Prolonged TCD Monitoring for Microembolus Detection in Acute Stroke Patients

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ABSTRACT

Microembolism might be a cause for early stroke recurrence. These can present as microembolic signals (MES) on transcranial Doppler (TCD) monitoring. Objectives: To identify the utility of TCD monitoring for the occurrence of MES in the early stages of ischemic stroke. – To determine the different cerebroembolic sources (Carotid, cardiac and MCA) using TCD. Setting: specialized university hospital stroke unit. Patients: 150 consecutive patients were studied, in the first 72 hours after ischemic stroke. 43 patients fitting the inclusion criteria were included and divided into three groups: carotid (10 patients), cardiac (15 patients) and MCA (18 patients) groups. In addition 10 normal controls were studied. Methods: all patients were assessed by a neurologic history and examination, CT on admission, MRI and MRA, ECG, Transthoracic ± transesophageal echocardiography, carotid duplex and TCD monitoring for one hour. Results: 60% of the carotid group showed MES; 66% of whom being in the ipsilateral MCA. 53% of the cardiac group showed MES; 75% being bilateral. Among the MCA group 27% had MES in the symptomatic MCA. MES were not detect in any of the normal controls. Conclusion: TCD is a promising tool for detection of early cerebral embolization in ischemic stroke and might have its implications on therapeutic options. (Egypt J. Neurol. Psychiat. Neurosurg., 2005, 42(2): 291-300).

INTRODUCTION

The increased incidence of recurrent ischemic events during the days and weeks following a TIA or cerebral infarct has long been recognized. “Stroke in evolution”, “progressive stroke”, and “early recurrent stroke” are terms frequently used to describe the development of new neurologic symptoms.¹

However, it is not a regular practice that the attending neurologist monitors for intravascular flow changes or embolization that might be the direct cause for early stroke recurrence.

The ability to diagnose microembolisation is of clinical relevance to a potentially preventable cause of stroke. Yet, the most commonly used diagnostic procedures: CT brain and MRI, carotid duplex and echocardiography, do not offer a direct, real-time evidence of cerebral embolism. Transcranial Doppler sonography (TCD) can supply the required data and has become an acceptable method for detecting cerebral microemboli arising from the carotids or the heart. Growing evidence shows that identifying these microemboli can enhance our pathophysiologic understanding of ischemic strokes and their recurrence in early stages of stroke.²³

MATERIAL AND METHODS

One hundred and fifteen consecutive patients presenting to the stroke unit at Ain Shams University Specialized Hospital, with acute ischemic stroke were prospectively studied.

Inclusion criteria: - acute ischemic stroke within the first 72 hours of onset, - in the territory of the anterior circulation, - only one detectable
source of embolization, - the presence of insonable temporal windows.

Exclusion criteria: - stroke duration exceeding 72 hours, - hemorrhagic stroke, - infarction in the posterior circulation territory, - more than one potentially embolic source, - undetermined source, - lacunar infarcts, - uninsonable temporal windows, - patients intolerant to monitoring.

All patients were assessed by a clinical history, neurological examination and CT on admission to exclude hemorrhage. Subsequently, the routine stroke protocol of our unit was performed including MRI with diffusion weighted image (DWI), magnetic resonance angiography (MRA), ECG, transthoracic ± transesophageal echocardiography, carotid duplex and TCD.

In addition, screening for other laboratory risk factors was done.

All patients received intravenous anticoagulant therapy after excluding hemorrhage by CT on admission. This treatment was replaced by antiplatelet therapy if cardiac embolization was excluded by investigations (this usually happened after TCD monitoring was done). So patients were considered anticoagulated if the aPTT was ≥1.5 times the control, or if the INR was ≥2.

TCD was done in the first 72 hours, mean time from stroke onset was 32.2 hours, that is why most patients were not therapeutically anticoagulated.

According to the results of investigations the patients having an acute infarction in the anterior circulation territory, identified by DWI, were assigned to four groups.

ICA group: patients with carotid artery disease; either diffuse atherosclerosis, stenosis , thrombus or plaque, with normal ECG and echocardiography. Cardiac group: patients with arrhythmias, or other potentially cardioembolic disorders as detected by ECG or echocardiography, with no stenotic segments on carotid duplex. MCA group: patients with an acute infarction on DWI in the domain of the MCA, with the homolateral MCA stenotic or occluded segmentally, with normal ECG, echocardiography and carotid duplex. Patients with whole length MCA occlusion on MRA were excluded since insonation could not be done proximal and distal to the stenotic segment. Normal control group: of 10 age-matched normal persons with no history suggestive of cerebrovascular diseases, normal carotid duplex and echocardiography.

Transcranial Doppler examination:

TCD was done using a Multi Dop X-4 (DWL) machine, with the patient lying supine. A 2-Mhz hand-held probe was applied to the transtemporal windows to identify the MCAs bilaterally, and to localize the stenotic segment. MCA stenosis was diagnosed if its peak systolic velocity was ≥ 80 cm/s with the presence of one of the following features: circumscribed increase in velocity, the presence of murmur, widening spectrum, or asymmetric MCA flow velocity of more than 30 cm/s asymmetry.

For embolus monitoring, two multigate 2-Mhz probes fixed in a standard headset were applied to the predetermined MCA position bilaterally. These probes are capable of simultaneous insonation at two different depths of the same vessel. A special software for the detection of MES was used. The distance between 2 insonation depths ranged from 8 to 10 mm, sample volume 10 mm., sweep speed 5 seconds and a low gain were used. An embolus detection threshold greater than or equal to 5dB was used for all patients. The machine used a 128-point Fast Fourier Transformation analysis and a graded color scale to display the intensity of the received Doppler signal.

Monitoring time was 1 hour and both MCAs were insonated simultaneously whenever possible or separately.

In the MCA group the bigate probe was adjusted so as to insonate the segments proximal and distal to the stenotic segment simultaneously, in order to exclude the possibility of emboli originating proximal to the stenotic MCA from an unidentified source in the carotid or the heart.
The same observer performed all the TCD examinations, being blinded to the patient’s clinical and radiological data. The observer was present during monitoring to watch for patients’ movements and for online MES detection. The TCD machine was equipped by a software for automated embolus detection. All studies were saved on hard disk for off-line analysis by an independent observer. Because of technical limitations data recorded did not include audio channel. MES were identified by their characteristic visual appearance and acoustic properties according to published criteria.\(^6,7,8\)

Only MES agreed upon by the two observers and the automated detection were included in assessment.

**Carotid duplex:**

The extracranial carotids were examined by Duplex Ultrasound using a Diasonic 2D Gateway machine with a 5 MHz pulsed Doppler trasducer with the patient in the supine position and the neck extended. Examination was carried out in both the longitudinal and transverse planes B-mode then colour duplex study and waveform analysis were done. The incidence angle was between 30-59\(^{\circ}\). The following findings were reported on: intimal surface thickening, presence or absence of plaques, and whether mobile or not, and presence of stenotic segments. Colour flow was noted at the point of maximum stenosis and post-stenotic segment. Doppler waveform, spectral broadening and velocity values were recorded. Velocity measures of interest were: peak systolic velocity in both ICA and CCA, end diastolic velocity and peak systolic velocity ratio PSVR of ICA: CCA. A threshold for ICA/CCA PSV 2.1 was considered for ICA stenosis of 50% or more.\(^9\)

**RESULTS**

According to our criteria for patient selection, 72 patients were excluded: 44 had more than one potentially embolic source, 19 had an undetermined source or lacunar stroke, 5 couldn’t tolerate the examination and 4 had uninsonable windows.

**Forty three** patients completed the study. They had a mean age of 68.4 (range 38-72 years), 24 men and 19 women. And 10 normal controls with a mean age of 66.2 (range 40-74), 6 men and 4 women.

Nineteen of the forty three patients (44.18%) had MES. Total number of MES was 310, mean 7.2/hr.

**Carotid group:** ten patients had carotid pathology by carotid duplex. 6/10 (60%) had MES; 4/6 (66.6%) had unilateral MES in the ipsilateral MCA (Fig. 2 A), and 2/6 (33.3%) had bilateral MES. Patient characteristics are shown in table 1.

**Cardiac group:** Fifteen patients had cardiac pathology, 8/15 (53.3%%) showed MES; 6/8 (75%) had bilateral emboli (Fig. 2 B), and 2/8 (25%) had unilateral emboli. Patient characteristics are shown in table 2.

**Prevalence, laterality and number of MES among carotid versus cardiac groups:**

Prevalence was 6/10 (60%) among the carotid group 8/15 (53.3%) versus the cardiac group, \(p: 0.9\). Unilateral MES were detected in 4/6 (66.6%) in the carotid versus 2/8 (25%) in the cardiac group, \(p: 0.3\). The mean number of MES per hour was 15±19.3 in the carotid and 35.16±34.1 in the cardiac group, \(p: 0.3\).

**MCA group:** eighteen patients with MCA stenotic segments without any detectable carotid or cardiac pathology, were examined. MES were detected in 5/18 (27.7%). All emboli were seen in the symptomatic MCAs, all were distal to the stenotic segment, ensuring an origin in the MCA. The count ranged from 2 – 15 / hour, total 39 embolic signals.

Diffusion weighted images DWI of the MES positive patients showed multiple infarcts in the territory of the involved MCA in 4/5 (80%), while only 2/13 (15.3%) of the MES negative patients showed multiple infarcts on DWI. \(P: 0.04\) (Fig. 1 A & B)
Normal control group:
None showed MES for a monitoring time of 30 minutes.

Anticoagulated versus non-anticoagulated patients:
24/43 patients could not be assessed for anticoagulant effect being on low molecular weight heparin with no diagnostic laboratory tests. The remaining 19 received heparin:
5 (26.3%) were therapeutically anticoagulated, and 14 (73.6%) were not therapeutically anticoagulated. Thus we compared patients with testable anticoagulation profile (i.e. excluding those on low molecular weight heparin). Among these 2/5 (40%) of anticoagulated patients showed MES, while 8/14 (57.1%) non anticoagulated patients showed MES. $P: 0.8$.

However the total number of MES was less in the anticoagulated group 2.4/hour as compared with the non anticoagulated group 8.8/ hour (Table 3).

Table 1. ICA group characteristics.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Patients n: 10</th>
<th>Patients with MES</th>
<th>Unilateral/ Bilateral MES</th>
<th>Number of MES/hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse atherosclerosis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 50% stenosis</td>
<td>1</td>
<td>1</td>
<td>Unilateral</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 50% + mobile plaque</td>
<td>3</td>
<td>1: unilat. plaqu</td>
<td>Unilat. Bilat.</td>
<td>13</td>
</tr>
<tr>
<td>≥ 50% stenosis</td>
<td>2</td>
<td>1: unilat. plaqu</td>
<td>Unilat.</td>
<td>3</td>
</tr>
<tr>
<td>≥ 50% + mobile plaque</td>
<td>2</td>
<td>1: bilat. plaqu</td>
<td>Bilat.</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>6</td>
<td></td>
<td>60</td>
</tr>
</tbody>
</table>

Table 2. Cardiac group characteristics.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Patients n: 15</th>
<th>Patients with MES</th>
<th>Unilateral/ Bilateral MES</th>
<th>Number of MES/hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICM</td>
<td>3</td>
<td>1</td>
<td>Unilat.</td>
<td>10</td>
</tr>
<tr>
<td>Thrombus</td>
<td>4</td>
<td>3</td>
<td>Bilat.</td>
<td>94</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>4</td>
<td>1</td>
<td>Bilat.</td>
<td>54</td>
</tr>
<tr>
<td>LVA</td>
<td>1</td>
<td>1</td>
<td>Bilat.</td>
<td>21</td>
</tr>
<tr>
<td>AF</td>
<td>2</td>
<td>1</td>
<td>Unilat.</td>
<td>1</td>
</tr>
<tr>
<td>Artificial valve</td>
<td>1</td>
<td>1</td>
<td>Bilat.</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>8</td>
<td></td>
<td>211</td>
</tr>
</tbody>
</table>

ICM: ischemic cardiomyopathy, LVA: left ventricular aneurysm, AF: atrial fibrillation.
Fig. (1): A. Left MCA shows an occluded segment with no distal runoff, however distal flow could be detected by TCD. Right MCA shows atherosclerotic changes. B. DWI shows multiple acute infarctions in the left MCA territory.

Table 3. MES in anticoagulated versus non anticoagulated patients (group receiving heparin) n: 19.

<table>
<thead>
<tr>
<th>Status</th>
<th>Total</th>
<th>MES +ve</th>
<th>MES –ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulated</td>
<td>5</td>
<td>2 (40%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Non anticoagulated</td>
<td>14</td>
<td>8 (57.1%)</td>
<td>6 (42.9%)</td>
</tr>
</tbody>
</table>
Fig. (2 A): A right carotid stenosis, rt. MCA emboli.

Fig. (2 B): Cardioembolic case, bilateral emboli.
DISCUSSION

MES are frequent phenomena in patients with acute stroke arising from variable sources, both in the very early stages and several days after the onset of symptoms. We performed microembolic signal monitoring during the acute phase of stroke as some studies reported decreasing prevalence of MES as time elapses from the acute episode.\(^3,10\) Also, we monitored for one hour, while most other studies' monitoring time was 30 minutes. The effect of prolonged monitoring has been previously demonstrated\(^11,12\).

Our study showed a (44.18\%) prevalence of MES among the whole stroke group, this agrees with other studies who detected a prevalence of 42\% and 38\%\(^{13,14}\). Our figures are more than others who reported 31.3\% and 33.3\%\(^{15,16}\), 28.6\%\(^{17}\), 16\%\(^{17}\). However, other studies showed a higher overall prevalence, 51\%.\(^3\)

The carotid group in our study had a 60\% prevalence of MES. Other studies reported a 100\% prevalence in >60\% stenosis\(^{18}\), 91.6\%\(^{19}\), 50\% in acute cases\(^{11}\), 44\% in acute stroke patients with a maximum number in stenosis 70-90\%\(^3\), 39\% in >40\% carotid stenosis\(^{19}\), 28.6\% and 28\% in non acute stroke patients\(^{15,17}\). The variability in prevalence might be due to the difference in study samples, some of them being acute stroke patients\(^{11,19}\), others being chronic patients\(^{15,17}\). Also some studies include symptomatic stenotic arteries\(^{11,14}\) and others include non-symptomatic arteries\(^{15}\).

No difference was detected in the number of patients having MES among different grades of stenosis, yet those having a mobile plaque showed a bigger number of embolic signals in both groups with < and > 50\% stenosis. This agrees with reports stating that there is no association between the degree of stenosis and embolisation and that plaque ulceration was the main source of microembolism\(^{17}\), on the other hand Stork et al found that plaque morphology was unrelated to MES.\(^{20}\)

The cardiac group showed a 53.3\% prevalence of MES, 75\% being bilateral. Prevalence varied in different studies: 90\% in patients with prosthetic valves\(^{18}\), 36\% in patients with different potentially cardioembolic lesions, being bilateral in 38\%\(^3\) and 31\% in another group of cardiac patients\(^{21}\). The difference in results is attributable to the different populations studied, since some cardiac diseases are more emboligenic than others as prosthetic valves. Also, most of the studies involved chronic patients. Others included anticoagulated patients\(^{19}\).

The bilaterality of MES in cardiac cases was reported in other studies versus predominantly unilateral MES in carotid disease\(^{3,11,15}\), accordingly TCD embolus detection can localize the embolic source\(^{15}\). In previous studies prevalence of MES was reported to be higher in carotid than cardiac pathology.\(^{11}\)

We found that the prevalence of MES was higher among the carotid than the cardiac group while the number of MES was higher in cardiac than carotid cases, which contradicts findings of other studies.\(^{11,15}\) Yet one study included only chronic stroke patients, while the other had a monitoring time of 30 minutes. We studied patients in the first hours after stroke and monitored our patients for 1 hour, which might have increased the yield of the procedure. It has been reported that high intensity transient signals are less frequent in cardiac than in carotid embolism, disappear a few days after the embolic event\(^{22}\) and there is a negative relationship between the time since the symptoms and the number of MES per hour\(^{13}\).

In our study we excluded patients with more than one potentially embolic source. This might explain why the number of MES in carotid disease was less than cardiac disease as any contributing cardiac pathology has been excluded from the carotid group. In other studies cardiac disorders were not excluded as contributing to the MES in carotid cases.

MCA group: Our group of patients showed the number of cases having intracranial
atherosclerosis to be higher than those with extracranial atherosclerosis. It is known that extracranial carotid stenosis is an important and treatable cause of stroke in Caucasians. In contrast, intracranial internal carotid artery and middle cerebral artery (MCA) stenosis are the predominant vascular lesions found in stroke patients among Asians, Africans, and Hispanics. A previous study on Egyptian patients showed that 76% had intracranial vascular abnormalities in the MRA while only 12.3% patients had evidence of carotid stenosis.

We detected MES in 27.7% of the MCA stenosis group, with a count range 2 – 15 / hour. Our findings are similar to those of another study except that our MES count is less in number. This is possibly because we excluded patients with other potential causes of embolism such as carotid stenosis and cardiac disease by investigating those sources and by monitoring for emboli proximal to the MCA stenosis. For MCA stenosis in acute stroke, these are important factors to consider in order to avoid mistakenly studying patients with differing origin of embolism. Most of the patients positive for MES had multiple infarcts in agreement with previous reports. Multiple acute lesions on DWI were regarded as good markers of an underlying embolic mechanism for ischemic stroke.

Control group: none of our control group showed MES. Others reported either a low prevalence among controls 5%, or in none of normal group. In our study we excluded any cardiac or carotid pathology by echocardiography and carotid duplex, while Georgiadis et al. depended on a negative history, which might explain the difference in results.

Anticoagulant effect: Anticoagulant therapy affected mainly the number of MES per hour rather than the prevalence of embolic signals. The effect of anticoagulant therapy on MES was controversial in different studies, ranging from no effect, to a possible effect on the frequency and/or prevalence of MES. One study showed that the number of MES tended to decrease after ticlopidine therapy.

Conclusion:
The reason for the different proportions of patients with MES found in different studies is unclear. A number of factors may be important, including different treatment regimens, time from last symptoms, duration of recording and criteria of embolus detection.

Our results confirm previous reports on the clinical relevance of asymptomatic embolization in the setting of an acute stroke varies among different stroke categories. Embolus monitoring can help determine the source of embolization, the earlier we monitor for emboli the more likely that we can detect embolism, also prolonged monitoring increases the yield of the technique.

The effect of anticoagulant therapy is not clear in our study and also in others. We could not identify the differential effect of anticoagulants on different stroke subtypes due to the small number of patients in each of the two groups of coagulated and anticoagulated patients.

REFERENCES


الفحص المطول بالدوبلر عبر الدماغ تكشف السدادات الشريانية لدى مرضى الجلطات المخية الحادة

يُعتبر استقبال إشارات عالياً للالدماح من خلال موجات الدوبلر عبر الدماغ من العلامات المميزة للسدى الشرياني في حالات الجلطات المخية الحادة.

أهداف البحث:
- اختيار إمكانية التعرف على الإشارات المميزة للسدى الشرياني عن طريق الدوبلر عبر الدماغ.
- التعرف على المصادر المختلفة للسدى الشرياني من الشريان السباتي أو القلب أو الشريان الدماغي الأوسط.

تمت دراسة 150 مريضاً في الأثنين وسبعين ساعة تالية للجلطة. وقد انتهت شروط البحث على 43 مريضاً تم تقسيمهم إلى ثلاثة مجموعات حسب مصدر السدى: سبائية من القلب أو من الشريان الأوسط والгруппة الرابعة كانت المجموعة الضيقة وتكونت من عشرة أشخاص أصحاء. وقد فحص جميع المرضى كلياً بالأشعة المقطعية. الرنين المغناطيسي، رسم القلب، الجذع الصوتية على القلب. الدوبلر الشرياني السباتي ودوبلر الدماغ لمدة ساعة. أظهرت النتائج وجود سدادات شريانية في 10% من المجموعة الأولى، 50% من المجموعة الثانية، 20% من المجموعة الثالثة بينما لم تظهر فائراً من مجموعة الأصحاء.

يستخلص من البحث أن الفحص المطول بالدوبلر عبر الدماغ يعتبر من الوسائل الواعدة لتشخيص السدادات الشريانية في حالات الجلطات الحادة مما قد يعكس على الخطة العلاجية لهؤلاء المرضى.