Countable and non-countable microembolic signals by TCD in first-ever stroke or TIA patients with PFO

G. Telman *, E. Kouperberg, E. Sprecher, D. Yarnitsky

Department of Neurology, Rambam Health Care Campus, Haifa, Israel
Technion Faculty of Medicine, Haifa, Israel

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Abstract

Background: There are data in the literature indicating that the number of microembolic signals (MES) in patients with patent foramen ovale (PFO) is directly related to stroke incidence and recurrence. We thus hypothesized that the amount of artificially induced microembolic signals monitored by contrast transcranial Doppler (cTCD) would be greater in younger patients with PFO and stroke (when cryptogenic strokes related to the PFO are frequent).

Patients and methods: The final analysis included 109 patients with first-ever ischemic stroke or TIA with PFO, as detected by Transesophageal Echocardiography (TEE), and MES, as measured by cTCD. Thirty-seven patients (aged 19–45 years) were defined as the “younger” group, and the other 72 patients (aged 46–77 years) were defined as the “older” group. Eighty-six patients (78.9%) suffered from stroke, including 28 in the younger group and 58 in the older group. The pattern of microembolization was defined as “countable” when the observers were able to calculate the number of MES. In the case of a “shower” of MES on TCD examination, the pattern of monitoring was defined as “non-countable.”

Results: Ischemic heart disease, and hyperlipidemia were found to be significantly more frequent in the group of older patients. Twenty-three patients (62.2%) in the younger group had cryptogenic stroke or TIA (no risk factors found), as compared to 26 patients (36.1%) in the older group (p = 0.009). There were 23 patients with a non-countable pattern of MES in the older group, as compared with 5 such patients in the younger group (p = 0.04). There was no difference found in the number of MES between the groups in those patients with a countable pattern of MES (13.3 ± 11.8 in the younger group vs. 13.7 ± 11.7 in the older group).

Conclusions: In stroke and TIA patients above 45 years of age, PFOs producing a large amount of MES on TCD examination are frequent. Thus, there is no correlation between a large amount of MES and stroke or TIA in young patients.

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1. Introduction

There is a great deal of debate in the literature regarding the significance of patent foramen ovale (PFO) in stroke pathogenesis generally and in cryptogenic strokes particularly. This controversy is emphasized by the title of one of the many reviews devoted to this subject — “Patent foramen ovale: the never-ending story” [1]. In many cases, the presence of PFO is only an accidental finding and is related to a high prevalence in the general population, with no relation to stroke. Thus, the main research effort in this area should be focused on identifying the subsets of patients in whom PFO does play a significant role in stroke pathogenesis.

The aim of the present study was to examine the hypothesis that the amount of microembolic signals (MES), as measured by contrast transcranial Doppler (cTCD), may be associated with PFO-related stroke. A likely assumption is that there is an association between a large amount of MES and the chance of occurrence of PFO-related stroke.
Therefore, in younger patients, in whom cryptogenic strokes are frequent and a present PFO could be the only possible pathogenic factor for stroke, we would expect a higher amount of MES on cTCD examination than in older patients.

2. Patients and methods

2.1. Patients

All of the patients included in this study were hospitalized in a single neurological department from July 1999 through July 2007. PFO was found in 128 patients with first-ever TIA or CVA who underwent TEE (Transesophageal Echocardiography) as part of the routine work-up protocol. They were subsequently referred for cTCD examination. We did not find an acoustic window for TCD examination in 12 of the patients, and there were no MES on cTCD in 7 of the patients in this cohort. The rest of the patients (109) with MES on cTCD examination were included in the final analysis, including 60 males (55%) and 49 females (45%). The cohort was divided into two groups according to age. Thirty-seven patients (33.9%) under 45 years of age were defined as the younger group (mean age 37.6±6, range 19–45), while the other 72 patients, ranging in age from 46–77, were defined as the “older” group (mean age 55.3±7.1). Eighty-six patients (78.9%) had suffered a stroke, including 28 in the younger group and 58 in the older group.

2.2. Transcranial Doppler

Air microemboli were artificially generated by an intravenous injection of 9 ml of saline vigorously agitated with 1 ml of air into the cubital vein. The injection was done during a Valsalva maneuver (VM), such that release of the glottis closure coincided with the end of the injection. All TCD examinations were conducted with the patients in a supine position.

We performed insonation over both middle cerebral arteries (MCA), and the data from the side with a greater amount of MES were used for final analysis. In those cases when only one acoustic window was accessible for cTCD examination, we used its results for final analysis. Those patients with accessible acoustic windows but without MES on TCD were excluded from the study.

The results of monitoring were interpreted independently and blindly off-line by two observers (E.K. and G.T.). The TCD machines of Rimed Intraview (Israel) and Viasys Nikolet (USA) were used for monitoring. The parameters of monitoring were as follows: depth of insonation 51–63 mm; sample volume 3 mm; power of insonation 100%; range 154 cm/s; 256-point fast Fourier transformation; and threshold of embolus detection 8 dB. A special holder for MCA monitoring was used. MES were detected according to generally accepted criteria [2]. The effectiveness of VM (%) was controlled by reedition of peak systolic velocity (PSV) during the VM related to the base PSV, as generally accepted [3]. The results of monitoring were defined as “countable” when the observers were able to calculate the precise number of MES. In the case of a “shower” pattern of MES, the results of monitoring were defined as non-countable.

3. Statistical analysis

Distributions of risk factors and countability in both groups were compared using chi-square tests. Effectiveness of VM and MES counts were compared using t-tests. JMP (SAS Institute, Cary, NC, USA) was employed for statistical analyses.

4. Results

Hyperlipidemia, and ischemic heart disease (IHD) were found to be significantly more frequent among the older patients (see Table 1). There was no difference found in the proportion of stroke and TIAs between the two groups, with 28 stroke patients (75.5%) in the younger group and 58 (80.6%) in the older group (NS). Twenty-three patients (62.2%) in the younger group had cryptogenic stroke or TIA (no risk factors found), as compared to 26 such patients (36.1%) in the older group (p=0.009). The effectiveness of VM was similar in both groups. The reduction of PSV during VM was 32.7% in the younger patients and 34.8% in the older patients (NS). There were 23 patients (31.9%) with a non-countable pattern of MES in the older group, as compared with 5 (13.5%) such patients in the younger group (p=0.04). There was no difference found in the number of MES between groups in those patients with a countable pattern of MES (13.7±11.7 in the older patients and 13.3±11.8 in the younger patients; NS).

5. Discussion

There is extensive evidence in the literature indicating that the prevalence of PFO is greater in young stroke patients than among healthy persons [4–6], and this tendency is the most obvious in young stroke patients with cryptogenic stroke [7–9]. In line with these data are some observations discussed below, indicating a possible correlation between the amount of MES and stroke incidence and recurrence in patients with PFO. Therefore, in terms of lifetime occurrence, it is expected that people with a higher number of MES will have a stroke at a younger age. Using cross-

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Younger patients (n=37)</th>
<th>Older patients (n=72)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>9 (24.3%)</td>
<td>25 (34.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (5.4%)</td>
<td>8 (11.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2 (5.4%)</td>
<td>15 (20.8%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>10 (27%)</td>
<td>24 (33.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>IHD</td>
<td>2 (5.4%)</td>
<td>14 (19.4%)</td>
<td>0.05</td>
</tr>
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</table>
sectional data to examine patients who already had a stroke, it is expected that a higher MES count will be found in the younger patients than in the older ones, especially if there is a predominance of cryptogenic strokes in the group of younger patients. In order to examine this hypothesis, we compared the pattern of artificial microembolization after VM in stroke patients with PFO among those younger and older than 45 years of age. There is a debate in the literature arguing for [10–12] and against [13,14] a correlation between the size of both PFO and right-to-left shunt, as measured by TEE, on the one hand, and severity of stroke and stroke recurrence, on the other hand. The data on the interrelation between the number of microemboli, as measured by cTCD, and stroke occurrence and recurrence are more limited. Anzola et al. [15] followed up 59 patients with PFO and stroke. The amount of shunting measured by the number of MES was the only significant independent variable associated with stroke recurrence. Serena et al. [16] quantified the magnitude of right-to-left shunt as “no shunt,” “small” (< 10 MES), and “large” (more than 10 MES), with the latter including “shower” (> 25 signals) and “curtain” (uncountable signals) patterns. The authors found that the detection of curtain or shower patterns was associated with a higher risk of stroke, with an odds ratio of 3.5. According to the results of a recently published YAMIS study [17], “major” shunts (defined by cTCD as > 50 microbubbles spontaneously or > 10 microbubbles spontaneously together with > 80 after provocation) were associated with stroke in young adults (odds ratio of 2.8).

We realize that there are numerous morphologic and structural factors influencing the final number of MES in MCA, including the structure of the cardiac chambers; the presence of a septal aneurism; the pressure gradient across the septum; the configuration of the cerebral blood vessels; the systemic blood pressure, the rheological characteristics of the blood and some others. The search for a possible relation between these factors and the pattern of microembolization by TCD seems to be important and may contribute to the topic of our study. Unfortunately, a limitation of the present study is that we could not extract detailed retrospective data about PFO size and morphology from TEE protocols in some of the patients. In addition, there are some dynamic factors that can influence the final number of MES in repeated TCD examinations in the same patient. For example, the efficacy of VM, the number of air microbubbles in the solution injected, and the rate of injection can all vary from one test to another. In order to minimize the influence of all the abovementioned factors, we did not rely solely on the precise number of MES, but defined the pattern of microembolization as “countable” MES or “non-countable” MES (i.e., “shower” pattern of artificial MES). Special care was taken to control for the dynamic factors in our study, with similar efficacy of Valsalva, injection rate, and dual-person (E.K. and G.T.) performance of air bubble generation in an effort to produce a similar number of air microbubbles.

The main result of our study was that a non-countable pattern of microembolization was found significantly more frequently in the older group of patients, despite the highly significant predominance of patients with cryptogenic strokes in the younger group. Thus, our findings seem to indicate that the pathogenesis of stroke in young PFO patients is determined by multiple and different factors and is not directly related to the amount of MES found on TCD examination. Further investigations are needed to set apart those PFO bearers who are especially prone to stroke development.

References

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