Predictive and Clinical Value of Cerebral Microemboli Detection in Cardiac Patients

Ashraf El-Mitwalli¹, Mohamed El-Sayed Abd El Hamid², Wael Rifaie³, Mohamed Mosbah²
Departments of Neurology¹, Internal Medicine², Cardiology³, Mansoura University

ABSTRACT

Background and Aim: Cardioembolic strokes have a worse prognosis and produce larger and more disabling strokes than other ischemic stroke subtypes. We sought to evaluate the prevalence of High-intensity-transient-signals (HITS) in patients having different cardiac sources of emboli and the value of transcranial Doppler (TCD) in stroke prediction. Subjects and Methods: consecutive cardiac patients were subjected to ECG, transthoracic echocardiography, and TCD examination. Results: a total of 45 cardiac patients were investigated; twenty patients with rheumatic heart disease, 10 with prosthetic valves, and 15 with myocardial ischemia. In all patients, the presence of HITS was not affected by the patients’ age, gender, the presence of risk factors, the platelet count or the INR level. Cerebral strokes were significantly higher in patients with HITS than those without. In patients with prosthetic heart valves, 60% was HITS-positive with a mean rate of 14.2±6.49/30 minutes, which was significantly higher than myocardial ischemia and rheumatic heart disease patients. In myocardial ischemia group, a higher prevalence of HITS was found with left ventricular ejection fraction (LVEF) <55% and left ventricular thrombus. In rheumatic heart and ischemic heart disease groups ≥80% of patients treated with antithrombotics and/or thrombolytics did not show any HITS, while in mechanical heart valves only 20% of patients received anticoagulants plus aspirin was HITS-negative. Conclusion: Cerebral strokes are significantly higher in cardiac patients with detected HITS than those without. In patients with prosthetic heart valves, anticoagulants didn’t significantly decrease or clear HITS. (Egypt J. Neurol. Psychiat. Neurosurg., 2008, 45(1): 107-115)

INTRODUCTION

About 15% to 30% of ischemic strokes are of cardiac origin¹, they have a worse prognosis and produce larger and more disabling strokes than other ischemic stroke subtypes, and this observation is derived from emboli originating in cardiac chambers, which are on average of large size², but it is thought to be one of the more preventable types of strokes³. Thus, a predictor for the potential risk for cerebral embolism would be of great value in stroke prevention, especially in patients with potential cardiac sources of embolism.

Transcranial doppler, MRI, echocardiogram, Holter monitoring, and electrophysiological studies increase our ability to identify the source of cardioembolism⁴. Transcranial Doppler (TCD) has an established diagnostic and potential therapeutic role in acute stroke management⁵ and offers the possibility of detecting continuing subclinical microemboli in patients at risk of embolism⁶. It has been used also for monitoring of the efficacy of antithrombotic treatment on the occurrence of HITS⁷⁸. Emboli signals are detected for an indefinite period of time after prosthetic valve insertion, carotid artery stenosis, acute stroke, and atrial fibrillation, and during angiography⁹.

Patients with potential cardiac sources of embolism are at higher risk for stroke⁰¹¹¹². Studies have shown also a higher prevalence of Microemboli signals (MES) in patients with an increased risk of stroke¹³. This study was designed to evaluate the prevalence of HITS in patients having different cardiac sources of emboli estimated either by transesophageal or transthoracic echocardiography and the role of transcranial doppler ultrasonography in stroke prediction.
SUBJECTS AND METHODS

This study was conducted on consecutive cardiac patients admitted to Mansoura University Hospitals, Mansoura, Egypt.

Subjects
The patients were classified according to the clinical and echocardiographic findings into three age and sex matched groups:

1. Group I (Rheumatic heart disease with native valve group).
2. Group II (Rheumatic heart disease with prosthetic valve replacement).
3. Group III (Myocardial ischemia).

Patients were excluded from the study if there is a possibility suggestive of other sources of emboli rather than cardiac sources, those who had recent cardiac procedures and patients with inadequate temporal bone acoustic window or too restless to allow long-time monitoring.

Methods
All the patients were subjected to the following: Careful history taking, thorough clinical examination, routine laboratory investigations, full 12-lead ECG, and plain x-ray chest.

Transthoracic echocardiographic examination: Two-dimensional transthoracic echocardiography was performed in all patients with a 3.5-MHz probe using a Hewlett-Packard Sonos 1500. Left ventricular ejection fraction (LVEF) was assessed with a visual quantitative grading system. Patients were divided into subgroups according to LVEF function: those with normal LVEF > 55% and those with decreased LVEF < 55%. LV thrombus was diagnosed when an echogenic mass adjacent to but distinguishable from LV endocardium was detected in an area of wall-motion abnormality. The echocardiograms were interpreted by cardiologist blinded to the results of the TCD recordings.

Transcranial Doppler examination: Transcranial doppler monitoring was performed with a DWL Multidop X4 with a 2-MHz probe. The patients were examined in the supine position by the same investigator. The middle cerebral arteries (MCA) were insonated at a depth between 50 and 55 mm according to standard criteria for a period of 30 minutes. The probe was fixed on the head with a specially designed spectacle frame; this guaranteed a minimum of artifact disturbances and a constant angle of insonation. For demonstration of high-intensity-transient-signals (HITS), all of the following criteria were required: 1) random occurrence, 2) brief duration (<0.1 second), 3) high intensity (minimum 3 dB above background intensity), 4) primarily unidirectional quality within the Doppler spectrum, 5) causing a spike in the power/intensity trace, and 6) accompanied by an audible "chirp" or "pop".

All HITS were recorded on hard disk. The investigator did not know the cardiological status of the patient, or the diagnosis.

Brain CT examination: using Philips Tomoscan (USA) was performed for patients who presented by stroke or other neurological signs.

Statistical analysis
The reported data were processed using SPSS ver. 15 under Microsoft Windows XP. Continuous data were expressed in the form of mean±SD. Student t test was used to compare numerical data, while categorical data were compared using chi-square test. P value < 0.05 was considered significant.

RESULTS

From May 2005 through March 2006, a total of 45 cardiac patients were investigated and classified according to clinical and echocardiographic findings into the following age and sex matched groups:

- Group I: 20 patients with rheumatic heart disease; 14 males (70.0%) and 6 females (30.0%) and mean age of 49.2±5.89 years.
- Group II: 10 patients with prosthetic valves; 7 males (70.0%) and 3 females (30.0%) and mean age of 48.1±4.83 years.
- Group III: 15 patients with myocardial ischemia; 10 males (66.7%) and 5 females (33.3%) and mean age of 66.2±7.44 years.
In all patients, the presence of HITS was not significantly affected by the patients’ age, gender (Table 1), and the presence of risk factors, the platelet count or the INR level.

**Frequency and number of HITS:**
Six patients (60%) with prosthetic heart valves was HITS-positive with a mean rate of 14.2±6.49/30 minutes, which was statistically significantly higher compared with both myocardial ischemia patients (20% showed HITS with a rate of 1.7±1.15/30 minutes: p=0.01) and with rheumatic heart disease patients (25% showed HITS with a rate of 2.4±1.14/30 minutes: p=0.003) (Table 2, Fig. 1).

**Cerebrovascular events**
Of the rheumatic heart disease group, eight patients (40%) were presented with cerebrovascular events; 4 out of the 5 patients with HITS-positive had stroke while 4 only out of the 15 patients without HITS presented with cerebral stroke (p=0.03). In mechanical heart valves, all the patients presented with acute cerebral stroke had HITS on TCD (p=0.0001), also in myocardial ischemia group, the 2 patients who had completed stroke had HITS on TCD monitoring and the patient with TIA had no HITS (0.02) (Table 3).

**EEG and Echographic findings**
The myocardial ischemia group showed significantly higher prevalence of HITS with LVEF <55% (p=0.024) and also with the presence of left ventricular thrombus (p=0.002)

**The use of antithrombotic, anticoagulant and thrombolytic therapy**
In native rheumatic heart valve disease group, 9 out of 11 patients (82%) treated with aspirin either alone(5 patients 45%) or combined with heparin (6 patients 55%) did not show HITS, also in ischemic heart disease group, 12 out of 15 patients (80%) treated with aspirin combined with either heparin or streptokinase did not show HITS, both showed significantly lower frequency of HITS using antithrombotic anticoagulants (p=0.017, p=0.014) respectively compared with mechanical heart valves; only one out of 5 (20%) patients received anticoagulants plus aspirin was HITS-negative (Table 4).

**Table 1. Age and sex distribution and HITS frequency in all groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Rheumatic Heart</th>
<th>Prosthetic heart valve</th>
<th>Myocardial ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>age</td>
<td>sex</td>
<td>age</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>&gt;50</td>
<td>male</td>
</tr>
<tr>
<td>HITS</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>no HITS</td>
<td>10</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>p</td>
<td>0.29</td>
<td>0.57</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The presence of HITS was not correlated to the patients’ age or sex

**Table 2. HITS frequency and number.**

<table>
<thead>
<tr>
<th></th>
<th>Frequency n/ total (%)</th>
<th>Number/30 minutes (mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic heart disease</td>
<td>5/20 (25%)</td>
<td>2.4± 1.14</td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>6/10 (60%)</td>
<td>14.2± 6.49</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>3/15 (20%)</td>
<td>1.7±1.15</td>
</tr>
</tbody>
</table>

The prosthetic heart valve group showed the highest frequency of HITS.
Fig. (1): HITS frequency in the studied patients.

Table 3. Cerebrovascular events and HITS in all groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Rheumatic Heart</th>
<th>Prosthetic heart valve</th>
<th>Myocardial ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HITS Positive</td>
<td>HITS Negative</td>
<td>Stroke or TIAs</td>
</tr>
<tr>
<td>Stroke or TIAs</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>No stroke</td>
<td>1</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>p value</td>
<td>0.0335</td>
<td>0.0001</td>
<td>0.0238</td>
</tr>
</tbody>
</table>

The stroke prevalence is significantly higher in patients with HITS.

Table 4. The effect of antithrombotic and thrombolytic therapy on the HITS.

<table>
<thead>
<tr>
<th>Group</th>
<th>Rheumatic Heart</th>
<th>Prosthetic heart valve</th>
<th>Myocardial ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin ± Heparin (n=11)</td>
<td>Aspirin ± Heparin Streptokinase (n=15)</td>
<td>Aspirin ± Heparin Streptokinase (n=15)</td>
<td></td>
</tr>
<tr>
<td>HITS-positive</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>HITS-negative</td>
<td>9</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>p value</td>
<td>0.017</td>
<td>0.014</td>
<td></td>
</tr>
</tbody>
</table>

Patients received thrombolysis and/or antithrombotic therapy showed marked lower prevalence of HITS in rheumatic heart and myocardial ischemia compared with prosthetic heart valve group.
A- Transthoracic Echocardiography showing thickened calcified tips of mitral valve leaflets with limited mobility and characteristic disatolic doming with valve area by planimetry $1.2 \text{ mm}^2$

B- Transthoracic Echocardiography showing stenotic mitral valve and pressure half life $0.6 \text{ cm}^3$ with detected gradient of $22.4/15.5$ trivial mitral regurgite detected by continuous wave Doppler

C- Brain CT scan axial cut: left basal ganglionic ischemic infarcts

D- TCD: High-intensity-transient-signals (HITS)

Fig. (2): A 41 year-old female with rheumatic double mitral valve disease.

**DISCUSSION**

In the present study, 25% of rheumatic heart disease patients showed high intensity transient signals (HITS) with a mean HITS count of $2.4 \pm 1.14$. Georgiadis et al. detected HITS in 15% of patients with native valve disease. HITS detected in a rate ranging from 50% to 89% in various prosthetic heart valves subtypes. In our study, HITS were detected in 60% of prosthetic valve patients with a mean HITS count of $14.2 \pm 6.49$. These data are closer to other studies of prosthetic valve series 50% and 55%. In myocardial ischemia, HITS were found in 20% of them, a frequency closer to that detected by Nadareishvili et al., who found 17% of their patients with AMI had cerebral microembolism.
In our patients’ series, there was no relationship between HITS frequency and patients’ age, gender, these results are close to those obtained by Georgiadis et al.\(^{20}\). Regarding the relation between HITS and platelet count and INR in patients with rheumatic valve disease, no difference could be detected between HITS-positive and HITS-negative patients in agreement with another study.\(^{22,23}\) Furthermore, Batista et al.\(^{22}\) added that, the potential effectiveness of HITS as an additional guide to INR values to increase oral anticoagulant dosage, in patients with INR ≥ 2 appear to be limited.

There is an unsolved debate about the predictive value of HITS; some studies stated that a doubtful predictive value of HITS detection and the various mechanisms by which risk factors contribute to the development of cerebrovascular events\(^{20}\) and its detection provides pathophysiological rather than clinically relevant information.\(^{24}\) while others found a strong association of HITS in the acute phase of stroke with known potential arterial and cardiac embolic sources. HITS have an independent predictive value of poor outcome.\(^{25}\) TCD-detected microemboli are associated with an increased prevalence of prior cerebrovascular events; presence of TCD-detected microemboli could be a risk factor for cerebrovascular ischemia.\(^{26}\) There has been frequent report on transcranially detected HITS with prosthetic valves, the incidence of thromboembolic events is increased following heart valve replacement.\(^{27}\) In our study, we reported a significantly higher prevalence of stroke in HITS-positive patients compared with HITS-negative patients in all groups.

The present study is an example of indirect evidence that HITS are predictors of stroke in patients with MI as we detected a significantly higher rate of stroke in MI patients with HITS - positive than in patients without detected HITS in agreement with Nadareishvili et al.\(^{21}\); Also, in our study; HITS were more frequently seen in patients with LV thrombi.

The risk of stroke after myocardial infarction (MI) is increased compared with the risk among those without MI\(^{24}\); about 60% of stroke patients had AMI\(^{29}\). A nearly significant increase of HITS was documented in patients with anterior AMI\(^{28}\). Decreased LVEF was an independent risk factor for stroke in a post hoc analysis of the SAVE study, and every decrease of 5% in LVEF increased the risk of stroke by 18%.\(^{20}\) LV thrombus is a major cause of cerebral embolism in MI\(^{31}\). In a study of 77 patients with anterior AMI, 46% had LV thrombi and the frequency increased progressively with the extent of myocardial dyskinesia and LV end-diastolic pressure.\(^{32}\)

Anticoagulation treatment appears to decrease the prevalence of HITS,\(^{33}\) the rapid and significant decline of HITS in stroke and TIA patients suggests the possible efficacy of dual antiplatelet therapy with aspirin and clopidogrel in patients with HITS.\(^{34}\) Asymptomatic HITS were significantly less common in subjects taking warfarin.\(^{35}\) In patients with recent stroke of arterial origin, intravenous acetyl salicylic acid can rapidly reduce cerebral microemboli as detected by TCD.\(^{36}\) In a case report, TIAs completely ceased after the initiation of an antiplatelet therapy with aspirin, HITS were not detected in later TCD studies.\(^{37}\)

In patients with prosthetic heart valves, no correlation detected between the number of emboli signals and the intensity of oral anticoagulation.\(^{18}\) Eicke et al.\(^{19}\) found no correlation of HITS with the anticoagulant treatment or the development of clinical events and concluded that HITS are frequent events in patients with prosthetic valves. No difference could be detected between HITS-positive and HITS-negative cases regarding treatment with acetyl salicylic acid.\(^{38}\)

Our results also considered an extension to the current debate about the efficacy of antiplatelets, antithrombotic or thrombolytics in cessation or clearance of HITS. Significantly lower prevalence of HITS in both rheumatic heart and myocardial ischemia groups but HITS were not affected by the use of anticoagulants or antiplatelets in prosthetic heart valve patients, this could be explained by that, HITS originating from prosthetic cardiac valves are mainly gaseous and cannot serve as an indicator of the valves thromboembolic activity.\(^{39}\)
Conclusion:
Cardiac emboli are significant contributors to the development of cerebrovascular strokes. Detection of HITS using TCD in cases with potential cardioembolic sources may represent a predictor of clinical embolic events. Cerebral strokes are significantly higher in patients with detected HITS than those without. In patients with prosthetic heart valve, anticoagulants didn't significantly decrease or clear the HITS frequency.

Recommendations:
Larger studies of longitudinal design and strict inclusion criteria are recommended to determine the influence of HITS on prognosis and outcome of such patients. Other observational studies are also recommended to identify the risk factors leading to emboli formation in cardiac patients of different pathologies.

HITS detection can be potentially relevant to the selection of antithrombotic treatment in acute stroke associated with cardioembolic disease. Further studies are necessary to assess its effectiveness as an additional guide to monitor oral anticoagulant intensity.

REFERENCES


النوب والأهمية الإكلينيكية لاستكشاف الجلطات الدماغية دقيقة الموجة في مرضى القلب


الأنساد الشرياني ذو المصدر الثاني من السببات الأساسية لحدوث الجلطات الدماغية وفحص الدماغي بأشعة الدوبلر. لجعل الإشارات الصادرة عن الانسدادات المرجحة تكون قليلاً المصدر، في الدراسة الحالية هذا، إلى دراسة القيمة الإكلينيكية للكشف عن الإشارات الدماغية علاجية للإشارات الدماغية في مرضى الجلطة أو مرضى القلب ذو المصدر للإنساد الشرياني. لهذا الغرض، فحصنا 45 مريضاً من بينهم 31 رجلاً و14 امرأة قسموا إلى ثلاث مجموعات الأولية: مرضى صمام القلب الروماتويدي: 20 مريضاً، الثانية مرضى صمام القلب الصناعي (10 مرضى) .الثالثة مرضى صمام شرايين القلب (15 مريضاً). أظهر فحص الدوبلر الدماغي معدل أعلى وعدد أكبر من الإشارات عالية الشدة في مرضى المجموعة الثانية مقارنة بأفرادهم في المجموعتين الأخرين. في المجموعات الثلاث لم تجد أية فرق إحصائي ملموسة بين المرضى الإيجابيين للإشارات علاجية الشدة ومرضى السليمين لها بالنسبة العمر والجنس. بعد الصفحات الدموية والآي. أ. إن أنه من الملموسة أن المرضى الإيجابيين للإشارات عالية الشدة أمثالوا بعدد أعلى من الجلطات الدماغية. وقد أظهرت الدراسة قلة معدل الإشارات الدماغية علاجية الشدة في المرضى الذين استخدموا العناصر الملموسة للتنبؤ، والذين للعائلات في كل المجموعتين الأولى والثانية، أما في المجموعة الثانية فلم يكن هناك اختلاف ذو دالة إحصائية وقد يعزى ذلك إلى أن معظم هذه الإشارات ذات طبيعة غازية. في المجموعة الثالثة تبين أن المرضى الإيجابيين للإشارات علاجية الشدة أمثالوا بانخفاض نسبة الفترة القافزة للطيفين الأيسر وكذا بعدد أعلى من جلطات الطيفين الأيسر.

الخلاصة: يمكن القول أن استكشاف الإشارات العددية الدقيقة علامة الشدة بواسطة فحص الدوبلر الغازية يساعد في تشخيص وعلاج إشارات شرياني ذوي المصدر القلبي المحيط بالأنساد الشرياني بدرجة تفاوت باختلاف طبيعية المرضى القلبي. المرضى الإيجابيون للإشارات عالية الشدة يمتلكون عساواً بمحصلة أسوأ، ومرضى عصبي السليمين للإشارات عالية الشدة.