

# 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% ( $\pm 21$ ) fibrin, 34% ( $\pm 21$ ) RBCs, and 4% ( $\pm 2$ ) 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 ( $\pm 8$  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

**A**cute 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 frequently noted during evaluation. Most therapeutic strategies for acute ischemic stroke focus on clot disruption or resolution of thrombosis.<sup>1</sup> In fact, the only 2 Food and Drug Administration-approved therapies include pharmacological thrombolysis with intravenous tissue plasminogen activator and endovascular thrombectomy with various devices.<sup>2-4</sup> Intravenous tissue plasminogen activator does not depend on overt delineation of thrombus, yet subtle neuroimaging findings suggesting thrombosis in proximal intracranial arteries

are often viewed as confirmatory evidence of a potentially extensive or destructive event that warrants aggressive treatment.<sup>5-7</sup> 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.<sup>8-10</sup>

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

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and blooming artifact (BA) on gradient-echo or other susceptibility-weighted MRI sequences.<sup>5–7,10–17</sup> Many of these studies have correlated these findings as a poor prognostic factor in clinical outcome and diminished likelihood of revascularization.<sup>7,10–13,17,18</sup> 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.<sup>8</sup> 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.<sup>19</sup> 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 artery (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.<sup>20</sup> 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.<sup>3</sup> Thrombectomy cases included in our analyses were conducted as part of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI trials and as part of routine clinical care following the US Food and Drug Administration clearance of the Merci Retriever System.<sup>3,21–23</sup> The MERCI 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.<sup>3,21,22</sup> 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.<sup>24–26</sup> 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.<sup>24</sup>

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. Pseudocolorization 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  $\chi^2$  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.).

**Table.** Clinical Characteristics of Study Population

Clinical Characteristic	Population Variable (n=50)
Age, years, mean $\pm$ SD	66 $\pm$ 21
Sex	
Female	48%
Race	
White	82%
Black	10%
Asian	6%
Hispanic	2%
Diabetes	12%
History of hypertension	66%
Coronary artery disease	26%
Atrial fibrillation	14%
History of smoking	12%
Baseline NIHSS score	Median 19 (IQR, 15–22)
Intravenous tPA	14%
Intra-arterial tPA	2%
Day 90 mRS	Median 3 (IQR, 1–5)

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

## 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).

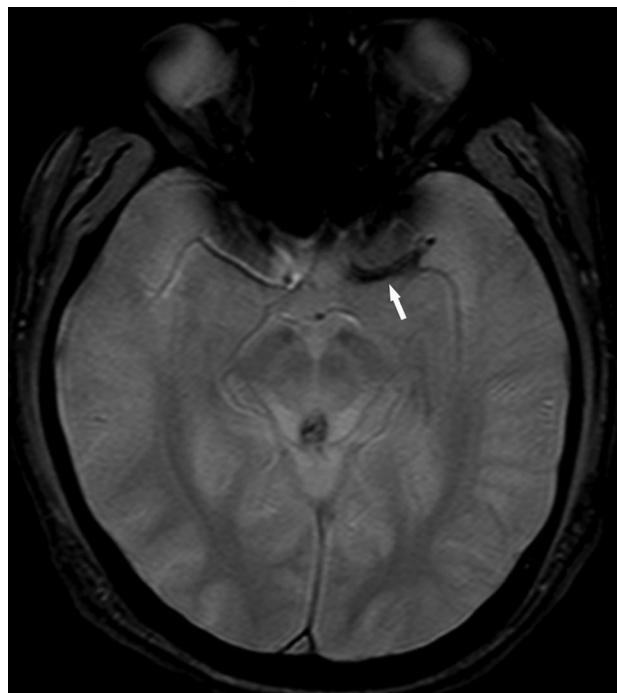
A total of 20 CT scans was included for analysis of which 10 demonstrated HMCAS (Figure 1). The HMCAS revealed a mean HU of 61 ( $\pm 8$  SD) across all cases. There were 32 MRI scans reviewed with 17 (53%) demonstrating BA (Figure 2). The 2 patients who had both CT and MRI at our institution before 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.

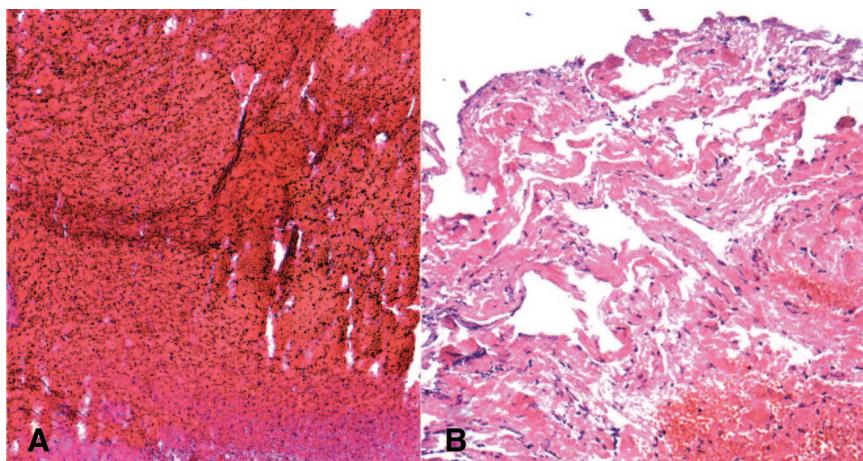


**Figure 1.** Noncontrast CT scan of the head reveals a right hyperdense middle cerebral artery sign (HMCAS, arrow) associated with acute left hemiparesis.

Across all retrieved thrombi, mean (SD) proportion of components was 61% ( $\pm 21$ ) fibrin, 34% ( $\pm 21$ ) RBCs, and 4% ( $\pm 2$ ) 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.



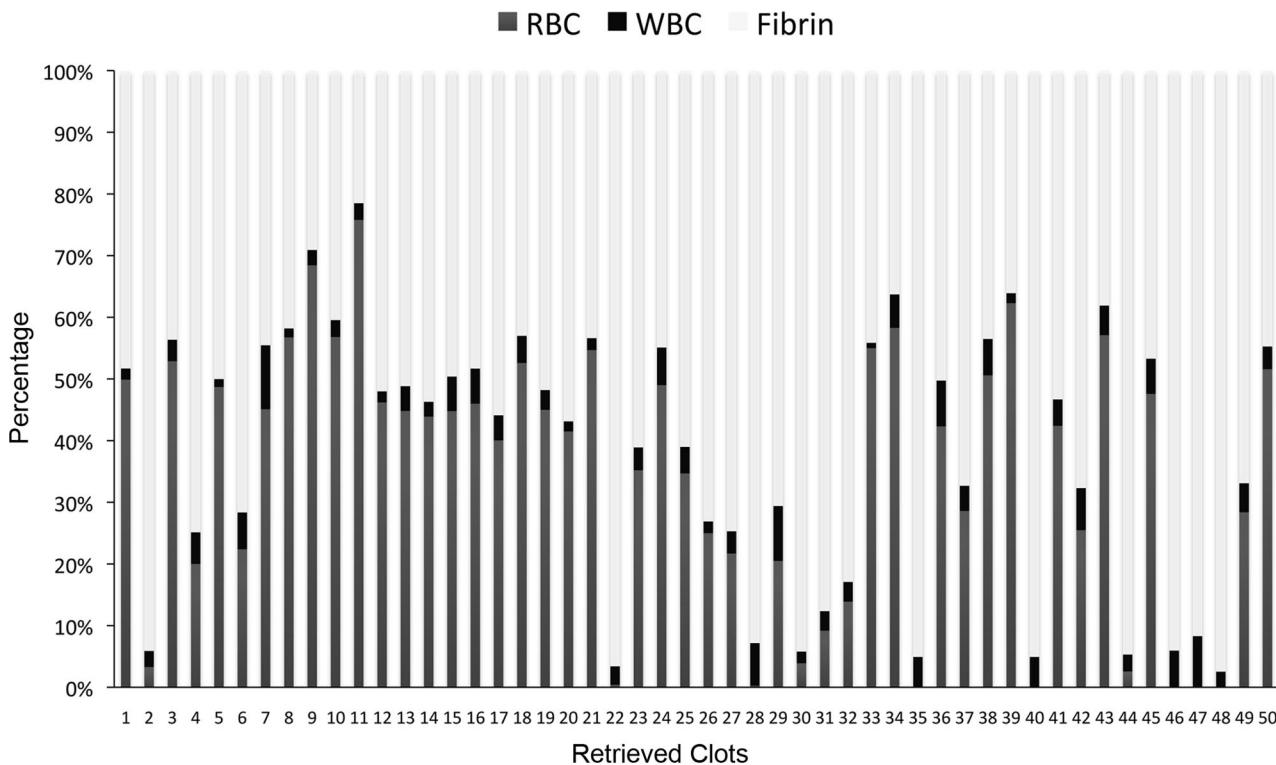
**Figure 3.** Classification of retrieved thrombi as red blood cell-dominant (**A**) and fibrin-dominant (**B**).

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.<sup>27</sup>

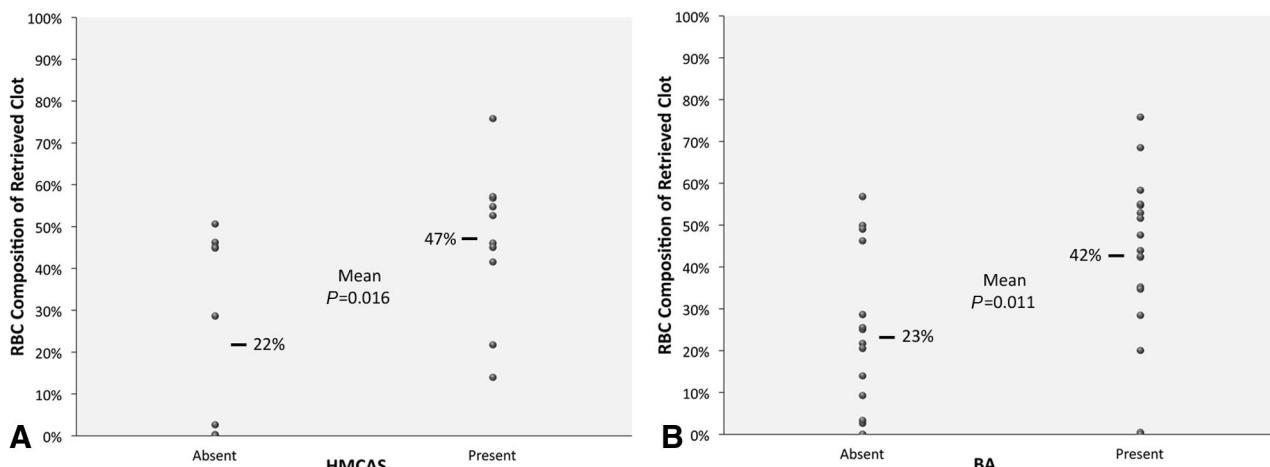
No correlation was noted between the type of baseline imaging modality (ie, CT or MRI) and gross or histopathologic findings. There were also no differences between the timeline between baseline diagnostic imaging acquisition to clot retrieval (mean $\pm$ SD, 86 $\pm$ 32 minutes) and the resultant thrombus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

## Histopathologic Composition of 50 Retrieved Clots



**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.



**Figure 5.** Red blood cell (RBC) composition of retrieved clots correlates with early vessel signs, including (A) the hyperdense middle cerebral artery sign (HMCAS) and (B) blooming artifact (BA).

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.<sup>5,15</sup> 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 are 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.<sup>8</sup> Furthermore, de-

tailed 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.<sup>5-7,11</sup> HMCAS detection is undoubtedly influenced by variable methodology, including blinding, quantitative measures of HU, and other baseline factors.<sup>20</sup> 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.<sup>12-14</sup> Relatively greater thrombus burden associated with cardioembolism may increase BA conspicuity.<sup>13</sup> 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.<sup>14</sup> 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.<sup>28</sup> Early vessel findings in other territories such as the posterior cerebral artery still await pathological correlation.<sup>10,13,14,29,30</sup>

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.<sup>10,20,31</sup> Because we did not discern any correlation between HU density and RBC quantitative 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.<sup>32</sup> 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.<sup>8</sup> A subsequent report also described marked heterogeneity in thrombi.<sup>9</sup> Prediction of clot composition from CT or MRI may 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.<sup>25</sup> Stasis has previously been invoked in determining thrombus composition at the embolic source yet not at the recipient site.<sup>10,33</sup> 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.<sup>25,26</sup> 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.<sup>7,10,11,13,16–18</sup> 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.

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# Stroke

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## Full Article

## 급성 뇌졸중에서 혈전 성상을 반영하는 CT와 MRI의 조기 혈관 징후

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

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 Harry V. Vinters, MD; Victor J. Marder, MD; Jeffrey L. Saver, MD

(*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 기울기에코 (gradient-echo) MRI의 색변집 인공음영(blooming artifact, BA)의 급성 허혈뇌졸중에서 얻어진 혈전의 병리학적 특성과의 연관성을 보기 위한 첫 상관 관계 연구이다.

**방법:** 급성 중대뇌동맥 허혈뇌졸중 증례 50개의, 기계적 혈전제거술 시행 이전에 촬영한 비조영증강(noncontrast) CT와 기울기에코 MRI 영상을 임상 자료 및 병리학적 자료를 모르는 상태로 분석하였다. 혈전제거술을 시행한 폐색 부위의 혈전에 대하여 조직병리학적 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% ( $\pm 21$ ), RBC 34% ( $\pm 21$ ), WBC 4% ( $\pm 2$ )였다. 제거된 혈전 중에서, 22개(44%)의 주성분은 섬유소였고 13개(26%)는 RBC였으며, 15개(30%)는 혼합형이었다. HMCAS는 CT를 촬영한 20명의 중대뇌동맥 뇌졸중 환자 중 10명에서 관찰되었으며, 평균 Hounsfield Unit 밀도는 61 ( $\pm 8$  SD)이었다. BA는 기울기에코 MRI 검사 32건 중 17건에서 관찰되었다. HMCAS는 섬유소가 주된 성분인 혈전보다 RBC가 주성분이거나 혼합형인 경우에 더 흔히 관찰되었다(100% vs. 67% vs. 20%,  $P=0.016$ ). RBC의 평균 비율은 HMCAS와 연관된 혈전에서 더 높았다(47% vs. 22%,  $P=0.016$ ). BA는 섬유소가 주성분인 혈전과 비교하였을 때 RBC가 주성분이거나 혼합형인 경우에 더 흔히 관찰되었다(100% vs. 63% vs. 25%,  $P=0.002$ ). BA와 연관된 혈전에서 평균 RBC 비율이 더 컸다(42% vs. 23%,  $P=0.011$ ).

**결론:** CT상의 HMCAS와 기울기에코 MRI에서의 BA는 혈관 폐색을 유도한 혈전의 병리학적 특성을 반영한다. RBC 성분이 HMCAS와 BA의 발현을 결정하는 것으로 보이며, HMCAS나 BA가 관찰되지 않는 경우는 아마도 섬유소가 주된 성분인 혈전을 시사하는 것으로 생각된다.

**급성** 허혈뇌졸중(ischemic stroke)은 다양한 기저 질환의 결과로, 결국 한 동맥이 막힘으로써 발생한다. 근위

부 두개내동맥(proximal intracranial artery)의 폐색과 그 이후 단계적으로 발생하는 허혈 과정의 병리생리학적 기전은

급성기에는 거의 포착된 적이 없다. 그러나, 폐색의 원인으로 혈전 생성 역할을 한다는 점에 대하여서는 뇌졸중 검사나 평가를 시행하는 동안 종종 관찰되었다. 급성 혀혈뇌졸중의 대부분의 치료적 방침은 혈전을 파괴하거나 혈전 생성을 해결하는 데 초점이 맞추어져 있다.<sup>1</sup> 사실, 정맥내 조직플라스미노겐활성제(tissue plasminogen activator, tPA)를 사용한 약물학적 혈전용해술과 여러 가지 기구를 이용한 혈관내 혈전제거술 두 가지 치료만이 식품의약국(Food and Drug Administration)의 승인을 받았다.<sup>2~4</sup> 근위부 두개내동맥의 혈전 생성을 시사하는 미묘하고 미세한 신경영상 소견이 적극적인 치료를 필요로 하는 광범위한, 또는 파괴적인 사건의 확정적인 증거로 종종 생각되기는 하나, 정맥내 tPA의 투여는 혈전이 뚜렷하게 관찰되는지의 여부에 따르지는 않는다.<sup>5~7</sup> 뇌졸중에서 혈관내 혈관재개통술(endovascular revascularization procedure) 이전에 CT나 MRI와 같은 비침습적 영상에서 근위부 폐색을 시사하는 소견이 나타난다. 그러나, 그러한 폐색의 특징은 다른 방법에 의하여 확인되었다. 급성 혀혈뇌졸중에서 두개내동맥의 혈전제거술은 혈전의 구성 성분이나 혈전 생성의 성상, 또는 폐색된 이후 부위로의 혈류를 막는 그 어떤 물질에 대하여서도 직접적인 분석이 가능하다는 것이 특별한 점 중 하나이다.<sup>8~10</sup>

이전의 연구에서 혈전 생성을 시사하는 CT와 MRI에서의 초기 혈관 징후의 존재, 고밀도 중대뇌동맥 징후(hyperdense middle cerebral artery sign, HMCAS)와 기울기에코(gradient-echo) MRI 또는 자화율 강조 MRI (susceptibility-weighted MRI) 영상의 색변침 인공음영(blooming artifact, BA)이 연구되었다.<sup>5~7,10~17</sup> 이들 연구 중 많은 수에서 이러한 징후가 임상적으로 나쁜 예측인자와 연관되며 혈관재개통의 효과를 감소시킬 가능성성이 있다고 하였다.<sup>7,10~13,17,18</sup> 그러나 대부분의 연구에서 혈관조영술 결과와의 연관성이나 폐색된 부위의 특성과 관련된 실제 병리학적 연관 관계는 보지 않았다.

본 연구자들은 급성 뇌졸중에서 근위부 두개내동맥 순환에서 제거한 혈전의 병리학적 변화를 기술한 바 있으며, 이번에는 혈전의 구성 성상을 예측하는 데 도움이 될 수 있는 신경영상 소견과의 상관 연구를 보고하고자 한다.<sup>8</sup> 이번 보고는 HMCAS와 BA를 포함한 초기 혈관 징후의 존재 및 특성의 기저를 이루는 동맥경화반이나 혈전의 구성 요소를 분석한 결과를 기술하였다.

## 방법

2001년 5월~2007년 3월, 85명의 급성 혀혈뇌졸중 환자가 본 센터에서 혈관내 혈전제거술을 시행받기 전에 CT나 MRI 검사를 시행하였다. CT나 MRI를 이용한 비침습적 영상은 비조영 CT나 기울기에코 시퀀스(gradient-recalled echo, GRE)를 포함한 MRI 프로토콜에 따라 급성 뇌졸중 증례를 위

한 표준 진단 알고리즘에 의하여 얻어졌고, 이는 이전에 기술한 바 있다.<sup>19</sup> GRE 영상은 절편 두께 5 mm, 절편 간격 0, 반복 시간(TR) 800 ms, 반향 시간(TE) 15 ms, 전위각(flip angle) 30°, 관측 범위(field of view) 240, 매트릭스 크기 256×144의 조건으로 얻었다. 이번 연구의 대상 선정 조건은 급성 중대뇌동맥(middle cerebral artery, MCA) 폐색과 함께 혈관내 혈전제거술 직전에 시행한 비조영 CT나 GRE MRI 결과가 있으며, 제거한 조직에서 혈전 병리 결과를 얻을 수 있는 경우로 정하였다. 연구 센터로 이송되기 전에 다른 기관에서 CT를 시행한 경우는 불완전한 유용성, 영상 질의 저하, DICOM (Digital-Imaging-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 조직을 얻을 수 없었던 경우가 연구 분석에서 제외되었다.

임상적, 방사선학적, 자세한 혈관영상학적 자료는 본 센터의 지속적인 연구의 한 부분으로 전향적으로 수집되었다. 이를 연구 자료는 일상적으로 모든 뇌졸중 환자에서 시행되어 얻어지고 중앙 데이터베이스에 기록된다. 신경영상 인가를 받은 두 명의 면허가 있는 혈관 신경과 전문의가 혈관내 혈전제거술 시행 직전에 시행한 비조영 CT나 GRE 영상을 임상, 혈관영상학적 변수 및 병리 분석 결과를 모르는 채 후향적으로 분석하였다. HMCAS의 존재 유무는 외관 관찰에 따라 두 명의 신경영상 전문가의 판독 의견 일치를 점수화하였다. 비대칭적으로 MCA의 밀도가 증가하거나 눈에 잘 띠는 경우를 HMCAS로 분류하였고, 이 결정에 HU 밀도 수치는 사용하지 않았다.<sup>20</sup> HMCAS 유무를 점수화한 이후, HU 밀도 측정을 MCA의 양측 분절에서 시행하였다. 축 방향(axial) GRE MRI 또한 외관 관찰 시 BA의 존재 유무를 의견 일치 방법으로 검토하였다. BA는 근위부 MCA에서 종종 혈관의 경계를 왜곡시키는, 저밀도로 보이거나 음영 소실로 보이는 부분으로 정의하였다. 만약 CT나 MRI의 인공물(artifact)로 인하여 HMCAS나 BA의 존재 유무 판단이 애매할 경우에는, 관련 영상 자료를 본 분석에서 제외시켰다.

혈전제거술 시행 이전에 디지털 감산 혈관조영술로 MCA 폐색을 확인하였다. MCA의 혈전이 동측의 내경동맥(internal carotid artery)이나 전대뇌동맥(anterior cerebral artery) 까지 퍼져 연결되어 있는 경우도 분석에 포함시켰다. 혈관조영술 방법과 혈전제거술 과정에 대하여서는 다른 곳에 기술하였다.<sup>3</sup> 이번 연구 분석에 포함된 혈전제거술 중례는 Mechanical Embolus Removal in Cerebral Ischemia (MERCI) 연구와 Multi MERCI 연구의 일부로, 그리고 Merci Retriever System의 미국 식품의약국 승인 이후 일상적인 임상 치료의 일부로 진행되었다.<sup>3,21~23</sup> MERCI와 Multi MERCI 연구는 뇌졸중 발생 8시간 이내에 근위부 두개내동맥 폐색 치료에서

**Table. Clinical Characteristics of Study Population**

Clinical Characteristic	Population Variable (n=50)
Age, years, mean $\pm$ SD	66 $\pm$ 21
Sex	
Female	48%
Race	
White	82%
Black	10%
Asian	6%
Hispanic	2%
Diabetes	12%
History of hypertension	66%
Coronary artery disease	26%
Atrial fibrillation	14%
History of smoking	12%
Baseline NIHSS score	Median 19 (IQR, 15–22)
Intravenous tPA	14%
Intra-arterial tPA	2%
Day 90 mRS	Median 3 (IQR, 1–5)

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

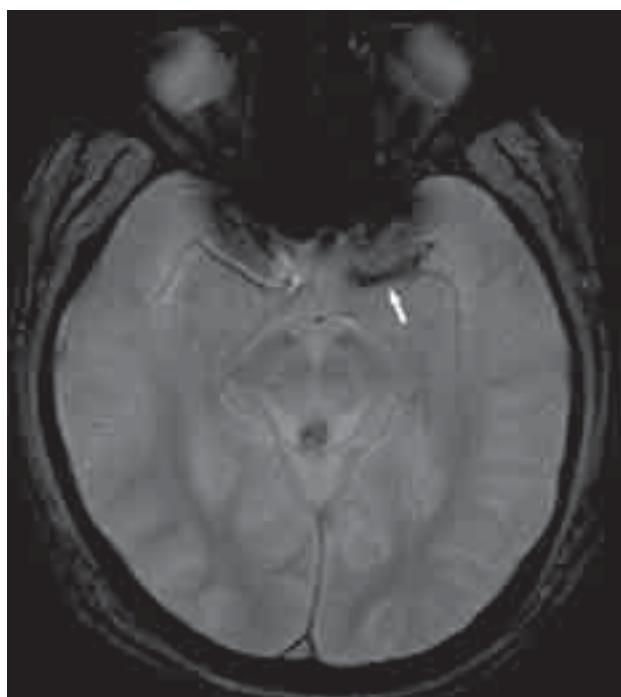
Merci Retrieval System (Concentric Medical, Inc., Mountain View, CA)의 혈관내 혈전제거술의 안전성과 효용성을 평가하였다.<sup>3,21,22</sup> 본 연구에서 시행된 기계적 혈전제거술은 Merci Retriever System과 그 이후 세대의 기구들을 사용하여 이루어졌다. 혈관조영술을 이용한 혈관 폐색 진단부터 혈전제거술이 완전히 끝날 때까지의 모든 과정에 대한 순차적인 혈관조영 사진을 동맥 폐색의 특성 및 관련된 결순환을 평가하기 위해 검토하였다.<sup>24–26</sup> 폐색 유무 및 폐색 부위 이후 영역의 폐색 부위 전방향 관류의 범위를 Thrombolysis in Cerebral Infarction 스케일을 이용하여 측정하였으며, 결순환을 통한 관류는 American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR)의 결순환 평가 시스템을 사용하여 측정하였다.<sup>24</sup>

각 단계별로 다양한 양의 혈전이 추출되면서 혈전제거술 과정이 진행되어, 혈전 제거는 순차적으로 이루어졌다. 기구가 통과함에 따라 혈전의 크기는 점차 줄어들고, 카테터를 제거하고 helical coil의 원위부로 혈전이나 특정 물질의 존재를 감지한다. 만약 별개의 혈전이 동정되지 않으면, 흡인된 물질들을 부드럽게 생리식염수로 세척하여 불분명한 작은 물질들을 확인한다. 원위부 혈전제거 카테터와 제거된 혈전의 구성에 대하여 혈전성 물질과의 관계를 사진으로 기록하였다. 혈전은 이후 거즈나 수술용 소독포에 옮긴 후 여러 관점에서 사진을 촬영하였다. 혈전의 길이를 지표(guide)를 이용하여 측정하였다. 이후 혈전 물질은 즉시 10% phosphate-buffered formalin에 고정하였다. 포르말린 고정한 조직은 파라핀에 넣어 고정한 후

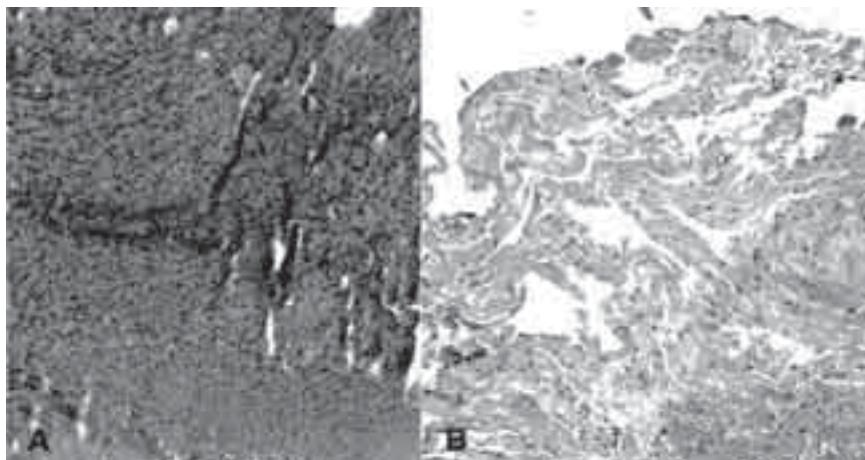


**Figure 1.** Noncontrast CT scan of the head reveals a right hyperdense middle cerebral artery sign (HMCAS, arrow) associated with acute left hemiparesis.

8 μm 두께로 절단하여 hematoxylin and eosin (H&E) 염색을 시행하였다. 각 조직 절편을 Olympus BX41 microscope with an attached MicroFire digital camera (Model



**Figure 2.** Gradient-echo MRI demonstrates blooming artifact (BA, arrow) in the left middle cerebral artery.

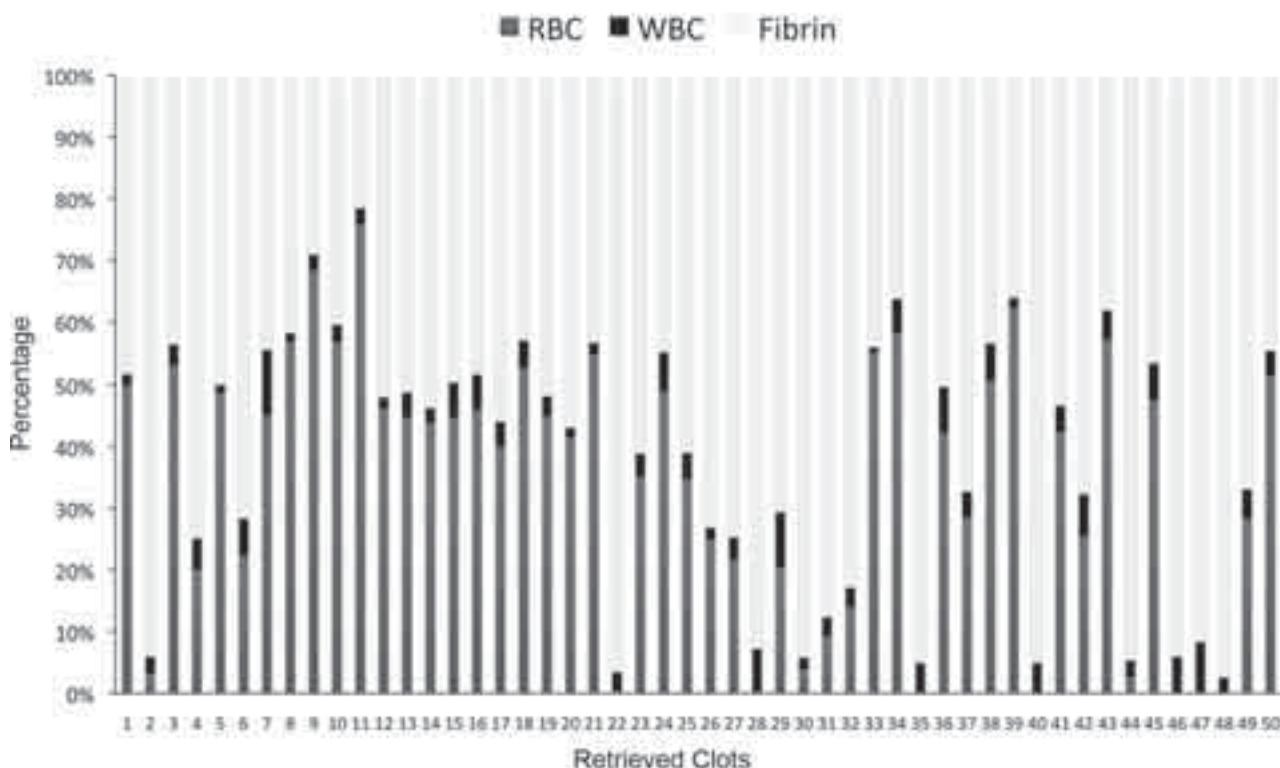


**Figure 3.** Classification of retrieved thrombi as red blood cell-dominant (**A**) and fibrin-dominant (**B**).

S99809)를 사용하여 촬영하였다. 이후 조직학적 분석을 임상 양상에 대한 정보 없이, 기능적 차이가 있는 과정들에 대한 특징 추출 분석(feature-detection analysis) 방법으로 시행하였다. 분석 대상 과정들에는 혈소판:섬유소 축적(흐르는 혈액에서의 혈전 생성), 선형 중성구와 단핵구 침착(표면 흡착 상호 작용), 적혈구 과다 축적(전혈 응고)이 포함되었다. 또한, 광학 현미경을 이용하여 혈전의 구성을 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 슬라이드는 Aperio Scanscope XT digital scanner (Aperio, Vista, CA)를 사용하여 400배로 정밀 촬영하였다. 각각의 디지털 영상 파일은 200 MB에서 5 GB에 이르는 크기로, 영상 분석 소프트웨어로 분석하기 위하여 작은 파일 크기로의 전환을 필요로 하였다. 이 과정은 Adobe Photoshop CS3 (Adobe Systems, San Jose, CA)를 이용하여 섬유소, RBC, 그리고 유핵 WBC를 유사 색상(pseudocolor)으로 변화시켜 시행하였다. 유사 색상화는 look-up table과 특정 성분의 계산을 통해 자동 한계점을 사용하여 각 혈전 구성 요소의 영상

#### Histopathologic Composition of 50 Retrieved Clots



**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 특정 색상을 부여하는 방법으로 진행하였다. 그 다음에 RBC, WBC, 섬유소의 각 영역별 분율을 계산하기 위해 Image J software (National Institutes of Health, Bethesda, MD)를 사용하였다. 이러한 병리 분석은 전체 혈전 제거 과정을 통해 추출된 각각의 혈전 조각 분석에 이용되었으며, 여러 개의 혈전 조각이 추출되었을 경우에는 각 혈전의 구성 요소들(RBC, WBC, 섬유소)의 분석 결과 평균값을 사용하였다.

임상 자료, 방사선학적 및 혈관조영술 자료, 병리 분석 자료에 대하여 기술 통계 분석 방법을 시행하였다. HMCAS와 BA를 포함한 조기 혈관 칭후의 존재 유무와 혈전 병리의 특성을 범주형 변수로 전환하여 통계 분석에 적용하였다. 각 특정 혈전 구성 요소의 분율은 연속형 변수로 간주하였다. CT와 MRI 상의 혈전 생성의 조기 혈관 칭후와 혈전 구성의 관계는 카이제곱검정 및 분산 분석 방법을 사용하여 확인하였고, 유의 수준은 0.05 미만으로 정하였다. 통계 분석은 SPSS software (Version 16.0; SPSS, Inc, Chicago, I.L.)를 이용하였다.

## 결과

선정 조건을 만족시킨 환자 50명의 평균 연령은 66세였고 48%가 여성이었으며, 82%가 백인이었다. 임상적 특성은 Table에 기술하였다. 혈관조영술에서 내경동맥 폐색은 52%, MCA 폐색은 48%에서 관찰되었다. Merci Retriever System만 사용한 경우(78%)와, 정맥내 치료를 함께 받은 경우(14%), 그 외 다른 치료(경동맥 tPA 투여[2%, 혈관성형술, 스텐트 삽입술]를 함께 시행한 경우가 있었다. 본 연구에 포함된 환자의 최종 Thrombolysis in Cerebral Infarction 점수의 중앙값은 2였다(2% 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 ( $\pm 8$  SD)이었다. 32건의 MRI 결과를 검토한 결과, 17건(53%)에서 BA가 관찰되었다(Figure 2). 2명의 환자는 본 연구 기관에서 혈관조영술 시행 전에 CT와 MRI를 모두 시행하였으며, HMCAS와 BA가 모두 관찰되었다. MRI 촬영의 금지 사유 여부를 즉시 평가할 수 없을 때, 선별 목적으로 MRI 검사 이전에 CT를 시행하였다. 이들 중례에서, 혈관 칭후는 정확히 같은 혈관의 해부학적 위치에서 관찰되었다.

추출된 혈전은 때때로 하나의 뎅어리인 경우도 있었으나 대부분은 여러 개의 조각으로 나뉘어졌다. 이들 여러 개의 조직들은 각 시술 과정의 다양한 단계에서 얻어졌으며, 혈전이 제거된 시기도 다양했다. 혈전의 양과 재관류 또는 재개통 상태와는 관련성이 없었다. 혈관내에서 폐색을 일으킨 혈전의 기원은 혈전제거술과 카테터 조작 특성상 명확하게 평가할 수 없었

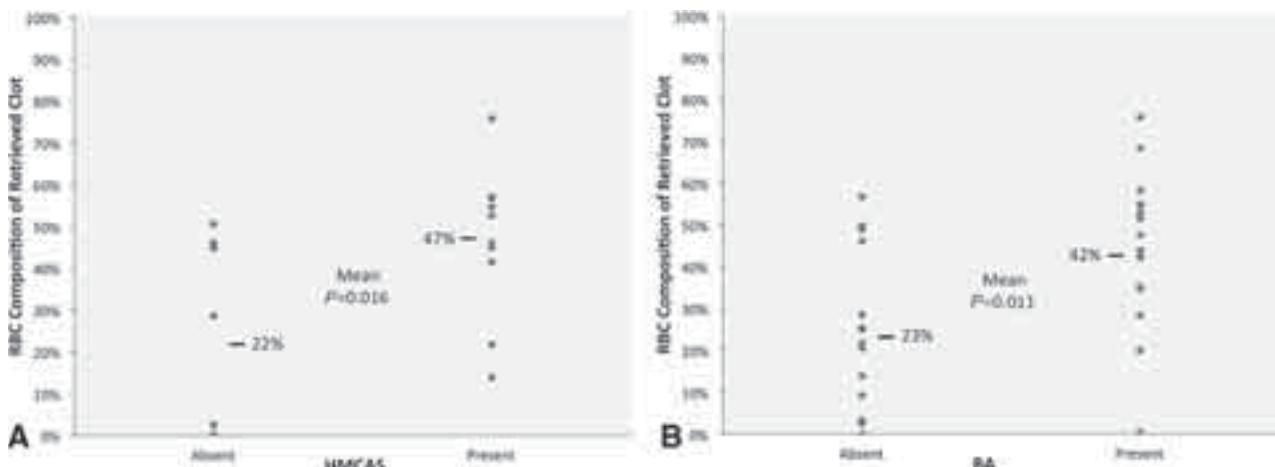
다. 그러나 일부 중례에서는, 육안 검사와 조직병리학적 검사상 쉽게 혈전 기원의 위치를 관찰할 수 있었다.

제거된 혈전 중에서, 섬유소는 61% ( $\pm 21$ ), RBC는 34% ( $\pm 21$ ), WBC는 4% ( $\pm 2$ )의 평균 구성 비율을 보였다. 제거된 혈전 중에서, 22개(44%)가 섬유소-우성으로 분류되었으며, 13개(26%)는 RBC-우성, 15개(30%)는 혼합형으로 분류되었다 (Figure 3). 전반적인 병리학적 분포는 Figure 4에 표시한 대로 모든 중례에 걸쳐 관찰되었다. WBC 구성은 모든 중례에서 일관적으로 미미하였다. 여러 조각으로 나뉘어진 중례에서도, 성공적으로 혈전이 제거된 경우와 그 구성이 다르지 않았다. 본 연구 기간 6년 중, Merci Retriever System을 이용하여 첫 혈전제거가 이루어지고 실제 임상에 소개되기까지 2년간, 혈관내 시술의 기술적인 면의 다양성으로 인하여 야기될 수 있는 병리학적인 소견의 변화는 없었다. 본 연구자들은 최근 이 시술 과정 이후 나쁜 예후를 보인 환자들의 특성을 기술한 부검 연구 결과를 발표하였다.<sup>27</sup>

영상 검사 기법(CT 또는 MRI)과 육안 검사 결과 또는 조직병리학적 검사 결과의 연관성은 관찰되지 않았다. 진단적 영상 결과를 얻은 시점과 혈전이 제거된 시점 간의 시간(평균  $\pm$  SD, 86  $\pm$  32분)과 혈전 성분 및 구성비 결과의 차이는 없었다.

CT상의 HMCAS는 RBC-우성 또는 혼합형 혈전에서 섬유소-우성인 혈전에서보다 더 잘 관찰되었다(100% vs. 67% vs. 20%,  $P=0.016$ ). 평균 RBC 구성 비율은 HMCAS가 관찰된 경우에서 더 높았으나(47% vs. 22%,  $P=0.016$ ), HU 밀도는 혈전의 구성과 관계가 없었다. BA 또한 RBC-우성 또는 혼합형 혈전에서 섬유소-우성 혈전에서보다 더 자주 관찰되었다(100% vs. 63% vs. 25%,  $P=0.002$ ). 모든 중례에서 일관적으로 낮은 비율을 보인 WBC 성분은 HMCAS나 BA의 존재와 관계가 없었다. BA에서 평균 RBC 비율이 더 높았다(42% vs. 23%,  $P=0.011$ ). 조기 혈관 칭후(HMCAS 또는 BA)의 존재 유무는 임상적 특징 또는 방사선학적 요인과 관련이 없었다. 다변량 회귀 분석 결과 RBC 구성 비율을 제외하고는 HMCAS나 BA의 예측인자는 없었다(Figure 5). CT와 MRI를 모두 촬영 한 두 중례에서, HMCAS와 BA의 완전한 일치가 정량 분석에서 RBC의 구성 비율이 증가한 RBC-우성 혈전과 연관되어 있었다. HMCAS나 BA가 없는 경우는 작고 섬유소가 많은 혈전 조직에서 조금 더 흔하였다.

본 연구 결과에서 영상 검사 결과(HMCAS나 BA), 또는 혈전의 조직병리학적 특성과 뇌졸중의 중증도 또는 이후의 예후와의 연관 관계는 없었다. 혈전의 조직병리학적 특성은 뇌졸중의 원인이나 기전(심인성색전증[cardioembolism] 또는 죽상 경화증[atherosclerosis])과도 관련되어 있지 않았고, 성공적인 추출 가능성과도 관련이 없었다. 이와 유사하게, 영상 결과 또는 조직병리학적 특성은 혈전제거 시점에 대하여서도 차이가 없었다.



**Figure 5.** Red blood cell (RBC) composition of retrieved clots correlates with early vessel signs, including (A) the hyperdense middle cerebral artery sign (HMCAS) and (B) blooming artifact (BA).

## 고찰

급성 허혈뇌졸중에서 CT나 MRI와 같은 비침습적 영상 검사 방법의 혈관 이상 소견은, 20년 이상의 기간 동안 혈전 성상의 병리학적 확인 없이 혈관 폐색을 유발한 혈전의 결과라 기술되어 왔다.<sup>5,15</sup> 본 연구 결과에서 CT상의 HMCAS와 GRE MRI상의 BA를 포함한 조기 혈관 징후가 그 혈전의 병리학적 특성을 반영한다는 초기 방사선학적-병리학적 결과의 연관 관계를 보여 주었다. HMCAS와 BA는 급성 뇌졸중 환자의 치료 우선 순위를 정하는 과정에서 자주 관찰되며, 혈관내 혈전의 구성이나 종류에 대하여 추측하고, 다양한 혈관재개통술을 이용할 때의 예후 예측에 영향을 준다. 본 연구에서 관찰한 것과 같은 혈전 구성에 대한 정확한 기술은 임상적 특성, 비침습적 영상 검사, 혈관조영술, 조직병리학적 육안 검사 등에 기초하여 이루어져야 한다.<sup>6</sup> 뿐만 아니라, 혈전의 자세한 병리학적 검사는 기계적 혈전제거술에서만 가능하며, 정맥내 또는 동맥내 혈전용해술, 흡인, 또는 혈관성형술과 스텐트 삽입술에서는 가능하지 않다. 본 연구 결과에서 급성 허혈뇌졸중에서 혈관 폐색을 일으킨 혈전의 영상 검사에 관한 여러 가지 중요한 관찰 결과를 확인하였다.

혈전으로 인한 급성 MCA 폐색 시 조기 혈관 징후는 일부 환자에서만 관찰되며, 이러한 방사선학적 이상 소견이 관찰되지 않는다고 해서 혈전성 폐색 가능성은 제외시키지 않는 것이 더 중요할 것이다. HMCAS나 BA는 성공적으로 혈전제거술을 시행한 연구 대상 중례의 반 가량에서 관찰되었다. HMCAS를 처음 기술하였을 때에는 조금 더 높은 발생률을 보고하였으나, 대부분의 성공적인 연구들에서는 발견율을 50% 가량으로 보고하였고, 이는 이번 연구 결과와 비슷하다.<sup>5-7,11</sup> HMCAS의 발견은 HU의 정량적 측정이나 다른 요인들을 포함한 방법적인 변화에 의하여 영향을 받는다.<sup>20</sup> 심인성색전증 또는 큰동맥 죽상경화증으로 구별되는 뇌졸중의 발생 기전이 BA가 잘 발견되는 데 영향을 주었을 수 있으나, 이번 연구에서도 이전에 보고

된 것과 같은 BA 발견율을 보였다.<sup>12-14</sup> 심인성색전증과 연관되어 상대적으로 큰 혈전이 BA가 더 잘 보이도록 하였을 수 있을 것이다.<sup>13</sup> 이번 연구의 중례 중 47%에서 BA가 관찰되지 않았는데, 이는 일반적으로 섬유소가 많은 혈전과 연관되어 있었고, 이는 약물을 이용한 섬유소용해(fibrinolysis)의 잠재적 대상이 될 수 있다. HMCAS와 BA의 연관성을 본 경우는 제한된 자료만이 있는데, 이는 MRI의 일차적 사용과 혈전제거술의 빠른 대상 선정이 종종 CT를 찍을 필요가 없도록 하기 때문이다.<sup>14</sup> HMCAS는 혈전용해술 이전에 CT만을 통상적으로 사용한 경우 15%까지 낮게 보고되고, 치료적인 이득은 이 결과와 특별한 관련 없이 얻어지는 것 같다.<sup>28</sup> 후대뇌동맥(posterior cerebral artery)과 같은 다른 영역에서의 조기 혈관 징후에 대하여서는 병리학적 연관성에 대한 연구가 필요하다.<sup>10,13,14,29,30</sup>

HMCAS와 BA는 혈전의 구성 요소, RBC 성분을 반영하는데, 이는 아직 섬유소용해의 주된 목표는 아니다. RBC-우성으로의 혈전 분류는 HMCAS나 BA가 동정된 경우 모두에서 관찰되었다. 이들 조기 혈관 징후는 섬유소가 많은 혈전에서는 드물었다. RBC의 비율은 이 영상 소견과 밀접하게 관련되어 있었다. HMCAS 내의 HU의 측정은 최근에 발생한 색전과 관련되었으나, 이 밀도의 변화를 특정 혈전 구성 성분의 탓으로 생각하기는 어렵다.<sup>10,20,31</sup> HU 밀도와 RBC의 정량적 측정 간의 관계를 확인하지 못하였기 때문에, RBC가 많은 혈전 또는 '적색 혈전(red thrombus)'의 존재를 가리는 데 있어서 HMCAS의 유무를 단순히 육안으로 시행하는 외관 검사만으로 충분할 것으로 보인다. GRE MRI상의 BA의 감수성 효과(susceptibility effect)는 RBC 성분과 연관된 국소적 철자성 장의 왜곡(ferromagnetic field distortion)과 관련된 것으로 보인다. 그러므로, HMCAS와 BA는 지금까지 뇌졸중의 동맥 재개통술의 대부분에서 목표로 삼고 있는 섬유소 망(fibrin mesh)보다 RBC 덩어리를 조금 더 반영하는 혈전의 간접적 표지자이다. 그러나, 혈관내 시술 동안 기계적 혈전제거술의 조직이 추가적

인 구성 성분과 주변의 적색 혈전을 함께 걸려들게 하는 것이라는 가능성도 여전히 남아 있다.

진단적 영상 방법을 이용하여 ‘적색 혈전’과 ‘백색 혈전(white thrombi)’을 구분하고자 하는 시도는 다년간 이루어져 왔으나 달성되지 않았다.<sup>22</sup> 허혈뇌졸중을 일으킨 혈전의 초기 분석 결과에서, ‘적색 혈전과 백색 혈전’의 전통적 구분이 정말로 적용 가능한지에 대한 의문이 생겼으며, 이는 병리학적 조직에서 다양한 결과가 관찰되기 때문이었다.<sup>8</sup> 뒤이은 연구 결과 또한 혈전에서 주목할 만한 다양성을 보고하였다.<sup>9</sup> 아마도 그런 이유로 인하여 CT나 MRI를 통한 혈전 성상의 예측은 어려울 것이며, 특히 HMCAS나 BA가 폐색 부위 근위부와 원위부의 저류에 의하여 유도된 이차적 구성 성분보다는 색전의 근원을 반영한다고 가정하면 더욱 그러할 것이다. HMCAS와 BA가 RBC 성분을 강조한다는 이번 연구 결과 또한 그러한 증례에서 저류나 방금 생성된 혈전이 조금 더 흔하다는 것을 시사할 수 있다. HMCAS나 BA에 대하여 제거된 혈전 조각들의 공간적 근원을 재구성하는 것이 어려울지라도, 24%의 증례에서 제한적인 재관류(Thrombolysis in Cerebral Infarction 0 또는 1)만이 이루어졌다는 것은 RBC 성분이 저류에 의하여 증가한 것이라는 가능성을 제기한다. 이러한 가설은 대뇌허혈(cerebral ischemia)에서의 혈류 교란의 역할을 강조하는데, 이는 혈전 면에 부딪히고, 원위부는 결순환 관류를 통해 채워진다.<sup>25</sup> 저류는 혈전이 혈관 폐색을 일으킨 부위가 아니라 혈전 생성의 원인 부위에서 혈전의 생성을 결정한다고 언급되어 왔다.<sup>10,33</sup> 혈관조영술은 그러한 요인을 구분하는 데 필수적이다. 흥미롭기도, 제거된 혈전의 양과 이후 순차적인 재관류의 연관성은 발견하지 못하였는데, 이는 혈전 생성 이상의 또 다른 허혈의 병리생리학적 면을 시사하며, 이는 미래의 뇌졸중 치료 방법에 매우 중요한 역할을 할 것이다.

대뇌동맥의 혈류와 혈전의 상호 관계에 대한 고려 없이는 HMCAS와 BA를 이용하여 혈관재개통의 예후를 예측하는 데 내재적 결함이 존재한다.<sup>25,26</sup> 많은 연구에서 조기 혈관 징후의 예후 예측이나 혈관재개통에 대한 예측 정도를 규명하기 위해 시도하였으나, 그러한 예후들은 혈전의 구성이 혈류 장애의 원인으로써 뿐만 아니라 결과로써도 어떻게 작용하는지의 여부를 포함한 여러 다양한 원인에 의하여 결정되는 것 같다.<sup>7,10,11,13,16-18</sup> HMCAS와 BA와 RBC-우성 혈전의 병리 결과 간의 명백한 연관 관계에도 불구하고, 이러한 징후에만 의존하여 뇌졸중의 원인을 결정하거나 혈관재개통 방법을 계획하는 것은 피해야 한다. HMCAS나 BA의 영상 특징만으로는 혈전의 성공적 제거를 예측할 수 없다는 이번 연구 결과는, 영향을 줄 만한 다른 원인들에 대한 연구를 필요로 한다. 그것은, 재개통은 아마도 해당 증례의 여러 특징에 의하여 영향을 받기 때문이다. 추가적인 상관 관계 연구로 이들 영상 검사상의 징후와 혈류를 특성화하는 혈관조영술 결과의 특징을 포함하여 다양한 혈관내

접근 방법의 영향을 평가하여야 한다.

본 연구에서의 조기 혈관 징후와 혈전의 병리학적 특성 간의 포괄적인 분석은 몇 가지 제한점을 가지고 있다. 혈관조영술 시행 직전에 검사한 초기 영상 검사 결과의 유무 및 영상 질의 평가는 이미 기계적 혈전제거술에 적당한 환자로 제한된 코호트에서 추가적으로 결정되었다. 이번 연구 결과는 많은 증례를 제외함으로써 생긴 유의한 편향(bias)에 의하여 해석에 제한이 있다. 연구 결과가, 혈전제거술이 가능한 근위부 MCA에 혈전이 위치한 경우만으로 국한되었기 때문이다. 혈관 폐색이 회복되는 경우나 완벽하게 분해된 경우에는 연구를 진행할 수 없어서 분석에서 제외하였다. 혈관조영술 이전에 시행한 정맥내 tPA로 일부 혈전에 변화가 생겼거나, 시술 중에 표준 과정으로 주입하는 혜파린으로 인한 변화가 반영되었을 가능성도 남아 있다. 이미 기술한대로, 혈전 조각의 근원은 추측일 뿐이고, 그 외 함유된 조각은 그 구성에서 차이가 날 수 있다. 마지막으로 대부분의 혈전 조직이 그 성상 면에서 다양했기 때문에 혈전 종류의 분류 또한 불완전하다.

## 결론

이번 연구는 급성 허혈뇌졸중에서 관찰되는 조기 혈관 징후를 기저의 혈전 구성과 연관시킨 첫 번째 연구이다. HMCAS와 BA는 혈전성 MCA 폐색에서 흔히 나타나는 것은 아니고, 이 미세한 소견을 확인하지 못했다고 해서 동맥 재개통술을 시행하지 않아서는 안된다. 혈류에 대한 구성 및 분자생물학적 특성을 포함한 혈전 구성의 조금 더 자세한 면에 대한 후속 연구가 진행 중이다.

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# Original Contributions

## 缺血性卒中 CT 及 MRI 早期血管征象反映血栓成分 CT and MRI Early Vessel Signs Reflect Clot Composition in Acute Stroke

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**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。以红细胞为主型及混合型血栓比以纤维蛋白为主型血栓更常出现 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)

缺血性卒中常因诸多原因引起的动脉闭塞而发生。导致急性期近端颅内动脉闭塞及继发的下游缺血的病理生理学机制尚不明确，而血栓形成是血管闭塞的一个重要原因。脑梗塞的大部分治疗策略集中于裂解血栓或溶栓<sup>[1]</sup>。实际上，FDA 批准的治疗脑梗塞的方法仅有 tPA 和使用多种装置的血管内取栓术两种<sup>[2-4]</sup>。静脉溶栓并不依赖对血栓状况的详尽了解，而近端颅内动脉血栓形成时常预示广泛而严重的缺血事件需要采取侵入性治疗措施，这需要更细致的影像学支持<sup>[5-7]</sup>。大部分卒中血管内再通治疗之前，CT 及 MRI 等无创影像学检查都能提供相似的近端血管闭塞的证据，但要了解闭塞的详细特征则依赖其他手段。缺血性卒中颅内动脉血栓摘除术或取栓术则提供了直接研究血栓成分及性质或各种阻塞物的绝好机会<sup>[8-10]</sup>。

以往研究显示，早期血管征象的出现往往提示血栓形成，这些征象包括缺血性卒中大脑中动脉高密度征 (HMCAS) 以及 MRI 梯度回波序列或磁敏感加权成像显示的开花伪像 (BA)<sup>[5-7,10-17]</sup>。众多研究显示这些征象提示不良的临床预后及低再通率<sup>[7,10-13,17,18]</sup>。但是大部分研究都没有对阻塞部位的血管像或病理特征进行相关研究。

我们先前报道了一系列缺血性卒中颅内动脉近端血栓的病理变化。本研究首次结合神经影像进行相关性研究，可能有助于通过影像预测血栓成分。本研究首次对斑块和血栓成分及其对 HMCAS 及 BA 等血管早期征象的出现及特征的影响进行研究。

### 方法

自 2001 年 5 月至 2007 年 3 月间连续纳入本中

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心 85 名缺血性卒中患者，在进行血管内取栓术前进行 CT 或 MRI 评估，使用非增强 CT 及 MRI，包含 MRI 梯度回波序列 (GRE)，获取每位患者的标准图像<sup>[19]</sup>，GRE 序列无间隙扫描，层厚 5 mm，重复时间 800 ms，回波时间 15 ms，翻转角度 30°，256×144 矩阵。入选标准包括急性大脑中动脉 (MCA) 闭塞，能够获得非增强 CT 或 GRE MRI 影像，其后行血管内血栓取栓术，并能够成功获得血栓病理结果。在转到我们中心之前于外院做的 CT 检查，因为缺乏实用性，质量不高，而且无法在非医学数字化影像及通讯 (Digital Imaging and Communications in Medicine, DICOM) 格式图像上测量 HU (Hounsfield Unit) 密度值，因此，未在我们中心行 CT 或 MRI 检查以及取栓术未获得血栓病理标本的病例均排除在外。

本中心前瞻性纳入患者的临床、放射学及详细的血管造影信息，这些数据被常规记录并保存在中心数据库。取栓术之前获得的 GRE MRI 影像由两位血管神经病学专家在临床、造影信息及血栓病理双盲的情况下进行回顾性的分析，他们均通过资格认证同时神经影像学鉴定合格。两位神经影像专家经肉眼阅片意见一致后才能确认 HMCAS 存在，以 MCA 区域非对称性的明显或显著增高的密度影来对 HMCAS 进行分级，不使用 HU 密度值进行特异性测量<sup>[20]</sup>。在完成 HMCAS 的分级后，测量双侧 MCA 段 HU 密度值，用相同的模式进行 GRE MRI 扫描，通过肉眼分辨是否出现 BA，BA 被定义为 MCA 近端低信号影或信号丢失区，血管的边缘常常扭曲。若 HMCAS 及 BA 存在伪影而不清晰，该病例即被排除。

在取栓术前使用数字减影血管呈像 (DSA) 明确 MCA 闭塞的诊断。血栓扩展至同侧颈内动脉或大脑前动脉的 MCA 闭塞也纳入到分析之内。造影技术及取栓术的具体方案另外详述<sup>[3]</sup>。纳入分析的行取栓术的病例也包括在 MERCI (Mechanical Embolus Removal in Cerebral Ischemia) 及联合 MERCI 临床试验之中，病人的纳入是日常临床工作的一部分，使用 FDA 批准的 Merci 取栓系统进行取栓<sup>[3,21-23]</sup>。MERCI 及联合 MERCI 临床试验评价发病 8 小时内近端颅内动脉闭塞使用 MERCI 取栓系统 (Concentric Medical, Inc, Mountain View, CA) 进行血管内取栓的安全性及有效性<sup>[3,21,22]</sup>。在所有报道的病例中均使用 MERCI 取栓系统及其后延伸设备进行机械取栓。从诊断到取栓术后一系列的血管造影数据被保存并用

以分析动脉闭塞的特点及侧枝循环的血流<sup>[24-26]</sup>。使用脑卒中溶栓量表 (Thrombolysis in Cerebral Infarction scale) 评价阻塞的程度及下游灌注情况，侧枝灌注情况使用美国介入及神经放射治疗学会 / 介入放射学会 (ASITN/SIR) 侧枝血流评级系统<sup>[24]</sup>进行评价。

在整个取栓术的不同时期相继取出不同数量的血栓，在完成多次取栓并显示血栓负荷下降后，拔出导管，螺旋线圈的远端则用来检查是否还存在血栓及其他栓塞物。如果未发现分离的血栓，使用生理盐水轻轻冲洗吸出物以显示不易发现的小栓子碎片。照相记录血栓与远端取栓导管的关系及取出血栓的形状。然后将血栓置于纱布或手术衣之上，多视角拍照，使用标记帮助显示血栓的大体三位度量。然后立即使用 10% 的磷酸缓冲福尔马林液血栓样本固定，石蜡包埋固定，然后以 8 μm 厚度切片，苏木精 - 伊红染色液染色。固定 MicroFire 数码相机 (Model S99809) 的 Olympus BX41 于显微镜进行拍照。组织学检查过程中不接触相关的临床数据，完全基于形态学分析，包括血小板聚集 (流动血液中血栓形成)、线样中性粒细胞及单核细胞沉积 (表面粘附聚集)、富红细胞聚集体 (全血凝固)，血栓成分在光镜下也被分为红细胞为主、纤维蛋白为主，及混合型。使用全幅数字影像进一步进行组织病理分析，包括半自动定量及定量测量红细胞 (RBC)、白细胞 (WBC) 及纤维蛋白含量。使用 Aperio Scanscope XT 数字扫描仪 (Aperio, Vista, CA) 扫描放大 400 倍的苏木精 - 伊红染色液切片。获得的单幅数字图像文件非常大，从 200 MB 至 5 GB 不等，需要处理成小幅尺寸以便图像分析软件能够对成分含量进行量化。过程中使用 Adobe Photoshop CS3 (Adobe Systems, San Jose, CA) 给纤维蛋白、红细胞及有核白细胞附以伪彩，使用颜色查找表及全自动阈值为每种血栓成分附上特定伪彩来计算各种成分的含量，然后用 Image J 软件 (National Institutes of Health, Bethesda, MD) 定量各区域的红细胞、白细胞及纤维蛋白。用同样的方法对整个过程中取得的所有血栓片段进行定量，最后计算所有血栓片段的平均值以及平均血栓成分含量 (包括红细胞、白细胞及纤维蛋白)。

描述性数据分析广泛应用于各种临床血管造影及病例数据分析。早期血管征的出现与否、血栓病理的定量描述在数据分析中均使用等级变量进行分析。每种血栓成分含量的百分比使用连续变量，血栓在 CT 及 MRI 上早期血管征象及血栓成分之间关系使用卡方检验，变量数据分析有意义界定于

**表 研究样本临床特征**

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

$P<0.05$  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( $\pm 8$ )。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。

织病理学上可见的完整血栓可以很容易地进行空间定位。

平均 (标准差 [SD]) 成分为 61%( $\pm 21$ ) 的纤维蛋白, 34%( $\pm 21$ ) 的红细胞, 以及 4%( $\pm 2$ ) 的白细胞。

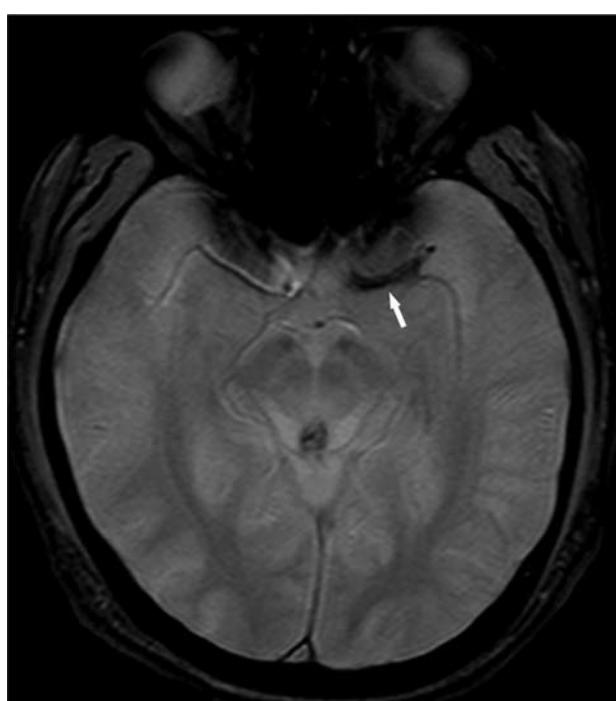


图 2 梯度回波序列 MRI 显示左侧大脑中动脉开花伪像 (BA, 箭头)。

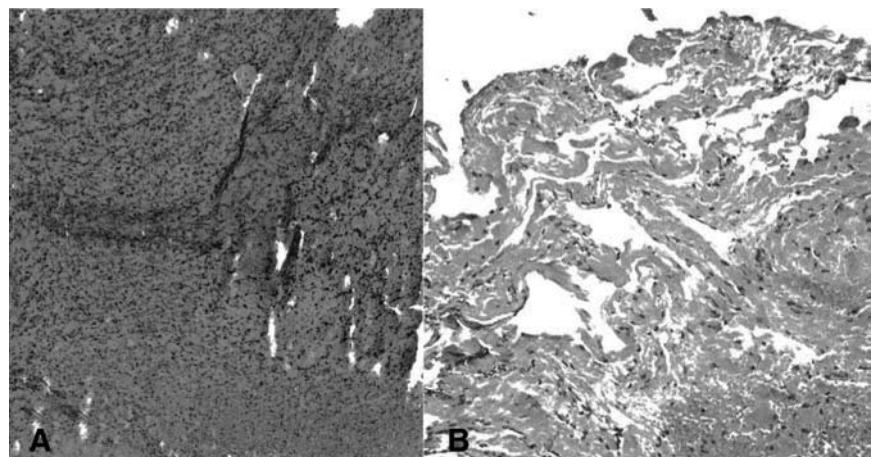


图 3 红细胞为主的血栓 (A) 和纤维蛋白为主的血栓 (B)

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<sup>[27]</sup>。

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 也较常常见于红细胞为主及混合型的血栓，而不是纤维蛋白

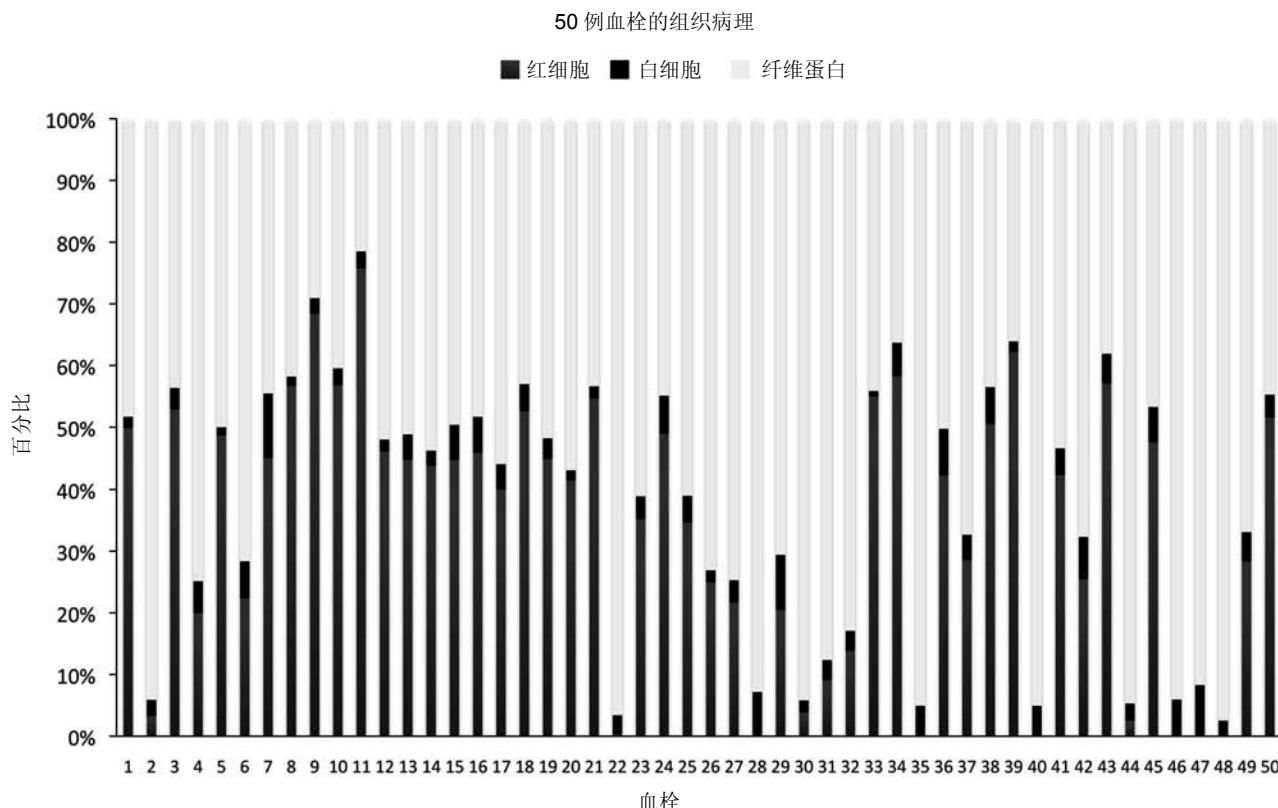


图 4 血栓按 1 到 50 编号纳入。组织病理学成分包括红细胞、白细胞以及纤维蛋白。

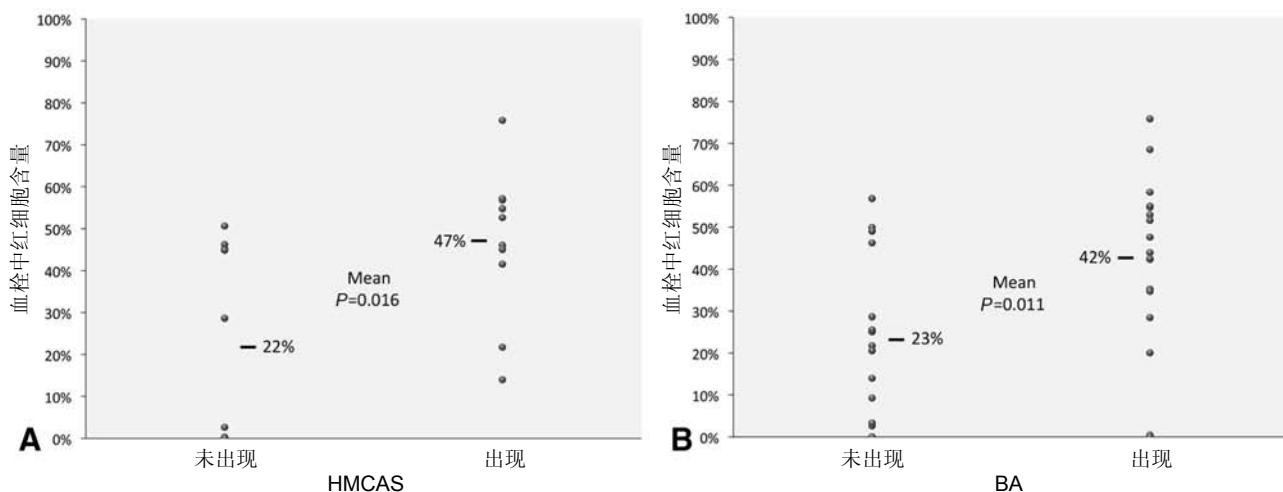


图 5 HMCAS 与红细胞含量的关系 (A) 以及 BA 与红细胞含量的关系 (B)。

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<sup>[5,15]</sup>，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。缺血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，以及其对不同血管再通治疗的效果是否会造成影响的诸多猜测。血栓成分的确定依赖于综合的评估，包括临床特征、非侵入性影像、血管造影以及病理学的系统检查<sup>[8]</sup>。而对血栓详细的病理学检查只有通过血栓取栓术才能实现，而不是动静脉溶栓、吸

引术、血管成形术及支架植入术。我们在进行缺血性卒中闭塞性血栓的研究中有许多新的影像学发现。

早期血管征象可能只在部分急性大脑中动脉血栓性闭塞病例中出现，但重要的是这些影像学征象缺失时往往不排除血栓性闭塞。本研究成功实施血栓取栓术的病例中约有一半出现 HMCAS 或 BA。早期文献报道 HMCAS 的出现率非常高，而更多后续研究报道的检出率约为 50%，与我们的研究相一致<sup>[5-7,11]</sup>。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本因子<sup>[20]</sup>。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<sup>[12-14]</sup>。相对来说，心源性栓塞的血栓负荷越重 BA 显示越清晰<sup>[13]</sup>。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<sup>[14]</sup>。有研究报道的连续纳入的患者溶栓前单使用常规 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<sup>[28]</sup>。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<sup>[10,13,14,29,30]</sup>。HMCAS 及 BA 反映的是血栓的成分之一 (红细胞) 的含量，而不是溶栓的重要指征。在出现血管征象的几乎所有病例中，血栓成分都是以红细胞为主，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

种血栓成分<sup>[10,20,31]</sup>。

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<sup>[10,20,31]</sup>，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 的磁敏感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<sup>[32]</sup>。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<sup>[8]</sup>，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<sup>[9]</sup>。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瘀滞诱发的继发成分时。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。尽管重建与 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<sup>[25]</sup>。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<sup>[10,33]</sup>。血管造影可能成为识别这些影响因素不可或缺的手段。有趣的是我们并未发现取栓量与其后的再灌注存在明显相关，提示在血栓形成机制之外可能还存在其他的病理生理学机制，可能成为未来卒中治疗策略。

如果不考虑血流及血栓的相互作用，HMCAS 及 BA 对血管再通的预测价值可能会大打折扣<sup>[25,26]</sup>。众多的研究尝试明确早期血管征象对卒中预后或对血管再通的预测价值，然而影响预后的因素众多，而血栓成分并非唯一因素，还要考虑血流受损<sup>[7,10,11,13,16-18]</sup>。尽管 HMCAS 与 BA 同红细胞为主的病理类型关系明确，但临床医师不能仅仅依据这些发现来明确卒中病因或制定血管再通策略。我们发现显示影像学特征不能单独准确预测取栓效果，仍需探究其他潜在影响因素，毕竟血管再通受多方面因素影响。进一步的研究需要着眼于联合血管造影及血流特征的基础上评估这些影像征象对不同血管治疗手段的影响。

尽管这次机会难得，但也存在一些局限，造影的基线影像数据的可用性及质量已经导致了选择性偏倚，仅仅局限于适合做取栓术的患者。我们的研究中排除了许多病例而存在较大的偏倚，因为手术只能取到近端 MCA 血栓，而这些结论仅适用于该段的血栓。弹性血栓及崩解的血栓被排除在外。部分血栓有可能是反映了血管造影前静脉组织纤溶酶原激活的作用，甚至是标准肝素治疗的结果。正如上述，血栓片段位置上存在选择偏倚，而且血栓成分也可能存在其他的不同。

## 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，并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。

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