CT and MRI Early Vessel Signs Reflect Clot Composition in Acute Stroke

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Background and Purpose—The purpose of this study was to provide the first correlative study of the hyperdense middle cerebral artery sign (HMCAS) and gradient-echo MRI blooming artifact (BA) with pathology of retrieved thrombi in acute ischemic stroke.

Methods—Noncontrast CT and gradient-echo MRI studies before mechanical thrombectomy in 50 consecutive cases of acute middle cerebral artery ischemic stroke were reviewed blinded to clinical and pathology data. Occlusions retrieved by thrombectomy underwent histopathologic analysis, including automated quantitative and qualitative rating of proportion composed of red blood cells (RBCs), white blood cells, and fibrin on microscopy of sectioned thrombi.

Results—Among 50 patients, mean age was 66 years and 48% were female. Mean (SD) proportion was 61% (±21) fibrin, 34% (±21) RBCs, and 4% (±2) white blood cells. Of retrieved clots, 22 (44%) were fibrin-dominant, 13 (26%) RBC-dominant, and 15 (30%) mixed. HMCAS was identified in 10 of 20 middle cerebral artery stroke cases with CT with mean Hounsfield Unit density of 61 (±8 SD). BA occurred in 17 of 32 with gradient-echo MRI. HMCAS was more commonly seen with RBC-dominant and mixed than fibrin-dominant clots (100% versus 67% versus 20%, P=0.016). Mean percent RBC composition was higher in clots associated with HMCAS (47% versus 22%, P=0.016). BA was more common in RBC-dominant and mixed clots compared with fibrin-dominant clots (100% versus 63% versus 25%, P=0.002). Mean percent RBC was greater with BA (42% versus 23%, P=0.011).

Conclusions—CT HMCAS and gradient-echo MRI BA reflect pathology of occlusive thrombus. RBC content determines appearance of HMCAS and BA, whereas absence of HMCAS or BA may indicate fibrin-predominant occlusive thrombi. (Stroke. 2011;42:1237-1243.)

Key Words: cerebral ischemia ■ CT ■ MRI ■ stroke ■ thrombus

Acute ischemic stroke may result from a diverse range of underlying disorders, often culminating in obstruction of an artery. The pathophysiological mechanisms that lead to obstruction of a proximal intracranial artery and resultant downstream ischemia are rarely discerned in the acute phase; however, the role of thrombosis as a cause of obstruction is often viewed as confirmatory evidence of a potentially extensive or destructive event that warrants aggressive treatment.5–7 Before most endovascular revascularization procedures for stroke, noninvasive imaging in the form of CT or MRI may similarly reveal features suggestive of a proximal occlusion, yet characterizing such an occlusion typically relies on other approaches. A unique aspect of thrombectomy or clot retrieval from an intracranial artery in the setting of acute ischemic stroke is the opportunity to directly investigate clot composition or the nature of thrombosis or any material that has blocked flow to critically dependent downstream regions of the brain.8–10

Prior studies have analyzed the presence of early vessel signs on CT and MRI suggestive of thrombosis, including the hyperdense middle cerebral artery sign (HMCAS) on CT.
and blooming artifact (BA) on gradient-echo or other susceptibility-weighted MRI sequences. Many of these studies have correlated these findings as a poor prognostic factor in clinical outcome and diminished likelihood of revascularization. Most of the studies, however, have not shown angiographic correlation or actual pathological correlation with the features of the underlying occlusive lesion.

We previously described the initial series of pathological changes in thrombi retrieved from the proximal intracranial arterial circulation in acute stroke and now provide the first neuroimaging correlative study that may be used to predict clot composition. This report describes the unique opportunity to investigate plaque or thrombus constituents that underlie the presence and characteristics of early vessel signs, including HMCAS and BA.

Methods

During the period from May 2001 through March 2007, 85 consecutive cases of acute ischemic stroke were evaluated with CT or MRI before endovascular thrombectomy at our center. Noninvasive imaging with CT or MRI was acquired per standard algorithm for acute stroke cases with noncontrast CT or a MRI protocol including gradient-recalled echo (GRE) sequences as previously described. GRE images were acquired with slice thickness of 5 mm and no gap. TR 800 ms, TE 15 ms, 30° flip angle, 240 field of view, and 256×144 matrix size. Selection criteria for this study included acute middle cerebral arterial (MCA) occlusions with available noncontrast CT or GRE MRI data acquired immediately before endovascular thrombectomy and available thrombus pathology resulting from any retrieved specimen. CT studies acquired at outside institutions before transfer to our center were not included due to incomplete availability, poor quality, and inability to measure Hounsfield Unit (HU) density on non-DICOM (Digital-Imaging-and-Communications-in-Medicine) format images. As a result, cases without CT or MRI acquired at our center and thrombectomies that did not yield a pathological specimen were excluded from our analyses.

Clinical, radiographic, and detailed angiographic data were prospectively acquired as part of ongoing work at our center. These data are routinely acquired and archived in a centralized database. Two board-certified vascular neurologists with accreditation in neuroimaging retrospectively reviewed the noncontrast CT or GRE sequences acquired immediately before endovascular thrombectomy blinded to clinical and angiographic variables as well as the results of pathological study. The presence or absence of HMCAS was scored on consensus reading by the 2 neuroimaging experts based on visual inspection. Conspicuity or increased density of the MCA in an asymmetrical fashion was used to categorize the HMCAS, although specific measures of HU density were not used in this determination. After HMCAS rating, HU density measures were obtained of bilateral segments of the MCA. Axial GRE MRI scans were also reviewed in a consensus fashion to determine the presence or absence of BA based on visual inspection. BA was defined as an area of hypointensity or signal loss in the proximal MCA, often distorting the margins of the vessel. If CT or MRI artifacts obscured delineation of HMCAS or BA, then the associated imaging data set of that case was excluded from our analyses.

Digital subtraction angiography was used to confirm the diagnosis of MCA occlusion before thrombectomy. MCA occlusions with extension of clot into the ipsilateral internal carotid or anterior cerebral arteries were included in our analyses. Angiographic techniques and the thrombectomy procedure have been described elsewhere. Thrombectomy cases included in our analyses were conducted as part of the Mechanical Embolus Removal in Cerebral Ischemia (MERCII) and Multi MERCII trials and as part of routine clinical care following the US Food and Drug Administration clearance of the Merci Retriever System. The MERCII and Multi MERCI trials evaluated the safety and efficacy of endovascular thrombectomy with the Merci Retrieval System (Concentric Medical, Inc, Mountain View, CA) in the treatment of proximal intracranial arterial occlusions performed within 8 hours of stroke symptom onset. Mechanical thrombectomy was performed with the Merci Retriever System and subsequent generation devices in all cases of this report. Serial angiography from the initial diagnostic runs throughout the procedure until completion of thrombectomy was reviewed to assess features of arterial occlusion and corresponding collateral flow. The presence of occlusion and extent of antegrade perfusion in the downstream territory was measured with the Thrombolysis in Cerebral Infarction scale, and collateral perfusion was graded with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral flow grading system. Clot retrieval occurred sequentially throughout the thrombectomy procedure with variable amounts of thrombus extracted at each stage. After each pass of the device that appeared to reduce clot burden, the catheter was withdrawn and the distal aspect of the helical coil inspected for the presence of thrombus or any particulate material. If no discrete thrombus was identified, the aspirated material was then gently flushed with saline to uncover any smaller fragments that may be obscured. Photographs documented the relationship of thrombotic material with respect to the distal thrombectomy catheter and architecture of the retained clot. Thrombi were then placed on gauze or surgical dressing and photographed from multiple perspectives. Gross measurements of linear thrombus dimensions were taken using a guide. Thrombus material was immediately fixed in 10% phosphate-buffered formalin. Formalin-fixed specimens were embedded in paraffin, cut at 8-μm thickness, and stained with hematoxylin and eosin. Histological sections were photographed with an Olympus BX41 microscope with an attached MicroFire digital camera (Model S99809). Histological examination was performed without knowledge of the clinical findings and was based on feature-detection analysis of functionally distinct processes, including platelet:fibrin accumulations (thrombosis in flowing blood), linear neutrophil and monocyte deposits (surface adherence interactions), and erythrocyte-rich accumulations (whole-blood coagulation). Clot composition was also categorized as red blood cell (RBC)-dominant, fibrin-dominant, or mixed by light microscopy. Further histopathologic analysis included semiautomated quantitative and qualitative measurements for the proportion of RBCs, white blood cells (WBCs), and fibrin composition from digitized whole slide digital images. Hematoxylin and eosin-stained slides were scanned in at 400× magnification using an Aperio Scanscope XT digital scanner (Aperio, Vista, CA). The resulting individual digital image files were large, ranging from 200 MB to 5 GB, and required processing to smaller file sizes so that image analysis software could be used to quantify proportions of components. This processing was done using Adobe Photoshop CS3 (Adobe Systems, San Jose, CA) to assign pseudocolors to fibrin, RBCs, and nucleated WBCs. Pseudo-colorization was conducted with a look-up table and automated thresholds to assign specific colors to imaging features of each clot component for calculation of specific content. Image J software (National Institutes of Health, Bethesda, MD) was then used to quantify the percentage of RBCs, WBCs, and fibrin by area. These pathology studies were repeated for each fragment of clot retrieved from the entire procedure. When multiple clot fragments were retrieved for analysis, the mean values across fragments were used for clot constituents (ie, RBC, WBC, fibrin). Descriptive statistical analyses were performed on all clinical, radiographic, angiographic, and pathological data. The presence or absence of early vessel signs, including the HMCAS and BA, and the qualitative descriptions of clot pathology were treated as categorical variables in the statistical analyses. Percentages of each specific clot component were treated as continuous variables. The relationship between early vessel signs of thrombosis on CT and MRI and clot composition was probed using both χ² and analysis of variance statistics with significance noted below the P<0.05 level. Statistical analyses were performed with the use of SPSS software (Version 16.0; SPSS, Inc, Chicago, IL).
Results

Among 50 patients who fulfilled entry criteria, the mean age was 66 years, 48% were female, and 82% were white. Clinical characteristics are summarized in the Table. Angiography demonstrated occlusions of the internal carotid artery in 52% and MCA in 48%. The Merci Retriever System was used either alone (78%) or in combination with intravenous (14%) or other treatments (intra-arterial tissue plasminogen activator [2%], angioplasty, stenting). The final median Thrombolysis in Cerebral Infarction score for patients included in this analysis was 2 (2% Thrombolysis in Cerebral Infarction 0, 22% 1, 40% 2, 36% 3).

A total of 20 CT scans was included for analysis of which 10 demonstrated HMCAS (Figure 1). The HMCAS revealed a mean HU of 61 (±21) across all cases. There were 32 MRI scans reviewed with 17 (53%) demonstrating BA (Figure 2). The 2 patients who had both CT and MRI at our institution before angiography were found to have both HMCAS and BA, respectively. Acquisition of CT before MRI was used for screening purposes in cases in which MRI contraindications could not be immediately assessed. In these cases, the vessel signs were situated in the exact same vascular anatomic location.

Extracted thrombi were occasionally retrieved as a single mass, although most were retrieved in multiple fragments. These multiple retrieval specimens were obtained at various stages of each procedure and the time to clot retrieval varied extensively. There was no correlation between the amount of thrombus retrieved and recanalization or reperfusion status. The orientation of the occlusive thrombus within the vessel could not be unequivocally established due to the nature of the clot retrieval procedure and catheter manipulation. In some cases, however, intact clots on gross examination and histopathology could be readily oriented in space.

Table. Clinical Characteristics of Study Population

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Population Variable (n=50)</th>
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<tbody>
<tr>
<td>Age, years, mean±SD</td>
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<tr>
<td>Sex</td>
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<td>Female</td>
<td>48%</td>
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<td>66%</td>
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<tr>
<td>Coronary artery disease</td>
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<tr>
<td>History of smoking</td>
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<tr>
<td>Baseline NIHSS score</td>
<td>Median 19 (IQR, 15–22)</td>
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<tr>
<td>Intra-venous tPA</td>
<td>14%</td>
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<td>Intra-arterial tPA</td>
<td>2%</td>
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<tr>
<td>Day 90 mRS</td>
<td>Median 3 (IQR, 1–5)</td>
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</tbody>
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NIHSS indicates National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; mRS, modified Rankin Scale; IQR, interquartile range.

Figure 1. Noncontrast CT scan of the head reveals a right hyperdense middle cerebral artery sign (HMCAS, arrow) associated with acute left hemiparesis.

Across all retrieved thrombi, mean (SD) proportion of components was 61% (±21) fibrin, 34% (±21) RBCs, and 4% (±2) WBCs. Of the retrieved clots, 22 (44%) were classified as fibrin-dominant, 13 (26%) RBC-dominant, and

Figure 2. Gradient-echo MRI demonstrates blooming artifact (BA, arrow) in the left middle cerebral artery.
15 (30%) mixed (Figure 3). A broad distribution of pathology was noted across all cases as depicted in Figure 4. WBC composition was consistently marginal across all cases. In cases with multiple fragments obtained, there was no change in composition with successive clots retrieved. Over the 6-year period of this study, from the first retrieval case ever performed with the Merci Retriever System to a period >2 years after introduction to clinical practice, there was no change in pathological findings that may have implicated potential variation in technical aspects of the endovascular procedure. We have recently published an autopsy study describing patients with poor outcomes after this procedure.27

No correlation was noted between the type of baseline imaging modality (ie, CT or MRI) and gross or histopathologic findings. There were also no differences between the timeline between baseline diagnostic imaging acquisition to clot retrieval (mean±SD, 86±32 minutes) and the resultant thrombus constituents or composition.

HMCAS on CT was more commonly seen with RBC-dominant and mixed than fibrin-dominant clot pathology (100% versus 67% versus 20%, \( P=0.016 \)). Mean percent RBC composition was higher in clots with HMCAS (47% versus 22%, \( P=0.016 \)), although HU density was not correlated with clot composition. BA was also more common in

**Figure 3.** Classification of retrieved thrombi as red blood cell-dominant (A) and fibrin-dominant (B).

**Figure 4.** Clot composition based on histopathology, including red blood cell (RBC), white blood cell (WBC), and fibrin percentage. Retrieved clots are numbered from 1 to 50 in order of historical entry into our study.
RBC-dominant and mixed clots compared with fibrin-dominant clots (100% versus 63% versus 25%, \( P = 0.002 \)). The consistently low percentage of WBC content across all cases was not a determinant of HMCAS or BA. Mean percent RBC was greater with BA (42% versus 23%, \( P = 0.011 \)). The presence of either early vessel sign (ie, HMCAS or BA) did not correlate with clinical or radiographic factors. Multivariate regression analyses did not identify predictors of HMCAS or BA other than RBC content (Figure 5). In the 2 cases with both CT and MRI, the complete concordance of HMCAS and BA was associated with RBC-dominant clots with elevated RBC composition on quantitative analyses. Absence of HMCAS or BA was more common with small, fibrin-rich specimens.

Our analyses revealed no correlation between imaging findings (HMCAS or BA) or thrombus histopathology with baseline variables, including stroke severity, or subsequent outcomes. Thrombus histopathology was unrelated to final determination of stroke etiology or mechanism (eg, cardioembolism or atherosclerosis) and was not predictive for successful extraction. Similarly, there were no differences in imaging or histopathologic features with respect to the timing of clot extraction.

**Discussion**

Noninvasive imaging modalities such as CT and MRI have delineated vessel abnormalities attributed to occlusive thrombus in acute ischemic stroke for >20 years without pathological corroboration of the nature of the underlying thrombus.\(^5,15\) Our findings provide the initial radiological–pathological correlation that early vessel signs (including the HMCAS on CT and BA on GRE MRI) reflect underlying clot pathology. The HMCAS and BA were commonly encountered in the triage of patients with acute stroke, resulting in much speculation to date about the type or composition of intravascular thrombus and related expected outcome with various revascularization strategies. Definitive statements about clot composition such as our observations must rely on comprehensive evaluation of clinical variables, noninvasive imaging, angiography, and gross examination with histopathology.\(^8\) Furthermore, detailed pathological examination of the thrombus is possible only with mechanical thrombectomy, unlike the situation with intravenous or intra-arterial thrombolysis, aspiration, or angioplasty and stenting. Our findings reveal several novel observations about imaging of occlusive thrombus in acute ischemic stroke.

Acute MCA occlusion due to thrombus may reveal early vessel findings in only a fraction of cases and perhaps more importantly, the absence of such subtle imaging abnormalities does not rule out thrombotic occlusion. The HMCAS or BA was noted in approximately half of all our cases with successful thrombectomy. Initial descriptions of the HMCAS cited a much higher incidence, yet most successive studies reported detection rates of approximately 50%, consistent with our findings.\(^5-7,11\) HMCAS detection is undoubtedly influenced by variable methodology, including blinding, quantitative measures of HU, and other baseline factors.\(^20\) Our results are also consistent with previously reported detection rates for BA, although stroke mechanism differentiated by cardioembolism or large artery atherosclerosis may affect conspicuity of BA.\(^12-14\) Relatively greater thrombus burden associated with cardioembolism may increase BA conspicuity.\(^13\) Absence of BA in 47% of our cases was generally associated with fibrin-rich thrombi, a potential target for pharmacological fibrinolysis. Only limited data were available to correlate HMCAS with BA because primary use of MRI and rapid triage to thrombectomy often obviate the need for CT.\(^14\) HMCAS has been reported in as low as 15% of cases evaluated with routine use of CT alone before thrombolysis depending on case series and therapeutic benefit may be achieved irrespective of this finding.\(^28\) Early vessel findings in other territories such as the posterior cerebral artery still await pathological correlation.\(^10,13,14,29,30\)

The HMCAS and BA reflect RBC content, a thrombus constituent, yet not the principal target of fibrinolysis. Classification of thrombi as RBC-dominant was noted in every case in which either HMCAS or BA was identified. These early vessel findings were increasingly infrequent with fibrin-rich thrombi. The percentage of RBC was also closely linked with these imaging findings. Measurement of HU within the
HMCAS yielded values consistent with recently lodged emboli, although it remains difficult to ascribe these density changes to a particular clot constituent. Because we did not discern any correlation between HU density and RBC quantitive measures, one may conclude that the mere presence or absence of HMCAS using simple visual inspection is likely sufficient in distinguishing the presence of a RBC-rich clot or "red thrombus." The susceptibility effect of BA on GRE MRI has been ascribed to local ferromagnetic field distortion associated with RBC components as well. The HMCAS and BA are therefore indirect markers of occlusive thrombi, reflecting trapped RBC more closely than the fibrin mesh targeted by most arterial revascularization procedures developed to date for stroke. It remains possible, however, that mechanical thrombectomy specimens ensnare additional constituents and adjacent red thrombi during the endovascular procedure itself.

The potential to distinguish "red thrombi" from "white thrombi" has been a longstanding and elusive expectation of diagnostic imaging modalities. Our previous findings on the initial analyses of clots causing ischemic stroke in humans questioned whether such traditional distinctions of "red versus white clots" are truly applicable, because much heterogeneity was observed among pathological specimens. A subsequent report also described marked heterogeneity in thrombi. Prediction of clot composition from CT or MRI might therefore be difficult, especially if one assumes that the HMCAS or BA reflects the original embolus rather than secondary components promoted by stasis proximal and distal to the occlusion site. Our findings on the HMCAS and BA that accentuate RBC content may also suggest that stasis and fresh thrombus are more common in such cases. Although it remains challenging to reconstruct the spatial orientation of the retrieved fragment with respect to the HMCAS or BA, limited reperfusion (Thrombolysis in Cerebral Infarction 0 or 1) in 24% of cases raises the possibility that RBC content was augmented by stasis. This hypothesis underscores the role of flow derangements in cerebral ischemia, up against the clot face, and in distal segments filled through collateral perfusion. Stasis has previously been invoked in determining thrombus composition at the embolic source yet not at the recipient site. Angiography may be indispensable in distinguishing such factors. Interestingly, we found no correlation between amount of clot retrieved and subsequent reperfusion, suggesting that other aspects of ischemic pathophysiology beyond thrombosis will be essential in future therapeutic strategies for stroke.

The prognostic significance of the HMCAS and BA in the setting of arterial revascularization may be inherently flawed without consideration of the interaction between flow and thrombi in cerebral arteries. Many studies have attempted to define prognostic aspects of early vessel findings or their predictive role in revascularization, yet such outcomes are likely multifactorial, including considerations of how thrombus composition is not just the cause, but also the result of impaired flow. Despite an unequivocal link between the HMCAS and BA with RBC-dominant pathology, undue emphasis should not persuade clinicians to establish stroke etiology or plan revascularization strategies based on this finding alone. Our finding that imaging features of HMCAS or BA cannot alone predict successful clot extraction warrants investigation of other potential influential factors, because recanalization may be affected by many features in a given case. Further correlative studies should evaluate the impact of these imaging signs with various endovascular approaches, incorporating angiographic features to characterize flow.

The unique opportunity that permitted this comprehensive analysis of early vessel findings with thrombus pathological findings also imposed several limitations. Availability and quality of baseline imaging immediately before angiography resulted in further selection of a cohort already limited to candidates deemed suitable for mechanical thrombectomy. Our findings are limited by significant bias associated with excluding many cases, because the results relate only to clots in the proximal MCA that could be retrieved. Resilient occlusions and those with complete disintegration could not be studied and were thereby excluded from our analyses. It remains possible that some thrombi reflected changes of intravenous tissue plasminogen activator before angiography or even changes associated with standard procedural heparin administration. As noted, the orientation of clot fragments is speculative and other retained fragments may have differed in composition. Finally, our classification of clot types is also imperfect because most specimens were heterogeneous in nature with considerable variation across cases.

Conclusions

Our novel observations provide the first correlative study of early vessel signs in acute ischemic stroke with underlying clot composition. The HMCAS and BA are not ubiquitous in thrombotic MCA occlusion and failure to discern these subtle findings should not deter arterial revascularization strategies. Further studies are underway to delineate more detailed aspects of clot composition, including molecular features and architecture with respect to flow.

Sources of Funding

This work has been funded by National Institutes of Health–National Institute of Neurological Disorders and Stroke Awards K23 NS054084 (D.S.L.) and P50 NS044378.

Disclosures

All authors were employed by the University of California (UC), which holds a patent on the retriever devices for stroke, at the time of this work. The UC Regents received payments based on the clinical trial contracts for the number of subjects enrolled in the MR and Recanalization of Stroke Clots Using Embolectomy MR (MR RESCUE) multicenter clinical trial and the Concentric Merci Registry. D.S.L. is a scientific consultant regarding trial design and conduct to Concentric Medical (modest) and CoAxia (modest). C.S.K. is Principal Investigator of the National Institutes of Health-funded MR RESCUE trial (P50 NS044378). S.T. is a scientific advisor of Reverse Medical (modest), which makes a device to treat acute stroke. G.R.D. is a medical advisor and stockholder of Concentric Medical. H.V.V. is supported in part by the Daljit S. and Elaine Sarkaria Chair in Diagnostic Medicine. J.L.S. is a scientific consultant to AGA Medical (modest). Boehringer Ingelheim (modest), Bristol Myers Squibb (modest), CoAxia (modest), Concentric Medical (modest), Ev3 (modest), FibroGen (modest), ImaRx (modest), Sanofi Aventis (modest), and Talecris (modest). He receives support for editorial work in MedReviews (modest).
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References


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Stroke. 2011;42:1237-1243; originally published online March 10, 2011;
doi: 10.1161/STROKEAHA.110.605576
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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CT와 MRI의 조기 혈관 징후

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(Stroke. 2011;42:1237-1243.)

Key Words: cerebral ischemia ■ CT ■ MRI ■ stroke ■ thrombus

배경과 목적: 본 연구는 CT의 고밀도 중대뇌동맥 징후(hyperdense middle cerebral artery sign, HMCAS)와 가을기에로
(gradient–echo) MRI의 색보강 인공영양(blooming artifact, BA)의 급성 혈혈뇌졸중에서 얻어진 혈전의 벌리학적 특성과의
연관성을 보기 위한 첫 삼관 관계 연구이다.

방법: 급성 중대뇌동맥 혈혈뇌졸중 증례 50개의, 기계적 혈전제거술 시행 이전에 완만한 비조영증강(noncontrast) CT와 기울
기로로 MRI 영상을 입상 자료 및 벌리학적 자료를 모르는 상태로 분석하였다. 혈전제거술을 시행한 혈색 부위의 혈전에 대하여
조직 벌리학적 분석을 시행하였는데, 절개한 혈전을 현미경으로 관찰하여 적혈구(red blood cell, RBC), 백혈구(white blood
cell, WBC), 섬유소(fibrin)의 구성 비율을 자동화된 방법으로 정성, 정량적 분석하였다.

결과: 환자 50명의 평균 연령은 66세였고, 48%가 여성이었다. 혈전의 평균(표준편차) 구성은 섬유소 61% (±21), RBC 34% (±
21), WBC 4% (±2)였다. 저편된 혈전 중에서, 22개(44%)의 주성분은 섬유소였고 13개(26%)는 RBC였으며, 15개(30%)는 혼합
형이었다. HMCAS는 CT를 활용한 20개의 중대뇌동맥 혈혈뇌졸중 환자 중 10명에서 관찰되었으며, 평균 Hounsfield Unit 밀도는
61 (±8 SD)이었다. BA는 기울기에로 MRI 검사 32건 중 17건에서 관찰되었다. HMCAS는 섬유소가 주된 성분인 혈전보다
RBC가 주성분이거나 혼합형인 경우에 더 훨씬 관찰되었다(100% vs. 67% vs. 20%, P=0.016). RBC의 평균 비율은 HMCAS와
연관된 혈전에서 더 높았(47% vs. 22%, P=0.016). BA는 섬유소가 주성분인 혈전과 비교하였을 때 RBC가 주성분이거나 혼
합형인 경우에 더 훨씬 관찰되었다(100% vs. 63% vs. 25%, P=0.002). BA와 연관된 혈전에서 평균 RBC 비율이 더 컸다(42%
vs. 23%, P=0.011).

결론: CT의 HMCAS와 가을기로로 MRI에서의 BA는 혈전 범색을 유도한 혈전의 벌리학적 특성을 반영한다. RBC 성분이
HMCAS와 BA의 발생을 결정하는 것으로 보이며, HMCAS나 BA가 관찰되지 않는 경우의 야마도 섬유소가 주된 성분인 혈전을
시사하는 것으로 생각된다.

질의 혈혈뇌졸중(ischemic stroke)은 다양한 기저 질환의 결과로, 결국 한 동맥이 막힘으로써 발생한다. 근위부 두개내동맥(proximal intracranial artery)의 범색과 그 이후 단계적으로 발생하는 혈혈 관류의 벌리생리학적 기전은

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급성기에는 거의 포착된 적이 없는, 그러나, 폐색의 원인으로 혈전 생성을 막는 점에 대하여서는 뇌졸중 검사나 평가를 시행하는 동안 종종 관찰되었다. 급성 혈혈뇌종증의 대부분의 치료의 방침은 혈전을 파괴하거나 혈전 생성을 제거하는 데 초점이 맞추어져 있다.1 신경, 정맥내 조직플라스마피로판활성제(tissue plasminogen activator, tPA)를 사용한 약물학적 혈전용해제와 여러 가지 기구를 이용한 혈관내 혈전제거술 두 가지 치료반인이 심장의약국(Food and Drug Administration)의 승인을 받았다.1-4 근위부 두개뇌동맥의 혈전 생성을 시사하는标志과 미세한 심장영상 소견이 적절적인 치료를 필요로 하지는 않지만, 또는 파괴적인 사례의 확장적인 종종 발생하는 하나, 정맥내 tPA의 두어는 혈전이 풀려고 관찰되는 지의 여부에 따르지 않는다.1-7 뇌졸중에서 혈관내 혈전재개통술(endovascular revascularization procedure) 이전에 CT나 MRI와 같은 비침습적 영상에서 근위부 폐색을 시사하는 소견이 나타난다. 그러나, 이러한 폐색의 특징은 다른 방법에 의하여 확인되었다. 급성 혈혈뇌종증에서 두개뇌동맥의 혈전제거술은 혈전의 구성 성분이나 혈전 생성의 성상, 또는 폐색된 이후 부위로의 혈류를 막는 이는 물질에 대하여서도 직접적인 분석이 가능하다는 것이 특별한 점 중 하나이다.1-6-10

이전의 연구에서 혈전 생성을 시사하는 CT방사선에서의 조기 혈관 정후의 존재, 고밀도 증대뇌동맥 정후(hyperdense middle cerebral artery sign, HMCA)와 기울기기(gradient-echo) MRI 또는 차용을 강조 MRI(susceptibility-weighted MRI) 영상의 세포막 인공조영(blooming artifact, BA)이 연구되었다.1-3,10-17 이들 연구 중 많은 수에서 이러한 정후가 임상적으로 나온 예측인자와 연관되어 혈관재개통의 효과를 감소시키는 가능성이 있다고 하였다.1,10-15,17-19 그러나 대부분의 연구에서 혈관조영술 결과와의 연관성이나 폐색된 부위의 특성과 관련된 실제 방사선학적 관찰 관찰에 보지 않았다.

본 연구자들은 급성 뇌졸중에서 근위부 두개뇌동맥 순환에서 제거한 혈전의 복잡한 변화를 기술한 바 있으며, 이변에는 혈전의 구성 성상을 예측하는 데 도움이 될 수 있는 심장영상 소견과 상관 연구를 보고하고자 한다.이번 보고는 HMCA와 BA를 포함한 조기 혈관 정후의 존재 및 특성의 가치를 이루는 동맥경화병이나 혈전의 구성 요소를 분석한 결과를 기술하였다.

방법

2001년 5월~2007년 3월, 85명의 급성 혈혈뇌종증 환자가 본 센터에서 혈관내 혈전제거술 시행받기 전에 CT나 MRI 검사를 시행하였다. CT나 MRI를 이용한 비침습적 영상은 비조영 CT나 기울기기 어시플(gradient-recalled echo, GRE)을 포함한 MRI 프로토콜에 따라 급성 뇌졸중 증후를 일관한 표준 알코리즘에 의하여 얻었고, 이는 이전에 기술한 바 있다.10-15 GRE 영상은 전면 두께 5 mm, 전면 간격 0, 반복 시간(TR) 800 ms, 반복 시간(TE) 15 ms, 전위각(flip angle) 30°, 관측 범위(field of view) 240, 해석 크기 256×114의 조건으로 얻었다. 이번 연구의 대상 선정 조건은 급성 중대뇌동맥(middle cerebral artery, MCA) 폐색과 함께 혈관내 혈전재거술 직전에 시행한 비교조영 CT나 GRE MRI 결과가 있으며, 재거한 조각에서 혈관 분리 결과를 얻을 수 있는 경우로 정하였다. 연구 선택에 이르기 전에 다른 분야에서 CT를 시행한 경우는 불완전한 유용성, 영상 질의 저하, DICHOM (Digital-Image-and-Communications—in-Medicine) 형식의 영상이 아니어서 Hounsfield Unit (HU) 밀도를 측정할 수 없다는 등의 이유로 제외하였다. 그 결과 CT나 MRI가 본 센터에서 시행되지 않고 혈전제거술에서 병리 조각을 얻을 수 없었던 경우가 연구 분석에서 제외되었다.

임상적, 방사선학적, 자세한 혈관영상학적 자료는 본 센터의 지속적인 연구의 한 부분으로 전향적으로 수집되었다. 이를 연구 자료는 임상적으로 모든 뇌졸중 환자에서 시행하여 얻었고 중앙 데이터베이스에 기록되었다. 심장영상 인자를 받은 두명의 면허가 있는 혈관 전문가와 혈관내 혈전제거술 시행 직전에 시행한 비교조영 CT나 GRE 영상을 입상, 혈관영상학적 변수 및 병리 분석 결과를 모으는 세 후향적으로 분석하였다. HMCA의 존재 유무는 외관 관찰에 따라 두명의 심장영상 전문가의 합의 입증된 결과를 확인하였다. 비대칭적으로 MCA의 밀도가 증가하거나 눈에 잘 띄는 경우를 HMCA로 분류하였고, 이 결과에 HU 밀도 수치는 사용하지 않았다.10-15 HMCA 유무를 점수화한 이후, HU 밀도 측정을 MCA의 양측 분절에서 시행하였다. 측방향(axial) GRE MRI 또한 외관 관찰 시 BA의 존재 유무를 의견 일치 방법으로 검토하였다. BA는 근위부 MCA에서 중장 혈전의 경계를 확인하기는, 지밀도로 보이거나 음영 소실로 보이는 부분으로 정의하였다. 만약 CT나 MRI의 인공조명(artifact)로 인하여 HMCA나 BA의 존재 유무 판단이 애매할 경우에는, 관련 영상 자료를 본 센터에서 재검토하였다.

혈전제거술 시행 이전에 다치며 감산 혈관조영술로 MCA 폐색을 확인하였다. MCA의 혈관이 동측의 내경동맥(internal carotid artery)이나 전대뇌동맥(anterior cerebral artery) 까지 파져 연결되어 있는 경우도 본 센터에 포함시켰다. 혈관조영술 방법과 혈전제거술 과정에 대하여는 다른 곳에 기술하였다.1 이 연구 분석에 포함된 혈전제거술 중에는 Mechanical Embolus Removal in Cerebral Ischemia (MERCI) 연구와 Multi MERCI 연구의 일부로, 그리고 Merici Retriever System의 미국 식품의약국 승인 이후 임상적인 입상 치료의 일부로 진행되었다.1-10 MERCI와 Multi MERCI 연구는 뇌졸중 발생 8시간 이내에 근위부 두개뇌동맥 폐색 치료에서
Merci Retrieval System (Concentric Medical, Inc, Mountain View, CA)의 혈관내 혈전제거술의 안전성과 효용성 평가하였다. 본 연구에서 시행된 기계적 혈전제거술은 Merci Retriever System과 그 이후 세대의 기구들을 사용하여 이루어졌다. 관관조영술을 이용한 혈관 폐색 진단부터 혈전제거술이 완전히 끝날 때까지의 모든 과정에 대한 순차적인 혈관조영 사진을 동맥 폐색의 특성 및 관련된 결과물 평가하기 위해 검토하였다. 본 폐색 유무 및 폐색 부위 이후 양학적 폐색 부위 전방향 관류의 범위를 Thrombolysis in Cerebral Infarction 스펙티드를 이용하여 측정하였으며, 결손 환을 통한 관류는 American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR)의 결손환 평가 시스템을 사용하여 측정하였다.

각 단계별로 다양한 양의 혈전이 추출되면서 혈전제거술 과정이 진행되며, 혈전 제거는 순차적으로 이루어졌다. 기구가 동행함에 따라 혈전의 크기는 점차 줄어들고, 카테터를 제거하고 helical coil의 원위부로 혈전이나 특정 물질의 존재를 감지한다. 만약 별개의 혈전이 동정되지 않으면, 흡인된 물질들을 무드하게 생리시험수로 세척하여 분명한 작은 물질들을 확인한다. 원위부 혈전제거 카테터와 제거된 혈전의 구성에 대해 혈전성 물질과의 관계를 사진으로 기록하였다. 혈전은 이후 가즈나 수술용 소독포에 옮긴 후 여러 관점에서 사진을 촬영하였습니다. 혈전의 길이를 지표(standard)을 이용하여 측정하였다. 이 후 결손물질은 즉시 10% phosphate-buffered formalin에 고정하였다. 포르말린 고정한 조직은 파라핀에 넣어 고정한 후

**Table. Clinical Characteristics of Study Population**

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Population Variable (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean±SD</td>
<td>68±21</td>
</tr>
<tr>
<td>Sex</td>
<td>Female 48%</td>
</tr>
<tr>
<td>Race</td>
<td>White 82%</td>
</tr>
<tr>
<td></td>
<td>Black 10%</td>
</tr>
<tr>
<td></td>
<td>Asian 6%</td>
</tr>
<tr>
<td></td>
<td>Hispanic 2%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12%</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>66%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>26%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14%</td>
</tr>
<tr>
<td>History of smoking</td>
<td>12%</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>Median 19 (IQR, 15-22)</td>
</tr>
<tr>
<td>Intravenous IPA</td>
<td>14%</td>
</tr>
<tr>
<td>Intra-arterial IPA</td>
<td>2%</td>
</tr>
<tr>
<td>Day 90 mRS</td>
<td>Median 3 (IQR, 1-5)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; IPA, tissue plasminogen activator; mRS, modified Rankin Scale; IQR, interquartile range.

Figure 1. Noncontrast CT scan of the head reveals a right hyperdense middle cerebral artery sign (HMCAS, arrow) associated with acute left hemiparesis.

Figure 2. Gradient-echo MRI demonstrates blooming artifact (BA, arrow) in the left middle cerebral artery.
S99809)를 사용하여 촬영하였다. 이후 조직학적 분석을 임상 양상에 대한 정보 없이, 기능적 차이가 있는 과정들에 대한 특 징 추출 분석(feature-detection analysis) 방법으로 시행하였다. 분석 대상 과정들은 혈소판-섬유소 촉적(호르는 혈액에서의 혈전 생성), 신혈 증성구와 단핵구 침착(표면 흡착 상호 작용), 적혈구 과다 촉적(혈관 응고)이 포함되었다. 또한, 광학 현미경을 이용하여 혈전의 구성은 적혈구(red blood cell, RBC)-우성형, 섬유소-우성형, 또는 혼합형으로 분류하였다. 추가적으로 RBC, 백혈구(white blood cell, WBC), 섬유소 구성의 반자동 정성, 정량 분석을 digitized whole slide digital images를 이용하여 시행하였다. H&E 염색된 슬라이 드는 Aperio Scanscope XT digital scanner (Aperio, Vista, CA)를 사용하여 400배로 정밀 촬영하였다. 각각의 디 지털 영상 파일은 200 MB에서 5 GB에 이르는 크기로, 영상 분석 소프트웨어로 분석하기 위하여 작은 파일 크기로의 전환 을 필요로 하였다. 이 과정은 Adobe Photoshop CS3 (Adobe Systems, San Jose, CA)을 이용하여 섬유소, RBC, 그리고 유백 WBC를 유사 색상(pseudocolor)으로 변화시켜 시행하였다. 유사 색상화는 look-up table과 특정 성분의 계 산을 통해 자동 반대로 사용하여 각 혈전 구성 요소의 영상

**Figure 3. Classification of retrieved thrombi as red blood cell-dominant (A) and fibrin-dominant (B).**

**Figure 4. Clot composition based on histopathology, including red blood cell (RBC), white blood cell (WBC), and fibrin percentage. Retrieved clots are numbered from 1 to 50 in order of historical entry into our study.**
특징에 특성 차이는 부여하는 방법으로 진행하였다. 그 다음에 RBC, WBC, 심유소의 각 영역별 분으로 계산하기 위해 Image J software (National Institutes of Health, Bethesda, MD)를 사용하였다. 이러한 분석은 전체 혈전 재기 과정을 통해 추출된 각각의 혈전 조각 분석에 이용되었으며, 여러 개의 혈전 조각이 추출되었음에는 각 혈전의 구성 요소들(RBC, WBC, 심유소)의 분석 결과 평균값을 사용하였다.

임상 자료, 방사선학적 및 혈관조영술 자료, 방사 분석 자료에 대하여 기술 통계 분석 방법을 시용하였다. HMCAS와 BA를 포함한 조기 혈관 폐쇄의 존재 유무와 혈전 병리의 특성을 비주성 변수로 전환하여 통계 분석에 적용하였다. 각 특정 혈전 구성 요소의 분율은 인체명 변수로 산정하였다. CT와 MRT상의 혈전 생성의 조기 혈관 폐쇄와 혈전 구성의 관계라는 카이 제곱검정 및 분산 분석 방법을 사용하여 확인하였고, 유의 수준은 0.05 미만으로 정하였다. 통계 분석은 SPSS software (Version 16.0: SPSS, Inc, Chicago, I.L.I)를 이용하였다.

결과

선정 조건을 만족시킨 환자 56명의 평균 연령은 66세였고 48.2%가 여성이었으며, 82.1%가 백인이었다. 임상적 특성은 Table 1에 기술하였다. 혈관조영술에서 내경동맥 폐쇄는 52.1% MCA 폐쇄는 48.7%에서 관찰되었다. Merch Retriever System만 사용한 경우(78.8%)와, 정맥내 치료를 함께 받은 경우(14%), 그 외 다른 치료(경동맥 tPA 투여[2%], 혈관통행술, 스트레트 삽입술)을 함께 시행한 경우가 있다. 본 연구에 포함된 환자의 최종 Thrombolysis in Cerebral Infarction 점수의 증감은 2점(Thrombolysis in Cerebral Infarction 0, 22% 1, 40% 2, 36% 3).

총 20건의 CT 결과가 분석에 포함되었으며, 10건에서 HMCAS가 관찰되었다(Figure 1). HMCAS의 평균 HU는 61±8 SD였다. 32건이 MRT 결과를 검토한 결과, 17건(53.1%)에서 BA가 관찰되었다(Figure 2). 2명의 환자는 본 연구 기관에서 혈관조영술 시행 전에 CT와 MRT를 모두 시행하였으며, HMCAS와 BA가 모두 관찰되었다. MRT 환자들의 급지 사유 여부를 즉시 평가할 수 없었을 때, 신경 병리로서 MRT 검사를 이전에 CT를 시행하였다. 이들 중에서, 혈관 폐쇄는 정확히 같은 혈관의 해부학적 위치에서 관찰되었다.

추출된 혈전은 대부분 하나의 단일적인 경우도 있었으나 대부분은 여러 개의 조각으로 나뉘어졌다. 이들 여러 개의 조각들은 각 시술 과정의 다양한 단계에서 얻었으며, 혈전이 제거된 시기도 다ختلف했다. 혈전의 양의 재판관 또는 재판관 상태와는 관계없이 없었다. 혈관내에서 폐쇄를 일으킨 혈전의 기원은 혈전제거술과 카테터 조작 특성상 명확하게 평가할 수 없었다. 그러나 일부 증례에서는, 육안 검사와 조직병리학적 검사 상 쉽게 혈전 기원의 위치를 관찰할 수 있었다.

제거된 혈전 중에서, 심유소는 61% (±0.6), RBC는 34% (±2.1), WBC는 4% (±2.0)의 평균 구성 비율을 보았다. 제거된 혈 전 중에서, 22개(44%)가 심유소-우성으로 분류되었으며, 13개(26%)는 RBC-우성, 15개(30%)는 혈관형으로 분류되었다(13). 전반적인 병리학적 보고는 Figure 4에 표시한 대로 모든 증례에 걸쳐 관찰되었다. WBC 구성은 모든 증례에 일반적으로 피피하였다. 여러 조각으로 나뉘어진 증례에서도, 성공적으로 혈전이 제거된 경우와 그 구성이 다르지 않았다. 본 연구 기간 6년 동, Merch Retriever System을 이용하여 제거한 혈전이 이루어지고 실제 임상에 소개되기까지 2년간, 혈관내 시술의 기술적인 면의 다양성으로 인하여 이상될 수 있는 병리학적인 소견의 변화는 없었다. 본 연구자들은 최근 이 시술 과정 이후 나온 예를 보고 환자의 환원을 기술한 부분 연구 결과를 발표하였다.17

영상 검사 기법(CT 또는 MRT)과 육안 검사 결과 또는 조직 병리학적 검사 결과의 연관성은 관찰되지 않았다. 단단한 영상 결과를 얻은 시점과 혈전이 제거된 시점 간의 시간(평균±SD, 86±32분)과 혈전 성분 및 구성이 결과의 차이는 없었다. CT상의 HMCAS는 RBC-우성 또는 혈관형 혈전에서 심유 소-우성을 혈전에서보다 더 잘 관찰되었다(100% vs. 67% vs. 20%, P=0.016). 평균 RBC 구성 비율은 HMCAS가 관찰된 경우에 더 높았으나(76% vs. 22%, P=0.016), 평균 복도는 혈전의 구성과 관계가 없었다. BA 또는 혈관형 혈전에서 심유소-우성 혈전에서보다 더 자주 관찰되었다(100% vs. 63% vs. 25%, P=0.002). 모든 증례에 일반적으로 낮은 비율을 보이는 WBC 성분은 HMCAS나 BA의 존재와 관계가 없었다. BA에서 평균 RBC 비율이 더 높었다(42% vs. 23%, P=0.011). 조기 혈관 폐쇄(HMCAS 또는 BA)의 존재 유 무는 임상적 특성 또는 방사학적 요인과 관련이 없었다. 다변량 회귀 분석 결과, RBC 구성 비율을 계획하는 HMCAS나 BA의 예측인자로 개발하였다(Figure 5). CT와 MRT를 모두 활용한 두 증례에서, HMCAS와 BA의 완전한 임상적 의미가 정량 분석에서 RBC의 구성 비율이 증가한 RBC-우성 혈전과 연관되어 있다. HMCAS나 BA가 없는 경우는 작고 심유소가 많은 혈전 조직에서 조금 더 혼합된다.

본 연구 결과에서 영상 검사 결과(HMCAS나 BA), 또는 혈전의 조직병리학적 특성과 뇌절증의 중요도 또는 이후의 예후와의 연관 관계는 없었다. 혈전의 조직병리학적 특성은 뇌절증의 원인이나 기전(심심장재반응 cardioembolism) 또는 촉상 경화증(atherosclerosis)과도 관련되어 있지 않았고, 성공적 인 추출 가능성과도 관련이 없었다. 이와 유사하게, 영상 결과 또는 조직병리학적 특성은 혈전제거 시기에 대하여도 차이가 없었다.
인 구성 성분과 주변의 적색 혈전을 함께 결합하게 하는 것이
라는 가능성이 여전히 남아 있다.

진단적 영상 방법을 이용하여 ‘적색 혈전’과 ‘백색 혈전
(white thrombi)’을 구분하고자 하는 시도는 다양한 이유가
있으나 달성되지 않았다. 혈관내피증은 발생한 혈전의 조
기 분석 결과에서, ‘적색 혈전과 백색 혈전’의 전등적 구분이
정밀로 적용 가능한지에 대한 의문이 생겼으며, 이는 병리학적
조직에서 다양한 결과가 관찰되기 때문이었다.3,4 뒤이은 연구
결과 또한 혈전에서 주목할 만한 다양성을 보고하였다.5 아마
도 그런 이유로 인하여 CT나 MRI 등 혈전 성상의 예측은
어려울 것이며, 특히 HMCAS나 BA가 백색 부위 근위부와 원
위부의 저혈류에 의하여 유도된 이차적 구성 성분보다는 섬유
의 근관을 반영한다고 가정하면 더욱 그러한 것으로, HMCAS와
BA가 RBC 성분을 강조한다는 이번 연구 결과 또한 그러한 중
래에서 저혈류 방면 생성된 혈전이 조금 더 혼합된 것을 시
사할 수 있다. HMCAS나 BA에 대하여 제거된 혈전 조직의
공간적 근관을 재구성하는 것이 어려울적으로도, 24%의 증례에
서 재활체적(Thrombolysis in Cerebral Infarction
0 또는 1)이 이루어졌다는 것은 RBC 성분이 저혈류에 의하여
중간한 것이며 같은 것을 제기한다. 이러한 기술은 대뇌혈
(cerebral ischemia)에서의 혈전 치료의 역할을 강화하는데,
이는 혈전 면에 부착하고, 원위부는 점화된 관류를 통해 채워
진다.5,6 저혈관은 혈전 재투과를 일으키는 주원이며 혈전
생성의 원인 부위에서 혈전의 생성을 결정한다고 언급되어 왔
다.5,33 혈관조영술은 이러한 요인을 구분하는 데 필수적이다.
흡미적으로, 제거된 혈전의 양과 이후 순차적인 재관류의 연관
성은 발견되지 않았는데, 이는 혈전 생성의 또 다른 혈
혈의 복합생물학적 면을 시사하며, 이는 미래의 뇌졸중 치료
방법에 매우 중요한 역할을 할 것이다.

대뇌혈관의 혈류와 혈전의 상호 관계에 대한 고려 없이는
HMCAS와 BA를 이용하여 혈관내피의 예후를 예측하는 데
내재적 결정요인 존재한다.5,3,3,3 많은 연구에서 조기 혈관 장부
의 예후 예측에 혈관내피유의 예후 점수를 규정하기 위해
시도하였으나, 이러한 예후요인의 혈전의 구조와 혈관형의
으로써 둘다 가능한 결과로도 어떻게 정상화하는지의 이론을
포함할 여러 다양한 요인에 의하여 결정되는 것 같다.5,3,3,3,3,3,3
HMCAS나 BA와 RBC-우성 혈전의 복합 결과 간의 명백한
연관 관계에도 불구하고, 이러한 결과에 또한 의존하여 뇌졸중의
원인을 결정하거나 혈관내피유의 예측을 계획하는 것은 필요하
한다. HMCAS나 BA의 복합 상태로는 혈전의 성공적인
제거를 예측할 수 없다는 이번 연구 결과는, 영향을 줄 만한 다른
원인들에 대한 연구를 필요로 한다. 그것은, 재관류 외에도
당장 증례의 여러 특성에 의하여 영향을 받기 때문이다. 추가
적인 상관관계 연구로 이들 영상 검사상의 장부와 혈류를 특
성화하는 혈관조영술 결과의 특성을 포함하여 다양한 혈관내
접근 방법의 영향을 평가하여야 한다.

본 연구에서의 초기 혈관 장부와 혈전의 복합하적 특성 간의
포괄적인 분석은 몇 가지 제한점을 가지고 있다. 혈관조영술
시행 직전에 검사한 초기 영상 검사 결과의 유무 및 영상 질의
평가가 이미 기계적 혈관재료학의 저항을 제한한 코호
트에서 추가적으로 결정되었다. 이번 연구 결과는 많은 증례를
제외함으로써 생긴 유의한 판별(bias)에 의하여 해석에 제한이
있다. 연구 결과가, 혈관재료학은 가능한 근위부 MCA에 혈전
이 위치한 경우만으로 국한된다고 판단된다. 혈관 패쇄는 희열
되는 경우나 완전히 반해했던 경우에는 연구를 진행할 수 없어
서 분석에서 제외하였다. 혈관조영술 이전에 시행한 정맥내
(tPA)로 일부 혈전에 병명이 생겨나지, 시술 중에 표준 과정으
로 주입하는 해파린으로 인한 변화가 반영되었을 가능성이 남
아 있다. 이와 같은데, 혈관 장부의 근관은 추적이 끝난 뿐이고,
그 외유적 증거는 그 구조와 차이가 남아 있다. 마지막으
로 대부분의 혈전 조직이 그 성상 면에서 다양했기 때문에 혈
전 종류의 분류 또한 불완전하다.

결론

이번 연구는 급성 혈관내피증에서 관찰되는 조기 혈관 장부
을 가진 혈전 구성과 관류시간 첫 번째 연구이다. HMCAS와
BA는 혈전성 MCA 패색에서 흔히 나타나는 것은 아니고,
이 미치는 영향을 확인하지 못했으며 해서 동맥 재관류를 시
행하지 않았다는 연구이다. 혈류에 대한 구성 및 분자생물학적
특성을 포함한 혈전 구성의 조건은 분명히 해석하기는 어렵다.

Sources of Funding
This work has been funded by National Institutes of Health—National
Institute of Neurological Disorders and Stroke Awards K23
NS054084 (D.S.L.) and P50 NS044378.

Disclosures
All authors were employed by the University of California (UC),
which holds a patent on the retriever devices for stroke, at the time of
this work. The UC Regents received payments based on the
clinical trial contracts for the number of subjects enrolled in the MR
and Recanalization of Stroke Clots Using Embolectomy MR (MR
RESCUE) multicenter clinical trial and the Concentric Merci Reg
istry. D.S.L. is a scientific consultant regarding trial design and
conduct to Concentric Medical (modest) and CoAxia (modest).
C.S.K. is Principal Investigator of the National Institutes of Health
funded MR RESCUE trial (P50 NS044378). S.T. is a scientific
advisor of Reverse Medical (modest), which makes a device to treat
acute stroke. G.R.D. is a medical advisor and stockholder of
Concentric Medical. H.V.V. is supported in part by the Daljit S.
and Elaine Sarkaria Chair in Diagnostic Medicine. J.L.S. is a scientifi
consultant to AGA Medical (modest), Boehringer Ingelheim (mod
est), Bristol Myers Squibb (modest), CoAxia (modest), Concentric
Medical (modest), Ev3 (modest), FibroGen (modest), ImaRx (mod
est), Sanofi Aventis (modest), and Talectis (modest). He receives
support for editorial work in MedReviews (modest).
References


背景与目的：本研究首次对缺血性卒中大脑中动脉高密度征（hyperdense middle cerebral artery sign，HMCAS）以及MRI梯度回波序列开花伪像（blooming artifact，BA）与血栓病理的相关性进行研究。

方法：连续纳入50例大脑中动脉缺血性卒中患者，在进行血栓取栓术前，进行非增强CT及MRI梯度回波序列检查，在临床信息及血栓病理双盲的情况下阅片，然后将血栓取栓术所得血栓切片后在显微镜下进行组织病理学分析，包括全自动定量及成分定量分级，这些成分包括红细胞、白细胞及纤维蛋白。

结果：纳入的50名患者的平均年龄为66岁，48%为女性，平均（标准差[SD])成分为61%(±21)的纤维蛋白，34%(±21)的红细胞，以及4%(±2)的白细胞。在50例患者血栓中，22例（44%）以纤维蛋白为主，13例（26%）以红细胞为主，15例（30%）为混合型。20例大脑中动脉卒中患者中有10例出现HMCAS，平均HU(Hounsfield Unit)密度值为61(±8 SD)。而在32例行MRI梯度回波序列的患者中有17例出现BA。纤维蛋白型及混合型血栓比红细胞型血栓更常出现HMCAS（100% vs 67% vs 20%，P=0.016）。出现HMCAS的血栓平均红细胞含量更高（47% vs 22%，P=0.016）。红细胞型及混合型血栓比纤维蛋白型血栓更常出现BA（100% vs 63% vs 25%，P=0.002）。出现BA的血栓红细胞含量更高（42% vs 23%，P=0.011）。

结论：HMCAS及BA能够反映闭塞性血栓的病理类型。红细胞的含量决定是否出现HMCAS及BA，如果两者均未出现，提示血栓成分可能以纤维蛋白为主。

关键词：脑梗塞，CT，MRI，卒中，血栓

(Stroke. 2011;42:1237-1243. 郑州大学附属第一医院神经内科 高远 宋波 译 许予明 校)
heart 85 patients with ischemic stroke, excluding patients with hemorrhagic stroke, who were treated with intravenous thrombolysis before undergoing endovascular thrombectomy. The study included patients with acute middle cerebral artery (MCA) occlusion who were able to undergo CT or MRI imaging, followed by endovascular thrombectomy and successful thrombus retrieval. In patients who underwent CT or MRI imaging before admission, the scans were not of sufficient quality to measure Hounsfield unit (HU) density values, and therefore, these patients were excluded from the study.

In the current study, we prospectively included patients' clinical, radiologic, and detailed angiographic information, which was recorded and stored in a central database. The GRE MRI images obtained before thrombectomy were reviewed by two vascular neurologists in a double-blind manner, after excluding patients with HMCAS or BA. The HMCAS was defined as a non-symmetrical or significant increase in density in the MCA region, without using HU density values. The BA was defined as a low signal area or signal loss in the MCA, with the vessel edges being distorted. In cases where HMCAS or BA were unclear or had artifacts, the case was excluded.

The thrombus images were obtained before the thrombectomy using DSA, and MCA occlusion was confirmed. Thrombus extension to the internal carotid artery or anterior cerebral artery was also included in the analysis. Further details of the thrombectomy and imaging protocols are provided in the previous publication [3].

The thrombus samples were obtained before and after thrombectomy and were fixed in 10% phosphate-buffered formalin, embedded in paraffin, and then cut into 8 µm thick slices, stained with Hematoxylin and Eosin (H&E). MicroFire Digital Camera (Model S99809) with an Olympus BX41 microscope was used to take photographs. The histologic evaluation was performed in a blinded manner without contact with the clinical data, and the analyses were based on morphologic features, including platelet aggregation (thrombus formation in flowing blood), neutrophil and monocyte deposition (surface adhesion), and erythrocyte aggregates (whole blood coagulation). The thrombus components were categorized as red cells, fibrin, or mixed-type. The digital images were further analyzed using a semi-automatic quantitative analysis software.

The descriptive data were analyzed using a variety of clinical angiographic and case data analyses. The presence or absence of early vascular signs and quantitative thrombus analysis in CT and MRI images were evaluated using the Image J software (National Institutes of Health, Bethesda, MD). The data were analyzed for each region of interest (ROI) with Image J, and the same method was used to analyze all thrombus samples obtained during the procedure and the average values of each thrombus component were calculated.
表 研究样本临床特征

<table>
<thead>
<tr>
<th>临床特征</th>
<th>样本变量 (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄，岁，平均值±标准差</td>
<td>66±21</td>
</tr>
<tr>
<td>性别</td>
<td></td>
</tr>
<tr>
<td>女性</td>
<td>48%</td>
</tr>
<tr>
<td>种族</td>
<td></td>
</tr>
<tr>
<td>白种人</td>
<td>82%</td>
</tr>
<tr>
<td>黑种人</td>
<td>10%</td>
</tr>
<tr>
<td>亚种人</td>
<td>6%</td>
</tr>
<tr>
<td>西班牙人</td>
<td>2%</td>
</tr>
<tr>
<td>糖尿病</td>
<td>12%</td>
</tr>
<tr>
<td>高血压病</td>
<td>66%</td>
</tr>
<tr>
<td>冠心病</td>
<td>26%</td>
</tr>
<tr>
<td>房颤</td>
<td>14%</td>
</tr>
<tr>
<td>吸烟史</td>
<td>12%</td>
</tr>
<tr>
<td>基线 NIHSS</td>
<td>中位数 19 (四分位间距 15-22)</td>
</tr>
<tr>
<td>静脉 tPA</td>
<td>14%</td>
</tr>
<tr>
<td>动脉 tPA</td>
<td>2%</td>
</tr>
<tr>
<td>90 天的 mRS</td>
<td>中位数 3 (四分位间距 1-5)</td>
</tr>
</tbody>
</table>

P<0.05 水平。使用 SPSS 软件 (版本 16.0; SPSS, Inc, Chicago, I.L.) 进行统计分析。

结果

在满足纳入条件的 50 名患者中，平均年龄为 66 岁，48% 为女性，82% 为白人，临床特征见上表。血管造影证实颈内动脉闭塞占 52%，MCA 闭塞占 48%。治疗方式有单用 MERCI 治疗 (78%)、MERCI 联合静脉溶栓治疗 (14%)、MERCI 联合其他治疗 (动脉内 tPA[2%])，血管成形术，支架植入术。本研究中患者最终脑梗塞溶栓评分 (Thrombolysis in Cerebral Infarction score, TCIS) 中位数为分值 2(TCIS 评分 0 分的占 2%，1 分占 22%，2 分占 40%，3 分占 38%)。

在本项研究纳入的 20 例 CT 扫描中，有 10 例出现了 HMCAS (如图 1)。所有出现的 HMCAS 平均 HU 密度值为 61(±8)。在 32 例 MRI 扫描中，有 17 例 (53%) 出现了 BA (如图 2)。共 2 位患者既有 HMCAS，也有 BA。对于不能很快评估是否有 MRI 禁忌的病人，可以在做 MRI 前进行 CT 检查作为筛查。在这些病例中，早期血管征象都出现在近乎相同的血管解剖位置上。

取出的血栓偶尔为一个整块，大部分为多个碎片。这些不同的标本在每项操作的不同时间段取出，而且血栓取出的时间也存在很多差异。取栓量与血管再通或再灌注之间没有联系。由于取栓术及本身及导管操作的特性，不能精确对血管内闭塞血栓进行空间定位。然而，在一些病例中，肉眼观察及组

图 1 头颅非增强 CT 显示右侧大脑中动脉高密度征 (HMCAS) 伴随左侧肢体无力。

图 2 梯度回波序列 MRI 显示左侧大脑中动脉开花伪像 (BA, 箭头)。
在50例患者血栓中，22例（44%）以纤维蛋白为主，13例（26%）以红细胞为主，15例（30%）为混合型（图3）。如图4展示，血栓中各种病理类型分布广泛，WBC在各种成分中始终含量最低。获取的多片段血栓，在成分上与完整血栓是一致的。在进行该研究的6年中，从MERCI取栓系统应用于临床获取第一例患者血栓到临床应用超过两年的时间里，未发现可能提示潜在的手术技术层面变化的病理改变。我们最近发表了一项尸检研究，描述了进行该术后预后不佳的一组病人[27]。

基线影像模式（比如CT或MRI），与大体或组织病理发现之间未发现明显联系。基线影像获取至取栓时间（平均数±标准差，86±32分钟）、血栓组分及成分含量未见明显差异。

CT上所见到的HMCAS更常见于以红细胞为主的血栓及混合型的血栓，而不是纤维蛋白为主的血栓（100% vs 67% vs 20%，P=0.016）。尽管HU密度值与血栓成分并不相关，但出现HMCAS时平均红细胞含量较高（47% vs 22%，P=0.016）。BA也较常见于红细胞为主及混合型的血栓，而不是纤维蛋白

原始图3 红细胞为主的血栓（A）和纤维蛋白为主的血栓（B）

原始图4 血栓按1到50编号纳入，组织病理学成分包括红细胞、白细胞以及纤维蛋白。
型的血栓（100% vs 63% vs 25%，P=0.002）。白细胞在所有病例中表现为一致的低含量，不是HMCAS及BA的决定因素。出现BA较无BA时血栓红细胞的平均百分比高（42% vs 23%，P=0.011）。不管是HMCAS还是BA均与临床放射影像因素不相关。多因素分析显示除了红细胞含量以外无其他的HMCAS及BA预测因子（图5）。2例同时行CT及MRI检查的患者，HMCAS及BA的一致率与红细胞为主型血栓相关。小的纤维蛋白型血栓不常出现HMCAS及BA。

分析显示影像学表现（HMCAS或BA）及血栓病理类型与基线变量包括卒中严重程度、预后等不相关。血栓的病理与最终的卒中发病机制不相关（如心源性栓塞或大动脉粥样硬化型），也不是取栓成功的预测因素。同样，影像及病理特征与取栓的时间也无相关性。

讨论

非侵入性的影像模式如CT及MRI用以显示阻塞性血栓的血管异常已超过20年的时间，一直没有将其与血栓实际病理相联系[5-15]，本研究首次进行了影像与病理的对照研究显示早期的血管征象能够反映血栓潜在的病理类型。缺乏性卒中患者常可以观察到HMCAS及BA，这引起人们对血栓类型及成分（如心源性栓塞或大动脉粥样硬化型），也不是取栓成功的预测因素。同样，影像及病理特征与取栓的时间也无相关性。HMCAS及BA中的红细胞含量关系（A）以及BA与红细胞含量的关系（B）。

识别HMCAS无疑受不同方法的影响，包括盲法、HU值定量测量以及其他的基线因子[20]。本研究BA的检出率与先前的报道相一致。心源性栓塞及动脉粥样硬化血栓形成等卒中不同的机制可能会影响BA显像的程度[12-14]，相对来说，心源性栓塞的血栓负荷越重BA显示越清晰[13]。47%的研究病例中未显示BA，这些血栓多以纤维蛋白为主，常是纤溶药物的潜在靶点。研究中同时观察到HMCAS与BA的病例较少，这是因为MRI的早期应用以及及时的血栓取栓术使CT检查变得并不必要[14]。有研究报道的连续纳入的患者取栓前单使用常规CT扫描的HMCAS发现率只有15%，对溶栓的治疗效果没有太大意义[28]。其他区域比如后循环血管早期血管征象尚待病理的相关证据[10,13,14,29,30]。HMCAS及BA反映的是血栓的成分之一（红细胞），而不是溶栓的重要指证。在出现血管征象的所有病例中，血栓成分多以红细胞为主，而在纤维蛋白为主的血栓中血管早期征象出现的频率极低。红细胞的含量与这些血管征象关系密切。HMCAS区域的HU密度值的测量值与新形成血栓的HU密度值相一致，但是现在仍很难将这些密度的改变归因于某一
由于未明确 HU 密度值与 RBC 计量之间存在什么关系，故不能使用 HU 值来代表红细胞的含量，仅用肉眼判断 HMCAS 的出现可能已经足够用来区分红细胞为主的血栓或者说“红血栓”。BA 的磁敏效应也归因于红细胞成分引起的局部磁场扭曲。HMCAS 及 BA 是阻塞性血栓的间接标志，他们主要与红细胞的聚集有关而不是纤维蛋白。然而也有可能，这其中的红细胞来自取栓过程中网罗的其他的成分及相邻的红血栓。

长期以来人们期待通过影像诊断模式来分辨红白血栓。我们先前的研究发现缺血性卒中血栓标本存在极大的异质性，这使我们对传统的红白血栓的分类方法产生了质疑。随后的一项研究也显示血栓样本间存在明显的差异。使用 CT 及 MRI 来预测血栓成分因而变得困难，尤其是当人们认为 HMCAS 及 BA 反映的是最初的栓塞物而不是栓塞部位远端或近端发出诱发的继发成分时。我们发现红细胞成分对出现 HMCAS 及 BA 更为重要可能也提示血液淤滞及新鲜血栓在这些病例中更常见。尽管体现了与 HMCAS 及 BA 相对应血栓的空间定位结构仍十分困难，24% 的患者存在溶栓后灌注低下，而有限的再灌注造成的血液淤滞使血栓中红细胞的成分比重变大。这一假说强调了血栓之外，血流恶化在大脑缺血及远端侧枝灌注中的重要作用。血流瘀滞以往一直被认为是决定心源性栓子的成分而不是原位血栓的成分。血管造影可能成为识别这些影响因素不可或缺的手段。血流瘀滞在早期血管征象对卒中预后或对血管再通的预测价值，HMCAS 及 BA 在大脑中动脉血栓性闭塞出现并不普遍，未证明这些征象可以作为溶栓的证据。需要进一步的研究阐明血栓成分的更多细节，包括分子特征及血流状况。

结论

本研究首次进行缺血性卒中早期血管征象与血栓成分的相关研究。HMCAS 及 BA 在大脑中动脉血栓性闭塞出现并不普遍，将这些征象可以作为溶栓的证据。需要进一步的研究阐明血栓成分的更多细节，包括分子特征及血流状况。


