Clinical Radiology 74 (2019) 399–404

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Parenchymal hyperdensity on C-arm CT images after endovascular therapy for acute ischaemic stroke predicts a poor prognosis

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ARTICLE INFORMATION

Article history:
Received 8 February 2018
Accepted 15 January 2019

AIM: To investigate whether hyperdense areas (HDAs) observed after endovascular treatment on multisection computed tomography (CT) are related to outcome.

MATERIALS AND METHODS: Data on 82 patients with acute anterior circulation ischaemic stroke resulting from intracranial large artery occlusion were analysed retrospectively All patients underwent mechanical thrombectomy and/or emergency angioplasty, and partial or complete recanalisation was successfully achieved. C-arm CT was performed immediately after endovascular treatment for all patients. Clinical and radiological data were compared between patients with and those without HDA and between patients with good and those with poor outcomes.

RESULTS: Compared with non-HDA patients, HDA patients were more likely to present with severe neurological deficits (admission National Institutes of Health Stroke Scale [NIHSS] score: 18 versus 16, $p=0.037$) and had a higher number of stent retriever passes performed (2.9±1.3 versus 1.4±1, $p<0.001$), longer onset-to-presentation times (229±78 versus 171±90 minutes; $p=0.002$), longer onset-to-recanalisation times (418±94 versus 331±105 minutes; $p<0.001$), and longer puncture-to-recanalisation times (103±47 versus 69±42 minutes; $p=0.001$). Fewer HDA patients had a good prognosis (35.7% versus 70%, $p<0.001$). Multivariate analysis showed the presence of HDAs was an independent negative prognostic factor (OR=0.208; $p=0.002$).

CONCLUSION: HDAs on C-arm CT appear to be common in patients with acute ischaemic stroke who underwent successful endovascular treatment. HDA presence suggests a poor prognosis despite successful reperfusion.

Introduction

Acute anterior circulation ischaemic stroke resulting from intracranial large artery occlusion (LAO) has high morbidity and mortality. Thus, effective treatment of intracranial LAO is important. Although mechanical thrombectomy is a safe, effective treatment for acute intracranial LAO,[1–6] hyperdense areas (HDAs) are commonly seen on multisection computed tomography (CT) after endovascular therapy.[7–9] The presence of one or more HDAs may indicate blood–brain barrier (BBB) dysfunction caused by ischaemia–reperfusion injury.[10,11] The presence of a HDA after intra-arterial thrombolysis has been previously associated with symptomatic haemorrhage[7,8,12,13] and clinical deterioration.[12,14] Hyperdensity on

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https://doi.org/10.1016/j.crad.2019.01.009
0009-9260/

post-procedural flat-panel CT was associated with a tendency toward a higher risk of death and a lower risk of good clinical outcomes,[13] but these findings were non-significant. It remains uncertain whether the presence of HDAs and the prognosis for patients who undergo endovascular therapy are related. Moreover, most previous studies examined the significance of HDAs on multisection CT.[7,8,12,14,15]

Therefore, the aim of the present study was to investigate the incidence and clinical significance of parenchymal hyperdensity on C-arm flat-panel detector CT (C-arm CT; rotational angiography) immediately after endovascular reperfusion therapy for patients with acute anterior circulation ischaemic stroke with partial or complete recanalisation.

Materials and Methods

Patient selection

The study included 82 consecutive patients with acute anterior circulation ischaemic stroke who underwent endovascular treatment at Zhangzhou Hospital between January 2015 and June 2016. All patients underwent C-arm CT (Philips Healthcare, Best, The Netherlands/Artis zee ceiling, Siemens Healthcare, Erlangen, Germany) immediately after endovascular treatment. HDAs were defined as newly appearing HDAs detected on the initial CT examination after reperfusion therapy. The study was conducted with the approval of the local medical ethics committee. Patients were included if the acute anterior circulation ischaemic stroke was caused by intracranial LAO that was confirmed by digital subtraction angiography (DSA), if the time of symptom onset to the time of presentation was 6 hours or less, if successful recanalisation (thrombolysis in cerebral infarction [TICI] scale score $\geq$2b) was achieved via mechanical thrombectomy and/or emergency angioplasty, if the pre-stroke modified Rankin scale (mRS) score was 0–1, and the National Institutes of Health Stroke Scale (NIHSS) score was $\geq$6, or the Alberta Stroke Program Early CT Score (ASPECTS) was $\geq$6. Patients were given recombinant tissue plasminogen activator (rt-PA) as a bridging therapy if they met the criteria for intravenous thrombolysis. Patients with procedure-related vessel perforations and/or unsuccessful reperfusion were excluded from the study.

Imaging data and clinical assessment

Procedural and imaging data were extracted. Two neuroradiologists who were blinded to patient data separately studied all images carefully and individually. Haemorrhage transformation (HT) was categorised into H1, H2, PH1, and PH2 according to the European Cooperative Acute Stroke Study (ECASS-1) classification.[16] Haemorrhage was assessed using gradient echo T2*-weighted (GE-T2*) images. When GE-T2*-weighted images were not available, a follow-up CT examination was undertaken to make the diagnosis.

The review included confirming the occlusion site, collateral status, reperfusion extent via DSA images, and identification of HDAs on the C-arm CT images. The occlusion site was categorised as carotid T, carotid L, isolated intracranial intracerebral artery (ICA), proximal M1, and distal M117. Brain tissue reperfusion was assessed radiologically immediately after the procedure, with successful reperfusion defined as a TICI score $\geq$2b. The American Society of Interventional and Therapeutic Neuroradiology collateral grading (ACG) system was used to assess the extent and rate of retrograde collateral flow to the target downstream territory in the anterior circulation.[17]

Patient clinical records were reviewed. The data collected included key variables such as age, sex, vascular risk factors, bridging therapy, outcome in terms of the 90-day mRS score, or death within 30 days of the endovascular treatment. Clinical examinations included admission NIHSS to assess patient neurological function and mRS to assess clinical outcomes at 90 days, with a good outcome defined as a mRS score $\leq$2. Patient symptom onset-to-presentation time, onset-to-recanalisation time, and arterial puncture-to-recanalisation time were also noted. For patients who were missing the time of symptom onset, the last known normal-to-onset time was taken as the symptom-to-onset time.

Patient groups and statistical analyses

Patients were divided into the HDA and non-HDA groups based on the presence or absence of HDA, and good prognosis and poor prognosis groups based on clinical outcome. Study endpoints were compared between the HDA group and non-HDA group and between patients with poor outcomes and those with good outcomes. Differences in continuous variables were examined with Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Differences in categorical variables were examined with a χ^2 test. Stepwise logistic regression analysis was used to determine which variables influenced the outcomes and were related to prognoses. Variables with significant differences ($p \leq 0.05$) between the good prognosis group and poor prognosis group were included in analyses. Odds ratios (ORs) were computed to determine the associated relationships. A *p*-value of $\leq$0.05 was considered significant. Interobserver reliability was evaluated on the basis of the *kappa* coefficient, with a *kappa* coefficient of 0.4–0.69 considered moderate reliability, 0.70–0.89 considered substantial reliability, and 0.9–1 considered excellent reliability. All statistical analyses were performed with Statistical Package for the Social Sciences, Version 17.0 (SPSS, Chicago, IL, USA).

Results

The interobserver reliability of the two blinded neuroradiologists was excellent (kappa coefficient, 0.9). One or more HDAs were present on the C-arm CT images of 42 (51.2%) of the 82 patients included in this study. Both follow-up CT and magnetic resonance imaging (MRI) were performed in 58 patients; only follow-up CT was performed in 17 patients, while no follow-up brain imaging was

performed in seven patients because of poor clinical status. Patient clinical characteristics are shown divided into the non-HDA (see Fig 1a) and HDA groups (see Fig 1b–d) in Table 1. Compared with patients without a HDA, patients with a HDA on C-arm CT were more likely to have severe neurological deficits at presentation (admission NIHSS 18 versus 16; p=0.037), more likely to have carotid T occlusion (40.5% versus 17.5%; p=0.022), underwent numerous stent retriever passes (2.9±1.3 versus 1.4±1.0; p<0.001), had relatively longer onset-to-recanalisation and puncture-to-recanalisation times (418±94 versus 331±105 minutes, 103±47 versus 69±42 minutes; p<0.05) and were more likely to have a poor outcome (70% versus 35.7%; p=0.002). HT was more frequent in patients with HDA than in those without HDA (68.4% versus 39.5%, p=0.011). PH-type HT showed a trend toward a slightly higher frequency in patients with HDA (18.4% versus 2.6%, p=0.062). By contrast, H-type HT (50% versus 36.8%, p=0.247) and symptomatic intracerebral haemorrhage (sICH; 4.8% versus 0%, p=0.474) were similar between the groups.

Poor outcomes were reported in 39 (47.6%) of 82 patients in this study. The clinical characteristics of patients in the poor outcome group and those in the good outcome group are shown in Table 2. Compared with patients with a good outcome, patients with a poor outcome were more likely to have severe neurological deficits (admission NIHSS 18 versus 16; p=0.004), more likely to have carotid T occlusion (41% versus 18.6%; p=0.026), more likely to have undergone numerous passes of the stent retriever (2.6±1.6 versus 1.7±1.1; p=0.008), more likely to have poor collateral flow (p<0.002), more likely to have longer onset-to-recanalisation times and longer puncture-to-recanalisation times (392±108 versus 361±108 minutes; 99±54 versus 75±39 minutes; p<0.05), and more likely to have HDA on CT (69.2% versus 34%). HT was less frequent in patients with good prognosis than in those with poor prognosis (42.9% versus 74.1%, p=0.009). PH-type HT (36.8% versus 55.6%, p=0.113), H-type HT (6.1% versus 18.5%, p=0.195), and sICH (0% versus 7.4%, p=0.327) were similar between the groups. Based on the results of multivariate

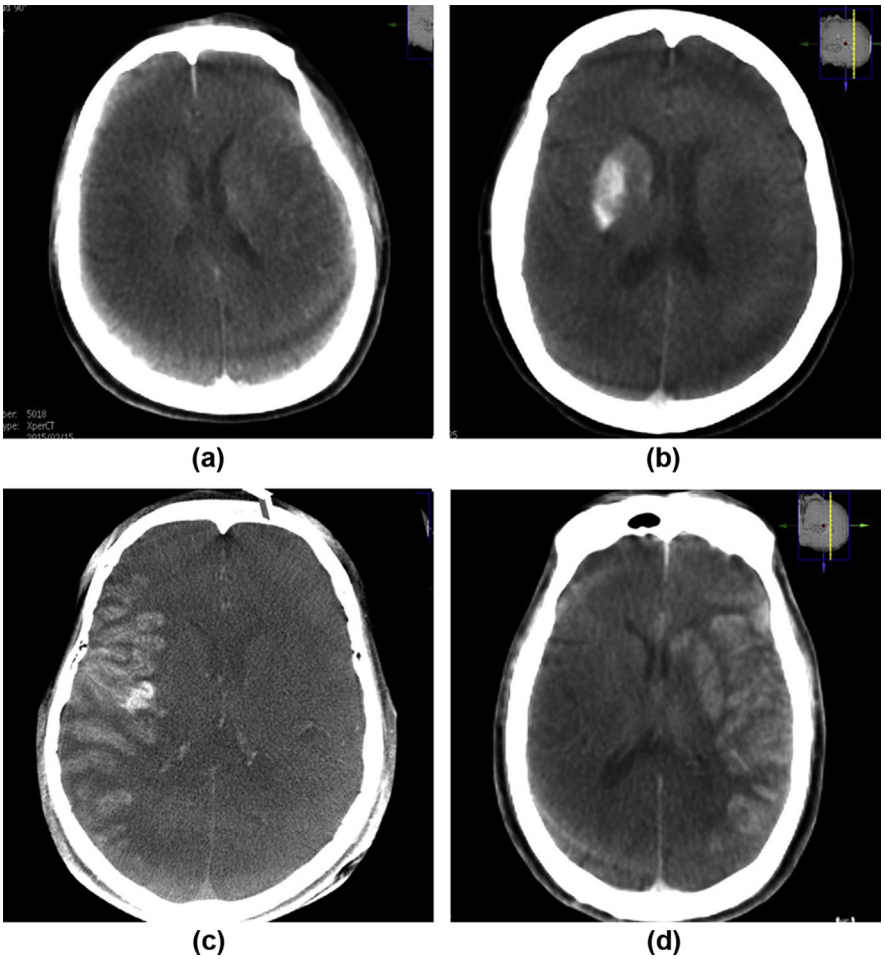

Figure 1 Illustrative case of no HDA or HDAs. (a) C-arm CT image post-endovascular therapy shows no HDA in a 75-year-old male patient with acute ischaemic stroke with admission NIHSS 18 and 90 day mRS 0. (b) C-arm CT image post-endovascular therapy shows right basilar ganglia HDA in a 70-year-old female patient with acute ischaemic stroke with admission NIHSS 13 and 90 day mRS 0. (c) C-arm CT image post-endovascular therapy shows right cortical HDA in a 66-year-old male patient with acute ischaemic stroke with admission NIHSS 23 and 90 day mRS 6. (d) C-arm CT image post-endovascular therapy shows left basilar ganglia and cortical HDAs in a 64-year-old male patient with acute ischaemic stroke with admission NIHSS 22 and 90 day mRS 6.

Table 1
Clinical characteristics of study patients grouped on the basis of HDA.

	HDA present (n=42)	No HDA present (n=40)	p-value
Sex (male, n)	22 (52.4%)	23 (57.5%)	0.6411
Age (mean, years, mean±SD)	66±11	62±10	0.135
Hypertension (n [%])	21 (50%)	19 (47.5%)	0.821
Diabetes mellitus (n [%])	5 (11.9%)	8 (20%)	0.316
Hyperlipidaemia (n [%])	6 (15%)	8 (20%)	0.556
Atrial fibrillation and/or rheumatic heart disease	22 (52.4%)	24 (60%)	0.487
Admission NIHSS score (median, IQR)	18 (15,22)	16 (14,20)	0.037
HAS positive on CT (n [%])	28 (66.7%)	24 (60%)	0.531
ASPECT (median, IQR)	10 (10,10)	10 (10,10)	0.296
No. of stent retriever passes (time, mean±SD)	2.9±1.3	1.4±1.0	<0.001
Intravenous thrombolysis (n [%])	14 (33.3%)	17 (42.5%)	0.392
Onset-to-presentation time (min, mean±SD)	229±78	171±90	0.002
Onset-to-recanalisation time (min, mean±SD)	418±94	331±105	<0.001
Puncture-to-recanalisation time (min, mean±SD)	103±47	69±42	0.001
Occlusion site (n [%])			
ICA			
Carotid T	17 (40.5%)	7 (17.5%)	0.022
Carotid L	3 (7.1%)	5 (12.5%)	0.656
Isolated intracranial ICA	0 (0%)	3 (7.5%)	0.112
M1			
M1-proximal	6 (14.3%)	10 (25%)	0.221
M1-distal	14 (33.3%)	13 (32.5%)	0.936
M2	2 (4.8%)	3 (7.5%)	0.895
ACG grade (n [%])			0.118
0	7 (16.7%)	2 (5%)	
1	15 (35.7%)	10 (25%)	
2	17 40.5%)	19 (47.5%)	
3	3 (7.1%)	8 (20%)	
4	0 (0%)	1 (2.5%)	
Haemorrhage transformation			
H or PH	26 (68.4%)	15 (39.5%)	0.011
H type	19 (50%)	14 (36.8%)	0.247
PH type	7 (18.4%)	1 (2.6%)	0.062
sICH	2 (4.8%)	0 (0%)	0.474
90-day mRS ≤2 (n [%])	15 (35.7%)	28 (70%)	0.002

HDA, hyperdense area; SD, standard deviation; IQR, interquartile range; NIHSS, National Institute Health Stroke Scale; HAS, hyperdense artery sign; CT, computed tomography; ICA, internal carotid artery; ICA-T, terminal ICA, M1 at its origin, plus A1 at its origin; ICA-L, terminal ICA plus M1 at its origin; M1, M1 segment of the middle cerebral artery; M2, M2 segment of the middle cerebral artery; ACG, American Society of Interventional and Therapeutic Neuroradiology collateral grading system; TICI, thrombolysis in cerebral infarction; mRS, modified Rankin Scale.

Table 2
Clinical characteristics of study patients grouped on the basis of outcome.

	Good prognosis (n=43)	Poor prognosis (n=39	p-value
Sex (male, n)	23 (53.5%)	22 (56.4%)	0.827
Age (mean, years, mean±SD)	63±12	66±10	0.259
Hypertension (n [%])	20 (46.5%)	20 (51.3%)	0.825
Diabetes mellitus (n [%])	5 (11.6%)	8 (20.5%·)	0.271
Hyperlipidemia (n [%])	7 (16.7%)	7 (18.4%)	0.556
Atrial fibrillation and/or rheumatic heart disease	26 (60.5%)	20 (51.3%)	0.403
Admission NIHSS score (median, IQR)	16 (14,18)	18 (16,22)	0.004
HAS positive on CT (n [%])	29 (67.4%)	23 (59%)	0.427
ASPECT (median, IQR)	10 (10–10)	10 (10–10)	0.807
No. of stent retriever passes (time, mean±SD)	1.7±1.1	2.6±1.6	0.008
Intravenous thrombolysis (n [%])	13 (30.2%)	18 (46.2%)	0.138
Onset-to-presentation time (min, mean±SD)	196±91	206±87	0.613
Onset-to-recanalisation time (min, mean±SD)	361±108	392±108	0.193
Puncture-to-recanalisation time (min, mean±SD)	75±39	99±54	0.024
Occlusion site (n [%])			
ICA			
Carotid T	8 (18.6%)	16 (41%)	0.026
Carotid L	5 (11.6%)	3 (7.7%)	0.820
Isolated intracranial ICA	0 (0%)	3 (7%)	0.275
M1			
M1-proximal	9 (20.9%)	7 (17.9%)	0.743
M1-distal	16 (37.2%)	11 (28.2%)	0.386
M2	3 (7%)	2 (5.1%)	1.000
ACG grade (n [%])			0.002
0	1 (2.3%)	8 (20.5%)	
1	9 (20.9%)	16 (41%)	
2	26 (60.5%)	10 (25.6%)	
3	6 (14%)	5 (12.8%)	
4	1 (2.3%)	0 (0%)	
Haemorrhage transformation			
H or PH type	21 (42.9%)	20 (74.1%)	0.009
H type	18 (36.7%)	15 (55.6%)	0.113
PH type	3 (6.1%)	5 (18.5%)	0.124
sICH	0 (0%)	2 (7.4%)	0.123
HDA presence (n [%])	15 (34.9%)	27 (69.2%)	0.002

SD, standard deviation; NIHSS, National Institute Health Stroke Scale; IQR, interquartile range; HAS, hyperdense artery sign; CT, computed tomography; ICA, internal carotid artery; M1, M1 segment of the middle cerebral artery; M2, M2 segment of the middle cerebral artery; ACG, American Society of Interventional and Therapeutic Neuroradiology collateral grading system; TICI, thrombolysis in cerebral infarction; HDA, hyperdense area.

logistic regression, HDA on C-arm CT (OR=0.208; 95% CI: 0.078–0.554 p=0.002) was independently associated with poor outcomes.

Discussion

The present study is clinically important because the presence of a HDA on a C-arm CT image was predictive of poor outcome (OR=0.208, p=0.002). A HDA on a CT image indicates BBB dysfunction caused by ischaemia–reperfusion injury[9–11] and suggests that the severely ischaemic parenchyma had already experienced infarction by the time of the intra-arterial contrast medium injection.[18] In studies on patients treated with intra-arterial thrombolysis with and without recanalisation success, the presence of a HDA was related to sICH[7,12,13] and clinical deterioration.[12,14] In the present study, haemorrhage was more frequent in the HDA group than in the non-HDA group (68.4% versus 39.5%, p=0.011), but the sICH rate was not significant different between the two groups (5.3% versus 0%, p=0.474), the reason of similar sICH rate between groups may be due to low overall sICH rate, and the low sICH rate may be due to the study population. The reasons that the presence of a HDA was related to poor prognosis in studies of patients treated with intra-arterial thrombolysis are listed as follows. First, intra-arterial thrombolysis is less

effective than mechanical thrombectomy in the recanalisation of intracranial large vessel occlusion (LVO) ischaemic stroke. When contrast medium is injected into the occluded vessel, it does not enter the circulation and manifests as a HDA on CT imaging. Second, failed recanalisation is also related to poor outcome. HDAs were also common after mechanical thrombectomy in a quarter of patients with acute ischaemic stroke and were associated with an increased risk of sICH and a poor outcome;[9,13] however, the poor clinical outcome may be related to unsuccessful reperfusion haemorrhage.[9,13] It remains unknown whether there is any relationship between the presence of a HDA and the prognosis of acute ischaemic stroke (AIS) after successful recanalisation. To the authors' knowledge, there is only one published study on the relationship between a HDA and the prognoses of patients with ischaemic stroke for whom partial or complete recanalisation was achieved by mechanical thrombectomy with retrievable stents.[15] In the present study, the presence of a HDA was not related to an increased risk of sICH or a negative outcome.[15] The differences between these studies might be due to the inclusion of seven patients with acute posterior circulation infarction, with six of these seven patients having acute basilar artery occlusion.[15] Acute basilar artery occlusion often results in severe neurological deficits and a poor outcome.[19,20] The previous study also had a smaller sample size (48 patients versus 82 patients) and no assessment of 90-day outcomes.

The presence of a HDA is common after intra-arterial reperfusion in stroke patients. HDAs appear in 31.2–60% of cases;[15] however, the rate was higher (51.2%) in the present patient population. The higher rate in the present study could be because C-arm CT was performed with an angiography machine immediately after the endovascular procedure; thus, whether the HDA was due to contrast enhancement that would eventually be resolved over time is unknown.[12] Cases with acute posterior circulation infarction were not included in the present study because a HDA on CT images is less likely in these cases than in cases of acute anterior circulation ischaemic stroke.[15,21] Patients in whom recanalisation was not achieved were excluded from the present study. Potentially, reperfusion injury occurs more easily in patients with partial or complete recanalisation than in patients with failed recanalisation, thus explaining the presence of a HDA. Finally, microcatheter contrast medium injection may increase the HDA rate, possibly due to contrast toxicity or pressure transmission by injection.[22]

In the present study, onset-to-recanalisation times were longer in the HDA group than in the non-HDA group. In studies of intra-arterial therapy, relatively long symptom onset-to-recanalisation times were associated with worse functional outcomes.[23,24] With relatively prolonged ischaemia times, damage to brain tissue is greater; thus, the presence of a HDA is more likely. This hypothesis was confirmed by the present study.

The possible limitations of the present study include the small sample size. Additionally, this study was performed in a single centre and was retrospective in nature. Moreover, C-arm CT was performed with an angiography machine; thus, the image quality was not as high as that provided by multisection CT. The spatial resolution of C-arm CT is similar to that of multisection CT;[25] however, in this study, imaging was performed under general anaesthesia, which allowed us to capture images that were clear enough for identification of parenchymal hyperdensity. Furthermore, consistency between the two radiology assessment reports was good. HDA was associated with HT in patients with AIS who received endovascular therapy.[13,26] Regardless of whether a HDA identified on a C-arm CT image was achieved with contrast enhancement, contrast medium extravasation or reperfusion haemorrhage, repeated CT was performed to differentiate these lesions;[12] however, the focus of the present study was to determine the correlation between the presence of a HDA and clinical prognosis and not on the correlation between HDA and sICH.

A positive correlation was also found between the presence of a HDA and clinical outcome, suggesting that the presence of HDAs can be considered an independent prognostic indicator; however, it cannot be claimed that the results can be generalised across the patient population with acute anterior circulation ischaemic stroke who undergo endovascular reperfusion treatment. Thus, a multicentre, clinical registry is needed to confirm the present findings.

In conclusion, the presence of one or more HDAs on C-arm CT images is common and was observed in 51.2% of patients with ischaemic stroke who underwent endovascular treatment. Moreover, the presence of HDAs was an independent predictor of a poor prognosis despite successful reperfusion therapy.

Conflict of interest

All authors disclose that there were no potential conflicts of interests.

Acknowledgements

This research benefitted from a grant from the Startup Fund for scientific research, Fujian Medical University (grant no.: 2016QH088).

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