THE ROLE OF TILT-TABLE TEST IN DIFFERENTIAL DIAGNOSIS OF UNEXPLAINED SYNCOPE

Marko Mornar Jelavić1, Zdravko Babić2, Hrvoje Hećimović3, Vesna Erceg4 and Hrvoje Pintarić5

1Center for Internal Medicine and Dialysis, Zagreb-East Health Center; 2Coronary Care Unit, Department of Cardiology, 3Clinical Department of Neurology, 4Department of Cardiology, 5Cardiac Catheterization Laboratory, Department of Cardiology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

SUMMARY – The aim of this retrospective study (February 2012 – September 2014) was to assess the role of head-up tilt-table test in patients with unexplained syncope. It was performed on 235 patients at Clinical Department of Cardiology, Sestre milosrdnice University Hospital Center. Patients were classified according to test indications: group A (convulsive syncope, n=30), group B (suspected vasovagal syncope, n=180), and group C (paroxysmal vertigo, n=25). The groups were analyzed and compared according to demographic data (age and gender), referral specialist (cardiologist, neurologist, and others), and test results (positive/negative) with specific response (cardioinhibitory, vasodepressor, or mixed). Groups A and B were referred most frequently by neurologists and cardiologists (p<0.05). The test was positive in 34 (14.5%) of all evaluated patients (5 in group A and 29 in group B), of which 13 (38.2%) had cardioinhibitory, 11 (32.4%) mixed and 10 (29.4%) vasodepressor response. In the cardioinhibitory subgroup, three patients (23.1%, 2 males/1 female, mean age 28.5 years) with normal electroencephalography were on antiepileptics. During head-up tilt-table testing, they had bradycardia (heart rate 30.0±5.0 beats/min) and prolonged asystole (13.7±11.0 seconds) with development of typical convulsions. These three subjects got a permanent pacemaker (atrial/ventricular stimulation, heart rate control) and anticonvulsive therapy was slowly withdrawn with no syncpe recurrence during 24-month follow up. In conclusion, head-up tilt-table test has an important role in the evaluation of patients with unexplained syncope and in differential diagnosis of vasovagal syncope. The indication for pacemaker implantation, strictly following the European Society of Cardiology guidelines, proved to be effective in preventing syncpe relapses in patients with cardioinhibitory convulsive syncope.

Key words: Syncope – diagnosis; Syncope – prevention and control; Syncope, vasovagal – diagnosis; Seizures; Tilt-table test; Pacemaker, artificial; Epilepsy

Introduction

Syncope is defined as a brief and transient loss of consciousness and postural tone with spontaneous and complete recovery. During syncope, there is global cerebral hypoperfusion and loss of consciousness is often preceded by prodromal symptoms, most commonly nausea, dizziness, profound sweating, paresthesia, blurred vision and tinnitus. Previous studies have shown that about 30% of adult population have ≥1 syncope during lifetime; some studies indicate that this ratio is 2:1 in favor of young women1-7. The most frequent form of syncope is vasovagal syncope. It is mediated by excessive vagal stimulation, or disbalance between sympathetic and parasympathetic autonomic activity. Vasovagal syncope is classified into cardioinhibitory, vasodepressor, and mixed syncope. It occurs repeatedly in predisposed individuals with precipitating factors such as emotional stress (especially
in warm, stifling spaces), fear, extreme fatigue, pain, prolonged standing, etc. Other causes of syncope include cardiac problems (arrhythmias and structural heart diseases), orthostatic hypotension and orthostatic intolerance syndromes, and neurologic (transient ischemic attack, carotid vascular disease, migraine, epilepsy, Parkinson’s disease), metabolic (hypoglycemia, shock, alcoholism) and psychogenic symptoms. Convulsive syncope may be accompanied by neurologic symptoms (convulsions, eye deviation and/or urinary incontinence). Clinical semiology can often resemble epileptic seizures. This can lead to misdiagnosis, and according to some studies, up to 30% of patients taking antiepileptic drugs have syncope and not epileptic seizures. Head-up tilt-testing (HUTT) is accepted as the gold standard for diagnostic procedure of vasovagal syncope. In this study, we investigated the following: 1) the role of HUTT in patients with unexplained syncope; 2) the importance of HUTT in differential diagnosis of vasovagal syncope, especially in patients with convulsive syncope; and 3) the importance of proper selection of patients for pacemaker implantation and its impact on the quality of life improvement by stopping syncope recurrences in patients with cardioinhibitory convulsive syncope.

**Patients and Methods**

This retrospective study was performed in 235 consecutive patients undergoing HUTT between February 2012 and September 2014. The investigation was indicated by cardiologists, neurologists, or other specialists and performed at Department of Cardiology, Sestre milosrdnice University Hospital Center. The investigation was performed in accordance with ethical standards laid down in the Declaration of Helsinki and approved by the appropriate institutional committee. Patients were included independently and classified in three groups according to HUTT indications, as follows: 1) group A: 30 patients with convulsive syncope, 12 of them were currently taking antiepileptic drugs (AEDs) because of suspected epilepsy. They all underwent prior thorough electroencephalographic (EEG) evaluation that classified them with normal interictal, irritative and epileptic EEG findings; 2) group B: 180 patients with suspected vasovagal syncope; and 3) group C: 25 patients with paroxysmal vertigo.

The groups were analyzed and compared according to their baseline demographic data (age and gender), specialists who referred them, HUTT results (positive/negative), and responses defined and classified by the Vasovagal Syncope International Study (VASIS) criteria, as follows: 1) mixed (VASIS-1): heart rate (HR) decreases by >10% but does not decrease to <40 beats/min for >10 seconds. Blood pressure (BP) falls before HR; 2) cardioinhibition (VASIS-2A): minimum HR >40 beats/min for >10 seconds, or asystole occurs for <3 seconds. BP falls before HR; 3) severe cardioinhibition/asystole (VASIS-2B): minimum HR <40 beats/min for >10 seconds, or asystole occurs for >3 seconds. BP falls before or coincident with HR; and 4) pure vasodepression (VASIS-3): HR does not fall >10% from maximum rate during HUTT. Additionally, in patients with positive HUTT we analyzed symptoms developed during its conduction (weakness, loss of consciousness, jerks, tongue bite, incontinence, eyeballs and head movement).

The exclusion criteria were cerebrovascular diseases (chronic cerebrovascular disease, cerebrovascular malformations), cerebral tumor or bleeding of any date, migraine and Parkinson’s disease or dementia, confirmed by extensive prior neurological evaluation (clinical examination, Doppler ultrasound of carotid and vertebrobasilar arteries, computed tomography and magnetic resonance imaging brain scan). We also excluded patients with previously confirmed psychogenic or metabolic disorders.

The HUTT was performed in accordance with the European Society of Cardiology (ESC) guidelines. The procedure started with the patient in supine position on a special table during 20 minutes. During this time, the patient received 0.9% NaCl infusion. Electrocardiographic (ECG) recording and monitoring of BP and HR was done every 5 minutes. After that, the patient was lifted to vertical position for 60 minutes (or until typical symptoms occurred) with ECG recording and measurement of BP and HR every 5 minutes. Finally, they were positioned back horizontally and the test was finished.

In accordance with the ESC guidelines, some patients fulfilled the criteria for implantation of a dual-chamber, rate modulated (DDDR) permanent pacemaker.
pacemaker. It was programmed to DDD pacing mode and also received rate drop response pacing, a feature of the pacemaker that instituted rapid DDD pacing if the device detected a rapid decrease in heart rate. The programmed option specified that the initial rate drop response parameters should be a drop size of 20 beats, a drop rate of 70/min, and an intervention rate of 100/min for 2 minutes. In addition, all pacemakers were programmed with a lower rate at 50 bpm and a minimum atrioventricular delay of 200 ms to avoid inappropriate pacing and to favor spontaneous cardiac rhythm. After implantation, patients were scheduled for regular check-up at 3 months and then at every 6 months for the next 2 years.

Statistical analysis

Qualitative data are presented as absolute numbers and percentages. We used χ²-test with Yates correction for its analysis. Quantitative data are presented with median and interquartile ranges. Differences between two groups were tested by Mann-Whitney U test and Student’s t-test. Differences among three groups were tested by nonparametric analysis of variance (Kruskal-Wallis ANOVA). The level of statistical significance was set at p<0.05. Processing was done using the STATISTICA 6.0 software (StatSoft Inc., USA).

Results

The HUTT was positive in 34 (14.5%) of all study subjects (N=235), 14 (41.2%) males and 20 (58.8%) females. The following test findings were recorded:

1) there were no significant differences among three groups according to demographic data and HUTT results (Table 1). Subjects in groups A and B were referred most frequently to the HUTT by neurologists and cardiologists (p<0.05), and those in group C by other specialists (such as general practitioners) (Fig. 1);

2) characteristics of patients with positive HUTT are presented in Table 2. Most had VASIS-2A/2B, and not VASIS-1 or VASIS-3 responses, without significant age and gender differences. The test was positive in five group A patients and 29 group B patients. There were significant differences in symptoms during HUTT between them, i.e. tonic-clonic jerks and eye deviation (p<0.05); and

3) group B subjects (patients with suspected vasovagal syncope) and group C subjects (patients with paroxysmal vertigo) had their diagnosis affirmed with HUTT testing.

We further analyzed group A patients with convulsive clinical semiology. Among 30 group A subjects, there were 12 patients taking AEDs. Out of these 12 patients taking AEDs, three (two males/one female, mean age 28.5 years) patients had positive HUTT (25%). They had a mean of 2.3±0.6 convulsive syncope per year, repeatedly normal interictal EEG and no prior cardiac problem. During HUTT, they developed cardioinhibitory VASIS-2B vasovagal response with bradycardia (HR 30.0±5.0 beats/min) followed by prolonged asystole (13.7±11.0 seconds). Clinically, they all had loss of consciousness with tonic-clonic jerks and eyeball deviation with upward gaze that lasted until restoration of the normal cardiac rhythm.

In accordance with ESC guidelines17,18, in these three patients we implanted a DDDR pacemaker (Medtronic Kappa, Medtronic Inc., Minneapolis, Minnesota, USA).

Table 1. Baseline characteristics of patients undergoing HUTT (N=235)

<table>
<thead>
<tr>
<th>Findings</th>
<th>Parameter</th>
<th>Group A (n=30)</th>
<th>Group B (n=180)</th>
<th>Group C (n=25)</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td>Age †</td>
<td>33.5 (27.0-59.0)</td>
<td>44.5 (29.0-63.5)</td>
<td>45.0 (30.5-52.5)</td>
<td>44.0 (29.0-61.0)</td>
<td>0.490</td>
</tr>
<tr>
<td></td>
<td>Male, n (%)‡</td>
<td>12 (40.0)</td>
<td>64 (35.6)</td>
<td>9 (36.0)</td>
<td>85 (36.2)</td>
<td>0.896</td>
</tr>
<tr>
<td></td>
<td>Female, n (%)‡</td>
<td>18 (60.0)</td>
<td>116 (64.4)</td>
<td>16 (64.0)</td>
<td>150 (63.8)</td>
<td>0.896</td>
</tr>
<tr>
<td>HUTT results</td>
<td>Positive, n (%)‡</td>
<td>5 (16.7)</td>
<td>29 (16.1)</td>
<td>0 (0)</td>
<td>34 (14.5)</td>
<td>0.094</td>
</tr>
<tr>
<td></td>
<td>Negative, n (%)‡</td>
<td>25 (83.3)</td>
<td>151 (83.9)</td>
<td>25 (100)</td>
<td>201 (85.5)</td>
<td>0.094</td>
</tr>
</tbody>
</table>

Group A = patients with convulsive syncope; group B = patients with suspected vasovagal syncope; group C = patients with paroxysmal vertigo; HUTT = head-up tilt-table test; † data are presented as median and range, compared with Kruskal-Wallis (ANOVA) test; ‡ data are presented as absolute number and percentage, compared with χ²-test.
Fig. 1. Comparison of specialist referral to tilt-table testing in patients with convulsive syncope (A), suspected vasovagal syncope (B) and paroxysmal vertigo (C).

Fig. 2. Electroencephalographic findings in patients with convulsive syncope: 12 patients on antiepileptic drugs (A) and 18 patients with no medication (B).

Table 2. Characteristics of patients with positive HUTT (N=34)

<table>
<thead>
<tr>
<th>Findings</th>
<th>Parameter</th>
<th>Group A (n=5)</th>
<th>Group B (n=29)</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td>Age†</td>
<td>34.0 (28.0-46.3)</td>
<td>35.0 (24.8-65.0)</td>
<td>34.5 (28.0-65.0)</td>
<td>0.789</td>
</tr>
<tr>
<td></td>
<td>Male, n (%)‡</td>
<td>2 (40.0)</td>
<td>12 (41.4)</td>
<td>14 (41.2)</td>
<td>0.664</td>
</tr>
<tr>
<td></td>
<td>Female, n (%)‡</td>
<td>3 (60.0)</td>
<td>17 (58.6)</td>
<td>20 (58.8)</td>
<td>0.664</td>
</tr>
<tr>
<td>HUTT response</td>
<td>VASIS-1, n (%)‡</td>
<td>1 (20.0)</td>
<td>10 (34.5)</td>
<td>11 (32.4)</td>
<td>0.903</td>
</tr>
<tr>
<td></td>
<td>VASIS-2A, n (%)‡</td>
<td>0 (0)</td>
<td>2 (6.9)</td>
<td>2 (5.9)</td>
<td>0.672</td>
</tr>
<tr>
<td></td>
<td>VASIS-2B, n (%)‡</td>
<td>3 (60.0)</td>
<td>8 (27.6)</td>
<td>11 (32.4)</td>
<td>0.361</td>
</tr>
<tr>
<td></td>
<td>VASIS-3, n (%)‡</td>
<td>1 (20.0)</td>
<td>9 (31.0)</td>
<td>10 (29.4)</td>
<td>0.975</td>
</tr>
<tr>
<td></td>
<td>Pause, n (%)‡</td>
<td>3 (60.0)</td>
<td>8 (27.6)</td>
<td>11 (32.4)</td>
<td>0.361</td>
</tr>
<tr>
<td></td>
<td>Pause duration (sec)§</td>
<td>13.7±11.0</td>
<td>8.8±6.0</td>
<td>10.0±7.3</td>
<td>0.338</td>
</tr>
<tr>
<td>Symptoms during HUTT</td>
<td>Weakness, n (%)‡</td>
<td>5 (100)</td>
<td>29 (100)</td>
<td>34 (100)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Loss of consciousness, n (%)§</td>
<td>3 (60.0)</td>
<td>7 (24.1)</td>
<td>10 (29.4)</td>
<td>0.274</td>
</tr>
<tr>
<td></td>
<td>Tonic-clonic jerks, n (%)‡</td>
<td>3 (60.0)</td>
<td>0 (0)</td>
<td>3 (8.8)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Tongue bite, n (%)‡</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Incontinence, n (%)‡</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Eye deviation, n (%)‡</td>
<td>2 (40.0)</td>
<td>0 (0)</td>
<td>2 (5.9)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Head movement, n (%)‡</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
</tbody>
</table>

Group A = patients with convulsive syncope; group B = patients with suspected vasovagal syncope; HUTT = head-up tilt-table test; VASIS = Vasovagal Syncope International Study; VASIS-1 = mixed vasovagal response; VASIS-2A = cardioinhibition/asystole <3.0 sec; VASIS-2B = severe cardioinhibition/asystole ≥3.0 sec; VASIS-3 = pure vasodepression; †data are presented as median and range, compared with Mann-Whitney U test; ‡data are presented as absolute number and percentage, compared with χ²-test; §data are presented as mean ± standard deviation, compared with Student’s t-test.
Acta Clin Croat, Vol. 54, No. 4, 2015

M. Mornar Jelavić et al. Head-up tilt-table testing in unexplained syncope

In this study, we confirmed the role of HUTT in the evaluation of patients with unexplained syncope. We demonstrated its importance in differential diagnosis of vasovagal syncope, especially in patients with convulsive syncope. We also demonstrated the significance of permanent pacemaker implantation for the quality of life by reducing the number of syncopes in patients with cardiac disease and no medications. They had VASIS-1 and VASIS-3 vasovagal response. We suggested them a conservative approach (hygienic-dietetic measures and avoidance of provoking factors), which was effective and they had no syncope recurrence. Another 16 patients had negative HUTT. Thirteen (72.2%) patients had normal interictal and three (16.7%) patients had irritative EEG findings (Fig. 2).

Discussion

In this study, we confirmed the role of HUTT in the evaluation of patients with unexplained syncope. We demonstrated its importance in differential diagnosis of vasovagal syncope, especially in patients with convulsive syncope. We also demonstrated the significance of permanent pacemaker implantation for the quality of life by reducing the number of syncopes in patients with cardiac disease and no medications. They had VASIS-1 and VASIS-3 vasovagal response. We suggested them a conservative approach (hygienic-dietetic measures and avoidance of provoking factors), which was effective and they had no syncope recurrence. Another 16 patients had negative HUTT. Thirteen (72.2%) patients had normal interictal and three (16.7%) patients had irritative EEG findings (Fig. 2).

Sandhu et al. found that most patients (72.0%) were referred to HUTT by cardiologists. Several authors report that HUTT may be useful in the evaluation of patients with unexplained syncope. Galeta et al. report on 139 (36.6%) patients with VASIS-1, 57 patients (15.0%) with VASIS-2A/2B and 130 (34.2%) patients with VASIS-3 response to HUTT. VASIS-3 and VASIS-1 responses were the most frequent causes of syncope in older and younger subjects, respectively. It could be explained with physiological aging, associated with reduction of the sympathetic-parasympathetic control of cardiac rhythm. Pietrucha et al. found no gender differences in the type of vasovagal response to HUTT.

We found a slightly lower prevalence of patients with positive HUTT testing (14.5%). More frequently we found VASIS-2A/2B than VASIS-3 and VASIS-1 response, with no significant age or gender differences.

Current ESC guidelines recommend HUTT for differential diagnosis of convulsive syncope. According to literature data, up to 25% of patients with recurrent loss of consciousness and nonspecific EEG findings are taking anticonvulsants because of suspected but not diagnosed epilepsy. A significant minority of these patients have vasovagal syncope.

Among our 12 patients that were on AEDs, only one (8.3%) patient had prior epileptic EEG findings. In three (25.0%) patients with normal EEG we detected VASIS-2B response with severe bradycardia and asystolic pauses >3.0 seconds. During syncope, they had typical symptoms described to epileptologists. In accordance with diagnostic test responses (VASIS-2B) and not responding to hygienic-dietetic measures, these patients got indication for implantation of a permanent DDDR pacemaker. Implantation of permanent pacemakers in patients with asystole and younger than 40 years is recommended. Studies have shown effectiveness of the permanent pacemaker implantation, especially a new contractility-driven DDDR pacing and closed-loop stimulation compared with conventional DDI pacing, in these patients. This is in accordance with our results.

Ruiter and Barrett have reported good results in preventing syncope in VASIS-1 and VASIS-3 patients by increasing fluid intake and with physical counter-pressure. In our two patients with suspected epilepsy but normal EEG findings, VASIS-1 and VASIS-3 vasovagal response, conservative approach was successful in preventing syncope recurrence during the 24-month follow up period.

Two major mechanisms of transient loss of consciousness are global cerebral hypoperfusion that results in syncope and asynchronous discharge of cerebral neurons that leads to seizure. In some studies, simultaneous EEG monitoring was performed during the HUTT and most authors showed diffuse brain wave slowing down during a syncopal episode.
In vasodepressor response, there is an appearance of theta waves at the onset of syncope, followed by increase in the EEG amplitude with reduction of frequency in delta range. Return to supine position is associated with restoration of a normal EEG pattern.

In cardioinhibitory response, there is generalized slowing and occurrence of delta activity. A sudden reduction of brain activity leads to disappearance of cerebral EEG activity (a ‘flat’ EEG). Upon returning the patient to supine position, the EEG slowly returned to normal during full recovery of consciousness.

The main limitation of this study was that we did not perform prolonged simultaneous EEG/ECG monitoring in patients with convulsive syncope. According to other authors, it is important in the diagnosis of arrhythmogenic epilepsy in which partial epileptic discharges profoundly disrupt normal cardiac rhythm, including bradyarrhythmias and cardiac asystole. The appropriate treatment is double-headed, including an antiepileptic drug and implantation of a permanent pacemaker. Also, we had a short follow up period.

In conclusion, syncope requires a multidisciplinary team and individualized approach. HUTT has an important role in diagnostic evaluation of patients with recurrent unexplained syncope. It is indicated in the differential diagnosis of vasovagal syncope, especially in patients with syncope accompanied by convulsive elements. These subjects will benefit from specific therapy, thus improving their quality of life.

References


Sažetak

ULOGA TILT-TESTA U Diferencijalnoj dijagnostici neobjašnjene sinkope

M. Mornar Jelavić, Z. Babić, H. Hećimović, V. Erceg i H. Pintarić

Cilj ovoga retrospektivnog istraživanja (veljača 2012. – rujan 2014. godine) bio je ispitati ulogu tilt testa u bolesnika s neobjašnjenoj sinkopom. Prvenstveno je na 235 bolesnika u Zavodu za kardiologiju KBC-a “Sestre milosrdnice”. Bolesnici su klasificirani prema indikaciji za izvođenje testa: skupina A (konvulzivna sinkopa, n=30), skupina B (suspektna vazovagalna sinkopa, n=180) i skupina C (paroksizmalni vertigo, n=25). Skupine su analizirane i uspoređivane prema njihovim demografskim podacima (dob, spol), specijalistima koji su ih uputili na pretragu (kardiolozi, neurolozi, ostali) te rezultatima (pozitivan/negativan) i specifičnim odgovorima (kardionhibicija, vazodepresija ili mješoviti) tilt testa. Skupine A i B najčešće je na testiranje uputio neurolog i kardiolog (p<0,05). Test je bio pozitivan u 34 (14,5%) bolesnika (5 u skupini A i 29 u skupini B), od kojih je 13 (38,2%) imalo kardionhibicinski, 11 (32,4%) mješoviti i 10 (29,4%) vazodepresivni odgovor. U kardionhibicijskoj podskupini troje bolesnika (23,1%, 2 muškarca/1 žena, srednje dobi 28,5 godina) je imalo normalan nalaz electroencephalografije i uzimali su antiepileptike. Tijekom izvođenja testa zabilježili smo bradikardiju (30,0±5,0 ot-kucja/min) i produženu asistoliju (13,7±11,0 sekunda) uz pojavu tipičnih konvulzija. U sve troje bolesnika ugrađen je trajni elektrostimulator (atrijska/ventrikulska stimulacija, kontrola frekvencije) i ukinuta je antikonvulzivna terapija, nakon čega su tijekom 24 mjeseca praćenje bili bez recidiva sinkope. U zaključku, tilt test ima važnu ulogu u procjeni bolesnika s neobjašnjenoj sinkopom i u diferencijalnoj dijagnostici vazovagalne sinkope. Indikacija za ugradnju elektrostimulatora, strogo slijedeći smjernice Europskoga kardiološkog društva, pokazala se učinkovitom u sprječavanju recidiva sinkopa u bolesnika s kardionhibicijom konvulzivnom sinkopom.

Ključne riječi: Sinkopa – dijagnostika; Sinkopa – prevencija i kontrola; Sinkopa, vazovagalna – dijagnostika; Napadaji; Test tilt-table; Srijani elektrostimulator; Epilepsija