

Tilt-table test in patients with convulsive syncope

Tilt-table test kod bolesnika s grčevitom sinkopom

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Summary

Aim: To investigate the role of head-up tilt-test (HUTT) in evaluation of patients with convulsive syncope, especially of those resistant on antiepileptic drugs.

Patients and methods: This retrospective study (February 2012 – September 2014) was performed on 30 consecutive patients at the Department of Cardiology, Sestre milosrdnice University Hospital Center. They were grouped as follows: Group A (convulsive syncope resistant on antiepileptics, n = 12) and Group B (convulsive syncope with no medications, n = 18). The groups were analysed by their demographic data (age, gender), referral specialists (cardiologists, neurologists, others) and HUTT results (positive/negative) with specific response (cardioinhibitory, vasodepressor, or mixed).

Results: Groups A and B were referred to the HUTT only by neurologists ($p < 0.05$). 5 patients were positive (16.7%). In Group A, 3 patients (60.0%) had cardioinhibitory response, while 2 patients in Group B had mixed (20.0%) and vasodepressor (20.0%) response.

All three patients (2 male/1 female, mean age 28.5 years) in Group A with cardioinhibitory response had normal electroencephalography and were on antiepileptics. During HUTT, they had bradycardia (heart rate 30.0 ± 5.0 beats/min) and prolonged asystole (13.7 ± 11.0 seconds) with development of typical convulsions. They got a permanent pacemaker (atrial/ventricular stimulation, heart rate control) and anticonvulsive therapy was slowly withdrawn. They had no syncope recurrence during 24 months of follow-up.

Conclusion: HUTT has an important role in the evaluation of patients with convulsive syncope resistant on anticonvulsive drugs. Indication for a pacemaker implantation proved to be effective in preventing syncope relapses in these patients.

Key words: cardioinhibitory syncope, seizures, tilt-up table-test, permanent pacemaker, epilepsy

Sažetak

Cilj: Istražiti ulogu tilt-up testa (HUTT) u evaluaciji bolesnika s konvulzivnom sinkopom, a posebice u bolesnika rezistentnih na antikonvulzivnu terapiju.

Bolesnici i metode: Ova retrospektivna studija (veljača 2012. – rujan 2014.) provedena je na 30 uzastopnih bolesnika u Zavodu za kardiologiju KBC-a Sestre milosrdnice. Bolesnici su grupirani kako slijedi: Grupa A (konvulzivna sinkopa rezistentna na antiepileptike, n = 12) i Grupa B (konvulzivna sinkopa bez terapije, n = 18). Grupe su analizirane prema njihovim demografskim podacima (dob, spol), specijalistima koji su uputili na pretragu (kardiolozi, neurolozi, ostali), te rezultatima (pozitivan/negativan) i specifičnim odgovorima (kardio-inhibicija, vazodepresija, ili mješoviti) HUTT-a.

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Rezultati: Grupe A i B upućivane su na HUTT isključivo od strane neurologa ($p < 0,05$). Test je bio pozitivan u 5 (16,7%) bolesnika. U grupi A, tri bolesnika (60%) je imalo kardioinhibitorni odgovor, dok je u grupi B dva bolesnika imalo miješani (20%) i vazodepresorni (20%) odgovor.

Sva tri bolesnika (2 muškarca i 1 žena, prosječne dobi 28,5 godina) s kardioinhibitornim odgovorom u Grupi A imala su normalan nalaz elektroencefalografije i uzimali su antiepileptike. Tijekom izvođenja testa zabilježili smo bradikardiju (30 ± 5 otkucaja/min) i prolongiranu asistoliju ($13,7 \pm 11$ sekundi), uz pojavu tipičnih konvulzija. Dobili su trajni elektrostimulator (atrijska/ventrikularna stimulacija, kontrola frekvencije) i postepeno im je ukinuta antikonvulzivna terapija. Tijekom 24 mjeseca praćenja bili su bez recidiva sinkope.

Zaključak: HUTT ima važnu ulogu u evaluaciji bolesnika s konvulzivnom sinkopom rezistentnom na antiepileptike. Indikacija za ugradnju elektrostimulatora pokazala se učinkovitom u sprječavanju recidiva sinkopa kod navedenih bolesnika.

Cljučne riječi: kardioinhibitorna sinkopa, napadaji, tilt-up test, trajni elektrostimulator, epilepsija.

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Introduction

Syncope is defined as a brief and transient loss of consciousness and postural tone with spontaneous and complete recovery. During syncope, there is a 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 their lifetime; some studies indicate that this ratio is 2:1 in favour of young women.¹⁻⁷ The most frequent form of syncope is a vasovagal syncope. It is mediated by excessive vagal stimulation, or disbalance between sympathetic and parasympathetic autonomic activity. Vasovagal syncope is classified into cardioinhibitory, vaso-depressor, and mixed. 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 (hypoglycaemia, shock, alcoholism) and psychogenic symptoms.^{1-5,8} Convulsive syncope may be accompanied with neurological 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 antiepileptics have syncope and not epileptic seizures.⁹⁻¹³ Head-up tilt-testing (HUTT) is accepted as the gold standard for the diagnostic procedure of vasovagal syncope.^{14,15} In this study, we wanted to investigate the role of HUTT in the evaluation of patients with convulsive syncope,

especially those resistant on antiepileptics. We also wanted to evaluate the importance of proper selection of patients for pacemaker implantation and its influence on improving life quality by stopping syncope recurrences in patients with cardioinhibitory convulsive syncope.

Patients and methods

This retrospective study was performed in 30 consecutive patients with convulsive syncope who had been on HUTT (February 2012 – September 2014). It was performed at the Department of Cardiology, University Clinical Hospital "Sestre milosrdnice", in accordance with the ethical standards laid down in the Declaration of Helsinki and approved by the appropriate institutional committee.

The patients were classified into two groups as follows:

1. Group A – 12 patients currently taking antiepileptic drugs (AEDs) because of suspected epilepsy. They all had a prior thorough electroencephalographic (EEG) evaluation that classified them with normal interictal, irritative and epileptic EEG findings;
2. Group B – 18 patients with no specific therapy and performed EEG evaluation.

The groups were analysed and compared by their baseline demographic data (age, gender), specialists who referred them, HUTT results (positive/negative) and responses, defined and classified by Vasovagal Syncope International Study (VASIS) criteria,¹⁶ 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;
4. Pure vasodepression (VASIS-3): HR does not fall >10% from maximum rate during HUTT.

Additionally, in patients with a positive HUTT we analysed 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 tumour 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 guidelines of the European Society of Cardiology (ESC).^{17,18} Procedure started in the patient supine position on a special table during 20 minutes. During this time patients received 0.9% NaCl infusion. Electrocardiographic (ECG) recording and monitoring of BP and HR was every 5 minutes. After that, the patient was lifted to a vertical position for 60 minutes (or until typical symptoms occurred) with ECG recording and measurement of BP and HR every 5 minutes. Finally, the patient was positioned back horizontally and the test was finished.

In accordance with ECG guidelines,^{17,18} some patients fulfilled the criteria for implantation of a dual-chamber, rate modulated (DDDR) permanent 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 after 3 months and then every 6 months for the next 2 years.

Statistical analysis

Qualitative data were expressed as absolute number and percentage. We used Fischer's exact test for analysis. Quantitative data were expressed as median and corresponding interquartile range. Differences between two groups were tested by Mann-Whitney U test. Limit of statistical significance was considered at $p < 0.05$. Processing was done using the STATISTICA 6.0 for Windows software.

Results

Groups A and B were referred to the HUTT only by neurologists ($p < 0.05$). There were no significant differences between them in demographic data and the HUTT results (Table 1). HUTT was positive in 5 (16.7%) subjects. We recorded the following results:

In Group A, 3 (25%) patients (2 males/1 female, mean age 28.5 years) had positive HUTT. They had on average 2.3 ± 0.6 convulsive syncopes per year, repeatedly normal interictal EEG and no prior cardiac problem. During HUTT, they developed cardioinhibitory VASIS-2B vasovagal response with bradycardia ($HR 30.0 \pm 5.0$ beats/min) followed by a 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 to ESC guidelines,^{17,18} they got a DDDR pacemaker (Medtronic Kappa, Medtronic Inc, Minneapolis, Minn). During 6 months of follow-up, we detected a drop rate 50/min in 2 patients, drop size 50/min, and total of 10 pacemaker interventions. We recorded drop rate 55/min, drop size 25/min, and total of 80 pacemaker interventions in 1 patient, and several episodes of non-sustained ventricle tachycardia. After 24 months of their follow-up, no subject had any syncope and AEDs were slowly withdrawn.

Other 9 patients taking AEDs had negative HUTT. Five patients (41.7%) had normal interictal, 1 (8.3%) epileptic and 3 patients (25.0%) had irritative EEG findings (Table 1).

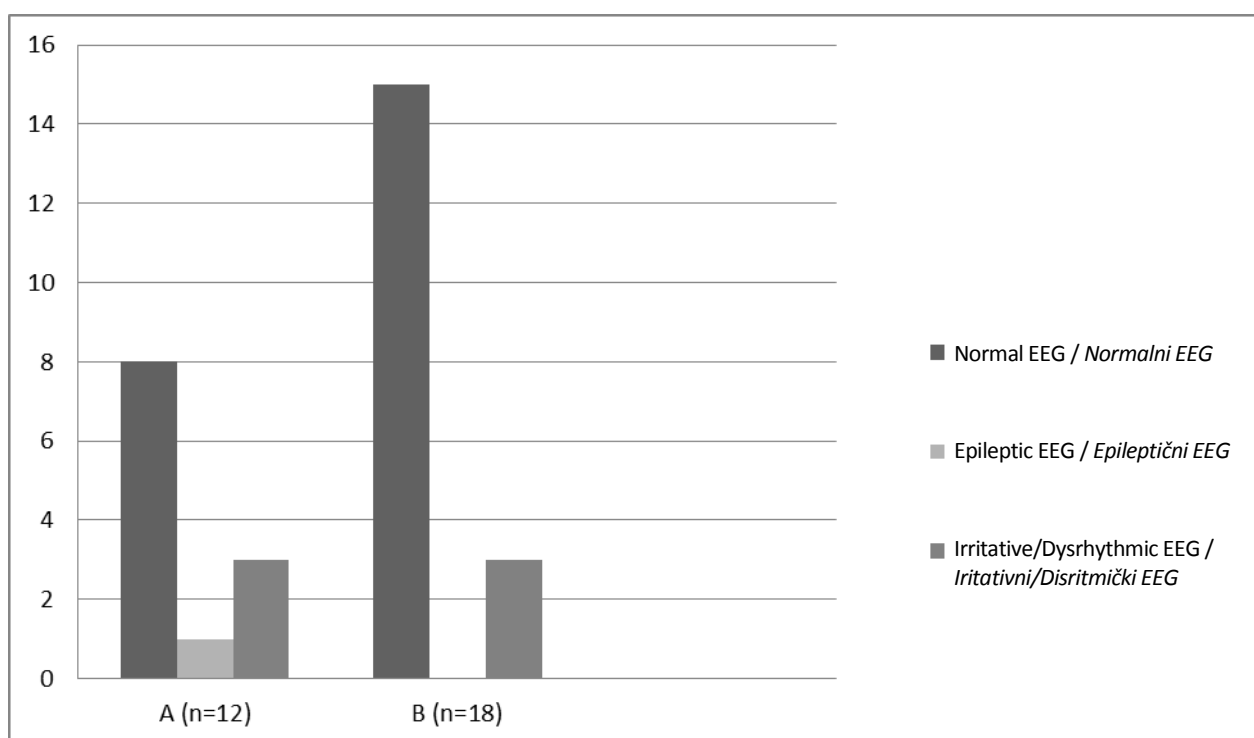
In Group B, 2 (11.1%) patients (females, aged 50.5 (30.0-71.0) years) had positive HUTT. They had normal interictal EEG and no cardiac disease and no medications. They had VASIS-1 and VASIS-3 vasovagal response. We suggested them a conservative approach (hygienic-dietetic measures and avoidance of provoking factors) that was effective and they had no syncope recurrence. Other 16 patients had negative HUTT. Thirteen (72.2%) patients had normal interictal and 3 (16.7%) patients had irritative EEG findings (Table 1).

Table 1 Baseline characteristics of patients who underwent HUTT* (n = 30)
 Tablica 1. Osnovne karakteristike pacijenata koji su podvrgnuti HUTT (n = 30)

| FINDINGS NALAZI | PARAMETERS PARAMETRI | A (n=12) | B (n=18) | p value p vrijednost |
|---|--------------------------------------|------------|--------------|-------------------------|
| Demographic data Demografskii podaci | Age [†] /Dob | 43 (20-74) | 32.5 (19-73) | 0.826 |
| | Male, n (%) [‡] Muškarci | 4 (33.3) | 8 (44.4) | 0.709 |
| | Female, n (%) [‡] Žene | 8 (66.7) | 10 (55.6) | 0.709 |
| HUTT results HUTT rezultati | Positive, n (%) [‡] | 3 (25.0) | 2 (11.1) | 0.364 |
| | Negative, n (%) [‡] | 9 (75.0) | 16 (88.9) | 0.364 |

*Abbreviations: A – patients with convulsive syncope taking antiepileptics; B – patients with convulsive syncope and no medications; HUTT – Head-up tilt-table test. [†]Data are expressed with median and corresponding interquartile range, compared with Mann-Whitney U test; [‡]Data are expressed with absolute number and percentage, compared with Fischer's exact test for small samples.

Skracenicice: A – pacijent s konvulzivnom sinkopom koji uzima antiepileptike; A- pacijenti s konvulzivnom sinkopom bez lijekova; HUTT – Head-up tilt-table test. [†]Podaci izraženi u prosjecima i odgovarajućim interkvartnim rasponom u usporedbi s Mann-Whitney testom; [‡]Podaci izraženi u apsolutnom broju i postotku u usporedbi s Fischer točnim testom za sve primjerke



Picture 1 Electroencephalographic findings in patients with convulsive syncope: 12 patients with antiepileptic drugs (A) and in 18 patients with no medication (B)

Slika 1. Elektroencefalografski nalazi kod pacijenata s konvulzivnom sinkopom: 12 pacijenata na antiepileptičkim lijekovima (A) te 18 pacijenata bez lijekova (B)

Discussion

In this study, we confirmed the importance of HUTT in the evaluation of patients with convulsive syncope. We also demonstrated a significance of permanent pacemaker implantation on life quality by reducing the number of syncopes in patients with cardioinhibitory convulsive syncope and subsequent withdrawal of AEDs.

Current ESC guidelines recommend HUTT for differential diagnosis of convulsive syncopes.¹ It is considered in the literature that up to 25% of patients with recurrent loss of consciousness and non-specific EEG findings are taking anticonvulsants because of suspected, but not diagnosed epilepsy. A significant minority of these patients have vasovagal syncope.⁹⁻¹³

Among our 12 patients that were on AEDs, only 1 (8.3%) patient had prior epileptic EEG findings. In 3 (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. The implantation of permanent pacemakers in patients with asystole and younger than 40 years is recommended.^{17,18} Studies have shown the effectiveness of permanent pacemaker implantation in these patients, especially a new contractility-driven DDDR pacing and closed-loop stimulation compared with conventional DDI pacing.^{1,19-21} This is in accordance with our results.

Ruiter et al. reported good results in preventing syncope at VASIS-1 and VASIS-3 patients, by increasing fluid intake and by physical counter-pressure.¹⁹ In our 2 patients with suspected epilepsy, but normal EEG findings, VASIS-1 and VASIS-3 vasovagal response, the conservative approach was successful in the prevention of syncope recurrence during our follow-up period of 24 months.

Two major mechanisms of transient loss of consciousness are global cerebral hypoperfusion which results with syncope and asynchronous discharge of cerebral neurons which leads to seizure.²²

In some studies simultaneous EEG monitoring was performed during the HUTT and most authors showed diffuse brain waves slowing during a syncopal episode.²³⁻²⁷

In vasodepressor response, there is an appearance of theta waves at the onset of syncope, followed by the increase of EEG amplitude with the reduction of frequency in delta range. Return to the 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 the disappearance of cerebral EEG activity (a 'flat' EEG). Returning the patient to the supine position, EEG slowly returned to normal, during full recovery of consciousness.

The main limitation of this study is that we have not performed prolonged simultaneous EEG/ECG monitoring in patients with convulsive syncope. According to other authors, it is important in the diagnosis of arrhythmogenic epilepsy where partial epileptic discharges profoundly disrupt normal cardiac rhythm, including bradyarrhythmias and cardiac asystole. The appropriate treatment is double-headed, including an antiepileptic drug and the implantation of a permanent pacemaker.^{28,29} We also had a short follow-up period.

To conclude, syncope requires a multidisciplinary team and individual approach. HUTT has a role in the diagnostic evaluation of patients with syncope accompanied with convulsive elements. These subjects will benefit from specific therapy, thus improving their quality of life.

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