Is pacemaker therapy the right key to patients with vasovagal syncope?

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SUMMARY
Introduction Vasovagal syncope is the most common type of reflex syncope. Efficacy of cardiac pacing in this indication has not been the subject of many studies and pacemaker therapy in patients with vasovagal syncope is still controversial.
Objective This study aimed to assess the efficacy and safety of pacing therapy in treatment of patients with vasovagal syncope, to determine contribution of new therapeutic models in increasing its success, and to identify risk factors associated with a higher rate of symptoms after pacemaker implantation.
Methods A retrospective study included 30 patients with pacemaker implanted due to vasovagal syncope in the Pacemaker Center, Clinical Center of Serbia, between November 2003 and June 2014. Head-up tilt test was performed to diagnose vasovagal syncope. Patients with cardioinhibitory and mixed type of disease were enrolled in the study.
Results Mean age was 48.1 ± 11.1 years and 18 (60%) patients were men. Mean follow-up period was 5.9 ± 3.0 years. Primarily, implantable loop recorder was implanted in 10 (33.3%) patients. Twenty (66.7%) patients presented cardioinhibitory and 10 (33.3%) mixed type of vasovagal syncope. After pacemaker implantation, 11 (36.7%) patients had syncope. In multiple logistic regression analysis we showed that syncope is statistically more likely to occur after pacemaker implantation in patients with mixed type of vasovagal syncope (p = 0.018). There were two (6.7%) perioperative surgical complications.
Conclusion Pacemaker therapy is a safe treatment for patients with vasovagal syncope, whose efficacy can be improved by strict selection of patients. We showed that symptoms occur statistically more often in patients with mixed type of disease after pacemaker implantation.
Keywords: vasovagal syncope; pacemaker therapy; head-up tilt test

INTRODUCTION
Vasovagal syncope, previously called neurocardiogenic syncope, is the most common type of reflex syncope, usually seen in young patients without cardiovascular history [1]. It is preceded by prodromal symptoms of strong initial sympathetic activation in two thirds of patients. Symptoms such as sweating, pallor, nausea, blurred vision, and confusion are presented for about 60 seconds [2]. Vasovagal syncope is caused by an overemphasized response of autonomic nervous system to various stimuli, such as strong emotions and orthostatic stress [2]. There are different initiators of vasovagal syncope, from extended standing, warm and stifling environment, and showering with hot water, to painful stimulus, fear, or psychological stress [3]. Therefore, peripheral as well as central mechanisms have been included in pathophysiology of vasovagal syncope [1].

After taking history, for the confirmation of diagnosis of vasovagal syncope, the head-up tilt test (HUTT) should be performed. HUTT is a noninvasive orthostatic stress test, and according to guidelines of European Society of Cardiology, cardiac pacing is indicated in patients over 40 years of age with recurrent vasovagal syncope, who show prolonged asystole during ECG recording and/or tilt testing, and are informed of the conflicting results of trials (class IIa of recommendations) [4]. The main dilemma remains whether patients with vasovagal syncope need specific therapy. It is generally accepted that patients with single syncope and without high risk occupations should be educated to recognize and avoid situations that can trigger syncope [1, 2, 4]. Counterpressure maneuvers and orthostatic training may be helpful [1, 2, 4]. According to guidelines of European Society of Cardiology, cardiac pacing is indicated in patients over 40 years of age with recurrent vasovagal syncope, who show prolonged asystole during ECG recording and/or tilt testing, and are informed of the conflicting results of trials (class IIa of recommendations) [4]. Efficacy of cardiac pacing in this indication has not been the subject of many studies and pacemaker therapy is still controversial.

OBJECTIVE
This study aimed to assess the efficacy and safety of pacing therapy in treatment of patients with vasovagal syncope, to determine in high risk settings (for example occupational implications such as pilots or professional drivers), or in situations when we must discriminate reflex syncope and orthostatic hypotension (class IIa of recommendations) [4]. The main dilemma remains whether patients with vasovagal syncope need specific therapy. It is generally accepted that patients with single syncope and without high risk occupations should be educated to recognize and avoid situations that can trigger syncope [1, 2, 4]. Counterpressure maneuvers and orthostatic training may be helpful [1, 2, 4]. According to guidelines of European Society of Cardiology, cardiac pacing is indicated in patients over 40 years of age with recurrent vasovagal syncope, who show prolonged asystole during ECG recording and/or tilt testing, and are informed of the conflicting results of trials (class IIa of recommendations) [4]. Efficacy of cardiac pacing in this indication has not been the subject of many studies and pacemaker therapy is still controversial.
diagnosis of vasovagal syncope was based on clinical history and results of tilt testing. During the testing, we used a protocol divided into three phases: Stabilization phase – the patient is rested supine for five minutes;

- Passive phase – the patient is tilted upright at an angle of 60° for 20 minutes;
- Provocation phase – one dose of 400 μg of sublingual glyceryl trinitrate spray is administered, after which the patient continues the test for 15 minutes.

HUTT was considered positive when asystole longer than three seconds and/or fall in systolic blood pressure higher than 50 mmHg was recorded. All patients were divided into these three hemodynamic types, based on the results of tilt testing:

- Cardioinhibitory type – when bradycardia and asystole longer than three seconds were recorded;
- Vasodepressor type – when fall in systolic blood pressure higher than 50 mmHg was recorded;
- Mixed type – when asystole and hypotension were recorded.

Patients with cardioinhibitory and mixed type of vasovagal syncope were enrolled in the study. Patients who were followed up less than six months were excluded. Pacemakers manufactured by Medtronic (Minneapolis, MN, USA) and St Jude Medical (Saint Paul, MN, USA) were implanted, in VVI and DDD mode of stimulation. Devices with and without special algorithms for treating reflex syncope were implanted. Pacemaker was implanted left or right prepectoral and electrodes were placed endovascularly, after cephalic vein cut-down or puncture of the subclavian and/or axillary vein. In patients with previously explanted implantable loop recorder (ILR), the device was explanted, after which the pacemaker was implanted during the same intervention. Data were collected from the pacemaker medical records and patients’ files from device controls in the Outpatient Department of the Pacemaker Center. All the patients were contacted by phone to check whether there were symptoms after the intervention.

For data processing we used descriptive and analytic statistic methods. From descriptive methods mean and standard deviation were used for continuous variables, and absolute and relative numbers for categorical variables. Multiple binary logistic regression analysis was used to identify the characteristics associated with a higher rate of syncope after pacemaker implantation. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 20 software (IBM Corp., Armonk, NY, USA). The efficacy of pacing therapy was determined according to frequency of symptoms recurrence after pacemaker implantation. Therapy safety was assessed based on frequency of perioperative complications in our and other studies, where pacemakers were implanted using standard surgical technique in similar or different indications.

**METHODS**

This was a retrospective, observational study, which included patients with pacemaker implanted due to vasovagal syncope, in the Pacemaker Center, Clinical Center of Serbia, between November 2003 and June 2014. The diagnosis of vasovagal syncope was based on clinical history and results of tilt testing. During the testing, we used a protocol divided into three phases: Stabilization phase – the patient is rested supine for five minutes;

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**RESULTS**

Thirty patients were included in this study. Mean follow-up period was 5.9 ± 3.0 years. Mean age was 48.1 ± 11.1 years and 18 (60%) patients were man. Patient and procedure characteristics and the incidence of risk factors are presented in Tables 1 and 2. Preoperatively, all the patients had syncope, HUTT was performed in all of them and based on the results, cardioinhibitory type of vasovagal syncope was diagnosed in 20 (66.7%) patients and mixed type in 10 (33.3%). Pacemaker in VVI mode of stimulation was implanted in six (20%) and in DDD mode of stimulation in 24 (80%) patients. Eight (26.6%) patients got device with special algorithm for treating reflex syncope. Primarily, ILR was implanted in 10 (33.3%) patients, after which, based on ILR records, implantation of pacemaker was indicated. After pacemaker implantation, during the follow-up period, 11 (36.7%) patients had syncope and 19 (63.3%) had no symptoms. Mean follow-up period from pacemaker implantation to the first syncope was 1.0 ± 0.4 years. In multiple logistic regression analysis we identified the type of vasovagal syncope as an independent risk factor for the occurrence of syncope after the pacemaker implantation (Table 3). We showed that the occurrence of syncope is statistically more likely after the pacemaker implantation in patients with mixed type of vasovagal syncope (p = 0.018). There were two (6.7%) instances of perioperative surgical complications, and a reintervention was required in one patient. We recorded no ventricular arrhythmias, ventricular tachycardia/fibrillation, and one patient died during the follow-up period.

**DISCUSSION**

Vasovagal syncope is a rare indication for pacemaker implantation. Medical doctors, even they are aware that according to guidelines there is an indication for pacing therapy, unwillingly make decision to implant the device because patients are usually young persons, who consider themselves healthy. If we look at guidelines, especially at the level of evidence, it will be completely clear why there are doubts about the role of cardiac pacing therapy in management of vasovagal syncope. Efficacy of cardiac pacing in this indication has not been the subject of many studies, and results and findings of those trials are inconsistent [4]. Firstly, efficacy of pacemaker therapy was confirmed in a few small randomized studies, with control group without specific therapy (VPS I, VASIS, SYDIT) [5, 6, 7]. However, the superiority of pacing therapy has not been confirmed in double-blind placebo-controlled trials (VPS II, SYNPACE) [8, 9].
In our study, after pacemaker implantation, during the follow-up period, 36.6% of patients had syncope. Comparing to the results of the VPS II study where 31% of patients had syncope during follow-up, our results are in line for additional explanation. Pacemaker in VVI mode of stimulation was implanted in six (20%) patients and five of them had syncope during the follow-up. Although, in our study, mode of stimulation has not been identified as a risk factor associated with a statistically higher rate of symptoms after pacemaker implantation (p = 0.068), experience tells us that patients with pacemaker in VVI mode of stimulation have syncope after intervention significantly more often. We interpret our results as a consequence of the insufficient number of enrolled patients with this mode of stimulation to achieve statistical significance. In addition, eight (26.6%) of our patients received a device with a special algorithm for treating VVS. This algorithm allows rapid increasing of heart frequency in case of significant drop in heart rate and thus prevents vasodilatation, a drop in blood pressure, and, finally, the occurrence of syncope [10, 11]. However, it is accepted that timely detection of paradoxical neural reflex, which is responsible for the occurrence of vasovagal syncope, at its afferent part, is most important for preventing syncope. Thus, the traditional function of pacemaker, preventing bradycardia development and acting at the efferent part of the neural reflex, is changed. Based on this idea, new pacemaker algorithms, which allow the pacemaker to react in accordance with cardiac contraction dynamics, measuring the change in intracardiac impedance, are developed. Increased myocardial contractility, that occurs in the initial pathophysiological segments of the development of vasovagal syncope, due to increased releasing of catecholamines and still insufficient venous return in the right ventricle, can be detected [12, 13, 14]. This allows us to stop the vicious circle that leads to the occurrence of vasovagal syncope with the pacing at this, afferent part of paradoxical reflex. In our study, only one patient with an implanted device with this special algorithm had syncope during the follow-up period. Unfortunately, in our center, we have not had the opportunity to implant more pacemakers with this algorithm, but we believe that their use in the future will improve the results of pacing therapy in this indication. Relatively high percentage of symptom recurrence in our study population must be considered from the viewpoint of the length of the patient’s follow-up. Described studies had, in most cases, a twelve-month follow-up, and we had an average follow-up of 5.9 ± 3.0 years, which provides greater significance to our results. Additionally, mean age of our patients was under 49 years and was significantly lower than in other studies. Even before our study, many researchers questioned whether vasovagal syncope in the elderly had different pathophysiological mechanisms of development compared to younger people and whether that could provide greater efficacy of pacing therapy in this indication. Therefore, they noted that studies which promote the importance of pacemaker therapy in management of vasovagal syncope had enrolled patients with mean age significantly higher than that in studies whose results have challenged the effectiveness of pacing in this indication [15]. It should be noted that the nature of symptoms was different in patients who continued to have syncope after the pacemaker implantation. These patients stated that syncope after the pacemaker implantation compared to those before the intervention were less sudden, preceded by prolonged prodromal symptoms; also, none of these patients sustained any injuries. It is important to mention major conclusions of the meta-analysis, which included nine studies that assessed the role of pacemaker therapy in treatment of patients with vasovagal syncope, and which was published in 2007 [16]. In addition to the known fact that in the group of double-blind studies it is not possible to prove the efficacy of pacing therapy, it is also highlighted that results were not significantly changed when research was limited only to patients with cardioinhibitory type of vasovagal syncope confirmed during the HUTT [16]. In our study, however, three (15%) patients with cardioinhibitory type of disease had syncope and we showed that syncope after pacemaker implantation is statistically less likely to occur in patients with cardioinhibitory type of vasovagal syncope than in those with mixed type of the disease.

**Table 1. Patient and procedure characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Age</td>
<td>48.1 ± 11.1</td>
</tr>
<tr>
<td>Syncope before PM implantation</td>
<td>30 (100)</td>
</tr>
<tr>
<td>HUTT before PM implantation</td>
<td>30 (100)</td>
</tr>
<tr>
<td>ILR implanted before PM implantation</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>PM with special algorithm</td>
<td>8 (26.6)</td>
</tr>
<tr>
<td>Syncope during follow-up</td>
<td>11 (36.7)</td>
</tr>
</tbody>
</table>

**Table 2. Incidence of risk factors**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>5 (16.6)</td>
</tr>
<tr>
<td>Atrial fibrillation before implantation</td>
<td>5 (16.6)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Hyperlipoproteinemia</td>
<td>5 (16.6)</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>6 (20)</td>
</tr>
</tbody>
</table>

**Table 3. Correlation between patient characteristics and clinical data with symptoms’ recurrence**

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1.135</td>
<td>0.443</td>
</tr>
<tr>
<td>Type of VVS</td>
<td>4.658</td>
<td>0.018</td>
</tr>
<tr>
<td>Type of PM</td>
<td>-3.732</td>
<td>0.068</td>
</tr>
<tr>
<td>Previously implanted ILR</td>
<td>-2.478</td>
<td>0.194</td>
</tr>
<tr>
<td>PM with algorithm for treating VVS</td>
<td>0.942</td>
<td>0.588</td>
</tr>
</tbody>
</table>

* Dependent variable: syncope
B – regression coefficient; Sig. – significance; VVS – vasovagal syncope; PM – pacemaker; ILR – implantable loop recorder
It is necessary to develop new ideas that will lead to better selection of patients with vasovagal syncope, who will gain from the pacemaker therapy. One such idea, used in our study, is related to the early implantation of ILR in patients with recurrent vasovagal syncope, in order to select patients with highly suspected cardioinhibitory type of disease, and then based on ILR records determine specific therapy [17]. Therefore, ILR is implanted in patients with recurrent vasovagal syncope and then the patients are observed for any development of significant bradycardia or significant asystolic pauses, which would be the indication for pacemaker implantation. In two large studies, ISSUE 2 and ISSUE 3, the rate of symptom persistence in a group of patients with an implanted pacemaker and in those without specific therapy, was compared [18, 19]. In both studies, with ISSUE 3 being a double-blind study with a placebo control group, statistically significant reduction of absolute and relative risk of symptom persistence in patients who were under specific therapy was demonstrated [18, 19, 20]. In our study, this new approach to patient selection, by early implantation of an ILR, was applied in 10 patients, and two (20%) of them had syncope during the follow-up period.

Our results indicate that pacemaker implantation is a safe procedure. There were two (6.7%) perioperative surgical complications, and a reintervention was required in one patient. In one perioperative surgical complication, atrial lead dislodgement occurred, which was resolved during the same hospitalization by implanting a new atrial lead. In the second case, iatrogenic apical pneumothorax was diagnosed; the patient was monitored by a thoracic surgeon, and after a somewhat prolonged hospitalization in our center, the patient was discharged in good general condition. In the patient who died during the follow-up period, noncardiovascular cause of death was found. Therefore, pacemaker implantation, like any other surgical procedure, has some risks, but it is important to emphasize that mentioned complications do not diverge in their type or in frequency from what is expected [21, 22].

CONCLUSION

Our study has shown that pacemaker therapy is a safe treatment for patients with vasovagal syncope, whose efficacy can be improved by a strict selection of patients. We have shown that syncope is statistically more likely to occur after the pacemaker implantation in patients with mixed type of vasovagal syncope. Our results and permanent enrolment of new therapeutic models and new pacemaker algorithms assure us that efficacy of pacemaker therapy in this indication will be advanced in the near future.

REFERENCES


КРАТАК САДРЖАЈ

Увод
Вазовагалне синкопе представљају најчешћи тип рефлексних синкопа. Постоје бројне дилеме везане за лечење болесника са вазовагалном синкопом, а пејсмејкер терапија у овој индикацији је још увек контроверзна.

Циљ рада
Циљ рада је био да се испита ефикасност и безбедност пејсмејкер терапије у лечењу болесника са вазовагалном синкопом, да се процени допринос нових терапијских модела повећању њене успешности и да се одреде фактори ризика повезани са повећаном учесталошћу симптома након уградње пејсмејкера.

Методе рада
Ретроспективном студијом обухватање је 30 болесника са вазовагалном синкопом којима је у Пејсмејкер центру Клиничког центра Србије у Београду од новембра 2003. године до јуна 2014. године уграден трајни антибрадикардички пејсмејкер. Дијагноза је постављена на основу резултата head-up tilt теста. Укључени су болесници са диагнозом кардиоинхибиторног или комбинованог типа болести.

Резултати
Просечна старост болесника била је 48,1 ± 11,1 година, а 18 (65,0%) болесника је било мушког пола. Пресечан период праћења износио је 5,9 ± 3,0 године. Код 10 (33,3%) болесника најпре је уграђен имплантабилни loop рекордер. Код 20 (66,7%) болесника постављена је дијагноза кардиоинхибиторног, а код 10 (33,3%) комбинованог типа болести. У периоду праћења 11 (36,7%) болесника је имало синкопу. Користећи мултилу логистичку регресиону анализу, показали смо да се синкопа након уградње пејсмејкера чешће јавља код болесника са комбинованим типом болести (p = 0,018). Регистроване су две (6,7%) перипроперуалне хируршке компликације.

Закључак
Пејсмејкер терапија је безбедна метода лечења болесника са вазовагалном синкопом, чија ефикасност може бити унапређена ригорозном селекцијом болесника. Показали смо да се након уградње пејсмејкера симптоми статистички чешће јављају код болесника са комбинованим типом вазовагалне синкопе.

Кључне речи: вазовагална синкопа; пејсмејкер терапија; head-up tilt тест