Microembolic Signals is Associated With Insulin Resistance Among Acute Ischemic Stroke Patients

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Background: Microembolic signals (MES) and insulin resistance (IR) is common in patients with acute ischemic stroke (AIS). Patients with active MES tend to be more seriously ill and prone to aggravating disease progression. IR is an important risk factor for stroke which has been found to be associated with the severity of stroke. This study aims to investigate the clinical correlation between intracranial MES and IR in AIS patients. *Methods:* A total of 119 patients with AIS were enrolled in this study. The IR index (HOMA-IR) was calculated according to the homeostasis model and divided into 4 levels, where IR was defined by HOMA-IR index in the top quartile (Q4). Transcranial Doppler Sonography was performed in all patients within 72 hours after the stroke onset to monitor arterial MES in the lesion side of the brain for 30 minutes. *Results:* It is found that the positive rate of MES increased with the increase of IR level. The positive rate of MES in IR group was 55.2% (16/29), and that in non-IR group was 32.2% (29/90). In addition, HOMA-IR in patients with MES− were significantly lower than those in patients with MES+ (1.6 [Interquartile range: 0.9-2.5] compared with 2.2 [Interquartile range: 1.3-4.1], $P < .05$).In multiple logistic regression analysis, we calculated the OR of MES as compared with the HOMA-IR. The result of OR value is 1.38 (95% confidence interval: 1.05-1.82, $P = .02$). *Conclusions:* IR is positively related to MES in patients with AIS. Higher level of IR might contribute to plaque destabilization and the formation of MES, which finally leading to the occurrence of stroke.

Key Words: Insulin resistance—microembolic signal—ischemic stroke—transcranial doppler sonography—middle cerebral artery

Introduction

Acute ischemic stroke (AIS) has become one of the main causes of human death and disability. A survey showed that the mortality rate of China hospitalized patients with AIS was 3.3%∼5.2% at 1 month after the onset, and at 3 months the mortality rate was 9%∼9.6% with 34.5%∼37.1% death/disability rate, and at 12 months the mortality rate was 11.4%∼15.4% along with 33.4%∼44.6%

Abbreviations: CI, Confidence Interval; IQR, Interquartile Range; NIHSS, National Institute of Health Stroke Scale; SD, Standard Deviation; OR, Odds Ratio; MES, Microembolic Signal; IR, Insulin Resistance; AIS, Acute Ischemic Stroke; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; TCD, Transcranial Doppler Sonography; TC, Total Cholesterol; TG, triglyceride; LDL-C, Low-Density Lipoprotein Cholesterol;HDL-C, High-Density Lipoprotein Cholesterol; HCY, homocysteine; hsCRP, high-sensitivity C-reactive protein (hsCRP); HbA1c, glycated hemoglobin; Lp-PLA_2, Lipoprotein-Associated Phospholipase A_2; FPG, Fasting Plasma Glucose; FINS, Fasting Insulin

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death/disability rate.[1,2] The principles of AIS should lay emphasis on early diagnosis, early treatment, early rehabilitation, and appropriate prevention for various risk factors. Studies have shown that insulin resistance (IR) is an independent risk factor for ischemic stroke.[3] It can be characterized by decreased sensitivity of the body to insulin with formation of hyperinsulinemia and hyperglycemia and enhanced ability of platelet adhesion and aggregation at the same time.[4,5] Hyperinsulinemia and hyperglycemia cause the following pathological changes, such as disordered lipid metabolism,[6] abnormal coagulation function and endothelial cell dysfunction,[7,8] which then lead to disordered hemodynamic and vascular disease followed by the emergence of accelerated atherosclerosis,[9] and thus eventually triggering bad cardiovascular events.[10] IR is not only thought to be associated with the onset of cerebral infarction, but also has varying degrees of effect throughout the clinical course of ischemic stroke, because it will increase the severity of cerebral infarction, and be related to the recurrence of cerebral infarction, the risk of death and other adverse events.[11–13]

Cerebral thrombosis has been regarded as the main pathogenesis of AIS for a long time. With the development of medical imaging and related disciplines, transcranial Doppler sonography (TCD) has become a kind of real-time detection technology which is very sensitive to microembolic signal (MES). MES are abnormal components passing through the bloodstream other than normal blood cells, such as blood clots, platelet aggregates, arteriosclerotic plaque particles, fat or air. The study has found that MES is also an important cause of AIS,[14] especially watershed infarction, since patients with watershed infarction often have hypoperfusion which would cause formation of MES and decreased clearance rate of MES, making it easier for MES to locate at the end of the small artery and then leading to infarction in the cortex and junction area.[15,16] It is pointed out that patients with AIS in the acute stage have very high frequency of MES, which can easily lead to infarction progression and recurrence.[17] Therefore, MES cannot be neglected in the process of clinical diagnosis and treatment, for it directly threatens patients' health and life safety, and restricts the improvement of patients' quality of life. It has been proved that the occurrence of MES is related to carotid artery stenosis, atrial fibrillation, artificial heart valve implantation, stent placement,[18,19] but there are few studies on the relationship between MES and some high risk factors associated with ischemic stroke.

The purpose of this study is to explore the correlation between MES and IR in patients with AIS, to find the contributing factors of embolism, and to provide a new way to early prevent the occurrence and recurrence of ischemic stroke.

Methods

Subjects

Patients who were diagnosed with AIS at the Second Affiliated Hospital of Nantong University from December 2017 to June 2018 were consecutively selected. All patients underwent CT examination to exclude cerebral hemorrhage and were confirmed by magnetic resonance imaging as having AIS.

The diagnostic criteria for AIS needed symptoms or signs of focal neurological deficits lasting more than 24 hours, or imaging manifestations of cerebral infarction. Complete data of imaging examination, blood biochemistry examination, and various assessment scales. The informed consent form was signed.

Exclusive patients included clinical asymptomatic patients with lacunar infarction only detected by imaging; patients whose intracranial or extracranial stenosis was not the responsible vessel for the symptoms of this ischemic stroke; patients who were given thrombolytic therapy or endovascular treatment during the acute phase; patients with potential cardiogenic embolism indicated by electrocardiogram, dynamic electrocardiogram and color Doppler ultrasound of the heart (such as atrial fibrillation, rheumatic valvular heart disease, heart valve replacement, bacterial myocarditis, intracardiac thrombosis or tumor, recent myocardial infarction and atrial septal artery tumors); patients with potential hematopoietic microemboli (such as polycythemia vera, anticardiolipin phospholipid syndrome, systemic lupus erythematosus, etc.); diabetic patients currently treated with insulin; patients with ischemic stroke caused by nonatherosclerotic vascular stenosis from clinical perspective; patients with malignant tumors, intracranial infections, severe liver and kidney dysfunction, and autoimmune diseases; patients with poor TCD window penetration and uncooperative examination.

Vascular Risk Factors

The following demographic data of all enrolled patients were recorded: age, gender, body mass index (BMI), history of hypertension, history of diabetes, history of cerebrovascular disease, history of smoking and drinking. Smoking history was defined as smoking more than 10 cigarettes a day in the past 5 years. Drinking history was defined as consuming more than 50 g alcohol per day or 350 g alcohol per week lasting for more than 6 months. Hypertension was present if the systolic blood pressure was persistently at or above 140 mmHg, and the diastolic blood pressure was persistently at or above 90 mmHg or if the patient was currently undergoing antihypertensive drug therapy. Hyperlipidemia was present if the total cholesterol concentration was at or above 5.18 mmol/L (200 mg/dL) or the triglyceride concentration was at or above 2.26 mmol/ L (200 mg/dL), or if the patient was currently using lipid-lowering drugs. Diabetes was diagnosed by demonstrating fasting blood glucose at or above 7.0 mmol/L (126 mg/dL) or oral hypoglycemic agents. The severity of the disease was assessed by the National Institute of Health stroke scale (NIHSS) with a score of or

less 4 indicating mild stroke and greater than 4 indicating moderate to severe stroke.

The blood samples were collected from all patients on the first day of the admission under the fasting state or after a 12-hour overnight fast. The fasting plasma glucose level was measured by the glucokinase method, and the insulin level was measured by a radioimmunoassay. Routine analysis included total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, Apolipoprotein A, Apolipoprotein B, homocysteine (HCY), high-sensitivity c-reactive protein (hsCRP), glycated hemoglobin (HbA1c), Lipoprotein-associated Phospholipase A_2 (Lp-PLA_2). The BMI was calculated by the formula kg/m^2. The homeostasis model assessment of IR was calculated as follows: HOMA-IR = fasting insulin (FINS) (mU/L) × FBG (mmol/L)/22.5. TCD was performed to monitor MES within 72 hours after stroke onset. In the monitoring process, if TCD could not detect any blood flow signals due to patient's poor temporal window, then this patient was excluded from the series. What's more, patients with heart valve replacements were also excluded because of the artificial signals on the Doppler spectrum.

Microembolic Signal Detection

MES monitoring was performed using Embo-dop TCD produced by Germany DWL according to the standard scanning scheme which could automatically identify gas and solid emboli, and calculate the relative strength and number of solid emboli. During the monitoring process, the patient was quiet and relaxed, and was placed in the supine position. The 2 Mhz probe was used to routinely detect all blood vessels in the skull, and the 2 Mhz single depth monitoring probe was used on the clear side of the temporal window to obtain the best blood flow signal of MCA. The monitoring time was 30 minutes, the sampling depth of MCA was 50-58 mm, and the sampling volume was 6-8 mm, and the relative threshold of the embolus was set to be at or over 7.5 dB. The whole monitoring was performed within 72 hours of the patient's admission. At the same time of automatic MES monitoring, an experienced TCD physician closely observed the spectrum changes and manually recorded any suspicious MES signals, and reidentified all recorded abnormal signals in an offline state. MES signal recognition was according to standard consensus criteria: (1) short duration lasting less than 300 ms; (2) signal intensity ratio of background signal at or over 3 dB; (3) single direction appearing in the blood flow spectrum; (4) sharp birdsong or whistling sounds.[20]

Statistical Analysis

Statistical analysis was performed using STATA 13.1 (STATA Corp, College Station, TX). Continuous variables with normal distribution were presented as mean ± standard deviation or medians (interquartile ranges [IQRs]), and were compared by *t*-test or Mann−Whitney U test. Enumeration data was presented as percentage and was compared by χ^2-test. The dichotomy logistic method was adopted to analyze the relationship between MES and HOMA-IR. Multiple logistic regression analysis was performed to seek a balance among the statistically significant factors, like age, alcohol, smoking, previous stroke, etc. The accuracy and specificity of HOMA-IR for MES were evaluated via the receiver-operating characteristic curve (ROC curve). $P < .05$ was considered statistically significant.

Results

Baseline Demographics

This study includes 119 patients which can be divided into IR group and non-IR group. IR group (Q4) has 29 cases, and non-IR group (Q1-Q3) has 90 cases. And there are 45 MES+ cases and 74 MES− cases in all patients. The clinical characteristics of the patients according to HOMA-IR quartiles (Q4 compared with Q1-Q3) are shown in Table 1. A value of 3.0 was the cut-off point of the HOMA-IR index Q4 distribution. The HOMA-IR measured time after the onset of symptoms was 15.4 ± 3.9 hours (MES+ group) and 16.3 ± 4.1 hours (MES− group), no difference was observed($P = .24$). It is clear that no significant differences were observed in age, gender, history of hypertention, hypercholesterolemia, smoking, alcohol and stroke between HOMA-IR Q4 and Q1-Q3 ($P > .05$). Additionally, no differences were observed in serum levels of TG, TC, LDL-C, HDL-C, Apolipoprotein A, Apolipoprotein B, HCY and Lp-PLA_2 ($P > .05$). However, individuals in IR group were more likely had diabetes. Besides, they have higher NIHSS score at admission, BMI, fasting plasma glucose, FINS, HbA1c, hsCRP, TyG index and MES frequency ($P < .05$). Table 2 shows the clinical characteristics, vascular risk factors, past history and laboratory results within 72 hours of the TCD study. MES were detected in 45 of 119 patients (37.8%). There is no statistical difference of TCD performed time after the onset of symptoms between MES+ group and MES− group. The mean time of MES+ group is 48.6 ± 10.9 hours while MES− group is 46.1 ± 9.8 hours($P = .20$). MES+ patients were significantly younger than MES− patients (mean age 69.4 years; $P = .04$). Besides, MES+ group more frequently included patients with a history of smoking, alcohol or stroke. Variables such as TC, TG, LDL, HDL, fasting plasma glucose, Apo-A, Apo-B, HCY, hsCRP, HbA1c,TyG index, history of hypertention, hypercholesterolemia and diabetes mellitus displayed no association with MES. Whereas there were significant difference in HOMA-IR, NIHSS score at admission and FINS between the MES+ and the MES− patients.

Table 1. *Clinical characteristics in relation to the insulin resistance states*

Variable	HOMA-IR Q1-Q3 (n = 90)	HOMA-IR Q4 (n = 29)	P value
Age (mean ± SD), y	68.8 ± 11.4	65.0 ± 13.1	.14
Male, n (%)	63(70.0)	15(51.7)	.07
Hypertension, n (%)	62(68.9)	20(69.0)	1.00
Diabetes mellitus, n (%)	17(18.9)	16(55.2)	<.01*
Hypercholesterolemia, n (%)	28(31.1)	12(41.4)	.31
Alcohol, n (%)	30(33.3)	9(31.0)	.82
Cigarette smoking, n (%)	32(35.6)	11(37.9)	.82
Previous stroke, n (%)	21(23.3)	10(34.5)	0.23
MES positive, n (%)	29(32.2)	16(55.2)	.03*
NIHSS score at admission, median (IQR)	3.5(2.0-6.0)	5.0(3.0-8.0)	.04*
BMI,(mean ± SD), kg/m^2	23.8 ± 3.2	27.3 ± 4.6	<.01*
FPG,(mean ± SD), mmol/L	5.4 ± 1.6	9.1 ± 3.3	<.01*
FINS,(mean ± SD), mU/L	6.2 ± 3.0	12.7 ± 5.2	<.01*
HbA1c,(mean ± SD), %	6.1 ± 1.3	7.9 ± 2.0	<.01*
Total cholesterol,(mean ± SD), mmol/L	4.3 ± 1.1	4.4 ± 0.8	.65
Triglyceride,(mean ± SD), mmol/L	1.5 ± 1.1	1.8 ± 1.2	.21
HDL cholesterol,(mean ± SD), mmol/L	1.2 ± 0.3	1.2 ± 0.3	.99
LDL cholesterol,(mean ± SD), mmol/L	2.6 ± 0.9	2.6 ± 0.6	1.00
Apolipoprotein A,(mean ± SD), g/L	1.0 ± 0.2	1.0 ± 0.2	.99
Apolipoprotein B,(mean ± SD), g/L	0.9 ± 0.3	1.0 ± 0.2	.10
HCY,(mean ± SD), mmol/L	13.6 ± 6.9	12.4 ± 4.5	.38
Lp-PLA_2,median (IQR), ng/mL	65.5 (25.5-189)	82 (20.8-281.3)	.55
hsCRP,median (IQR), mg/L	2.7(0.9-6.1)	5.8(1.5-10.0)	.04*
TyG index,(mean ± SD)	8.6 ± 0.7	9.3 ± 0.6	<.01*

Abbreviations: BMI, body mass index; FBG, fasting blood glucose; FINS, fasting insulin; HbA1c, glycated hemoglobin; HCY, homocysteine; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity c-reactive protein; LDL, low-density lipoprotein; Lp-PLA_2, Lipoprotein-Associated Phospholipase A_2; MES, microembolic signals; NIHSS, National Institute of Health Stroke Scale; TyG, triglyceride glucose.
*P < .05.

Frequency of MES is Associated With the Degree of HOMA-IR and Stroke Severity

The spectrum of MES examination is shown in Figure 1. MES were identified by typical visual appearance on the spectral display and characteristic sounds. The frequency of MES in Q1, Q2, Q3, and Q4 were 23.3%, 26.7%, 40.0%, and 55.2% (Fig 2). It was obvious that the frequency of MES increased with the rising level of IR. The frequency of MES in Q4 group was higher than those in Q1 and Q2 group ($P < .05$). The frequency of MES in Q3 group was also higher than those in Q1 and Q2 group, although there was no statistical difference ($P > .05$). Moreover, we compared MES frequency among groups both in the patients with mild and moderate-severe stroke. The frequency of MES in Q1, Q2, Q3, and Q4 group of the mild and moderate-severe groups were 4/19 (21.1%) versus 3/11 (27.3), 3/16 (31.3%) versus 5/14 (35.7%), 8/20 (40.0%) versus 4/10 (40.0%), 6/13 (46.2%) versus 10/16 (62.5%), respectively. We found that the frequency of MES in the moderate-severe group was higher than mild group in the Q1, Q2, and Q4 group, but there was no statistical difference ($P > .05$) (Fig 3). Further, the binary logistic regression was done for the relationship for MES and HOMA-IR, suggesting that MES was associated with IR ($P < .05$). HOMA-IR in patients with MES− were significantly lower than those in patients with MES+ (1.6 [IQR: 0.9-2.5] compared with 2.2 [IQR: 1.3-4.1], $P < .05$; Fig 4). Multiple logistic regression analysis was performed for MES, and odds ratios (ORs) of HOMA-IR and other risk factors was calculated. With an odds ratio of 1.38 (95% confidence interval: 1.05-1.82), IR had an association with the occurrence of MES (Table 3).

Further, ROC curves were used to evaluate the feasibility of whether HOMA-IR can predict the incidence of MES. The area under the ROC curve was 0.636 with HOMA-IR's optimal cutoff value of 1.88 (Fig 5). The sensitivity and specificity of this cut-off value were 62.22% and 60.81%, respectively.

Discussion

It has been confirmed that IR is a risk factor of stroke, which can promote the development of stroke by affecting lipid metabolism, damaging vascular endothelium and other pathological mechanism damages. MES can reflect the instability of arterial plaque. It has been reported that MES was related to the occurrence and recurrence of stroke. However, the clinical association between MES and IR is still unclear. This study firstly confirmed that

Table 2. *Clinical characteristics of patients with or without microembolic signals*

Variable	MES+ (n = 45)	MES− (n = 74)	P value
Age (mean ± SD), y	65.0 ± 12.3	69.6 ± 11.3	.04*
Male, n (%)	31(68.9)	47(63.5)	.55
Hypertension, n (%)	31(68.9)	51(68.9)	.99
Diabetes mellitus, n (%)	14(31.1)	19(25.7)	.52
Hypercholesterolemia, n (%)	16(35.6)	24(32.4)	.73
Alcohol, n (%)	21(46.7)	18(24.3)	.01*
Cigarette smoking, n (%)	22(48.9)	21(28.4)	.02*
Previous stroke, n (%)	16(35.6)	14(18.9)	.04*
HOMA-IR,median (IQR)	2.2(1.3-4.1)	1.6(0.9-2.5)	.01*
NIHSS score at admission, median (IQR)	5.0(3.0-7.0)	4.0(2.0-5.3)	<.01*
BMI,(mean ± SD), kg/m^2	25.8 ± 4.7	24.0 ± 3.1	.01*
FPG,(mean ± SD), mmol/L	6.7 ± 2.8	6.1 ± 2.5	.23
FINS,(mean ± SD), mU/L	9.3 ± 5.5	6.9 ± 3.7	<.01*
HbA1c,(mean ± SD), %	6.7 ± 1.6	6.5 ± 1.7	.53
Total cholesterol,(mean ± SD), mmol/L	4.4 ± 1.0	4.3 ± 1.0	.60
Triglyceride,(mean ± SD), mmol/L	1.7 ± 1.2	1.6 ± 1.1	.64
HDL cholesterol,(mean ± SD), mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.00
LDL cholesterol,(mean ± SD), mmol/L	2.7 ± 0.8	2.5 ± 0.8	.19
Apolipoprotein A,(mean ± SD), g/L	1.0 ± 0.2	1.0 ± 0.2	1.00
Apolipoprotein B,(mean ± SD), g/L	1.0 ± 0.3	0.9 ± 0.3	.08
HCY,(mean ± SD), mmol/L	12.9 ± 4.2	13.5 ± 7.4	.62
Lp-PLA_2,median (IQR), ng/mL	86.0(20.0-309.0)	60.5(28.5-168.5)	.45
hsCRP,median (IQR), mg/L	3.8(0.9-7.4)	2.8(1.0-7.0)	.43
TyG index,(mean ± SD)	8.8 ± 0.7	8.7 ± 0.8	.50

Abbreviations: BMI, body mass index; FBG, fasting blood glucose; FINS, fasting insulin; HbA1c, glycated hemoglobin; HCY, homocysteine; HDL, high-density lipoprotein; hsCRP, high-sensitivity c-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; Lp-PLA_2, Lipoprotein-Associated Phospholipase A_2; MES, microembolic signals; NIHSS, National Institute of Health Stroke Scale; TyG, triglyceride glucose.

*$P < .05$.

MES detected in middle cerebral artery (MCA) are related to IR among AIS patients.

The detection rate of MES in AIS ranges from 5% to 80%, and the closer the onset time is, the higher the detection rate is.[21] Therefore, the time of TCD monitoring is fixed within 72 hours after the onset in order to obtain a higher MES detection rate in our study. The result shows the frequency of MES was 37.8% and we found it was associated with the severity of stroke. The current researches on MES have mainly focused on the correlation between MES and internal carotid artery stenosis.[19,22] Wu et al points out that the frequency of MES is related to the degree and symptoms of arterial stenosis.[18] To be more specifically, patients with severe intracranial artery

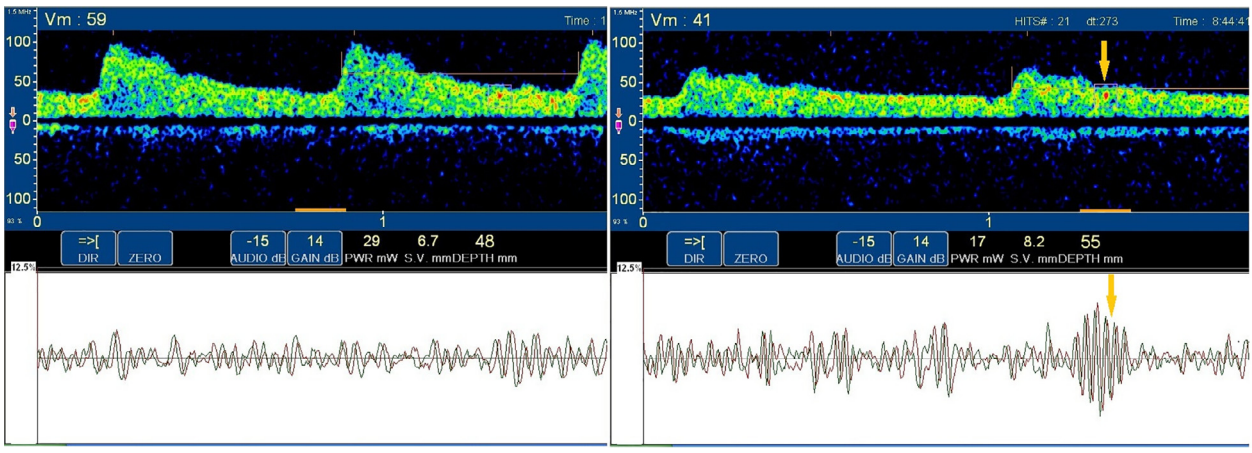

Figure 1. ***The spectrum of microembolic signal (MES) examination.*** *A was the spectrum of MES negative (MES−) in a patient. B was the spectrum of the MES positive (MES+). We could see the typical MES (the arrow).*

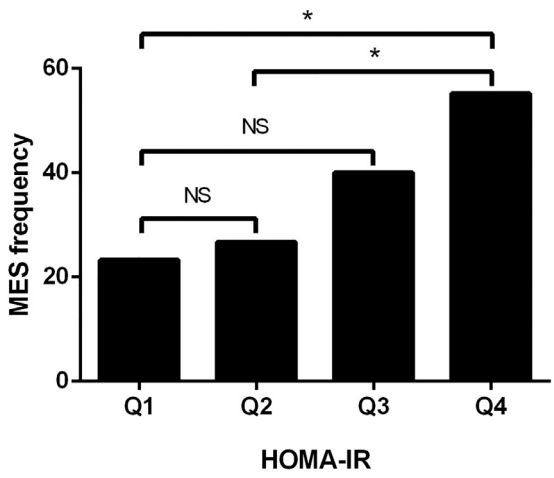

Figure 2. ***MES frequency in different grade IR.*** *The frequency of MES in Q1, Q2, Q3, and Q4 were 23.3%, 26.7%, 40.0%, and 55.2%.*P < .05, NS P ≥ .05.*

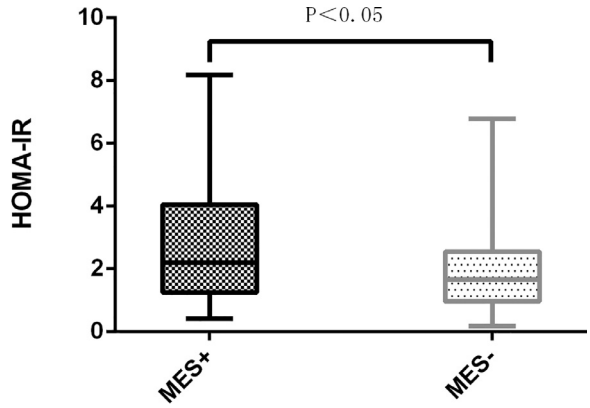

Figure 4. ***Distribution of HOMA-IR in patients with MES+ and MES−*** *Horizontal lines represent medians and IQRs. P values refer to Mann−Whitney U tests for differences between groups.*

stenosis have significantly higher frequency of MES than those with mild stenosis. It is also found that patients with symptomatic MCA stenosis have higher MES proportion than those with asymptomatic MCA stenosis, suggesting that asymptomatic MCA atherosclerotic plaques are relatively stable. Similarly, Chen et al have confirmed the above experimental results again.[23] Also, they find that patients with MES+ have a higher risk of stroke recurrence. At last, they point out that MES could predict the recurrence of ischemic stroke in patients with symptomatic MCA stenosis.

It is generally believed that MES mainly occurs in stroke patients with artery atherosclerosis and cardiogenic embolism (TOAST classification). Therefore, MES monitoring will help in determining the cause of stroke, and can predict the risk of stroke progression, recurrence and other adverse outcomes as well.[24] As for the causes of the progression of ischemic stroke due to MES, the following mechanisms may exist: (1) The MES can further aggravate the originally narrow lumen, which would further reduce the local blood flow and gradually increase the thrombus lesions; (2) The continuous shedding of MES can result in occluded small blood vessels around the infarction area, insufficient collateral circulation blood flow, and aggravated ischemic penumbra; (3) The large MES can cause arterial-arterial embolism. Because of this, Liberman et al find that patients with watershed infarction have higher MES detection rates.[19] It is well known that patients with watershed infarction often have hypoperfusion, thus it is useful and beneficial for their treatment to increase intracranial perfusion and relax antihypertensive target.[25,26] While if MES is the main cause, then more aggressive antiplatelet or even anticoagulant therapy may be beneficial for treatment.

As an important predictor of atherosclerosis, IR is one of the significant mechanisms of stroke and it has important clinical significance. Studies have found that the mechanism of IR-induced stroke may be related to the hyperinsulinemia, hyperglycemia, dyslipidemia and abnormal coagulation function, which damages microvessels and large blood vessels,[27−29] speeds up the atherosclerosis[30] and promotes fibrous plaque formation.[4,5] However, there was no report on the relationship between IR and MES. In our study, we compared the MES frequency between the IR group and non-IR group as well as the HOMA-IR between the MES+ group and MES− group, it is found that the MES occurrence frequency is

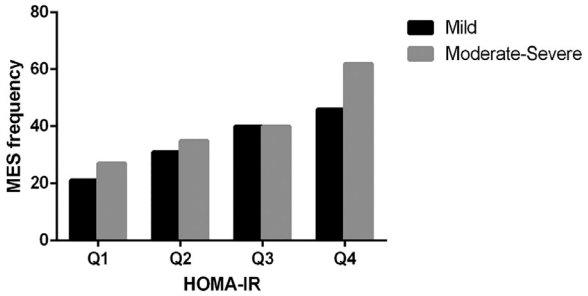

Figure 3. ***MES frequency in different grade IR of the patients with mild or moderate-severe stroke.*** *HOMA-IR in Quartile 1 (<1.10), Quartile 2 (1.10-1.79), Quartile 3 (1.79-2.97) and Quartile 4 (>2.97).*

Table 3. *Multivariate logistic regression analysis model for MES*

Variable	OR	95% CI	P value
Age	0.96	0.92-1.00	.05
Alcohol	2.24	0.66-7.59	.19
Cigarette smoking	1.48	0.45-4.86	.52
Previous stroke	2.60	0.99-6.86	.05
NIHSS score at admission	1.16	1.05-1.27	<.01*
HOMA-IR	1.38	1.05-1.82	.02*

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; MES, microembolic signals; NIHSS, National Institute of Health Stroke Scale.

*$P < .05$.

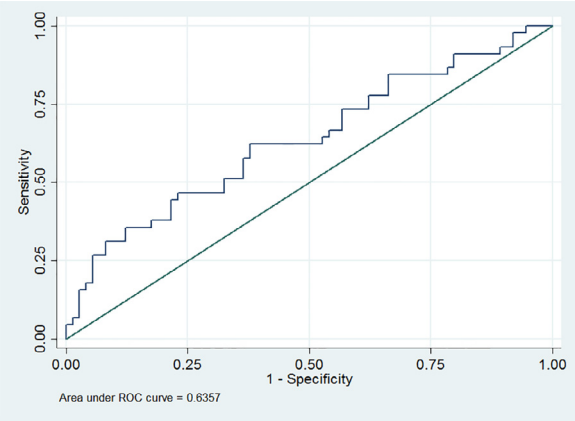

Figure 5. ***ROC analysis of HOMA-IR and MES incidence.*** *The area under the ROC curve was 0.636, and the optimal cut-off value for HOMA-IR was 1.88.*

closely related to HOMA-IR. The origin of MES is related to atherosclerotic plaque and the main source of MES might be ulceration and thrombosis induced by extracranial internal carotid artery stenosis, or intracranial artery stenosis.[31] IR is involved in these pathological processes exactly. Thus, we speculate that the formation of MES is related to IR and the experimental results confirm our hypothesis eventually.

Although this study has confirmed that the frequency of MES is positively related to IR level, it still needs further research to figure out that whether IR directly contributes to the formation of MES or affects the formation of MES by promoting arteriosclerosis and stenosis. However, it is valuable to find that patients with IR are prone to the formation of MES, so we need to pay attention to the treatment. The treatment of IR will be an important means to prevent AIS. Furthermore, it is of great significance to improve IR to reduce the incidence of poor prognosis in patients with AIS.

This study has the following limitations: (1) There was a selection bias in this study, for it only enrolled a small number of patients in a short period of time; (2) TCD recordings were done for only 30 minutes, while more long-term monitoring would probably have increased the detection rate of MES; (3) The detection rate of MES might also be higher, if TCD were performed earlier after the onset of symptoms, since MES detection rates were inversely proportional to the time after the onset of symptoms; (4) TCD sometimes could not have good monitoring because of patients' temporal bone windows. Thus, such patients are not included, and they are usually older and might be more prone to show emboli; (5) The gold standard of IR is hyperinsulinemic-euglycemic clamp, but it is difficult to implement clinically. Thus, we use HOMA-IR instead, it may have an effect on the results of the experiment; in addition, the HOMA-IR score is generally thought to reflect hepatic IR and whether IR as estimated by the HOMA-IR score reflects IR in the brain remains unknown.

Conclusions

The present study demonstrated that IR is positively related to the frequency of MES in MCA in patients with AIS and it is also clinically indispensable as a significant predictor of MES. Higher level of IR might contribute to plaque destabilization and the formation of MES, which finally leading to the occurrence of stroke. However, more researches are needed to further elucidate and clarify this link.

Authors' Contributions

XYZ was responsible for the concept and design of the study, data collection and analysis and the first draft of the paper and further manuscript. DMZ was responsible for overseeing the concept and design of the study and writing the paper. XYZ* and YZ was responsible for concept and design of the study, the data analysis and interpretation. FW was responsible for MES monitoring. All authors read and approved the final manuscript for publication.

Competing Interests

The authors declare that they have no competing interests.

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Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2018.12.033.

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