VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2008, Vol. 15, No. 5, pp. 446–450

ISSN 1897–5593

Can prodromal symptoms predict recurrence of vasovagal syncope?

Amir Farjam Fazelifar[1], Hosein Ali Basiri[2], Ali Tolooie[2], Majid Haghjoo[1], Hamid Barakpour[1], Zahra Emkanjoo[1], Hooman Bakhshandeh Abkenar[3], Mahboubeh Zeighami[4], Foroozan Asgari[4], Mohammad Ali Sadr-Ameli[1]

[1]Department of Pacemaker and Electrophysiology, Rajaie Cardiovascular Medical and Research Center, Tehran, Iran
[2]Department of General Cardiology, Rajaie Cardiovascular Medical and Research Center, Tehran, Iran
[3]Department of Epidemiology and Biostatistics Analysis, Rajaie Cardiovascular Medical and Research Center, Tehran, Iran
[4]Electrophysiology Nursing, Department of Pacemaker and Electrophysiology, Rajaie Cardiovascular Medical and Research Center, Tehran Iran

Abstract

Background: *Vasovagal syncope (VVS) is a common symptom with empirical therapy and high recurrence rate. Our goal was to determine whether the pattern of presyncopal prodromal symptoms can predict the recurrence probability of vasovagal syncope.*

Methods: *Seventy-nine consecutive patients (male/female: 53/26) with history of VVS and positive tilt table test (TTT) were enrolled in the study and completed the follow-up time for one year. They all had normal electrocardiograms and cardiac echocardiography without underlying disease. All of them were evaluated meticulously for prodromal symptoms (diaphoresis, nausea, palpitation and blurred vision) and frequency of syncopal spells in their past medical history. They received metoprolol at maximum tolerated dose and were taught tilt training as an empirical therapy after TTT.*

Results: *Fifty-four patients (68.4%) reported at least one of the four main prodromal symptoms. Median syncopal ± presyncopal spells were 4 episodes. Forty-two patients (53.2%) experienced recurrence of syncope or presyncope during the follow-up period. In recurrent symptomatic patients, diaphoresis had been more significantly reported in their past medical history ($p = 0.018$) and they had more syncopal spells before TTT ($p = 0.001$). Age, gender and type of TTT response did not have any effect on the recurrence of VVS.*

Conclusions: *Patients with a history of diaphoresis as a prodromal symptom and more pre-tilt syncopal attacks experience more syncopal or presyncopal spells during follow-up.* (Cardiol J 2008; 15: 446–450)

Key words: vasovagal syncope, prodromal symptoms, beta-blocker therapy

Address for correspondence: Amir Farjam Fazelifar, MD, Department of Pacemaker and Electrophysiology, Rajaie Cardiovascular Medical and Research Center, Vali-e-Asr Avenue, 1996911151, Tehran, Iran, P.O. Box 15745-1341, tel: 0098 21 2392 2931, fax: 0098 21 8878 4618, e-mail: fazelifar@gmail.com

Received: 9.07.2008 Accepted: 30.07.2008

Introduction

Prodromal symptoms and signs often precede vasovagal syncope (VVS). Despite its prevalence, significant gaps in our understanding of its pathophysiology and treatment remain [1]. Several pathophysiological mechanisms have been suggested to explain the development of arterial vasodilation in the setting of relative or absolute bradycardia. The optimal medical therapy of patients with VVS is still controversial. Many pharmacological and nonpharmacological approaches have been suggested, but due to the complex and variable mechanisms, the management of VVS is difficult and recurrence rates are high [2]. The purpose of this article is to evaluate the effect of prodromal symptom patterns on the recurrence of VVS.

Methods

Patients

We included 85 patients in this study, but only 79 patients were able to complete the follow-up period successfully. They were selected consecutively from patients referred to our arrhythmia clinic. All the patients had at least one episode of clinical history compatible with the diagnosis of VVS, with or without presyncopal spells during the previous year. A complete study (physical examination, 12-lead ECG, cardiac echocardiography, chest X-ray, bilateral carotid sinus massage, routine biological and hematological tests and neurology consultation) was performed to eliminate other possible causes of syncope during the inclusion phase. The inclusion criteria were: age ≥ 18 years with at least one syncopal event during the previous year consistent with the diagnosis of VVS, positive tilt table test (TTT) and absence of structural or electrical heart disease. Exclusion criteria were: presence of another possible etiology for syncope, documented autonomic dysfunction, unable to perform tilt training, contraindication or hypersensitivity for beta-blocker therapy or any other drug therapy that could make the patient inappropriate for the study.

Tilt test protocol and definitions

Positive TTT was one of the inclusion criteria. The study protocol was approved by the ethics committee of the hospital. Written informed consent was obtained from each patient. The test was performed by means of an electrically controlled tilt table with a footboard for weight bearing. Heart rate was continuously monitored. Instantaneous arterial blood pressure was recorded by digital servo-plethysmography (Finapress 2300, Ohmeda, Englewood, NJ, USA) with a digital cuff installed on the third finger of the right hand. No invasive instrumentation was used during the test. The patients had been fasting overnight, and medications that could interfere with the test (i.e., diuretics, vasodilators and beta-blockers) were withheld for at least two days before the study. The TTT was done after an initial observation with the patient in the supine position for 20 min. The test consisted of two consecutive tilted stages. In the first or passive stage, patients were tilted at 70° for up to 45 min without medication. If syncope did not develop, patients entered the active stage. They received 400 μg sublingual glyceryl trinitrate and continued to be tilted for another 15 min. If syncope occurred during the test, the tilt table was rapidly adjusted to return the patient to the supine position, and the study was terminated. We included all the patients with syncope or presyncope with systolic blood pressure ≤ 70 mm Hg with or without asystoly and/or bradyarrhythmia. We considered three types of syncope according to the changes in heart rate and blood pressure detected during the episodes: 1) vasodepressor, with an abrupt decrease of systolic blood pressure over 30 mm Hg (or 20% to 30% of the basal value); 2) cardioinhibitory, with a decrease in heart rate over 20% of the measurement taken immediately before the episode and 3) a mixed response, with both bradycardia and hypotension [3].

Study design

This is a prospective, case-series study. The primary hypothesis was that the presence or absence of prodromal symptoms may show different pathophysiological mechanisms for VVS. These differences can explain various responses to beta-blocker therapy in patients with VVS. During the first visit, all patients underwent a TTT. In patients with a positive response, beta-blocker (metoprolol) was started at maximal tolerated dose. All patients were informed about tilt training. The patients were then followed up for one year. Examinations were performed every three months. At each examination the clinical recurrence of syncope and/or presyncope and possible adverse effects were evaluated. In cases of recurrence, patients were reassured, physical examination and electrocardiogram were performed and possible adverse effects were evaluated. Frequency of recurrence of syncope and or presyncope was counted after twelve months follow-up period. Criteria for withdrawal from the study included: the patient's refusal to continue,

Table 1. Pattern of current prodromal symptoms reported by patients.

Palpitation	23 (29.1%)
Nausea	34 (43.0%)
Diaphoresis	57 (72.0%)
Blurred vision	43 (54.4%)
No symptom	21 (26.6%)

noncompliance and serious adverse effects. The primary end point of the study was finalization of follow-up period.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Statistical analysis

The statistical package used was SPSS 14.0 for windows. Mean (± standard deviation) and medians were calculated for continuous variables. Differences between groups were examined for statistical significance by a student *t*-test for continuous variables, with the Mann-Whitney *U*-test for variables nonparametrically distributed and by Fisher exact test for categorical variables. A value of $p < 0.05$ was considered significant. We used binary logistic regression analysis to find the potential predictors of recurrence of syncope and/or presyncope during the follow-up period.

Results

Baseline patient characteristics

Between August 2006 and March 2007, a total of 85 consecutive patients with unexplained syncope and normal electrocardiogram, echocardiography, neurology consultation and routine lab tests had positive TTT response. They did not have any contraindication for beta-blocker therapy or tilt training. Only 79 patients were able to complete the follow-up period. The enrolled patients consisted of 56 males and 23 females (mean age 45 ± 19 years, range 18–81 years). The pattern of prodromal symptoms are categorized in Table 1. Median pre-tilt syncopal and presyncopal events were 2 and 1 respectively (syncope spells: mean 2.7 ± 2.8, range 1–19 and presyncope spells: mean 2.7 ± 4, range 0–20).

Results of tilt table test

The most common type of response among patients who finished the follow-up period was vasodepressor type followed by mixed type and cardioinhibitory types (Table 2). The prevalence of positive tilt test in active or passive stage is summarized in Table 3. Pre-tilt blood pressure and heart rate were 118 ± 15.9 mm Hg and 75 ± 15 beat/min, respectively.

Table 2. Pattern of tilt-test induced vasovagal syncope.

Vasodepressor type	35 (44.3%)
Cardioinhibitory type	17 (21.5%)
Mixed type	27 (34.2%)

Table 3. Patten of positive stage of tilt table test.

Passive stage	46 (58.2%)
Active stage	33 (41.8%)

Results of follow-up period

The patients were followed up for twelve months (350 ± 16 days). Recurrence of syncope and/or presyncope occurred in 23 (29.1%) and 28 (35.4%) of patients, respectively. In total, 42 (53.2%) patients experienced at least one episode of syncope and/or presyncope during the follow-up period.

Predictors of recurrence of symptoms

Age ($p = 0.572$) and gender ($p = 0.463$) failed to predict the recurrence of syncope and/or presyncope. Diaphoresis, but not other prodromal symptoms and frequency of pre-tilt syncope and presyncope attacks were able to be used to predict recurrence of symptoms during the follow-up period (Table 4). Logistic regression analysis among patients with recurrence of syncope and/or presyncope showed diaphoresis [$p = 0.030$, Exp(B) = = 3.726, 95% CI for Exp(B): 1.139–12.194], and more pre-tilt (pre)syncope spells [$p = 0.002$, Exp(B) = = 0.718, 95% CI for Exp(B): 0.583–0.885] independently increase the risk of recurrence of syncope and/or presyncope during the follow-up period.

Discussion

Most patients who experience VVS are offered a variety of empirical pharmacological and nonpharmacological modalities. Tilt training is a well-known nonpharmacological therapy [4, 5]. Pharmacological treatment options are usually reserved for those who experience frequent syncope and/or when symptoms cause excessive lifestyle difficulties, threaten employment or result in unacceptable risk

Table 4. Predictors of recurrence of symptoms during follow-up.

Age		
Recurrence of symptoms	43 ± 20	p = 0.572
Asymptomatic during follow-up	46 ± 18	
Gender (male/female)		
Recurrence of symptoms	27/15	p = 0. 463
Asymptomatic during follow-up	26/11	
Prodromal symptoms (recurrence of symptoms/asymptomatic)		
Presence of palpitation	12/11	p = 0.910
Absence of palpitation	30/26	
Presence of nausea	19/15	p = 0.674
Absence of nausea	23/22	
Presence of diaphoresis	35/22	p = 0.018
Absence of diaphoresis	7/15	
Presence of blurred vision	26/17	p = 0.155
Absence of blurred vision	16/20	
Pre-tilt blood pressure [mm Hg]		
Recurrence of symptoms	116 ± 14.5	p = 0.113
Asymptomatic during follow-up	120 ± 17.2	
Pre-tilt heart rate [beat/min]		
Recurrence of symptoms	72 ± 13	p = 0.130
Asymptomatic during follow-up	78 ± 17	
Frequency of pre-tilt (pre)syncope spells		
Recurrence of symptoms	7.1 ± 5.5	p = 0.001
Asymptomatic during follow-up	3.3 ± 2.2	
Type of tilt table test response (vasodepressor/cardioinhibitory/mixed type)		
Recurrence of symptoms	21/6/15	p = 0.235
Asymptomatic during follow-up	14/11/12	
Positive stage of tilt table test (passive/active)		
Recurrence of symptoms	22/20	p = 0.262
Asymptomatic during follow-up	24/13	

of physical injury to the patient or others [2]. Among pharmacological agents, beta-blockers are the first drugs considered for the prevention of VVS. They are a logical choice, because elevated levels of epinephrine have been demonstrated in both spontaneous and tilt-induced faints [6–9]. Metoprolol, pindolol and atenolol have been the most frequently studied beta-adrenergic blockers in VVS [10–12]. Metoprolol was the first beta-blocker, tested in tilt-induced syncope. Asso et al. observed conversion of a positive tilt test to a negative response after parenteral administration of metoprolol [10]. Muller et al. [11] showed marked improvement in symptoms after oral metoprolol therapy in young patients with recurrent syncope. On the other hand, the Prevention of Syncope Trial (POST) showed that metoprolol was not effective in preventing VVS in the study population [13]. In this randomized, double-blind, placebo-controlled clinical trial, they demonstrated that metoprolol does not benefit patients with VVS, as a group. They were unable to demonstrate that age influenced the effect of the treatment [13]. Alegria et al. [14] also observed the apparent inefficacy of beta-blockers in a similar observational study. These mixed results and responses to beta-blockers can reveal different mechanisms underlying the interactions among decreased preload, sympathetic and parasympathetic modulation and vasodilatation. Many patients with VVS have pallor and diaphoresis, which may reflect very high circulating levels of epinephrine. In our study, patients with a history of diaphoresis had a worse response to beta-blocker therapy. Sympathetic system over-activity could be a compensatory

response in these patients, not as a primary underlying mechanism. It would be reasonable, therefore, to consider the Bezold-Jarisch paradigm a hypothesis that describes only one of many potential triggering mechanisms [15]. Greater frequency and number of syncopal and presyncopal spells in the patient's history are another independent risk factor that can predict early recurrence of syncope after the tilt test. The results of the current study confirm the findings of Sheldon's et al. study [16]. They show that patients who have fainted more are more likely to faint again. The multivariate proportional hazards analysis in Sheldon's et al. study demonstrated that the most powerful predictor of a recurrence of syncope is the logarithm of the number of preceding syncopal spells. The presence of diaphoresis and more pre-tilt syncopal and or presyncopal spells independently increased the risk of syncopal and/or presyncopal spells during the follow-up period.

Limitation of the study

The duration of the follow-up period was relatively short in our study. We were unable to analyze the circulating levels of epinephrine in patients with different prodromal symptoms. We excluded patients who had a history of VVS but had negative TTT. This exclusion criterion might have changed the results. Our study was not a randomized, controlled study, but could open the way to mechanism-targeted therapeutic trials, which may improve clinical outcomes.

Conclusions

Diaphoresis and greater frequency of spells in a patient's history are ominous predictors of symptom recurrence. Patients with a history of diaphoresis during VVS are less responsive to beta-blocker therapy. This finding might suggest another pathophysiology of the vasovagal state. Other pharmacological and/or nonpharmacological interventions may be needed in this group of patients.

Acknowledgments

The authors express their gratitude to the subjects. Expert secretarial help was provided by Roghayeh Kashefi.

The authors do not report any conflict of interest regarding this work.

References

1. Mosqueda-Garcia R, Furlan F, Tank J, Fernandez-Violante R. The elusive pathophysiology of neurally mediated syncope. Circulation, 2000; 102: 2898–2906.
2. Benditt DG, Fahy GJ, Lurie KG, Sakaguchi S, Fabian W, Samniah N. Pharmacotherapy of neurally mediated syncope. Circulation, 1999; 100: 1242–1248.
3. Madrid AH, Ortega J, Rebollo JG et al. Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a high symptomatic population: A prospective, double-blind, randomized and placebo-controlled study. J Am Coll Cardiol, 2001; 37: 554––559.
4. Gajek J, Zyśko D, Mazurek W. Efficacy of tilt training in patients with vasovagal syncope. Kardiol Pol, 2006; 64: 602–608.
5. Verheyden B, Ector H, Aubert AE, Reybrouck T. Tilt training increases the vasoconstrictor reserve in patients with neurally mediated syncope evoked by head-up tilt testing. Eur Heart J, 2008; 29: 1523–1530.
6. Chosy JJ, Graham DT. Catecholamines in vasovagal fainting. J Psychosom Res, 1965; 9: 189–194.
7. Benditt DG, Ermis C, Padanilam B, Samniah N, Sakaguchi S. Catecholamine response during haemodynamically stable upright posture in individuals with and without tilt-table induced vasovagal syncope. Europace, 2003; 5: 65–70.
8. Yamanouchi Y, Shehadeh AA, Fouad-Tarazi FM. Usefulness of plasma catecholamines during head-up tilt as a measure of sympathetic activation in vasovagal patients. Pacing Clin Electrophysiol, 1998; 21: 1539–1545.
9. Mitro P, Rybárová E, Zemberová E, Tkác I. Enhanced plasma catecholamine and cAMP response during the head-up tilt test in patients with vasovagal syncope. Wien Klin Wochenschr, 2005; 117: 353–358.
10. Asso A, Milstein S, Dunnigan A, Remole S, Benditt DG. Prognostic significance of parenteral metoprolol during head-up tilt testing. Circulation, 1991; 84 (suppl. II): II409 (abstract).
11. Muller G, Deal BJ, Strasburger JF, Woodrow Benson D. Usefulness of metoprolol for unexplained syncope and positive response to tilt testing in young persons. Am J Cardiol, 1993; 71: 592–595.
12. Nair N, Padder FA, Kutalek SP, Kantharia BK. Usefulness of pindolol for treatment of neurocardiogenic syncope. Am J Cardiol, 2004; 94: 1189–1191.
13. Sheldon R, Connolly S, Rose S et al.; for the POST Investigators. Prevention of Syncope Trial (POST). A randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. Circulation, 2006; 113: 1164–1170.
14. Alegria JR, Gersh BJ, Scott ChG, Hodge DO, Hammill SC, Shen W-K. Comparison of frequency of recurrent syncope after beta-blocker therapy versus conservative management for patients with vasovagal syncope. Am J Cardiol, 2003; 92: 82–84.
15. Fenton AM, Hammill SC, Rea RF, Low PA, Shen W-K. Vasovagal syncope. Ann Intern Med, 2000; 133: 714–725.
16. Sheldon R, Rose S, Flanagan P, Lou Koshman M, Killam S. Risk factors for syncope recurrence after a positive tilt-table test in patients with syncope. Circulation, 1996; 93: 973–981.