = 0.65, $p = 0.24$, and vs. rCBF within the DWI-segmented lesion, AUC = 0.64, $p = 0.22$).

When patients were stratified according to time post-ictus at admission (early = ≤ 4.5 h post-ictus, late = > 4.5 h post-ictus), for the early presentation group, those who developed HT had higher mean admission NIHSS score (11 ± 7 vs. 17 ± 4 , $p = 0.007$), and larger median admission DWI lesion volume (36.6 vs. 12.8 ml, $p = 0.024$). Likewise, the average volumes of hypoperfused brain based on the rCBF ≤ 0.48 and rMTT ≥ 1.3 thresholds were significantly higher in patients with HT versus those without (83.0 ± 30.8 vs. 53.6 ± 31.5 ml, $p = 0.005$, and 130.2 ± 36.8 vs. 91.1 ± 50.6 ml, $p = 0.006$, respectively). The mean rMTT values within the DWI-segmented infarct core (3.1 ± 0.8 vs. 2.5 ± 0.9 , $p = 0.04$) and within the MTT-segmented lesion (rMTT >1.3; 2.7 ± 0.4 vs. 2.3 ± 0.6 , $p = 0.02$) were also higher for those who

developed HT. For the late presentation patients, only mean rMTT within the MTT-segmented lesion (rMTT >1.3) was significantly different between the HT and non-HT groups (3.2 ± 1.0 vs. 2.3 ± 0.5 , $p = 0.017$).

Other Imaging and Clinical Variables Studied

All patients with HT had a proximal LVO, whereas among the patients who did not bleed, 54 (69%) had a LVO ($p < 0.01$).

Treatment with either IV or IA thrombolytics had no effect on the incidence of HT. Of the 22 HT patients, 9 (41%) received thrombolytic therapy (all IV), and of the 74 without HT, 35 (48%) received thrombolytic therapy (32 IV/3 IA) ($p = 0.50$ for IA t-PA, and $p = 0.45$ for IV t-PA). IV and IA lysis were started at a mean time post-ictus of 1.8 h (± 0.6) and 7.1 h (± 2.8), respectively.

Mechanical thrombectomy increased the likelihood of bleeding by nearly four times (OR 3.7, 95% CI 1.2–11.9, $p < 0.01$). 9/22 (41%) of the HT group were treated with mechanical thrombectomy, whereas 11/74 (15%) of the non-HT group received the same treatment. On average, mechanical thrombectomy was initiated 6.4 h (± 2.5) after stroke onset and HT occurred 9.8 h (± 7.7) after the procedure.

For the 20 patients who underwent mechanical thrombectomy, the time from ictus to start of treatment was an

Table 3. Univariate analysis

	Hemorrhage	No hemorrhage	p value
Number of patients	22 (23%)	74 (77%)	
Patients demographics			
Mean age	64	68	0.23
Female gender	9 (40%)	27 (36%)	0.80
Clinical characteristics			
Mean admission NIHSS score	16.5	10.9	0.001
Time from ictus (h:m)	4:14	3:42	0.33
Imaging findings			
Median DWI lesion volume (ml)	33.3 (14.8–73.9)	10.3 (4.3–48.5)	0.011
Mean rCBF within DWI lesion	0.44	0.57	0.02
Mean rCBV within DWI lesion	0.91	0.97	0.28
Mean rMTT within DWI lesion	3.09	2.48	0.01
Mean rPS within DWI lesion	1.99	1.91	0.67
Volume of ischemic lesion with rCBF < 0.48 (ml)	75.2	53.7	0.03
Volume of ischemic lesion with rMTT > 1.3 (ml)	120.4	89.5	0.04
Mean rCBF within ischemic lesion with rCBF < 0.48	0.269	0.289	0.06
Mean rMTT within ischemic lesion with rMTT > 1.3 ^a	2.78	2.30	0.001
Large vessel occlusion	22 (100%)	55 (74%)	0.01
Recanalization (n = 53)	9/17 (53%)	12/36 (33%)	0.23
Treatment modalities			
Mechanical thrombectomy ^a	9 (41%)	11(15%)	0.013
IV thrombolysis	9 (41%)	32 (44%)	0.50
IA thrombolysis	0	3 (4%)	0.45

^a Comparison of imaging and clinical characteristics between ischemic stroke patients with and without hemorrhagic transformation. NIHSS = National Institute of Health Stroke Scale; rCBF = relative cerebral blood flow; rCBV = relative cerebral blood volume; rMTT = relative mean transit time; rPS = relative permeability surface area product; IV = intravenous; IA = intra-arterial.

average of 1.9 h later for those with than for those without HT (4.9 ± 1.8 vs. 3.0 ± 2.4 h, $p = 0.075$). Importantly, for the subset of patients who underwent mechanical thrombectomy with HT, time from ictus to recanalization was significantly longer than for those without HT (8.7 ± 1.4 vs. 6.2 ± 1.7 h, $p = 0.006$).

ROC curve analysis showed an AUC = 0.75, $p < 0.01$ for the admission NIHSS score determination of HT. An admission NIHSS score <10 had a negative predictive value (NPV) of 100% ($n = 32$, 9 of whom were treated with IV lysis) for HT.

A binary logistic regression, using as inputs admission NIHSS, mechanical thrombectomy, and all of the CTP-based imaging variables that were significant in the univariate analysis (table 3), revealed only the two independent predictors of HT: (1) mean rMTT within the rMTT >1.3 segmented lesion (OR 3.7, $p = 0.007$), and (2) mechanical thrombectomy (OR 3.7, $p = 0.025$). Figure 1 shows a sample case.

When patients were stratified according to time post-ictus at admission (early = ≤ 4.5 h post-ictus, late =

>4.5 h post-ictus), NIHSS was the only independent predictor of HT in those admitted early (OR 1.2, $p = 0.015$), whereas both (1) mechanical thrombectomy (OR 4.3, $p = 0.048$) and (2) the mean rMTT within the MTT-segmented lesion (OR 2.5, $p = 0.08$) were the independent predictors in those admitted beyond 4.5 h.

Discussion

Our study has confirmed that the extent and degree of hemodynamic derangement in acute stroke patients can help identify those at highest risk for HT, and, more importantly, has shown that the detection of such severely ischemic tissue can be accomplished using CTP imaging with similar accuracy to that of DWI. These results suggest that CTP may have added value in the evaluation of acute stroke patients when MRI is not available or contraindicated.

Specifically, admission CTP CBF and MTT ischemic lesion volumes – relative thresholds of rCBF <0.48 and

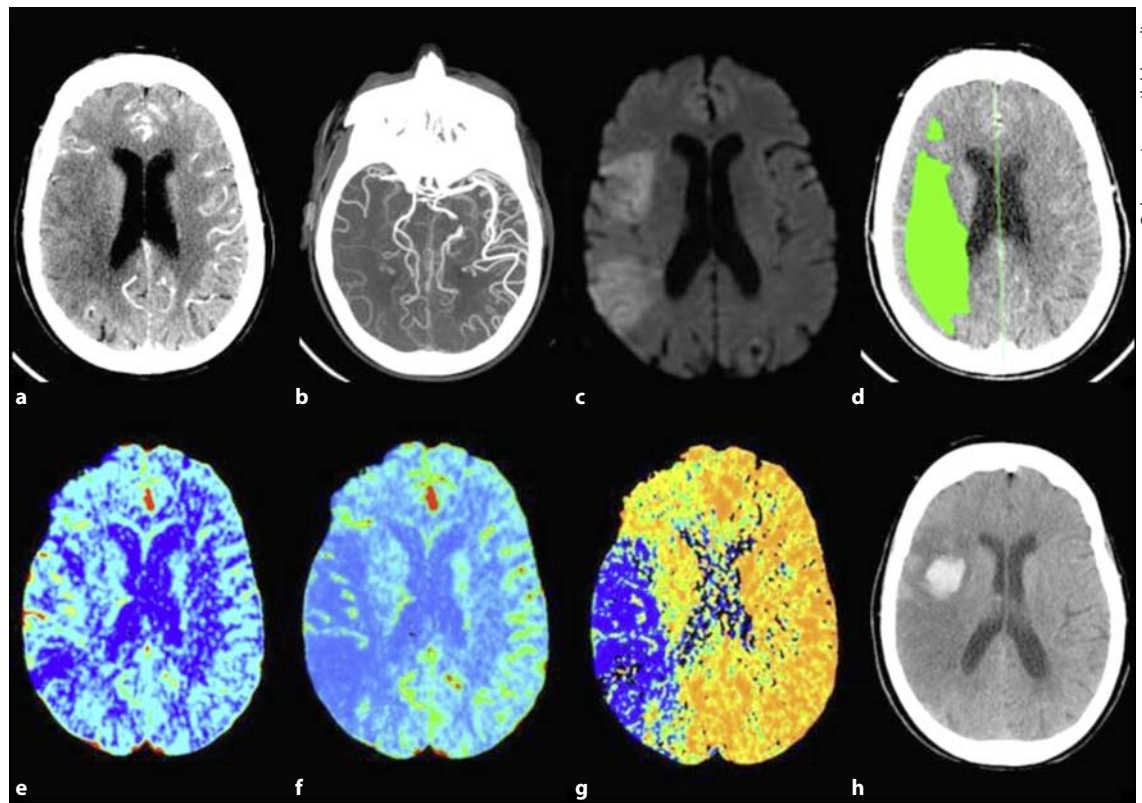


Fig. 1. An 81-year-old female presenting 6 h after the onset of left-sided weakness and right gaze preference; not a candidate for endovascular therapy: **a** 5-mm thick CTA source image shows poor tissue opacification of the right MCA territory, **b** CTA maximum intensity projection image shows proximal right MCA occlusion with poor collateralization, **c** DWI shows right MCA territory infarct core, **d** thresholded MTT lesion (rMTT >1.3), with 140 ml

total volume, **e** CBV map shows relative hyperemia (increased blood volume) of the cortical right MCA territory, **f** CBF map show decreased flow of the right MCA territory, corresponding to the DWI lesion, **g** MTT map shows corresponding area of prolonged transit time in the right MCA territory, mean rMTT = 4.3, and **h** 24 h follow-up NCCT shows HT at the anterior right MCA territory.

rMTT >1.3 – are strongly associated with HT. Indeed, the admission MTT lesion volumes showed a trend towards being slightly more accurate than the admission DWI lesion volumes in determining HT in our cohort, although this difference was not significant. These findings are in agreement with the concept that HT is a consequence of severe ischemic damage to vessel walls that leads to blood-brain barrier disruption and leakage [15]. CTP may better express the degree of ischemia associated with intense vessel wall damage than DWI, and hence have the potential to correlate more strongly with the development of HT. Our findings are supported by other studies that have reported reduced pretreatment CBF as a predictor of HT [7, 8].

Permeability surface area product maps are intended to reflect the degree of blood-brain barrier leakage, and although they have been shown to correlate with HT [3–

5], they are potentially fraught with substantial variability due to differences in acquisition and post-processing technique, including the size and molecular charge of the contrast agent used [16]. In our study, we hypothesize that the absence of correlation between rPS and HT can be attributed to our relatively short CTP acquisition protocol of 90 s. PS maps are typically calculated from CTP studies with acquisition times considerably over 120 s, to allow contrast sufficient time to leak into the interstitium.

Presence of a LVO was strongly associated with HT. As already noted, the degree of ischemia may play a role in small vessel friability, especially in the setting of maximal autoregulatory vasodilatation of the collateral bed. Because the number of patients in each subgroup was small, we did not reveal an association between HT and either recanalization or treatment with IV or IA thrombolysis. For those patients who received both IA thrombolysis

and mechanical thrombectomy, however, there was a strong association between HT and treatment, but importantly only for those treated after 4.5 h post-ictus (i.e. those with late recanalization). The correlation between recanalization and HT has been previously noted and is thought to reflect the fact that there needs to be some degree of reperfusion for bleeding to occur, although this point remains controversial [1, 17]. It may be that it is not recanalization per se, but rather *late* recanalization, which is a risk factor for HT [2, 15, 18, 19]. As discussed above, potential bleeding sources not only include the oligemic recanalized tissue bed, but also the flow augmented collateral vasculature [20]. Some authors have reported that good collateral circulation is associated with less severe blood-brain barrier disruption, and consequently a lower incidence of HT [21].

Admission NIHSS scores were significantly higher in the HT patients. In this regard, the NIHSS score may function as a marker of ‘clinical penumbra’, as the functional disabilities attributable to ischemia of eloquent cortex are believed to correlate with large volumes of severe flow derangement, as suggested by the CBF and MTT maps.

Our study has many limitations, arguably the most important of which was an insufficient number of patients with HT to stratify into symptomatic versus asymptomatic groups, or PH versus HI groups. Ours also has all the limitations and potential biases inherent with a retrospective study, especially with regard to the relationship between HT and treatment, as the risk of hemorrhage was almost certainly considered when excluding both the most and least ill patients from thrombolytic or endovascular therapies. Of note, our PS maps likely failed to show a correlation with HT due to an insufficiently

long acquisition time to accurately measure this parameter; many centers which perform CTP have similarly short acquisition times, especially given recent concerns regarding CTP radiation dose.

In conclusion, the associations that we have shown between HT of acute stroke and the volume/degree of admission ischemia support those of previous studies, can be accurately estimated using CT scanning only (both CTA and CTP) if DWI cannot be performed, and may be of modest clinical relevance – especially for their NPV in identifying patients (with low admission NIHSS scores, no LVO, and small admission ischemic lesions) at minimal risk for HT. Finally, although our retrospective pilot model suggests that late mechanical thrombolysis may be an independent risk factor for HT, this needs to be prospectively validated in a larger cohort of patients.

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Disclosure Statement

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