The Diagnostic Value of the Treadmill Exercise Test Combined with the Head Up Tilt Test for Diagnosing Vasovagal Syncope

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April 28, 2020

Abstract

Objective: Increased adrenergic tone can be a trigger of orthostatic stress of vasovagal syncope (VVS). This study aimed to explore the diagnostic value of treadmill exercise test (TET) combined with head up tilt test (HUTT) for VVS. Methods: A total of 73 patients with unexplained syncope or presyncope were enrolled. VVS was diagnosed in 57 patients according to the Calgary Score ([?]-2). Initially, all patients were subjected to the first HUTT. Then, patients with negative response in HUTT would further received TET on the next day. At last, patients who remained getting negative response in TET would be subjected to the second HUTT within 10min after TET. The symptoms of syncope, heart rate and blood pressure were recorded during the tests. Results: Syncope or presyncope occurred in 34 patients in the first HUTT. The sensitivity and specificity of HUTT for Calgary score-based VVS were 56.1% and 87.5%, respectively. Then, another 14 patients in TET and 9 patients in the second HUTT experienced syncope or presyncope during the tests. The sensitivity of TET combined with HUTT for VVS significantly increased to 94.7%, with the specificity only slightly decreasing to 81.3%. No patients required anticholinergics injection to restore vital signs during the tests. Conclusion: The combination of TET with HUTT is an effective and safe diagnostic strategy for VVS.

1. Introduction

Syncope, also known as fainting, is a transient and self-limited of loss of consciousness due to reduced blood flow to the brain. Vasovagal syncope (VVS) is one of the most common types of syncope [1]. The definitive diagnosis of VVS is based on a history of syncope, clinical manifestations, and a positive head-up tilt test (HUTT) after excluding cardiac and non-cardiac causes [2]. The HUTT is a non-invasive test for VVS, but the reproducibility and sensitivity are relatively low [3]. The sensitivity of the baseline head-up tilt test (BHUT) and nitroglycerin-stimulated head-up tilt test (NHUT) are 25% and 66%, respectively, while the specificity of the BHUT and NHUT are 86% and 99%, respectively [3]. Importantly, not all VVS patients have syncopal episodes during the HUTT. Increased adrenergic tone due to emotional stress, pain, or intensive exercise may trigger and contribute to VVS [4].

The treadmill exercise test (TET) is a common, non-invasive and cost-effective test widely used in the diagnosis of coronary atherosclerotic heart disease. It is known that vasovagal syncope may occur during a TET. As such, we hypothesized that increased adrenergic tone during exercise could be an additional trigger toward orthostatic posture and venous pooling stress. The combination of a TET and a HUTT may increase the reproducibility and sensitivity for diagnosis of VVS. Therefore, the purpose of this study was to explore the diagnostic value of TET combined with HUTT for diagnosing VVS in patients with unexplained syncope or presyncope.

2. Methods

2.1 Subjects

This study was approved by the Institutional Review Board of the Third Affiliated Hospital of Sun Yat-sen University, and also conformed to the principles of the Declaration of Helsinki. All subjects were informed about the experiments, and provided written consent before participation.

Seventy-six patients with unexplained syncope or presyncope were enrolled from September 2015 to September 2017. Patient clinical history and physical examination findings were recorded in detail, along with the results of laboratory tests such as complete blood count (CBC) and biochemical tests, and other examinations such as cardiac ultrasonography and electroencephalogram. The exclusion criteria included carotid sinus hypersensitive syndrome, sick sinus syndrome, pulmonary artery hypertension, hypertrophic obstructive cardiomyopathy, transient ischemic attack, epilepsy, brain infection, diabetes mellitus, atrial fibrillation, and contraindications for TET and HUTT. Two patients were excluded for sick sinus syndrome, and one patient was excluded for lack of a detailed clinical history.

For the remaining 73 patients, the Calgary Score was calculated based on 7 diagnostic questions regarding medical history, triggers, circumstances, and signs and symptoms of transient loss of consciousness [5]. The number, similarity, and triggers of each event were recorded. VVS was defined as syncope or presyncope occurring at least once in a patient with a Calgary syncope symptom scale of [?] -2 [5].

2.2 Experimental protocol

Patients completed a tour of the facility, and were familiarize with all of the testing procedures before beginning the experimental protocol. The protocol consisted of 3 phases. Initially, all patients received a HUTT. Patients with negative HUTT received a TET the next day. Finally, patients with a negative TET received a second HUTT within 10 minutes after the TET.

The HUTT was performed using a DT-1 HUT instrument (JUCHI Pharmaceutical Technology Co., Ltd. China) in a quiet, temperature-controlled (25-28°C) cardiovascular lab. Patients fasted for at least 4 hours, and refrained from taking interfering medications for at least 5 days prior to the testing. A BHUT was performed after 10 min of supine rest, and the table was tilted to 70° (passive tilt phase). Heart rate and blood pressure were recorded every 3 min. At the time when presyncope or syncope became apparent during the tilt-back, heart rate and blood pressure were recorded immediately. If the patient did not appear to have a positive reaction after monitoring for 45 min, the tilt bed was returned to the initial level.

Then, a NHUT was further performed as previously described [6]. Heart rate and blood pressure were recorded, 400 μg of nitroglycerin was placed under the patient's tongue, and the table was tilted to 70° within 10 s. Heart rate and blood pressure were recorded every 3 min. At the time when presyncope or syncope became apparent during tilt-back, heart rate and blood pressure were recorded immediately. If the patient did not appear to have a positive reaction after monitoring for 30 min, the tilt bed was returned to the initial position. Any symptoms of syncope, such as dizziness, nausea, feeling feverish, or visual or hearing difficulties were documented. If patients complained of visual ambiguity, partial or total blindness, or feeling faint, or they had syncope, the table was returned to the initial position immediately. The diagnostic criteria were based on the 1998 recommendations for the diagnosis of VVS using the HUTT published by China Journal of Cardiovascular Diseases editorial board [7]. Patients were classified as reflex syncope based on the Guidelines of Syncope by the European Society of Cardiology (ESC) [8].

Hemodynamic patterns were analyzed according to the modified Vasovagal Syncope International Study (VASIS) classification [9]. The classifications were: VASIS I, mixed response; VASIS IIa, cardio-inhibitory response without asystole; VASIS IIb, cardio-inhibitory response with asystole; VASIS III, vasodepressor response. The definitions of the classifications were as follows. VASIS I was defined as a decrease in heart rate $> 10\%$, minimal heart rate > 40 bpm or < 40 bpm for < 10 s with or without asystole occurring within 3 s, and a blood pressure decrease begins before a decrease in heart rate. VASIS IIa was defined as a minimal heart rate < 40 bpm for > 10 s, asystole occurring in < 3 s, and a blood pressure decrease before a heart rate decrease. VASIS IIb was defined as asystole occurring for > 3 s, and a decrease in heart rate either coincides with, or precedes a fall in blood pressure. VASIS III was defined as a decrease in heart rate to $<$ 10% of the maximal heart rate.

The standard TET was performed using the Bruce protocol on a T2100 treadmill exercise test system (GE, USA). Twelve-lead electrocardiograms were recorded during the test, including the warm-up period, exercise stage, and the recovery period. Blood pressure was measured throughout the test with a Tango blood pressure monitoring system (GE, USA), including the warm-up period, at the end of each stage, and every 3 min during the recovery period. Patients exercised up to the least their submaximal predicted heart rate for their age (submaximal predicted heart rate = 85% maximal predicted heart rate, with maximal predicted heart rate = 220 minus age). ST segment deviations were compared with the PQ isoelectric line, and were recorded with reference to the J-point along with 0.06 to 0.08 s after the inscription of the J-point [9]. Contraindications, termination criteria, and positive diagnostic criteria of the TET were in accordance with the 2002 ACC/AHA exercise test guidelines [10]. Contraindications included congenital heart disease, acute myocardial infarction within the past 6 months, unstable angina pectoris, cardiomyopathy, valvular disease, atrial fibrillation, left bundle branch block, and a cardiac pacemaker. The exercise test was halted if angina pectoris or a malignant arrhythmia occurred, blood pressure was [?] 220/110 mm Hg, ECG showed depression or elevation [?] 0.2mV in the ST segment, the heart rate reached the maximal predicted heart rate, or the patient complained of fatigue from exercising.

The diagnostic criteria for cardiovascular disease were: ST-segment depression [?] 2 mm or an elevation of [?] 1 mm, angina pectoris, ventricular tachycardia, exercise-induced hypotension (> -20 mm Hg drop in systolic blood pressure). If presyncope or syncope occurred, blood pressure was measured immediately. Two subjects recovered spontaneously. Twelve subjects were placed supine immediately after onset of presyncope or syncope. The symptoms were relieved within 1min to 10min, and the subjects' heart rate and blood pressure returned to normal.

2.3 Statistic analysis

Sensitivity and specificity were calculated to evaluate the diagnostic performance of TET combined HUTT for diagnosis of VVS based on the Calgary score. Continuous data were expressed as mean value +- standard deviation, and categorical data were presented as absolute number and percentage. Differences in continuous data were analyzed by Student's t-test, and categorical data were analyzed by Pearson's chi-square test. Values of $p < 0.05$ were considered as significance. SPSS version 18 software was used for all statistical analysis.

3. Results

A flow diagram of patient enrollment is shown in Figure 1. Sensitivity and specificity were calculated based on 57 patients with a Calgary Score [?] - 2. All patients participated in the first HUTT, and 34 patients experienced syncope or presyncope (3 in BHUT and 31 in NHUT). The 39 patients with a negative HUTT received a TET, and 14 experienced syncope or presyncope. The 25 patients with a negative TET received a second HUTT, and 9 patients experienced syncope or presyncope (2 in BHUT and 7 in NHUT). Thus, the sensitivity and specificity of the first HUTT was 56.1% (32/57) and 87.5% (14/16), respectively. The sensitivity of the first HUTT combined with the TET increased to 78.9% (45/57), without a change in the specificity of 87.5% (14/16). Finally, the combination of the first HUTT, TET, and the second HUTT demonstrated a sensitivity of 94.7% (54/57), and a specificity of 81.3% (13/16).

The mean age of patients who had a positive response in the first HUTT was 48.1 +-5.6 years, and 52.9% of them were male. Compared with patients who had a negative response in the first HUTT, patients with a positive response were older, had a greater number of episodes, were more likely to develop syncope during urination or changing position, and a greater number experienced loss of consciousness. However, more patients who have negative response induced by extensive exercise and suffered from abdominal pain, facially pallor and sweating in the syncope attack. Other baseline characteristics were not significantly different between the 2 groups ($p > 0.05$).

Compared to patients with a negative response in the HUTT combined with the TET, patients with positive response had a longer history of syncope, were more likely to have an episode with standing for a long time or walking, and were more likely to experience sweating and facial pallor. Other characteristics and symptoms

were not different between the 2 groups ($p > 0.05$). Patient characteristics are summarized in Table 1.

The characteristics of TET positive and negative patients are shown in Table 2. The 14 patients who had a positive TET had the following symptoms at recovery: fatigue, dizziness, sweating, graying of vision, and fatigue at recovery. Compared to patients with a negative TET, those with a positive TET had a greater maximal predictive heart rate, maximal heart rate, percent of maximal predictive heart rate, and exercise tolerance. Other exercise data were not different between positive and negative TET patients. However, the mean age of the positive patients was less than that of the negative patients. In addition, the systolic and diastolic blood pressure in the recovery phase were greater in positive patients than in negative patients. Of the patients with a positive TET, 5 became unconscious, 4 exhibited nausea, and one patient experienced vomiting. Presyncope or syncope occurred between 0:40 and 5:23 min during recovery, with duration of 2 to 10 min. The most common hemodynamic pattern was cardio-inhibitory type (VASIS II, 42.9%, 6 patients). During recovery, the onset of bradycardia was without hypotension in 6 patients, and the heart rate decreased more than 55 bpm (mean 78 +- 11.5 bpm). In 2 patients, the electrocardiogram showed sinus arrest and an escape rhythm (1 atrial escape rhythm and 1 junctional escape rhythm). Four patients had a mixed response (VASIS I, 35.7%). Their heart rate dropped to 50 bpm, and in 1 patient the electrocardiogram showed a junctional escape rhythm. Three patients had a vasodepressor type response (VASIS III, 21.4%). Their blood pressure (especially systolic pressure) decreased to $< 1/3$ of the average blood pressure after exercising.

Nine patients who received a second HUTT after a negative TET had a positive result (2 in BHUT and 7 in NHUT). In all 9 patient symptoms were relieved when they were returned to the supine position, and heart rate and blood pressure became normal within 10 min after lying down. The maximal heart rate, the percentage of maximal predictive heart rate, and exercise tolerance were all higher in the positive group than in the negative group. Patients who had a positive second HUTT had a longer history of syncope, were more likely to have an episode with standing for a long time or walking, and were more likely to experience sweating and facial pallor. These results indicate that the combination of TET and HUTT detected patients with adrenergic excitation, and exhibited more symptoms of sympathetic excitation.

4. Discussion

The results of this study suggest that a combination of TET and HUTT is more sensitive for detecting VVS than HUTT alone. Additionally, the combination of TET and HUTT can help rule out cardiogenic syncope and exercise-associated serious arrhythmias. Furthermore, patients with a positive test can recover spontaneously after lying down without anticholinergic therapy. Thus, the combination TET and HUTT is a sensitive and safe method for diagnosing VVS, and thus is worthy of clinical application.

VVS is a common disease of the autonomic nervous system, and can markedly decrease quality of life. VVS is triggered by increased adrenergic tone, which can occur due to pain, emotional distress, urination, and prolonged standing [12]. A loss of balance between the sympathetic and parasympathetic nerves causes a decrease of peripheral vascular resistance and inhibition of the heart [13]. The aim of provocative tests is to reproduce syncope or presyncope through stimulating the sympathetic nerves. The HUTT is a common test used to diagnose VVS, and is recommended by guidelines [14]. However, positive NHUT results range from 51% to 61.8% [15-17]. Exercise-induced VVS has been reported frequently [18]. The mechanism of exercise-induced VSS includes a parasympathetic reflex to catecholamine release and hypotension due to post-exercise peripheral vasodilation and decreased venous return. In one study, 3.1% of all asymptomatic volunteers were found to be hypotensive after exercise [19]. In another study, 22% syncope events occurred after exercise [20]. VVS can be provoked by increased sympathetic nerve stimulation, such as during strenuous exercise, and TET-induced VVS has been reported in normal heart patients [21]. The modified treadmill test has been reported to be a useful tool to diagnosis exercise-related syncope [22]. Therefore, based on the aforementioned findings we hypothesized that a combination of the TET and HUTT can improve the sensitivity of diagnosing VVS.

The results of this study showed that a greater number of younger patients had positive response to TET

combined with HUTT than HUTT alone. A study showed that the incidence of hypotension after exercise was 3.1% in healthy subjects < 55 years old, but only 0.3% in those older than 55 years [19]. In our study, patients with positive test results had a greater maximal predictive heart rate, maximal heart rate, and percent of maximal predictive heart rate as compared to those with negative results. This suggests that greater excitability of the sympathetic nervous system is associated with a higher rate of VSS.

In current study, we used the treadmill test to stress the cardiovascular system to a maximal age-predicted heart rate in order to increase the sensitivity of diagnosing syncope. The mean exercise tolerance is 13.15 +- 1.66 metabolic equivalents (METS). Reasons to stop the TET are fatigue or reaching the maximal predicted heart rate. Then test is then stopped when the goal is reached. The combination of TET with HUTT had a markedly high sensitivity of 94.7% for diagnosing VVS. On the other hand, the TET can detect coronary artery disease and arrhythmias, and thus exclude cardiogenic syncope. Doi et al. raised the concept that the TET is a useful diagnostic tool to detect exercise-related VVS, but is not useful for exercise-unrelated VVS [22]. The sensitivity and specificity for detecting exercise-related VVS are 78% and 95%, respectively. However, the sensitivity for detecting exercise-unrelated VVS is only 19%. The sensitivity of HUTT is 84%m so we combined TET with HUTT to resolve the problem of the low sensitivity for diagnosing exercise-unrelated VVS. In our study, only 3 patients developed syncope during the BHUT. Sublingual nitroglycerin was administered for the NHUT, as described by Raviels et al. [16], and sublingual nitroglycerin is more convenient and practical than isoproterenol. Nitroglycerin enhances venous pooling and stimulates adrenalin secretion, and thus results in a higher positive provocation rate [23]. The sensitivity of HUTT, including BHUT and NHUT, was 46.5%. Combined with TET, however, the sensitivity was increased to 94.7%. Taken together, these results indicate that TET combined with HUTT is a safe and simple way to diagnose VVS, and is well-tolerated by patients.

Both the HUTT and the TET are imperfect tools with no gold-standard. Based on the European Society of Cardiology guidelines for the use of diagnostic questionnaires for diagnosing syncope, we used the Calgary syncope symptom score as the reference standard in this study. The sensitivity and specificity of the Calgary score are good for diagnosis, but the specificity is lower when the history is undefined.

An important part of the TET is that patients must cease to exercise when they reach their maximal predicted heart rate or fatigue occurs. We monitored blood pressure and ECG results during the exercise and recovery periods, and our data showed that all of the patients demonstrated presyncope or syncope during the first 0-3 min of the recovery period, but not during the exercise period. To our best knowledge, this is the first study to examine using the TET combined with the HUTT for diagnosing VVS. The combined testing should be administered by a doctor and a nurse who were capable of managing syncope and complications, and cardiopulmonary resuscitation equipment should be immediately available [21].

Limitations of this study

A major limitation of this study is the small number of patients. We used the Calgary score as the reference standard for diagnosis of VVS; however, this is controversial. In addition, performing the combination of a TET and the HUTT is complicated and time consuming, and many not be useful in clinical practice. A simplification in which a TET is performed, and then a HUTT is performed within 10 min after the TET may also increase the diagnosis rate of VVS, and would be simpler and less time-consuming to perform.

Conclusion

Syncope induced by exercising can be stimulated by the TET. The combination of the TET and the HUTT is a safe a sensitive method of diagnosing VVS. Based on the results of this study, further research of the combined use of the 2 tests is warranted.

Acknowledgments

Research Funding – Supported in part by grants (Clinical and Translational Science Award R01 HL102387, P01 HL56693, and UL1 TR000445

(Clinical and Translational Science Award)

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