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Microembolic signals and clinical outcome in patients with acute stroke – a prospective study

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Abstract The occurence of microembolic signals (MES) in patients with transient ischemic attack (TIA) or stroke has already been described; the influence of the time interval between onset of symptoms and transcranial Doppler monitoring (TCD) on the MES rate or MES prevalence and the possible prognostic value of the early detected MES rate on the outcome of TIA or stroke symptoms in a 3 month interval are discussed. In a prospective study we evaluated 61 patients consecutively admitted to our stroke unit after their first ischemic neurological deficit involving the vascular territory of MCA and/or ACA. All of the patients underwent a 30-minute bilateral transcranial Doppler monitoring of their MCAs for the identification of MES. Monitoring was performed within 12.3 + –9.3 (average mean + –SD) hours of stroke onset for the first time, the second time 48 hours after first TCD monitoring. Prognosis for the recovery of neurological deficits was evaluated by using the Barthel index (BI) and Scandinavian Stroke Scale (SSS) at the time of admission of the patient to the stroke unit, and with Barthel indices after one month and after 3 months. As a result, 56% of all patients showed MES in at least one of the two registrations. MES were recorded not only on the symptomatic side. The MES prevalence between both TCD monitorings was significantly different (total MES prevalence: 1st TCD: 26 patients; 2nd TCD: 13 patients; $p < 0.04$; ipsilateral MES prevalence: 1st TCD: 19 patients; 2nd TCD: 9 patients; $p < 0.01$). The regression analysis showed a significant influence of the total MES rate on both neurological scores at admission (SSS: 0.03; Barthel index: 0.04), but not for the Barthel scores after one and three months. In conclusion, we found an influence of the time interval between onset of neurological symptoms of TIA or stroke on the MES rate and the prevalence of MES. The prevalence of MES or the MES rate, found after a short time interval to the onset of symptoms, did not have a prognostic value on the outcome of neurological deficits up to a three month follow-up.

Key words Embolism · Ultrasonics · Cerebral infarction

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Introduction

The diagnosis of embolic stroke is made on detection of a potential embolic source, usually after the neurological event. Reports indicate that persistent subclinical microemboli exist in patients with atrial fibrillation and stroke [21], carotid stenosis [1, 8, 16, 17], and other embolic sources [14] and vary according to stroke subtype. Microembolic signals (MES) are frequent events in patients with mechanical prosthetic valves [9], but did not appear to be a major prognostic for an impending cardioembolic stroke [6]. In vitro studies suggest that MES can be caused by air bubbles and fat or platelet-fibrinogen embolic particles [12, 15]. In vivo reports describe different types of clinically silent microembolic signals, found in an in vitro model [12] and in transcranial Doppler monitoring in patients with artificial prosthetic aortic valves [11].

The option to test and to treat patients very quickly is an advantage of stoke units. The time interval between the onset of neurological symptoms in cases of a TIA or stroke and admission to the stroke unit decreases, when emergency personnel (e.g. paramedics) are trained to recognize signs of cerebral ischemia very quickly. The personal staff at the stroke unit has to also be exercised in the management of the diagnostic and therapeutical tools. With improved management, a relatively short time interval between onset of cerebrovascular events and TCD monitoring can be achieved. A wide range of time intervals exists in former studies [1, 2, 4, 5, 7, 10, 19, 20, 23; Table 1] and different results of the influence of the time factor for the TCD monitoring (prevalence of MES, MES rate) are discussed [5, 19].

We undertook this study to evaluate the prevalence of MES in patients with acute TIA or stroke, reducing the

Table 1 Studies with acute stroke patients. Interval from onset of symptoms to the first TCD monitoring. Number of TCD follow-up examinations. Duration time for TCD monitoring. Prevalence of microembolic signals (MES)

Author	First TCD monitoring within hours of onset	Number of TCD monitorings (examination duration in minutes)	Prevalence of MES (%)	
			First	Overall
Babikian et al. [1], 1994 (n = 75)	? (only one TCD monitoring)	? (30 min; only 2 pat. 25 min)	20.8%	–
Babikian et al. [2], 1997 (n = 229 arteries)	Median of 9 days after onset	30 min.	Sympt. Art.: Asympt. Art.:	28.6% 12.4%
Daffertshofer et al. [4], 1996 (n = 254)	< 4 weeks	? (mean: 48 + -8 min)	9.3%	–
Delcker et al., 1998	12.3 hours (range 2 to 48 hours)	Onset, 48 hours	52%	56%
Del Sette et al. [5], 1997 (n = 75)	32 hours (range 1 to 72 hours)	Onset, 24 hours, 7 days (30 min)	5.3%	12%
Forteza et al. [7], 1996 (n = 69 arteries)	MES positive.: median 4 days; MES negative: median 12 days	?	Sympt. Art.: TIA: Stroke:	 44% 16%
Grosset et al. [10], 1994 (n = 41)	< 48 hours	? (30 min)	71%	–
Sliwka et al. [19], 1997 (n = 78)	< 1 week (range 1.5 to 168 hours)	Onset, 24 hours, 48 hours (30 min)	39.7%	40%
Takada et al. [20], 1996 (n = 29)	?	Admission, 1 day and 7 days	71%	60.3%
Tong and Albers [23], 1995 (n = 38)	< 48 hours	? (30 min)	11%	–

time interval from onset of neurological symptoms to the beginning of the TCD-monitoring. The influence of this short time interval on the MES prevalence and rate and the possible prognostic value of the early detected MES prevalence or rate on the clinical outcome of TIA or stroke symptoms over a three-month period were studied.

Subjects and methods

In a prospective study we evaluated 61 patients (aim number for the inclusion: 50 patients with sufficient bitemporal TCD insonation conditions) consecutively admitted to our stroke unit after their first ischemic neurological deficit involving the vascular territory of MCA and/or ACA. We considered both TIAs and complete strokes and excluded patients with cerebral hemorrhage and with vertebrobasilar episodes. In addition patients were excluded when their TCD (insonation conditions of bitemporal bone windows) were considered insufficient. Eleven patients had an insufficient temporal bone window. The remaining 50 patients consisted of 31 men and 19 women. All the patients were evaluated with the complete set of diagnostic tools of our unit, which included clinical history, neurological examination, CT scans or in selected cases cerebral MRI, carotid and vertebral Doppler- and color coded duplex (ACUSON 128XP, Mountain View, CA), transcranial Doppler sonography (DWL, Sipplingen, Germany), ECG monitoring, a complete cardiologic examination with an included transesophageal echocardiography (Table 2) and, very rarely, a cerebral angiography. All persons gave their informed consent prior to their inclusion in the study. Serum for the effect of the heparin treatment was checked maximally ten minutes before beginning both TCD-monitorings by examining the partial thromboplastin time (PTT). Prognosis for the recovery of neurological deficits was evaluated by using the Barthel index (BI) and Scandinavian Stroke Scale (SSS) at the time of the admission of the patient to the stroke unit, and with Barthel indices after one month and after 3 months. All clinical examinations and all score evaluations were performed by the same examiner.

Table 2 Pathological results (%) of the transesophageal echocardiography

Dilatated left ventricle	10%
Dilatated left atrium	20%
Right-left shunt	4%
Left-right shunt	2%
Mitral valve prolapse	4%
Left ventricular thrombi	2%
Left atrial thrombi	8%
Aortal plaques	20%
Atrial septal aneurysm	2%
Dilatative cardiomyopathy	2%
Atrial fibrillation	6%
Total of path. echocardiographies	52%

Subgroups determined by structural ischemic brain lesions

Brain imaging patterns were categorized as acute territorial stroke patterns indicating large vessel disease [13], acute hemodynamic stroke patterns (cortical or subcortical) indicating large vessel disease [13], lacunes (< 1.5 cm in diameter) and subcortical white matter lesions indicating small vessel disease [13].

Doppler and duplex sonography of the extracranial and intracranial arteries

The degree of carotid artery stenosis was estimated with the use of continuous-wave Doppler sonography and color-coded duplex

sonography using standard criteria. Intracranial arteries were insonated with transcranial Doppler sonography and transcranial duplex sonography using standard criteria.

TCD studies

All patients underwent 30-minute bilateral transcranial Doppler monitoring of their MCAs (Neuroguard system) for the identification of MES. Definite HITS counting was performed on-line by a single highly experienced examiner, who attended all examinations, and not by the "decision" of automated detection software. This approach is supported by another report [24] providing evidence that three different types of commonly used automated detection systems are less reliable than a human expert. Potential microembolic signals were identified as they occurred and were saved on floppy disk for subsequent analysis. We used the following criteria for the diagnosis of MES: They had an intensity of at least 9 dB above that of the background blood flow, unidirectionally high amplitude signals, a duration of < 300 milliseconds, and were accompanied by a "chirp" on the audio output [3]. The microemboli counts in bilateral MCAs during 30 minutes were added to the sum scores. The TCD-monitoring was performed after the admission of the patient for the first time, the second time 48 hours after the first monitoring.

Normal group

An age and sex matched control group of 16 probands without a vascular or cardiac history and with normal results in the extra- und intracranial Doppler and duplex sonography was used to find the normal prevalence and the normal MES rate. Like in the patient group, the TCD monitoring was performed twice with a time intervall of 48 hours.

Statistical methods

First a descriptive statistical analysis was performed. Pearson's correlation coefficient was calculated between MES rate and examined parameters (age, clinical scores, dose of heparin, PTT serum level). Group comparisons were made with either the chi-square test or Fisher's exact test (two-tailed). Regression analysis was performed with the dependant variables Barthel index (admission, after one and three months) or Scandinavian Stroke Score (admission) and the two nonindependant prognostic predictors MES rate and PTT.

Results

Microembolic signals

Patient group

We included 50 patients, men and women, with a mean age of 65.5 + –11.7 (mean + –SD; range, 37 to 86) years. Patients were treated with antiplatelet agents (n = 13) or anticoagulants (heparin n = 37). The time interval of first TCD registration was 12.3 + –9.3 (average mean + –SD) hours after stroke onset. 28 patients (56%) showed MES in at least one of the two registrations. MES were recorded not only on the symptomatic side (symptomatic side: first registration = 48% and second registration = 30%; asymptomatic side: first registration = 36% and second registration = 16%). The MES prevalence between both TCD monitorings was significantly different. At the first TCD monitoring the total MES prevalence existed in 26 patients, at the second monitoring in 13 patients: $p < 0.04$; ipsilateral MES prevalence (first monitoring in 19 patients, second monitoring in 9 patients: $p < 0.01$). Of the MES positive patients, 26 of 50 (52%) showed MES in the first registration, whereas 13 of 50 (26%) were positive in the second registration. Three patients (6%), who did not show MES in the first registration, became positive after 48 hours.

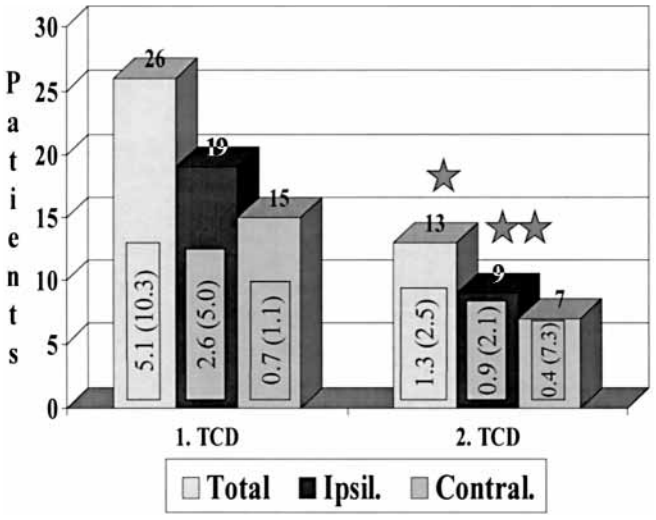

Fig. 1 Prevalence of microembolic signals (MES) in patients with acute cerebral ischemia. Total: Total MES rate of ipsilateral and contralateral MCAs; ipsil.: MES rate ipsilateral to cerebral ischemia; contral.: MES rate contralateral to cerebral ischemia. ★: $p < 0.05$; ★★: $p < 0.01$. Vertical numbers indicate the median of MES and 95% CI of the frequency

The analysis of the difference between the group with MES and the group without MES showed no statistically significant differences in the time of recording from onset, stroke risk factors (hypertension, pathological results in the transesophageal echocardiography, diabetes, dyslipidemia, smoking, and presence of ipsilateral carotid stenosis), and hematological parameters (partial thromboplastin time). Only a nonsignificant tendency for a higher MES prevalence existed in the patient group with microangiopathic lesions in brain imaging (16/26 versus 11/24 in patients with large vessel disease). There was no difference in prognosis between the group with MES and the group without MES (Barthel indices after one month and after three months). In Pearson's correlation coefficient no correlation existed between ipsilateral, contralateral, total MES rates, and neurological scores (SSS, Barthel indices). The regression analysis showed a significant influence of the total MES rate on both neurological scores at the admission (SSS: $p < 0.03$; Barthel index; $p < 0.04$), but not for the Barthel scores after one and three months. The partial thromboplastin time had no significant influence on this result.

Normal group

The age and sex matched control group had no MES in either of the TCD recordings, performed with a 48 hour interval.

Table 3 Pathological results (%) of extracranial continuous-wave (CW) Doppler and duplex sonography. *ICA* internal carotid artery; *ECA* external carotid artery; *CCA* common carotid artery; *VA* vertebral artery

Arteries	CW Doppler		Duplex	
	Right	Left	Right	Left
ICA	24%	16%	36%	40%
ECA	2%	2%	–	–
CCA	0%	0%	36%	38%
Bifurcation	0%	0%	52%	36%
VA	4%	6%	0%	6%

Neurological scores

At admission, the Scandinavian Stroke Scale was 43.0 + –15.7 (mean + –SD, with a range from 11.0 to 58.0). Barthel index at admission was 10.8 + -11.4 (mean + –SD, with a range of 0 to 30), after one month 12.1 + –10.7 (mean + -SD, with a range of 0 to 30), and after three months 14.7 + –10.0 (mean + -SD, with a range of 0 to 30).

Brain Imaging

When all 50 patients with an acute ischemic neurological deficit were analyzed on the basis of brain imaging studies (CT, MRI, or both), five patients had a normal result. In 24 patients, large vessel disease was suggested (territorial infarction, n = 23; hemodynamic stroke pattern, n = 5; four patients had combination of both). Twenty-six patients showed single or multiple lacunes, indicating some form of microangiopathic lesions (10 with additional white matter lesion on CT/MRI scans). In five patients of all 45 patients with pathological brain imaging, a combination of both brain imaging patterns with microangiopathic lesions and large vessel disease existed.

Doppler and duplex results of extracranial arteries

In the right internal carotid artery there was a stenosis > 50% in 12% and an occlusion in 12%, in the left internal carotid artery a stenosis > 50% in 12% and an occlusion in 4% (Table 3). Only arteriosclerotic plaques without any hemodynamic signs in the continuous-wave Doppler were found with duplex sonography in 36% (right ICA) and 40% (left ICA) of vessels. One stenosis > 50% was found in the external carotid artery; only plaques without a hemodynamic effect were seen in the common carotid artery of both sides. A stenosis or an occlusion of the vertebral artery existed in 4% (right side) or 6% (left side) of vessels.

Discussion

The occurence of MES is a frequent finding in our series, being present overall in 56% of our patients, but no MES occurred in the control group. We showed that a time factor does exist, which influences the HITS rate. The prevalence decreased from the first monitoring, performed after a mean interval of 12.3 hours, from 52% to a prevalence of 26% in the TCD recording after an additional 48 hours later. Other authors have also reported a high prevalence of MES in the acute or subacute phase of an ischemic event (19, 20). Del Sette et al. [5] evaluated 75 patients with a mean time intervall of 32 hours from the onset of the first focal ischemic neurological deficit and TCD monitoring of MCA and found an overall MES rate in only 12%. An explanation for this low MES prevalence could be the low number of patients with supposed cardioembolic stroke mechanisms [18]. Del Sette et al. [5] found an increase of the prevalence of MES after an additional 24 hours from 44% to 88% of MES positive patients and a following decrease of the MES prevalence to 11% of MES positive patients after one week. Takada et al. [20], studying 29 patients with acute stroke, reported a result similiar to ours, as they found a higher prevalence of MES with a shorter time interval between TCD monitoring and onset of the ischemic event (1 day to 28 days: 71% to 50%). The results of Sliwka et al. [19] with a time interval of less than one week agree with our results and shows a decrease in the number of MES in the follow-up examinations. Using the infrastructure of our stroke unit we reduced the time intervall between onset of neurological symptoms and TCD monitoring to a range from 2 to 48 hours. Therefore, most of the results of these studies speak for a high activity of thrombembolic process a short time after the onset of the ischemic event.

In our study, an influence of the MES rate on both the neurological scores (SSS, Barthel index) existed only at the time of the admission of the patient. Otherwise, the MES rate or the prevalence of MES at admission or 48 hours after the admission showed no effect as a prospective parameter for the outcome of neurological symptoms in the three-month follow-up period. The majority of patients were receiving some form of antiplatelet or anticoagulant therapy at the time of TCD testing and during the follow-up period. These medications may have affected the rate and the prevalence of microembolic signals. A significant influence of the thromboplastin time at the TCD monitoring times did not exist for our results. Our results agree with results of Del Sette et al. [5]. They describe a missing value of MES prevalence as a prognostic parameter at 30 days from onset, but with a longer interval between monitoring and stroke onset (up to 72 hours). The aim of both studies is to find a prospective parameter for the outcome of neurological symptoms, caused by a first focal ischemic deficit. Not included in either of the prospective studies is the rate of recurrent new ischemic events in the follow-up period. Therefore, another option is a connection between positive microemboli studies at baseline and recurrent cerebral ischemic events among those patients with a cerebral infarction, as described in a trend from Tegeler et al. [22].

In conclusion, we found an influence of the time interval between onset of neurological symptoms of TIA or

stroke on the MES rate. The prevalence of MES or the MES rate, found after a short time intervall to the onset of symptoms, did not have a prognostic value for the outcome of neurological symptoms up to a three month interval.

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