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MICRO EMBOLIC SIGNALS IN PATIENTS WITH CEREBRAL ISCHEMIC EVENTS

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Summary

Background and Purpose: The aim of this study was to evaluate the micro embolic signals (MES) occurrence in patients with ischemic stroke using transcranial Doppler monitoring to find out diagnostic relevance.
Methods: We prospectively performed bilateral multigated transcranial Doppler monitoring from both middle cerebral arteries in 359 patients with an acute (≤4 weeks) cerebral ischemic event, and in 182 control subjects without a cerebral ischemic event. MES were analyzed according to the standardized protocol.
Results: Patients with ischemic stroke had a significantly ($p<0,00001$) higher rate of MES occurrence (31,8%) than that of control subjects (5,5%). MES were detected significantly higher in patients diagnosed as partial or total anterior circulation infarcts (39,1%) than those of lacunar infarcts (26,0%) or than those of transient ischemic attacks (27,3%). Similar results were found according to neuroimaging findings [(normal (26,7%), lacunar infarction (26,7%), and territorial infarction (39,9%)] of the patients. Another result of this study is that MES was found to be an independent risk factor for ischemic stroke as well as proven ones.
Conclusions: Since MES were detected predominantly in patients with large-vessel territorial stroke, our results gave additional support to the reliability of MES detection by means of TCD. Secondly, MES was found to be an independent risk factor for ischemic stroke, and therefore our data underlines the importance of transcranial Doppler monitoring for detecting MES in ischemic cerebral events.
Key words: Cerebral embolism, risk factors, transcranial Doppler sonography.

Introduction

Especially for the older proportion of the population, stroke is one of the most common causes of death and loss of productive power. Ischemic stroke accounts for 80% of all strokes, and ischemic strokes are caused most frequently by emboli [1,2]. Transcranial Doppler (TCD) sonography can help with investigating cerebral embolism [3]. These microembolism were detected in various conditions including carotid arterial disease [4], prosthetic heart valves [5,6], carotid endarterectomy [7], and surgeries like cardiopulmonary by-pass [8], and atrial fibrillation [9,10].

The aim of this study is to evaluate the occurrence of MES in patients with ischemic stroke. Another objective is to disclose if MES is a risk factor for ischemic stroke. Finally, the data can help to define the reliability of MES detection by means of TCD.

Subjects and Methods

Cases

During a period of 18 months, 400 consecutive patients with first ischemic stroke and 200 control subjects were studied. Forty-one patients and 18 control subjects were excluded from the study because of missing data (8 patients vs 2 controls), failed diagnostic procedures such as carotid Doppler (9 patients vs 5 controls), and insufficient temporal bone window (24 patients vs 11 controls). Control subjects were defined as patients without an ischemic cerebrovascular disease. The remaining 359 patients (219 male and 140 female; mean age 57,7±0,6 years) and 182 control subjects (97 male and 85 female; mean age 55,9±0,9 years) had undergone the routine clinical and diagnostic workup including a general physical and neurological examination, a complete blood count, blood chemistry, electrocardiogram, transthoracic echocardiography, carotid ultrasonography, a transcranial Doppler sonography, and CT/MRI. Additional diagnostic information was obtained where available (e.g., MRI angiography or transesophageal echocardiography).

Clinical and neuroimaging classifications

Patients were allocated to one of three groups according to present symptoms and signs. Transient ischemic attacks (TIA); these patients presented focal neurological symptoms with abrupt onset and complete resolution within 24 hours. Partial and total anterior circulation infarcts (PACI/TACI); these patients presented the combination of new higher cerebral dysfunction; homonymous visual field defect; and ipsilateral motor and/or sensory deficits of at least two areas of the face, arm, or leg. Lacunar infarcts (LACI); these patients presented a pure motor stroke, pure

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sensory stroke, sensori-motor stroke, or ataxic hemiparesis [11]. Brain imaging patterns were categorized as acute territorial stroke patterns indicating large-vessel disease; lacunas (<1,5 cm in diameter) and subcortical white matter lesions indicating small-vessel disease; and no ischemic lesions [12].

TCD examinations

TCD examinations were carried out and analyzed by an experienced investigator who was unaware of the diagnosis of the patients or control subjects. TCD monitoring was performed with multigated transcranial Doppler system (Multidop X4, DWL and TCD8 software). Long term monitoring was performed while the patients were at rest in the supine position. The first parts of both MCAs were insonated simultaneously with a 2 MHz probe through the temporal bones at the 50-60 mm depth. An intergate distance was settled at 5 mm. After stabilizing the Doppler signals, probes were fixed tightly with an elastic headband. Thirty minutes of computerized bilateral recording was carried out on every patient.

The established criteria for accepting the high-intensity transient signals as MES were as follows: shorter than 100 ms, at least 3 dB greater than the base-line activity, mostly unidirectional, variable location in the TCD waveform, and having audible the characteristic "chirp" sound [13]. We, however, chose a higher decibel threshold (9 instead of 3 dB). Additionally, the proven MES was requested to the time lag in occurrence of the two signals in the multigate technology (figure 1) [14,15].

Estimated risk factors

In the patients and controls, the occurrence of a risk factor was determined by clinical examination, diagnostic procedures and evidence in their medical record.

Patients and control subjects were considered to have hypertension if they had the diagnosis of hypertension before the stroke or admission. In addition, if a control subject had a diastolic pressure more or equal to 95 mmHg or a systolic pressure more or equal to 160 mmHg on two or more occasions during study evaluation, the subject was considered to have hypertension. If a patient had a sustained blood pressure of 160/95 mmHg or more on at least two occasions during study evaluation or received antihypertensive treatment throughout the entire study evaluation, the patient was considered to have hypertension.

Patients who had transient hypertension (Cushing's reflex) and did not receive antihypertensive medication, were not considered to have hypertension.

Body mass index was calculated as weight in kilograms divided by height in meters squared, and obesity was defined if a subject had a body mass index of more than 25.

Diabetes mellitus was diagnosed if a subject had a previous diagnosis of diabetes mellitus or if the fasting blood glucose level was more than 120 mm/dl.

The diagnosis of atrial fibrillation was based on ECG recordings.

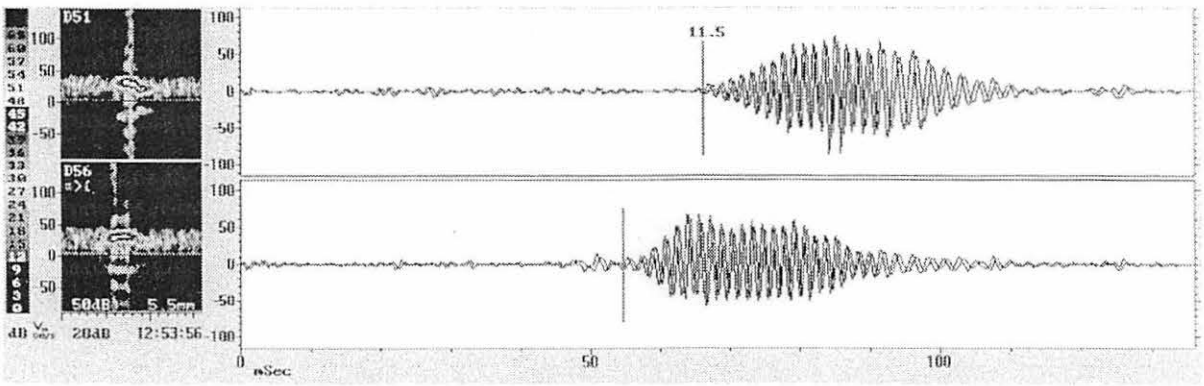

Figure 1

An embolic signal was detected at a depth of 56 mm, with a relative increase of 28 dB, and a second time at a depth of 51 mm. The background intensity increase was 50 dB. The software also detected the velocity of the embolic signal (60 cm/s). The time lag in occurrence of the two signals is visible as a pre-fast Fourier transform signal on the right side. There is a lag of 11,5 ms between the initials of the two signals. This difference indicates that the embolus has moved 6,9 mm from the first to the second sample volume [(11,5 ms)*(600 mm/1000ms)=6,9 mm]. The expected preset difference was 5 mm.

Coronary artery diseases consisted of angina pectoris (AP) and myocardial infarction (MI). These conditions were defined if a patient or control subject had a previous medical record of AP or MI, or had a characteristic chest pain or discomfort (short duration, relieving by rest or nitroglycerin). Additionally, the presence of ECG changes indicative of myocardial damage or the diagnostic increases of serum enzyme levels have been diagnosed as having coronary artery diseases.

A current smoker was defined if one smokes at least one cigarette a day within 6 months before stroke or admission.

Alcohol abuse was determined, if one drinks alcohol more than 15 cc a day within 6 months before stroke or admission.

High-grade carotid stenosis was diagnosed if a subject had a luminal narrowing of the internal carotid artery more or equal to 70%.

Statistical analysis

At the statistical analysis, t-test for group means and chi square test for group proportions were used. Univariate and multiple logistic regression analysis were used to estimate the odds ratio associated with each risk factor. The excepted statistically meaningfulness was set at $p<0,05$. The calculations were performed with the use of a statistical software package (Minitab 12 for Windows).

Results

MES were detected in 114/359 patients and in 10/182 control subjects ($p<0,00001$). The rate of MES varied between 0 and 149 signals within 30 min (6,3±0,9 MES/30 min) in patients and between 0 and 44 within 30 min (1,1±0,3 MES/30 min) in control subjects. The highest rates of MES were detected in both patients and controls that had prosthetic heart valves.

Table 1 summarized the clinical subgroups of patients. MES occurrences in the group of PACI/TACI were significantly higher than those groups of LACI and TIA.

The neuroimaging findings did not match entirely to the clinical subgroups of patients as shown in table 2. The reasons were due to some of patients with lacunar infarcts who were diagnosed initially as PACI, and some of the patients diagnosed as LACI who had no demonstrable lesion on follow up CT or MRI. Table 2 also shows significant differences between infarct types considering MES occurrence. MES were found significantly higher in the territorial infarction than either in the lacunar infarction or in the no ischemic lesion.

Table 1: MES in Clinical Subgroups.

	MES		
Clinical classifications	Yes	No	Total
Controls	10 (5,5%)	172 (94,5%)	182 (100%)
Patients*	114 (31,8%)	245 (68,2%)	359 (100%)
Transient ischemic attacks (TIA)	21 (27,3%)	56 (72,7%)	77 (21,4%)
Lacunar infarcts (LACI)	34 (26,0%)	97 (74,0%)	131 (36,5%)
Total and partial circulation infarcts (TACI/PACI)†	59 (39,1%)	92 (60,9%)	151 (42,1%)

The values in parenthesis are percentages
*p<0,00001 (Chi square) (patients versus controls)
†p=0,039 (Chi square)

Table 2: MES in Neuroimaging Subgroups.

Lesion type according	MES		
to CT and/or MRI	Yes	No	Total
Normal	24 (26,7%)	66 (73,3%)	90 (25,1%)
Lacunar infarct	35 (26,7%)	96 (73,3%)	131 (36,5%)
Territorial infarct*	55 (39,9%)	83 (60,1%)	138 (38,4%)

The values in parenthesis are percentages
*p=0,034 (Chi square)

Table 3: Distribution of risk factors for ischemic stroke.

Estimated risk factors	Patients n=359		Controls n=182	
	No.	%	No.	%
Hypertension	211	58,8	62	34,1
Micro embolic signals	114	31,8	10	5,5
Currently smoking	100	27,9	31	17,0
Diabetes Mellitus	69	19,2	23	12,6
Obesity	63	17,5	18	9,9
Atrial fibrillation	48	13,4	17	9,3
Coronary artery disease	36	10,0	7	3,8
Alcohol abuse	31	8,6	11	6,0
Prosthetic heart valves	20	5,6	8	4,4
High-grade carotid stenosis	19	5,3	1	0,5

The distribution of risk factors for ischemic strokes was summarized in the table 3. The most frequent risk factors among the cases of ischemic stroke were arterial hypertension (58,8%), MES (31,8%), and currently smoking (27,9%). In the univariate

logistic regression analysis (figure 2), MES, hypertension, currently smoking, coronary artery disease, obesity and high-grade carotid stenosis were significantly associated with the risk of ischemic stroke. Although prosthetic heart valves have the higher rate of MES occurrence, it was not significantly associated with the ischemic stroke. When multiple logistic regression analyses was performed (figure 3), the risk factors that remained independently significant were microembolic signals, hypertension and currently smoking.

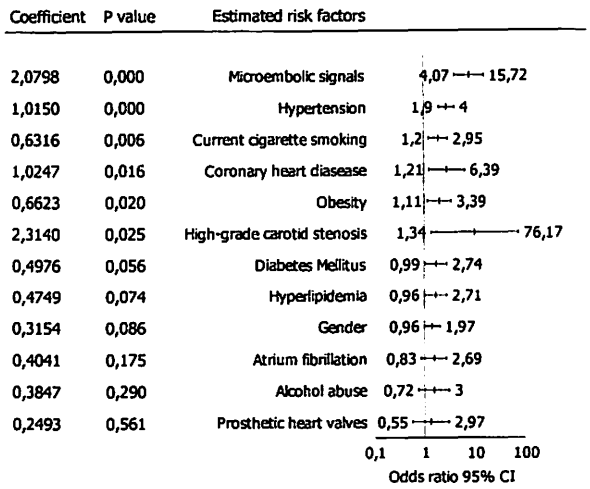

Figure 2: Univariate logistic regression analysis of estimated risk factors for ischemic stroke.

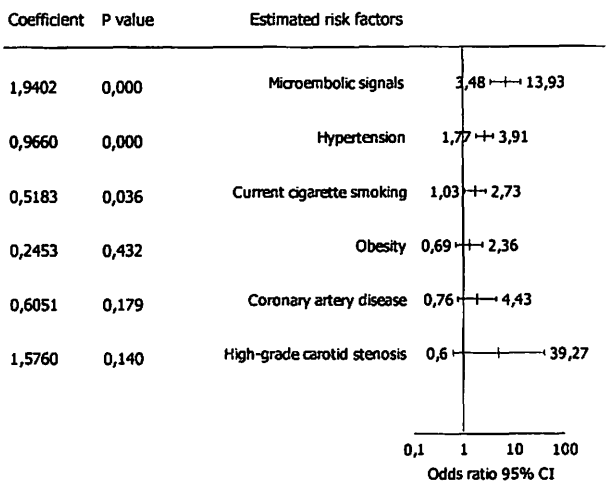

Figure 3: Multiple logistic regression analysis of estimated risk factors for ischemic stroke.

Discussion

The diagnosis of emboli sources in ischemic strokes has become an interesting subject by the investigation of MES by TCD. However, the relationship between neurological complications and MES showed by TCD is not exactly known. There are frequency and incidence studies of MES to show the relation of asymptomatic MES with possible clinical processes [6,16].

In recent years, many studies have shown that MES have clear importance on the pathogenesis of large vascular infarctions [14,17,18]. MES can be evaluated in patients who have an emboli source or nonlacunar large vascular disease [19-21].

The data presented here supports the potential clinical significance of MES in the pathogenesis of ischemic cerebral events in patients with clinical symptoms and neuroimaging signs indicating large-vessel disease. The MES occurrence in patients (31,8%, p=0,00001) was significantly higher than those of controls (5,5%). Additionally, the highest rate of MES occurrence was found in patients with territorial infarction (39,9%). This finding also reached a significant level (p=0,034) when comparing with the lacunar infarction or no ischemic lesion.

We, however, found MES in patients with lacunar infarct (26,7%) and no ischemic lesion (26,7%). These results, however, did not achieve a significant level compared with control subjects (5,5%). The possible explanation of these relatively higher MES occurrence in patients with lacunar infarct and no ischemic lesion is due to the relatively higher frequency of prosthetic heart valves in these patients (7,3% and 7,8% respectively) as well as in controls (4,4%). In contrast, patients with territorial infarction have a relatively lower rate of prosthetic heart valves (2,3%). It is shown that the patients with prosthetic heart valves characteristically show a high frequency of MES [6,22]. These MES are more likely gaseous particles generated by a cavitation mechanism indicating a benign nature of microemboli that arise from prosthetic heart valves [23-25]. Moreover, patients with lacunar infarction or no ischemic lesion mostly have a single MES, except those having prosthetic heart valves. The single MES most likely reflect very small particle [26] but rarely represent emboli large enough to cause occlusion of the small vessels. However, lacunar infarction has been noted in patients with potential sources of cerebral emboli in the heart or the cerebropetal artery [27].

Whereas, patients with territorial infarction have a significantly higher rate of high-grade carotid stenosis (9,4%, p=0,015) than those of patients with lacunar infarction (3,8%) or with no ischemic lesion (1,1%). MES detected in patients with high-grade carotid stenosis are usually solid, and represent emboli to have an increased risk of a

stroke [4,28,]. Reduction of both the number of embolic signals and the risk of stroke after endarterectomy of high-grade carotid stenosis support this suggestion [29,30].

This study also provides estimates of the relative risk of ischemic stroke associated with various factors. The use of standardized criteria ensured the reliability of the comparison of the risk factors. However, the selection of the patients with ischemic stroke in MCA territory gave limitation to our study. Additionally, our study is a hospital-based study, and therefore it is not entirely representative of the general population. Nevertheless, our data indicates that hypertension, current cigarette smoking, and microembolic signals detected on TCD in multiple logistic regression analysis were significantly associated with ischemic stroke in MCA territory. Similar to our findings, significant associations of hypertension [31] and cigarette smoking [32] have been reported in hospital-based studies and in population-based studies [33,34]. Obesity, coronary artery disease and high-grade carotid stenosis were significant risk factors for ischemic stroke in the univariate analysis, but were not significant in the multiple logistic analysis. The lack of an association between these factors and the risk of ischemic stroke in our study could be related to the fact that patients with ischemic strokes in the posterior circulation who excluded from this study.

No independently significant association with the risk of ischemic stroke for MES detected by TCD has been reported before. In our study, the estimated odds ratio of MES (6,96) indicates that the risk of ischemic stroke increases by 70% per positive result of MES detection. However, in the currently reported studies and in our study, no patient experienced new neurological symptoms during the TCD monitoring session [35]. The possible explanation of this bias could be related to poor understanding of the impact of microemboli detected by TCD on human brain function.

In conclusion, our study supports that the TCD has a predictive role of microemboli monitoring predominantly in patients with large-vessel territory stroke. Additionally, MES found an independent risk factor for ischemic stroke, and therefore our data underlines the importance of transcranial Doppler monitoring for detecting MES in ischemic cerebral events.

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