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Microembolic Signals in Acute Posterior Circulation Cerebral Ischemia

Sources and Consequences

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Background and Purpose—The clinical significance of microembolic signals (MES) in the posterior circulation remains unclear. The aim of this study was to investigate the sources and consequences of MES in acute posterior circulation cerebral ischemia.

Methods—We evaluated a total of 140 consecutive patients (93 males, mean age 62.9 years) who had acute posterior circulation cerebral ischemia. The MES monitoring was conducted at the basilar artery through the suboccipital window for a 30-minute period.

Results—MES were detected in 18 (12.9%) of the 140 patients. Clinical characteristics and laboratory data did not differ between the MES-positive and MES-negative groups. Intracranial vertebralbasilar artery (VBA) stenosis was independently associated with the presence of MES (odds ratio, 9.85; 95% confidence interval, 1.22–79.48; $P=0.032$), whereas the patients with vertebral artery stenosis that was limited to the extracranial portion did not show an association. Microembolic signals occurred significantly more frequently in patients with severe degree of VBA stenosis compared to those with nonsignificant stenosis (odds ratio, 9.88; 95% confidence interval, 1.23–79.07; $P=0.031$). In a subgroup analysis of the 79 patients who had lesions on diffusion-weighted images and relevant VBA stenosis, the MES-positive group showed more frequent embolic infarction ($P=0.010$) and multiple lesion patterns ($P=0.007$) than single perforating infarctions.

Conclusions—In acute posterior circulation cerebral ischemia, intracranial and severe VBA stenosis is associated with MES and may be its root causes. The presence of MES in VBA stenosis suggests that multiple and embolic type infarctions are the mechanisms of stroke. (*Stroke*. 2012;43:747-752.)

Key Words: diffusion-weighted image ■ microembolic signal ■ posterior circulation ■ stroke

Since the first description of microembolic signals (MES) by Spencer in 1990, numerous studies have been performed using MES detected by transcranial Doppler ultrasound (TCD) as markers of ongoing embolic phenomena.^{1–4} MES is thought to predict recurrent strokes in the internal carotid artery and middle cerebral artery.^{5–9} Previous studies have shown relationships between MES results and lesion patterns on diffusion-weighted magnetic resonance imaging (DWI) in patients with middle cerebral artery stenosis and suggested that multiple cerebral embolisms are one of the important infarction mechanisms in these patients according to TCD monitoring at the middle cerebral artery.¹⁰

The clinical relevance of MES in posterior circulation cerebral ischemia, however, remains unclear. Although a previous report that evaluated the significance of MES in intracranial artery stenosis included 2 patients with posterior cerebral artery stenosis, temporal windows were used for

TCD monitoring.¹¹ There have been no systemic studies of MES in the posterior circulation.

The present study was conducted to evaluate the clinical implications of MES in posterior circulation strokes using TCD monitoring at the basilar artery through the suboccipital window. We investigated factors associated with the presence of MES in posterior circulation ischemia. Furthermore, we demonstrated a relationship between MES and DWI findings in acute strokes of the posterior circulation with vertebralbasilar artery (VBA) stenosis to suggest a possible stroke mechanism in such affected patients.

Subjects and Methods

Subjects

We prospectively collected data from 259 patients who were admitted to the Neurology Department of Samsung Medical Center from January 2006 to July 2010 and performed MES monitoring for

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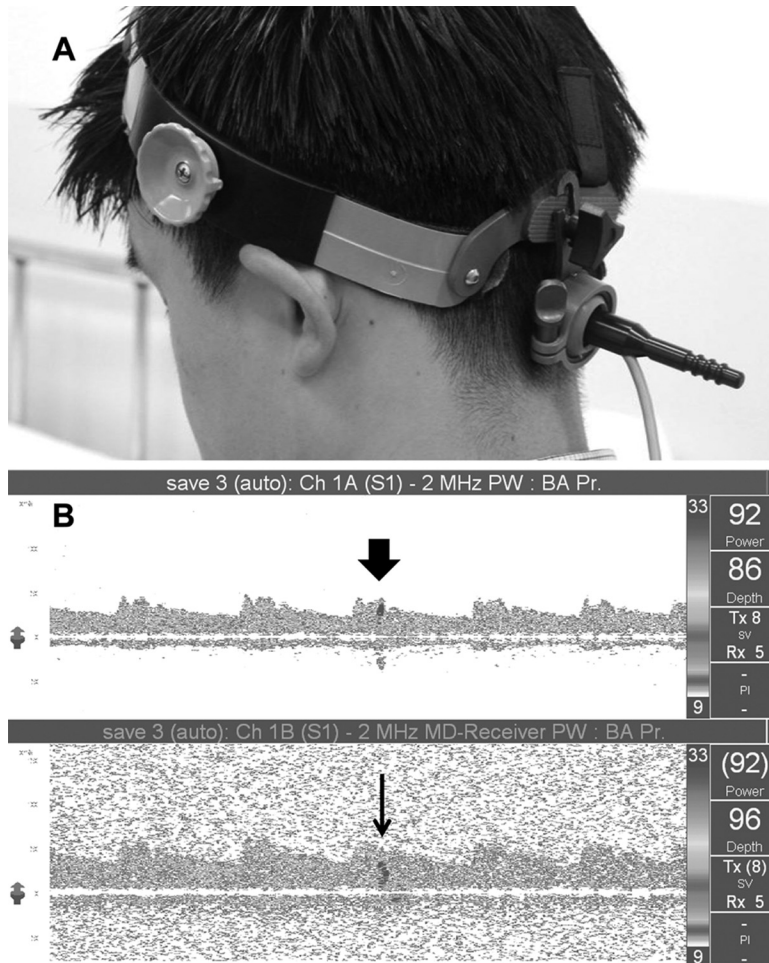


Figure 1. Transcranial Doppler monitoring at the basilar artery through the suboccipital window. **A**, A transducer is mounted to the head with a head frame that is rotated 90 degrees to maintain a tight and constant suboccipital angle. **B**, Transcranial Doppler screen shows microemboli passing through at depths of 86 mm (*wide arrow*) and 96 mm (*narrow arrow*) of the basilar artery. Display of spectra has been inverted to show waveform above baseline.

all patients at the basilar artery using TCD. We reviewed medical records and laboratory and radiological data including brain MRI and MRA. Our local Institutional Review Board approved this study.

All of the patients included in the study had acute posterior circulation ischemia including stroke, defined as a clinically relevant hypertensive lesion on DWI, or VBA territory transient ischemic attack, defined according to the classification of the Oxfordshire Community Stroke Project.¹² Patients also underwent MES monitoring using TCD within 7 days of the onset of an ischemic attack. Patients were excluded if TCD monitoring was performed >7 days from symptom onset (n=90), TCD was performed for anterior circulation territory infarction (n=4), the patient had a nonischemic event such as a migraine, Fabry disease, syncope, or intracranial hemorrhage (n=16), or there was no available MRI to evaluate the ischemia and cerebral vessels (n=9).

Lesion Patterns in VBA Stenosis

We performed a subgroup analysis of diffusion lesion patterns to evaluate the impact of MES in patients who had VBA stenosis. Because the embolic source can influence the ischemic lesion pattern, patients who had high risk sources of cardioembolism defined according to the Trial of Org10172 in Acute Stroke Treatment criteria were excluded from the subgroup analysis (n=6).

MRI and MRA

All patients underwent a MRI performed with a 3-T unit (Achieva; Philips Medical Systems) including DWI. DWI was obtained in 20 sections with b values of 0 and 1000 s/mm². The imaging parameters of the DWI were 2550 ms/75 ms (repetition time/echo time), 128×128 matrix, 24-cm field of view, and 5-mm/2-mm (slice thickness/intersection gap). Three-dimensional

time-of-flight MRA of the intracranial arteries and gadolinium-enhanced MRA of the extracranial arteries were obtained from all patients.

According to the lesion size and topographical distribution on DWI,^{13,14} a perforating infarct was defined as any single infarct with a diameter <15 mm involving the area supplied by perforators of the basilar artery, vertebral artery, posterior inferior cerebellar artery, anterior inferior cerebellar artery, or posterior cerebral artery.¹⁵ Embolic infarcts were defined as a single or multiple lesions larger than 15 mm located within the occipital lobe cortex, cerebellar cortex, or cerebellar border zone area. Acute infarcts were also classified as single or multiple (≥2 lesions).

The degree of VBA stenosis on MRA was categorized as either moderate (50%–70%) or severe (<70% or total occlusion) according to reduction in the diameter of the narrowest vessels. Significant arterial disease was identified if the relevant artery stenosis is >50%. For intracranial artery stenosis, the lumen reduction of the VBA was assessed on both the targeted maximal intensity projection MRA and the source images to reduce the overestimation of stenosis that is inherent in the time-of-flight MRA technique.¹⁶ The location of VBA stenosis was classified by the most distal significant stenotic portion into intracranial VBA (basilar artery and intracranial portion of vertebral artery: V4), extracranial vertebral (foraminal and postforaminal vertebral artery: V2 and V3), and vertebral artery orifice (origin to extracranial preforaminal artery: V1).¹⁶ Because contrast-enhanced MRA may exaggerate the degree of stenosis of the V1 segment, only severe stenosis or occlusion was considered to be significant in the V1 portion. Two stroke neurologists (J.C.H. and S.J.K.) reviewed the findings of DWI and MRA without knowledge of the TCD results. In cases of discrepancy, consensus readings were obtained.

Microembolic Signal Monitoring

MES monitoring by TCD (EME TC8080; Nicolet) was performed while patients were lying down. The distal basilar arteries were insonated through the suboccipital window for 30 minutes at a mean depth of 80 to 100 mm. A 2-MHz bigate transducer was mounted to the head with a TCD probe fixation head frame (Marc 500; Spencer Technologies). Because the head frame was originally built for transtemporal window monitoring, we rotated the head frame 90 degrees to maintain a tight and constant suboccipital angle (Figure 1A). The distances between the 2 insonation depths were set from 8 to 10 mm depending on signal quality. Insonation depths were adjusted to 6 mm in 6 patients with tortuous basilar arteries. Any suspected signal that was detected by automatic monitoring was simultaneously recorded by hand and manually validated. The definitions of embolic signals were as follows: typical visible and audible (click, chirp, and whistle) signals of short-duration, high-intensity signals within the Doppler flow spectrum that occurred randomly during the cardiac cycle, intensity increase of >5 dB above the background signal, and time delay for the microemboli to travel 2 insonation depths (Figure 1B). The presence and number of MES were assessed by 2 experienced readers (K.W.K. and E.J.L.) who were blinded to all clinical and imaging findings.

Statistical Analysis

The baseline characteristics of patients in the MES-positive and MES-negative groups were compared using either independent *t* tests or Mann-Whitney *U* tests for continuous variables and Pearson χ^2 and Fisher exact tests for categorical variables. In addition, multivariate logistic regression analysis was conducted to identify the independent contributors of MES, including clinically relevant and significant variables.

Differences in lesion multiplicity and patterns in DWI between the MES-positive and MES-negative groups were assessed using Pearson χ^2 test. The relationship between the number of MES and the number of lesions was assessed using Spearman correlation coefficient. Values of $P < 0.05$ were considered statistically significant. All statistical analyses were conducted using commercially available software (SPSS for Windows version 13.0; SPSS).

Results

Patient Characteristics

We included a total of 140 consecutive patients (94 males) who fulfilled the previously mentioned criteria. The mean age was 62.9 years (range, 31–91 years). MES were detected in 18 (12.9%; 95% CI, 8.3–19.5%) of the 140 patients. The median number of MES in the MES-positive group was 6 (range, 1–9). The mean interval between symptom onset and the TCD study was 3.8 days; the median interval between symptom onset and the MRI study was 2 days (range, 0–5 days). These values did not differ between the MES-positive and MES-negative groups.

The demographic and stroke risk factor profiles, including laboratory findings for the MES-positive and MES-negative groups, are summarized in Table 1. Clinical characteristics, vascular risk factors, and use of prestroke antithrombotic medication did not differ between the 2 groups. Of the 18 MES-positive patients, atrial fibrillation was detected in 1 patient, and the prevalence was the same as that in the MES-negative group. Laboratory parameters and coagulation factors on admission also were not significantly different across the groups.

The arterial stenosis features of the 2 groups are shown in Table 2. The MES-positive patients had a significantly higher prevalence of VBA stenosis compared to the MES-negative group ($P = 0.015$). There was a trend toward more frequent

Table 1. Patient Characteristics in the Microembolic Signal-Positive and Microembolic Signal-Negative Groups

	Microembolic Signal-Negative Group (n=122)	Microembolic Signal-Positive Group (n=18)	<i>P</i>
Age	62.1±12.5	66.8±12.8	0.187
Female, n (%)	37 (30.33)	9 (50)	0.097
Stroke risk factors			
Hypertension, n (%)	82 (67.2)	14 (77.8)	0.367
Diabetes mellitus, n (%)	42 (34.4)	7 (38.9)	0.711
Dyslipidemia, n (%)	49 (40.2)	10 (55.6)	0.161
Coronary heart disease, n (%)	19 (15.6)	2 (11.1)	0.496
Current smoking, n (%)	28 (23)	2 (11.1)	0.362
Previous stroke or transient ischemic attack, n (%)	22 (18)	4 (22.2)	0.746
Atrial fibrillation, n (%)	15 (12.3)	1 (5.6)	0.692
Laboratory findings			
C-reactive protein, mg/L	0.10 (0.05–1.34)	0.17 (0.04–0.33)	0.942
D-dimer, ng/ml	0.40 (0.26–0.70)	0.58 (0.33–1.15)	0.393
Fibrinogen, mg/dL	314 (252–353)	320 (258–378)	0.382
Prothrombin time, INR	1.08±0.31	1.00±0.07	0.151
Total cholesterol, mg/dL	174.52±41.82	177.89±36.38	0.904
LDL cholesterol, mg/dL	109.57±35.16	118.39±25.96	0.209
HDL cholesterol, mg/dL	45.07±12.24	52.11±14.15	0.133
Pre-stroke medication			
Antithrombotics, n (%)	47 (38.52)	7 (38.89)	0.498
Statin, n (%)	31 (25.4)	5 (27.8)	0.772
Time interval from symptom onset to TCD, days	3.62±1.94	4.33±1.85	0.173
Time interval from MRI to TCD, days	2 (1–3)	2 (1–4.25)	0.642

Data are expressed as mean (±standard deviation), proportion, or median (interquartile range).

INR indicates international normalized ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TCD, transcranial Doppler.

intracranial VBA stenosis in the MES-positive group, but the difference did not reach statistical significance ($P = 0.107$).

Multivariate Testing: Sources for Microembolic Signals

Independent predictors for the detection of MES were analyzed via multiple logistic regression analysis (Table 3). After adjusting for other variables, we found that intracranial VBA stenosis was independently associated with MES (OR, 9.85; 95% CI, 1.22–79.48; $P = 0.032$), whereas patients with vertebral artery stenosis that was limited to the extracranial portion or orifice showed no significant differences ($P = 0.099$ and $P = 0.201$, respectively) compared to patients with nonsignificant stenosis. MES occurred more frequently in patients with severe VBA stenosis compared to those with nonsignificant stenosis (OR, 9.88; 95% CI, 1.23–79.07; $P = 0.031$).

DWI Lesion Patterns With and Without MES in VBA Stenosis

Of the 140 patients, 79 who had lesions on DWI and relevant VBA stenosis were evaluated for lesion pattern analysis.

Table 2. Vertebrobasilar Artery Stenosis in the Microembolic Signal-Positive and Microembolic Signal-Negative Groups

	Microembolic Signal-Negative Group (n=122)	Microembolic Signal-Positive Group (n=18)	P
Significant vertebrobasilar artery stenosis (>50%), n (%)	81 (66.4)	17 (94.4)	0.015
Location of vertebrobasilar artery stenosis			0.107
No or <50% stenosis, n (%)	40 (32.8)	1 (5.5)	
Vertebral artery orifice, n (%)	14 (11.4)	2 (11.1)	
Extracranial vertebral, n (%)	11 (9.0)	2 (11.1)	
Intracranial vertebrobasilar artery, n (%)	57 (46.7)	13 (72.2)	
Degree of vertebrobasilar artery stenosis			0.014
No or <50% stenosis, n (%)	40 (32.8)	1 (5.5)	
50%–70% stenosis, n (%)	18 (14.7)	3 (16.6)	
>70% stenosis or occlusion, n (%)	63 (51.6)	14 (77.8)	

Analyses of cerebral infarcts and their relationships to the presence of MES are summarized in Table 4. DWI lesion pattern analysis revealed that embolic infarction was more frequent in the MES-positive group than in the MES-negative group (84.6% versus 45.5%; $P=0.010$). Single cerebellar border zone or perforating arterial infarctions did not occur in isolation but were always accompanied by cerebellar cortical or other vascular territorial lesions. Isolated thalamic infarcts were identified in 4 patients, all of whom were in the MES-negative group.

The multiple lesion pattern was significantly more frequent in the MES-positive group than in the MES-negative group ($P=0.007$). The number of MES was moderately correlated with the number of DWI lesions (Spearman correlation coefficient=0.364; $P=0.001$; Figure 2).

Table 3. Logistic Regression Analysis: Clinical and Stenotic Features Predicting Microembolic Signal

Variable	OR (95% CI) for Microembolic Signal	P
Age, per 1-y increase		0.449
Female		0.288
Time interval from symptom onset to TCD study, per 1-d increase		0.283
Location of vertebrobasilar artery stenosis		
No or <50% stenosis		Reference
Vertebral artery orifice stenosis	5.12 (0.42–62.40)	0.201
Extracranial vertebral artery stenosis	8.34 (0.67–103.55)	0.099
Intracranial vertebrobasilar artery stenosis	9.85 (1.22–79.48)	0.032
Degree of vertebrobasilar artery stenosis		
No or <50% stenosis		Reference
50%–70% stenosis	7.22 (0.69–75.45)	0.099
>70% stenosis or occlusion	9.88 (1.23–79.07)	0.031

OR indicates odds ratio; CI, confidence interval; TCD, transcranial Doppler.

Table 4. Analysis of Infarct Lesions in Vertebrobasilar Artery Stenosis in the Microembolic Signal-Positive and Microembolic Signal-Negative Groups

	Microembolic Signal-Negative Group (n=66)	Microembolic Signal-Positive Group (n=13)	P
DWI lesion pattern			0.010
Single perforating, n (%)	36 (54.5)	2 (15.4)	
Embolic, n (%)	30 (45.5)	11 (84.6)	
DWI lesion multiplicity			0.007
Single, n (%)	42 (63.6)	3 (23.1)	
Multiple, n (%)	24 (45.4)	10 (76.9)	

DWI indicates diffusion-weighted imaging.

Discussion

The detection of MES has been reported as the identification of active emboli of either arterial or cardiac origin. To date, most MES monitoring studies have focused on anterior circulation infarcts. A previous study confirmed the possibility and reliability of MES monitoring at the basilar artery using basilar artery TCD recording for the diagnosis of right-to-left shunts.¹⁷ Our study is the first to our knowledge to demonstrate the use of MES monitoring in patients with posterior circulation ischemia. MES monitoring at the basilar artery could be an alternative method in other research studying posterior circulation emboli, especially for subjects with an insufficient temporal acoustic window.

The fact that VBA stenosis was the main determinant of MES presence implies that VBA stenosis may be the source of arterial embolisms in posterior circulation infarcts. Previous studies have shown that VBA stenosis in either the extracranial or intracranial portion is an important cause of posterior circulation stroke and a predictor of recurrent stroke.^{18,19} However, some autopsy studies and prospective cohort studies have found that proximal extracranial vertebral artery lesions are seldom symptomatic.^{20,21} It is not clear whether vertebral artery orifice stenosis shown in MRA can be the source of arterial emboli in patients with intracranial VBA stenosis and posterior circulation infarcts. Our study shows that extracranial vertebral artery stenosis, especially vertebral artery orifice stenosis, is not related to MES signals, suggesting that orifice stenosis is a benign embolic source.

Several studies have noted that the prevalence of MES is significantly higher in patients with higher degrees of carotid stenosis.^{22,23} There have been a few studies demonstrating the relationship between intracranial artery stenosis and MES presence.^{10,24} The current study implies that a higher degree of VBA stenosis is associated with a higher prevalence of microemboli, which needs to be controlled.

The possible mechanisms for cerebral infarction in VBA stenosis include complete occlusion of the stenotic artery because of thrombosis formation, artery-to-artery embolism, hemodynamic compromise, small branch occlusion, or a combination of these factors.^{21,25} Discrimination between stroke mechanisms has clinical significance for the prevention of stroke attributable to VBA stenosis. Although several studies have examined DWI lesion patterns in patients with posterior circulation stenosis, there have been no studies

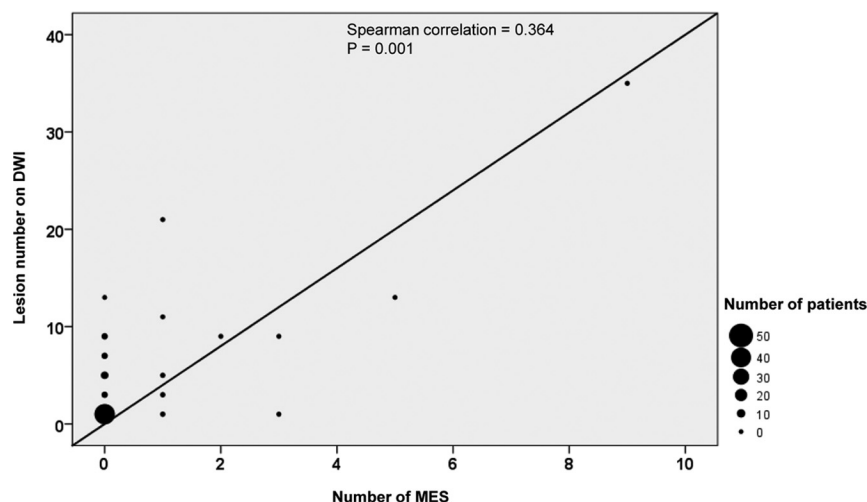


Figure 2. Relationship between number of microembolic signals (MES) and lesion on diffusion-weighted imaging (DWI).

characterizing the mechanisms of infarction in VBA stenosis.²⁶ The results of MES monitoring along with DWI lesion pattern analysis may be helpful for determining the mechanism of ischemic stroke in patients with arterial stenosis. Multiple acute lesions on DWI have been regarded as markers of an underlying embolic mechanism for ischemic stroke.^{27,28} Isolated small perforating artery lesions are thought to represent in situ branch occlusive disease or lacunar infarction. However, previous studies have suggested that DWI alone may be unable to differentiate lacunar infarcts or branch occlusive disease from other etiologies such as microembolic infarcts, especially in patients with posterior circulation infarcts.²⁹ The prevalence of MES and the relationship between MES and DWI lesions in middle cerebral artery territory stroke suggest an artery-to-artery embolic mechanism.^{10,24} Based on our study results, MES monitoring may provide additional information for accurate diagnoses of stroke causes, especially in posterior circulation strokes with small subcortical lesions.

Previous studies have evaluated the clinical importance of MES as an active intra-arterial embolic source in ischemic stroke patients.^{30,31} In a carotid artery stenosis study, the prevalence of MES was higher in patients with severe and ulcerative plaque stenosis.^{6,22} Several studies have provided evidence that MES detection plays a role in the prediction of future stroke events of the internal carotid artery and middle cerebral artery.^{9,32–33} Although our study did not include clinical data, the correlation we observed between MES number and DWI lesion number supports the clinical significance of MES for distinguishing vulnerable and unstable atherosclerotic stenosis and provides another clue for identifying optimal strategies to prevent ischemic stroke in patients with VBA stenosis.

This study has some limitations. The time interval from symptom onset to TCD monitoring was relatively long because of delayed admission. A previous study, however, has suggested that MES may be used as a marker of active thromboembolism after 7 days.³³ We did not discriminate dissection from atherosclerotic stenosis. It was difficult to completely differentiate atherosclerosis from dissecting pathology based on MRA findings.³⁴ Because transthoracic

echocardiography was not performed on all of patients, we were unable to exclude aortogenic embolisms. Suboccipital TCD window may present technical difficulties because of the tortuous basilar artery and head motion artifacts. Several studies have shown that intensive medical therapy reduces MES in carotid artery stenosis.^{35–37} Our study did not consider the effects of treatment on MES developments. Furthermore, although our analysis produced statistically meaningful results, most of the confidence intervals were wide. Further clinical studies with larger sample sizes are required to investigate the clinical implications and the effects of intensive medical treatment in patients with vertebrobasilar microemboli.

Conclusions

Our results demonstrate that VBA stenosis, particularly intracranial and severe-degree stenosis, is associated with MES in patients with acute posterior circulation ischemia and may be the underlying cause of MES. The presence of MES on basilar artery monitoring may suggest that multiple embolic infarctions are the stroke mechanism in patients with VBA stenosis.

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Disclosures

None.

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