Mechanisms of Acute Cerebral Infarctions in Patients with Middle Cerebral Artery Stenosis: A Diffusion-Weighted Imaging and Microemboli Monitoring Study

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Although most therapeutic efforts and experimental stroke models focus on the concept of complete occlusion of the middle cerebral artery as a result of embolism from the carotid artery or cardiac chamber, relatively little is known about the stroke mechanism of intrinsic middle cerebral artery stenosis. Differences in stroke pathophysiology may require different strategies for prevention and treatment. We prospectively studied 30 consecutive acute ischemic stroke patients with middle cerebral artery stenosis detected by transcranial Doppler and magnetic resonance angiography. Patients underwent microembolic signal monitoring by transcranial Doppler and diffusion-weighted magnetic resonance imaging. Characteristics of acute infarct on diffusion-weighted magnetic resonance imaging were categorized according to the number (single or multiple infarcts) and the pattern of cerebral infarcts (cortical, border zone, or perforating artery territory infarcts). The data of microembolic signals and diffusion-weighted magnetic resonance imaging were assessed blindly and independently by separate observers. Diffusion-weighted magnetic resonance imaging showed that 15 patients (50%) had single acute cerebral infarcts and 15 patients had multiple acute cerebral infarcts. Among patients with multiple acute infarcts, unilateral, deep, chainlike border zone infarcts were the most common pattern (11 patients, 73%), and for single infarcts, penetrating artery infarcts were the most common (10 patients, 67%). Microembolic signals were detected in 10 patients (33%). The median number of microembolic signals per 30 minutes was 15 (range, 3–102). Microembolic signals were found in 9 patients with multiple infarcts and in 1 patient with a single infarct ($p = 0.002$, χ^2). The number of microembolic signals predicted the number of acute infarcts on diffusion-weighted magnetic resonance imaging (linear regression, adjusted $R^2 = 0.475$, $p < 0.001$). Common stroke mechanisms in patients with middle cerebral artery stenosis are the occlusion of a single penetrating artery to produce a small subcortical lacuna-like infarct and an artery-to-artery embolism with impaired clearance of emboli that produces multiple small cerebral infarcts, especially along the border zone region.

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In the coronary circulation, acute coronary syndromes can be produced by a complete occlusion of 1 of the main arteries, which usually results in a Q wave myocardial infarct with segment elevation. Acute coronary syndromes can be produced by a partially or intermittently occluded artery that usually results in unstable angina or non-Q myocardial infarct. In the cerebral circulation, total occlusion of the middle cerebral artery (MCA) by an embolus originating from the carotid artery or the cardiac chambers occurs frequently in acute stroke patients. This observation provides the basis for most experimental stroke models and inspires the successful use of hyperacute thrombolytic therapy. However, the pattern and mechanism of cerebral infarction in partially occluded atherosclerotic cerebral arteries remain unknown. Atherosclerotic stenosis of the intracranial large artery, especially the MCA, occurs infrequently in stroke patients in whites. However, it is a common cause of stroke in patients with Chinese and African ancestry.[1–3] Possible mechanisms for cerebral infarction include thrombosis leading to complete occlusion, artery-to-artery embolism, hemodynamic compromise, local branch occlusion, or a combination of these factors. The elucidation of the mechanism responsible for cerebral infarction may have clinical implications for tailored treatment for or prevention of

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stroke from intracranial stenosis. For example, warfarin should be investigated as a treatment to prevent artery-to-artery thromboembolism, whereas intervention strategies such as angioplasty and induced hypertension should be studied to improve perfusion and cerebral hemodynamics. Anticoagulation and angioplasty are 2 treatments currently under study for this group of patients. However, there have been few studies that explore the pathophysiology of cerebral infarction in patients with intracranial atherosclerosis, especially during the acute stage.

Advances in neuroimaging such as transcranial Doppler ultrasound (TCD) and diffusion-weighted magnetic resonance imaging (DWI) may provide new insights into the interaction between atherothrombosis and cerebral infarction. DWI enables the detection of even small cerebral infarcts and the differentiation of acute ischemic lesions from old ones.[4,5] The visualization and monitoring of embolism in vivo were not possible until the development of TCD.[6] Until now, several studies both in vivo and in vitro have shown that microembolic signals (MESs) detected by TCD are likely to represent emboli passing through the insonated artery.[7–10] In this study, using the latest techniques of DWI along with MES monitoring, we explored the mechanisms of how a MCA stenosis produces acute cerebral infarction.

Patients and Methods

Using TCD, we prospectively screened consecutive acute stroke patients for MCA stenosis who were admitted to the Prince of Wales Hospital in Hong Kong. For patients with clinical features compatible with a stroke in the stenotic MCA territory, MES monitoring by TCD was performed within 3 days of onset of symptoms. The time of onset to TCD was 2.0 ± 0.76 days. Patients then underwent magnetic resonance imaging, including magnetic resonance angiography (MRA) and DWI examination, 2 to 3 days afterward. The time of TCD to DWI was 1.8 ± 0.61 days. A patient was excluded if there was an acute infarct in the territory outside of the studied MCA, complete MCA occlusion or less than 50% stenosis on MRA, or a poor temporal window; those patients who were agitated or confused and those with other potential sources of embolism such as severe (>50%) carotid stenosis or atrial fibrillation also were excluded. None of our patients had clinical evidence of mechanical valve replacement, left atrial or left ventricular thrombus, bacterial endocarditis, or recent myocardial infarction.

Transcranial Doppler Ultrasound Examination

We performed TCD using a TC 2020 machine (Nicolet-EME, Madison, WI) with a 2MHz transducer. The whole length of the MCA was examined through a temporal window. MCA stenosis was suspected if the systolic peak velocity showed segmental elevation of greater than 140cm/sec together with a signal of turbulent flow.[2,11,12]

The technique for MES monitoring was based on the setup and protocol of the ultrasound laboratory at the Department of Neurology, University of Münster, Münster, Germany. We conducted MES detection immediately after conventional TCD examination. The distal segment of the affected MCA was insonated through the temporal window for 30 minutes in all patients. A 2MHz bigate transducer was fixed to the head with the Marc 500 TCD probe fixation headframe (Spencer Technologies, Seattle, WA). The distance between 2 insonation depths was 8 or 10mm. A small sample 6mm in length and a low gain were used. A detection threshold greater than or equal to 5dB was used for all patients.[10] The machine used a 128-point Fast Fourier Transformation analysis and a graded color scale to display the intensity of the received Doppler signal. The FFT timeframe overlap was 61 to 71%. In addition, the audio Doppler signal of both channels was continuously recorded onto a four-channel digital audio tape recorder (TA-88; TEAC, Japan) at normal speed. The following definition for an embolic signal was used: a typically visible and audible (click, chirp, whistle), short-duration, high-intensity signal within the Doppler flow spectrum with its occurrence at random in the cardiac cycle and unidirectional, and an intensity increase of 5dB or more above the background signal.[13] In addition, there should be a time delay for the MES to pass the 2 insonation depths. The presence and number of MESs were assessed by an expert reader (T.H.) who was blinded to all clinical, laboratory, and other imaging data.

For patients with multiple MESs, we used 3 methods to confirm that MCA stenosis was the source of MES with a bigate transducer. Apart from monitoring the distal downstream of the MCA stenosis, we set the other monitoring depths at the ipsilateral anterior cerebral artery and contralateral MCA and proximal to MCA stenosis. The absence of MESs from these locations was regarded as evidence that MESs originated from the MCA stenosis.

Magnetic Resonance Imaging

We performed DWI in a 1.5T magnetic resonance scanner (Gyroscan ASC NT; Philips Medical Systems, Best, The Netherlands) with a standard head coil. The sequence used was a multishot navigated, spin-echo, echo planar imaging sequence with peripheral pulse gating, and diffusion-weighted b-values of 0, 313, and 1,252sec/mm^2 were used to obtain 9 slices in each of the 3 principal magnet directions with the following parameters: repetition time, pulse-dependent; diffusion echo delay time, 140 milliseconds; field of view, 23cm; number of signal average, 1; slice thickness, 6mm with a 1.2mm gap; matrix, 128 × 256; echo planar imaging, factor 9; and acquisition time, 1.5 to 2 minutes for each axis. The slices were chosen to cover the cerebrum. Acute infarcts on DWI were diagnosed when these lesions were shown to be hyperintense on the DWI integrated for the 3 diffusion sensitivity directions and hypointense on the apparent diffusion coefficient map. For images showing motion artifact in 1 diffusion sensitivity direction, infarct or subacute infarct was diagnosed only if the lesion showed all of the following features: (1) it had a much higher signal than on the image map with b = 0, (2) it was not caused by normal anisotropy of diffusion or artifact, and (3) it was seen on the DWIs in both of the remaining orthogonal diffusion sensitivity directions.

Studies have confirmed the validity and reliability of MRA for MCA stenosis.[14,15] A three-dimensional time-of-flight MRA of the intracranial arteries was performed with the following parameters: repetition time, 44 milliseconds; echo time, 7 milliseconds; flip angle, 20 degrees; 80 slices of 0.45mm thickness and overcontiguous sampling; field of view, 170mm; and matrix, 256 × 512. The severity of MCA stenosis on MRA was categorized as 50 to 75% (moderate) and greater than 75% (severe) on the basis of the amount of signal loss and the lumen reduction of MCA assessed on both the targeted maximal intensity projection MRA and the source images[11] to reduce the possibility of overestimation of stenosis inherent in the time-of-flight MRA technique.[16] We used the more robust and well-tested time-of-flight MRA instead of a gadolinium-enhanced technique because intracranial application of the latter has unavoidable venous contamination due to the short arterial-venous transit time.

We analyzed all acute infarcts within the MCA territory. The distribution of acute infarcts on DWI were categorized as cortical infarct, border zone infarct, or perforating artery infarct on the basis of the location of the infarct according to mapping templates by Damasio.[17] Border zone infarcts include anterior border zone infarct when the infarct occurred between the anterior cerebral artery and MCA territories, posterior border zone infarct when the infarct occurred between the MCA and posterior cerebral artery territories, and internal border zone infarct between the deep and superficial perforators of the MCA.[18] Acute infarcts also were classified as single or multiple on the basis of the number of infarcts according to the number of ischemic lesions. Traditionally, *multiple infarcts* have been defined as lesions that involve more than 1 major vascular territory and are topographically distinct.[19] However, this classification for multiple infarcts was not suitable for our study because we only included infarcts within the MCA territories under study. Multiple infarcts in this study were defined as more than 1 lesion that was topographically distinct (separated in space or discrete on contiguous slices). The MRA and DWI were read (S.G., W.M.M.L., Y.L.C.) without knowledge of the results of TCD.

Statistical Analysis

All data were analyzed by SPSS 9.0 software (Chicago, IL). χ^2 or Fisher's exact test was used for categorical statistical analysis. For the prediction of the number of cerebral infarcts on DWI, linear regression with adjusted R^2 was used. A p value of less than 0.05 was used to determine a statistically significant difference.

Results

We studied 30 consecutive acute stroke patients with MCA stenosis detected by TCD who had acute infarcts on DWI within the relevant MCA territories. The mean age was 68 years (range, 44–84). Twenty-five (83.3%) were men. The risk profile of the study group included hypertension in 16 patients (53%), diabetes mellitus in 12 (40%), and smoking in 20 (67%).

On MRA, 14 patients had moderate stenosis (50–75% diameter reduction), and 16 had severe stenosis (>75% diameter reduction). The total number of acute infarcts on DWI was 88 in 30 patients, ranging from 1 to 11 (mean, 3.3). Multiple acute, monoterritorial infarcts in 15 patients (50%) were shown with DWI. All 3 types of infarcts (border zone, cortical, and penetrating artery) were found. The patterns of cerebral infarcts and their relationship to the presence of MESs are summarized in the Table. Cortical infarcts, which usually were small (<5mm in diameter), were present in 9 of 15 patients (60%). All cortical infarcts were detected in the presence of additional infarcts at other sites within the MCA distribution; that is, no isolated cortical infarct was found. Multiple border zone infarcts were found in 11 of 15 patients (73%), and an isolated small border zone infarct was found in 5 of 15 patients (33%). The size of border zone infarcts varied from 2 to 15mm in diameter. In many patients with multiple lesions, cerebral infarcts appeared in a chainlike fashion (Figs 1–3). Some of the large lesions appeared to reflect the confluence of several small ones. Multiple penetrating artery infarcts were found in 10 of 15 patients (66.7%), and single penetrating artery infarcts were found in 5 of 15 patients (33.3%). Interestingly, all penetrating artery infarcts were lacuna-like and less than 15mm in diame-

Table. Relationship between Types of Infarction and Presence of Microembolic Signals

	Multiple Infarct		Single Infarct		
Infarct Type	n	MES+ (%)	n	MES+ (%)	Total MES+ (%)
BI	11	7	5	1	8/16 (50)[a]
BI	4	1	5	1	
BI + CI	4	4	0	0	
BI + CI + PAI	3	2	0	0	
Non-BI (%)	4	2	10	0	2/14 (14.3)[a]
PAI	2	1	10	0	
PAI + CI	2	1	0	0	
Total	15	9 (60)	15	1 (6.7)[b]	

[a]BI vs non-BI (P2 = 0.058, Fisher's exact test)
[b]Multiple vs single (p = 0.002, Pearson's χ^2).

BI = border zone infarct; CI = cortical infarct; MES = microembolic signal; PAI = penetrating artery infarct.

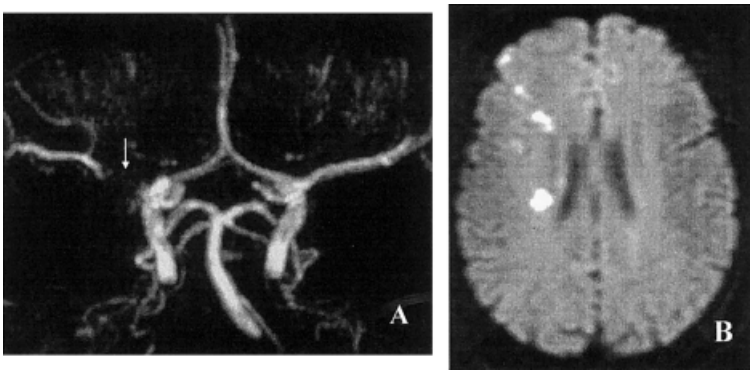


Fig 1. A 66-year-old woman had left-sided weakness. (A) Magnetic resonance angiography showed a severe stenosis in the right middle cerebral artery (arrow). *(B) Diffusion-weighted magnetic resonance imaging demonstrated multiple chainlike small infarcts along the right anterior border zone and internal border zone regions.*

ter. Border zone infarcts were found more frequently in patients with severe MCA stenosis (>75% diameter reduction) than in those with moderate stenosis (28.6%; Pearson χ^2, $p = 0.011$).

We detected MESs in 10 (33.3%) patients, with counts ranging from 3 to 102 MESs per 30 minutes (median, 15 MESs/30 min). MESs occurred more frequently in patients with multiple infarcts (9/15, 60.0%) than in patients with a single infarct (1/15, 6.7%; χ^2, $p = 0.002$). The number of MESs predicted the number of cerebral infarcts on DWI (adjusted $R^2 = 0.475$, $p < 0.001$; Fig 4). When we applied different models (compound, quadratic, cubic, and exponential) of prediction to the analysis in addition to linear regression, the quadratic and cubic were the best fit models for the observed data (adjusted $R^2 = 0.652$, $p < 0.001$ for both models). MESs tended to be detected more frequently in patients with border zone infarcts (50%) than in those without border zone infarcts (14.3%; Fisher's exact test, $p = 0.058$). We did not detect MESs in patients with a single penetrating artery infarct.

Discussion

To our knowledge, this is the first report of the combined use of MESs and DWI to explore the pathophysiology of cerebral infarct in acute stroke patients with moderate to severe MCA stenosis. Our results can be interpreted in 3 aspects: the frequency of MESs, the pattern of cerebral infarcts on DWI, and the relationship between MESs and DWI.

Frequency of Microembolic Signals

MESs are usually of short duration and high intensity, are displayed within the Doppler spectrum, and are detected by TCD. These signals correspond to embolic particles that pass through the insonated artery.[13] It has been suggested that they represent thrombus and platelet-fibrin aggregates.[9,20] MESs were found more frequently in symptomatic patients than in asymptomatic patients with internal carotid artery stenosis.[21–25] Moreover, the presence of MESs was associated with more severe stenosis and strongly associated with plaque ulceration and intraluminal thrombus.[26,27] The presence of MESs was also predictive of increased risk of future symptoms of cerebral ischemia in patients with symptomatic and asymptomatic internal carotid artery stenosis.[28–32] For patients with MCA stenosis, there were few studies to document the frequency and significance of MESs. MESs were detected in 3 patients (21%) with mostly chronic MCA stenosis.[33] In a pilot study, MESs were found infrequently (15%) in symptomatic acute stroke patients but not in asymptomatic patients with MCA stenosis.[34] Another study also reported the absence of MESs in the chronic stage of stroke among patients with MCA stenosis.[35] In our current study, MESs were found in 33.3% of patients with symptomatic MCA stenosis in the acute stage.

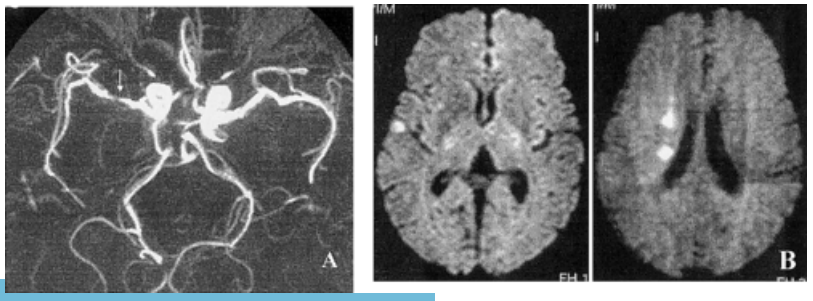


Fig 2. A 57-year-old man had left-sided weakness. (A) Magnetic resonance angiography showed severe right middle cerebral artery stenosis. (B) Diffusion-weighted magnetic resonance imaging showed multiple chainlike small infarcts in the internal border zone region (right panel) and a small infarct in the temporal cortex (left panel).

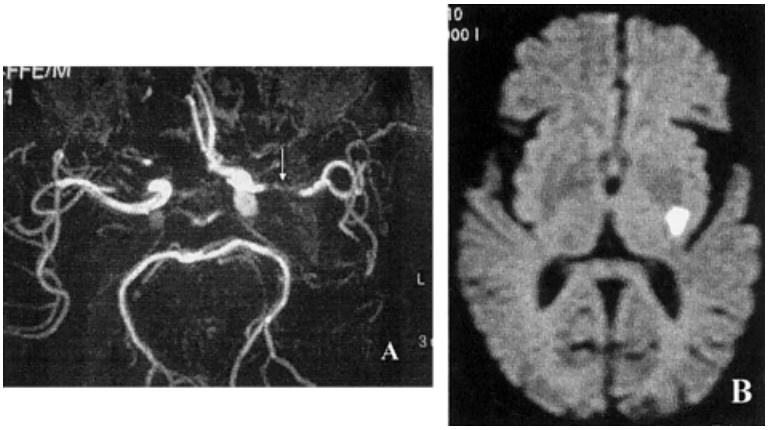


Fig 3. A 63-year-old man had sudden onset of right-sided weakness. (A) Magnetic resonance angiography showed severe stenosis on the left middle cerebral artery stem. (B) Diffusion-weighted magnetic resonance imaging demonstrated a single infarct in the left perforating artery area.

The higher detection rate may be related to the stricter inclusion criteria. We only studied acute stroke patients with evidence of acute cerebral infarct within the corresponding MCA distribution. Our data are also consistent with a previous histological report of artery-to-artery embolism from a stenotic MCA.[36] Another pathological study also showed thromboemboli composed of fibrin and platelets that had been found in distally occluded branches and at the thrombi formation on the surface of atheromatous plaques in the upstream MCA stem.[37] The presence of MESs in 33% of patients during a short recording time of only 30 minutes indicates that embolism is very common in patients with symptomatic MCA stenosis.

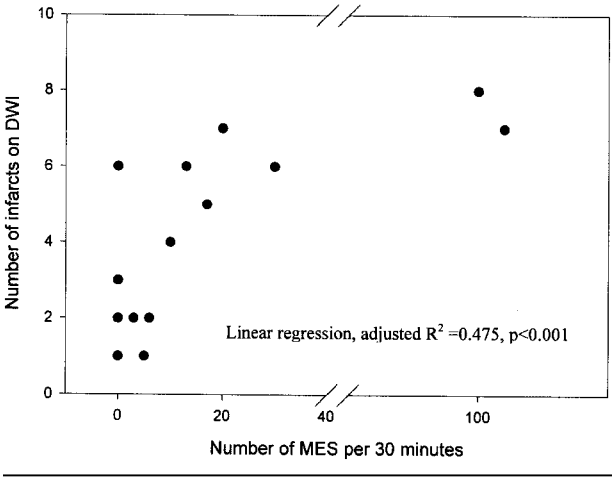
Pattern of Cerebral Infarcts on Diffusion-weighted Magnetic Resonance Imaging

DWI is a relatively new neuroimaging technique, in which an ischemic stroke lesion has an apparent low diffusion coefficient in an acute stage of 2 to 10 days. After that time, it normalizes and then becomes high in the chronic phase.[5] It was suggested that multiple lesions on DWI occurred simultaneously within a few days or up to a week. In addition, DWI is more sensitive for identifying small ischemic lesions, which usually are missed on conventional magnetic resonance imaging.[38] Therefore, multiple acute lesions on DWI were regarded as good markers of an underlying embolic mechanism for ischemic stroke. This was supported by the higher frequency of multiple acute lesions seen on DWI in patients with cardiac embolic source and internal carotid artery stenosis.[39,40] Multiple MCA territory infarcts may not always represent multiple emboli because collateral flow may spare islands of cortex. However, the infarcts that we observed were small and nonconfluent rather than big and confluent, with sparing of small islands of cortex. Therefore, the appearances were more suggestive of embolization as the origin. A highly significant relationship with MESs further supports the importance of embolism as the likely mechanism.

The finding of a high frequency (50%) of multiple acute infarcts on DWI according to our study suggests that embolism is a common underlying mechanism in patients with MCA stenosis. Two previous studies from Korea also found that MCA stenosis is the major underlying source for multiple MCA territory infarcts on DWI.[41,42]

All 3 subtypes of infarcts were found in the MCA territory distal to a stenosis. Different subtypes of infarct had different characteristics and may represent different pathophysiologies. Cortical infarct, which usually was less than 5mm in diameter in our study, was a common subtype in multiple infarcts (9/15, 60%). We did not find any isolated cortical infarct in this study. This observation suggests that small cortical lesions usually include silent lesions as well as additional symptomatic infarcts such as border zone infarct

Fig 4. Relationship between microembolic signals (MESs) detected by transcranial Doppler and cerebral infarcts on diffusion-weighted magnetic resonance imaging (DWI).



and penetrating artery infarct.[39] There are two possible outcomes when a small embolus is released to a distal artery. It may be cleared by adequate blood flow without causing brain damage. It also may lead to an ischemic lesion visualized on DWI because it could not be washed out or compensated for because of its size or frequency. There are numerous arterial anastomoses for each gyrus of cerebral cortex that may play a role in preventing and compensating for cortical infarct.[43] We presume that most small cortical emboli may flush out by adequate blood flow before forming a large ischemic lesion or are rescued by good collateral circulation. Most of these cortical infarcts are small and appear much more benign than the large cortical infarcts caused by acute MCA occlusion. This can be explained by the gradual development of sufficient leptomeningeal anastomosis between anterior or posterior cerebral arteries in the long process of atherosclerotic stenosis of the MCA.

Border zone infarct was seen as both single and multiple chainlike infarcts and a single infarct, but more commonly as multiple infarcts (73.3%) than as a single infarct (33.3%). This indicates that artery-to-artery embolism may play an important role for border zone infarct in patients with MCA stenosis. This hypothesis is further supported by the result of MES monitoring, which detected MESs in 50% of border zone infarct patients. Cholesterol crystals have been described as a cause of border zone infarct.[44] More recently, platelet emboli–occluded leptominingeal arteries in the border zone area have been demonstrated.[45,46] However, decreased cerebral blood flow in the anterior and posterior border zone regions in patients with internal carotid artery and MCA occlusions has been documented by positron emission tomography scanning.[47] Hemodynamic compromise may also instigate border zone infarct in patients with critical carotid artery stenosis or occlusion.[40,48] In a study of patients with internal carotid artery occlusion, low-flow infarcts were mostly small and often multiple and appeared as a chainlike pattern on magnetic resonance imaging.[49] Our study supports the hypothesis that hypoperfusion and embolism often coexist and may result in an impaired clearance of emboli in the border zone region.[50] Further study to document the outcomes and any recurrent events in the first year should strengthen our understanding of the clinical importance of finding MESs and multiple acute infarcts.

Penetrating artery infarct occurred both as a single infarct and as multiple infarcts. No penetrating artery infarct larger than 15mm was found in this study. The lesions' appearance was identical to that of classic lacunar infarcts caused by cerebral small vessel disease. It is accepted that the arterial lesion in lacunar infarct is the so-called lipohyalinosis in the small penetrating artery. Isolated penetrating artery infarct was seen in 10 patients; none had MESs. For this group, the atheroma in the MCA may occlude the origin of a penetrating artery and lead to a lacuna-like infarct.[51,52] Conversely, small embolic particles occasionally may lodge in a penetrating artery and result in lacunar infarction.[53] All 3 of our patients with both penetrating artery infarct and cortical infarct had MESs. This suggests that embolism might be the cause of small infarctions in the territory of deep perforators, which may not be evident in conventional magnetic resonance imaging or computed tomography.

Relationship between Microembolic Signals and Multiple Infarcts on Diffusion-weighted Magnetic Resonance Imaging

Multiple infarcts and MESs on DWI both are indicative of cerebral embolism. For DWI, most of the lesions may be produced by multiple emboli or the breakup of an embolus. The clinical importance of MESs is controversial because most of them are asymptomatic or lack evidence of brain damage.[24,54,55] In our study, we found a good relationship between the 2 techniques. We found MESs more frequently in patients with multiple infarcts than in patients with a single infarct. Lesions on DWI may occur at different times during the acute stroke period.[5] They may have occurred before the symptomatic event or continue after it. Both MES detection and DWI were performed after the symptomatic event, and DWI was conducted 2 to 3 days after MES monitoring. However, MES monitoring was performed only for 30 minutes, and the lesions on DWI represent the aggregate of cerebral infarcts produced by MESs. This hypothesis is supported by the observation that the number of MESs predicts the number of cerebral infarcts. Although MESs are labeled "asymptomatic" because of the lack of immediate clinical symptoms, our data strongly suggest that the presence of an MES is predictive of cerebral damage as shown in DWI. This observation agrees with recent data to support the clinical significance of MESs. A recent study showed that more than 50 MESs per hour have a predictive value for the occurrence of an ischemic stroke after endarterectomy.[8] Another study showed that the total number of MESs was significantly associated with stroke and hyperintense lesions on DWI after endarterectomy.[56]

An alternative explanation for the association between MESs and border zone infarcts is that both are related to the underlying MCA stenosis. Therefore, MESs are linked to border zone infarcts, but the relationship is not a causal one.

If ongoing thromboembolism is an important mechanism of stroke in patients with MCA stenosis, anticoagulation may have a role in acute management. A study of Hong Kong Chinese, who have a higher incidence of intracranial atherosclerosis, showed that the

use of low molecular weight heparin is associated with better outcome than a placebo among acute ischemic stroke patients.[57] A randomized controlled trial should be developed to investigate the benefit of antithrombotic treatment for patients with intracranial atherosclerosis.

In summary, our data show that multiple cerebral embolism is an important mechanism of cerebral infarcts in patients with MCA stenosis. Furthermore, the propensity for multiple border zone infarcts indicates that hemodynamic compromise, in conjunction with multiple small emboli, may result in deep border zone infarctions, possibly because of the failure to clear emboli in a poorly perfused brain area. Our data support further studies to investigate the use of antithrombotic therapy in patients with MCA stenosis, to test interventional therapy to improve cerebral perfusion, or to do both to prevent stroke in this particular group of patients.

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