

Tilt Training for Recurrent Neurocardiogenic Syncope

Effectiveness, Patient Compliance, and Scheduling the Frequency of Training Sessions

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SUMMARY

Unsatisfactory results obtained with medical therapy and dual-chamber pacing for prevention of recurrent neurocardiogenic syncope necessitated the development of new treatment modalities. Tilt-training, a novel treatment for recurrent neurocardiogenic syncope based on exercise sessions with prolonged upright posture (either on a tilt-table or standing on foot against a wall), was shown to be effective in preventing the recurrence of neurocardiogenic syncope. The purpose of this study was to demonstrate the long-term beneficial effects of a transient tilt training program lasting 2 months.

Thirty-two patients with recurrent neurocardiogenic syncope (mean number of syncope episodes in the last 6 months was 3.4 ± 2.3) constituted the study group. All of the patients were tilt test positive. The patients were taught a tilt training program with 2 phases (in-hospital training with repeated tilt procedures until 3 consecutive negative results were obtained and home exercises with standing against a wall) and home exercises lasted a maximum of 2 months. After this training program, the patients received no treatment and were followed for the recurrence of syncope. At the end of the follow-up period (376 ± 45 days), 81% of the patients were free of recurrent syncope.

This study revealed that similar successful results can also be obtained with a transient tilt training program as a first line treatment strategy. Less interference with the daily activities of the patients is the major advantage of this strategy. The ease of performance and high effectiveness rate will most likely result in more frequent utilization of this treatment modality. (Jpn Heart J 2004; 45: 833-843)

Key words: Recurrent neurocardiogenic syncope, Tilt training program

RECURRENT neurocardiogenic syncope, which is defined as a sudden, transient loss of consciousness due to neurally-mediated hypotension and bradycar-

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dia, annually accounts for about 3% of emergency department visits.¹⁾ Although neurocardiogenic syncope is not associated with an increased rate of mortality, quality of life deteriorates in conjunction with the frequency of recurrences. Functional impairment in recurrent neurocardiogenic syncope is thought to be similar to chronic illnesses such as rheumatoid arthritis, low back pain, and psychiatric disorders.^{2,3)}

Various forms of medical treatment have been proposed for recurrent neurocardiogenic syncope.⁴⁾ In general, while the results of medical treatment have been satisfactory in uncontrolled trials or in short-term controlled trials, with few exceptions, several long-term placebo-controlled prospective trials have been unable to show a benefit of the active drug over placebo.⁵⁾ Dual-chamber pacing with a rate drop response seemed to be effective in reducing the episodes of syncope but this treatment modality was found to be less effective on the occurrence of presyncope.^{6,7)} Unsatisfactory results obtained with medical therapy and dual-chamber pacing enforced the development of new treatment modalities. Tilt-training, a novel treatment for recurrent neurocardiogenic syncope based on exercise sessions with prolonged upright posture (either on a tilt-table or standing on foot against a wall), was shown to be effective in preventing the recurrence of neurocardiogenic syncope in 2 recent studies.^{8,9)} Based on these reports, the "European Society of Cardiology Task Force Report on Syncope, 2001" recommended this modality for the treatment of vasovagal syncope with class II indication.⁵⁾

The purpose of this study was to demonstrate the long-term beneficial effects of a 2 month transient tilt training program.

METHODS

Study group: Thirty-two consecutive patients (14 males, 18 females; age: 37 ± 12 years) with recurrent neurocardiogenic syncope (all of the patients had at least 2 syncope episodes in the last 6 months) and a positive nitrate-potentiated head-up tilt test constituted the study group. The mean number of syncope episodes in the last 6 months (before the tilt training program) was 3.4 ± 2.3 . None of the patients had been evaluated for syncope before, hence no patients received any treatment for neurocardiogenic syncope. All patients suffered from recurrent syncope (at least 2 episodes in the last 6 months) which was proven to be neurocardiogenic in origin by at least one positive nitrate-potentiated head-up tilt test. Diagnostic investigations, in addition to the head-up tilt test, included a detailed medical history from the patient, a detailed history from the eye witnesses of the syncope episodes, cardiovascular and neurological examinations, electrocardiograms (ECG), echocardiograms, and 24 hour continuous rhythm monitoring.

Patients with any abnormal findings which might be associated with other syncope etiologies were excluded from the study. Patients with suspected epilepsy and patients with structural heart disease (valvular, pericardial, myocardial diseases, etc.), coronary artery disease, comorbid conditions such as hypertension, and diabetes mellitus were also excluded. These diseases and/or comorbid conditions were ruled out by complete examination and relevant laboratory investigations including exercise ECG, echocardiograms, 24-hour Holter monitoring, biochemical tests, electroencephalograms, computerized tomographic scans, and magnetic resonance imaging.

Diagnostic head-up tilt test: No intravenous cannulation was performed in order to lessen the rate of false positive test results.^{10,11)} Resting phase in the recumbent position constituted a period of at least 5 minutes. At the end of the resting phase, the patients were tilted to a standard angle of 70 degrees for a period of 30 minutes. Time recording was started when the patients had assumed the upright position. During the procedure, an electrocardiogram was continuously monitored. Heart rate and blood pressure (noninvasively with a sphygmomanometer) were measured and recorded in the recumbent position, at the end of the resting period, 3 minutes after assuming the upright position, and every 5 minutes throughout the tilt test. If syncope developed, the tilt test was considered to be positive in the passive phase and the patient was immediately lowered to the supine position. Blood pressure and heart rate were recorded again as soon as the patient assumed the supine position. If no symptoms developed during this 30 minutes of passive tilting, the patients were lowered and a dose of 2.5 mg isosorbide dinitrate was administered sublingually. After 5 minutes, the patients were tilted to 70 degrees for another 15 minutes. If syncope occurred in this period, the test was considered to be positive in the provocation phase. The test was negative if no symptoms occurred during the passive and provocation phases. The terminology of Sutton was adopted for the neurocardiogenic syncope classification.¹²⁾ Syncope was further defined as the vasodepressor type: when there was a fall in arterial blood pressure, the heart rate remaining more than 60 beats/minute; cardioinhibitory type: when at the time of syncope, there was an asystole for 3 or more seconds; and mixed type: when there was a decrease in heart rate and blood pressure without asystole.

This head-up tilt test protocol was compatible with the class I recommendations of the "European Society of Cardiology Task Force Report on Syncope, 2001".⁵⁾

Tilt training: All patients with a positive head-up tilt test were referred to the tilt training program after a detailed explanation of the study (pathophysiology of neurocardiogenic syncope, aim of the program, etc.). Written consent was requested for complete compliance to the program. The program was mainly

composed of 3 phases: in-hospital tilt training, tilt training at home, and a follow-up period during which no exercises or other treatment modalities were performed.

In-hospital tilt training program: For the in-hospital tilt training phase, the same procedure used for the diagnostic head-up tilt test was performed daily (all sessions were performed on consecutive days) until the patients were without syncope in 3 consecutive sessions. The main objective of the in-hospital tilt training phase was to observe the acquired orthostatic tolerance of the patients for a safer home exercise period. Patients who could complete the in-hospital phase were referred to the home tilt training program. Patients who could not achieve 3 consecutive sessions without syncope were considered to be unresponsive to the in-hospital tilt training program (maximal number of in-hospital sessions was limited to 10 procedures). All patients were given an exercise schedule and a diary for recording the events that happened at home.

Tilt training program at home: Daily tilt training at home constituted 2 sessions of standing against a wall for a period of 15 minutes. The patients were instructed to stand with their feet 15 cm away from the wall and lean with the upper back against the wall without moving. This exercise was organized to be performed in a safe place (without risk of injury) with the attendance of a family member.

The patients continued this program for 1 month. During this period, the patients were encouraged to maintain the compliance with the program by weekly phone calls. At the end of the first month, all patients were called back to hospital for a nitrate-potentiated control head-up tilt test. After the control tests at one month, patients with a negative control tilt test were instructed to perform the home training program on alternate days. The tilt training program was halted in patients with a positive control tilt test. After 15 days, the tilt training program was further decreased to an exercise load of two days a week. After a period of 15 days with this program, a second nitrate-potentiated control tilt test was performed (this was the end of the home training phase).

Follow-up period: At the end of the 2 month home exercise program, the patients were instructed to stop the home exercises. No medications having possible beneficial effects on neurocardiogenic syncope were prescribed. The patients were followed for 376 ± 45 days with monthly phone calls and bimonthly office visits.

RESULTS

Diagnostic tilt test results: Diagnostic tilt tests were positive in the passive phase in 6 patients, and in the provocation phase in 26 patients. The diagnostic tilt tests were positive after a duration of 19.2 ± 9.5 minutes in the passive phase (6 patients), and the tests were positive 6.9 ± 2.9 minutes after provocation (26

patients). The syncope was the cardioinhibitory type in 5 cases, mixed type in 20 cases, and vasodepressor type in 7 cases. The most dramatic tilt response was observed in a patient with cardioinhibitory type syncope who was asystolic for a period of 21 seconds. This patient experienced myoclonic jerks in her extremities during the asystole period. The duration of pause (asystole) in the cardioinhibitory group ranged between 3 and 21 seconds (mean: 9.6 ± 7). Asystole was due to sinus arrest in all cases except one patient who developed junctional rhythm with a rate of 35 beats/minute before the occurrence of a pause lasting for 4 seconds. After assuming the recumbent position, all patients recovered spontaneously and returned to a stable sinus rhythm in about 20 seconds. No patient needed atropine for the resolution of bradycardia.

Tilt training results: Including diagnostic tests, training sessions, and control tests during the follow-up, a total of 220 in-hospital tilt table procedures were performed in 32 patients. In 20 patients, there was no syncope in the first session of the in-hospital tilt training procedure. In the remaining 12 patients, 7 patients had no syncope at the second training session. Finally, 2 out of 5 remaining patients achieved their first negative result in the third in-hospital session. Three other patients (9.3%) could not achieve any three consecutive results even after 8 repetitive sessions for each. These patients were considered to be intolerant to repeated orthostatic stress and they were thought to be unresponsive to the in-hospital tilt training program. The tilt training program was halted in these patients in order to prevent any possible physical injuries in case of syncope during home exercises. In the whole study group, a mean of 1.36 ± 0.61 training sessions was needed to achieve the first negative result. In 6 out of 29 patients who could achieve a first negative result, positivity resumed after 1 or 2 sessions without syncope. However, three consecutive negative results could be achieved in these patients with additional in-hospital training procedures.

Twenty-nine patients (90.6%) who could achieve 3 consecutive negative procedures (ie, patients with a successful in-hospital program) were referred to the home training program. These 29 patients were followed by weekly telephone calls for any problem associated with the exercises and for the program compliance for 1 month. Six patients wrote in their diaries that the tilt training program at home was impractical and interfered with their daily activities and that they skipped some exercise sessions (the frequency of skipped exercise sessions was no more than 2 sessions a week). During this one month home training, only one out of 29 patients experienced an episode of spontaneous syncope at a time other than exercise sessions. This patient was seen in the emergency department after the episode of syncope and no pathological signs were found that could be associated with other etiologies. The syncope episode was not typical for neurocardiogenic syncope and had occurred after an emotional reaction. For this reason

this episode was not considered to be a spontaneous neurocardiogenic syncope. This patient was found to be maintaining the tilt test negativity in the control head up tilt test at the end of the first month. Four patients recorded some complaints less severe than mild dizziness during some of the training exercises in their diaries.

All of the 29 patients referred to the home training program were controlled with a tilt test at the end of the first month. Tilt tests were positive in 5 patients (17%) and negative in the remaining 24 (83%). The home exercise program was halted in these 5 control tilt test positive patients and the remaining 24 patients were instructed to perform home exercises on alternate days for 15 days and 2 days a week for the following 15 days. Maintenance of negativity in the second control tilt test (after a period of 15 days with home exercise on alternate days and a period of 15 days with home exercises 2 days a week) was present in 15 patients (9 out of 24 patients who were tilt negative at the end of the first month were tilt test positive at the end of the second month). The overall laboratory success rate for active tilt training at the end of 2 months (success rate considered with control tilt test at the end of 2 months) was 51% (15 out of 29) and the clinical success rate (clinical well being and absence of recurrent neurocardiogenic syncope) was 100%.

Follow-up period: All of the patients ($n = 32$), including the 3 patients who were considered to be unresponsive to the in-hospital tilt training program, were followed for a period of 376 ± 45 days. Twenty-six patients were free of spontaneous syncope (81%). One of these 26 patients had frequent near-syncope attacks and the remaining ones were completely asymptomatic. Six patients experienced recurrence of spontaneous neurocardiogenic syncope. The mean number of recurrent syncope episodes during the entire follow-up period was 7.7 ± 8.6 . Only 1 of 3 patients considered to be unresponsive to the in-hospital tilt training program (these patients were not able to achieve 3 consecutive negative in-hospital tilt procedures and were not instructed to perform home exercises) had recurrent syncope. The other 2 patients were free of spontaneous syncope; however, one had frequent near syncope attacks. This patient had stated that after repeated tilt procedures she was able to recognize prodromal symptoms of syncope effectively and change her posture in order to prevent frank syncope.

One of 6 patients with recurrent spontaneous syncope had a positive result in the control tilt test at the end of 1 month. The other 4 patients who were tilt positive at the end of 1 month were free of syncope at the follow-up. One patient with a positive control tilt test result at the end of the second month had recurrent syncope. The other 3 patients with recurrent neurocardiogenic syncope were tilt test negative at the end of the first and second months. The follow-up results are summarized in the Figure.

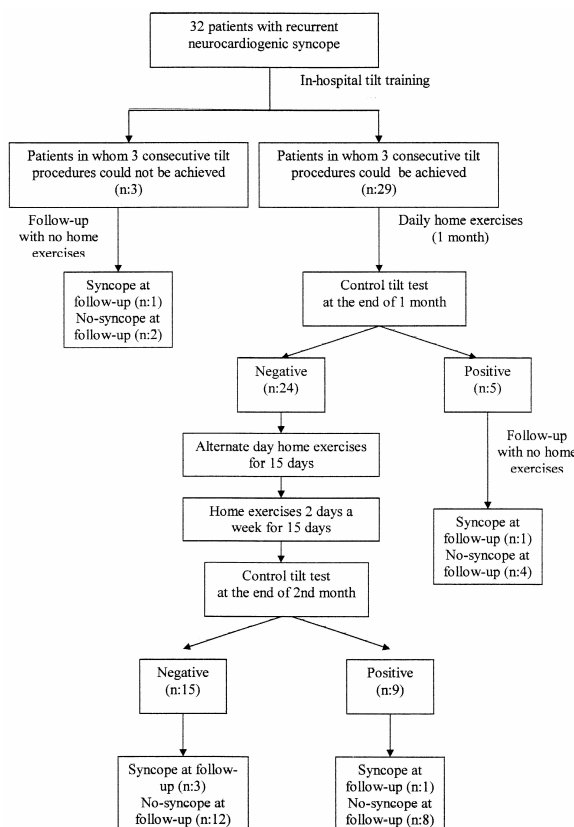


Figure. Summary of the method and results of the tilt training program.

DISCUSSION

The first authors to report the useful effects of repeat tilt tests on the recurrence rate of neurocardiogenic syncope were Morillo, *et al*¹³⁾ and Sheldon, *et al*.¹⁴⁾ In their disopyramide study, Morillo, *et al* observed that the incidence of positive stress test results decreased over time. Sheldon and coworkers also reported a reduced risk of syncope recurrence after a positive tilt test, and suggested that the tilt test might be considered not only as a diagnostic test but also as a clinical intervention as well.¹⁴⁾

There are many reports in the literature regarding the reproducibility of the tilt test.¹⁵⁻¹⁹⁾ In the majority of these reports, the reproducibility of a negative test was high and ranged between 85% and 94%, but a relatively lower rate of reproducibility was observed with a positive test (31-92%). It may be argued that the relatively lower probability of a second positive test may not be the lack of tilt test

reproducibility. In contrast, this phenomenon may be related to the training effect that is achieved even with one session of a diagnostic tilt test. After these pioneering observations regarding the possible training effect of repeated tilt tests, studies by Girolamo, *et al*⁹⁾ and Reybrouck, *et al*²⁰⁾ revealed that the training effect of continuing exposure to orthostatic stress (tilt training) effectively decreases the probability of syncope recurrence. These two studies consisted of patients with frequent syncope recurrence and some of the patients had also had malignant neurocardiogenic syncope resistant to different medical treatments. It was demonstrated that the tilt training method was quite efficient in preventing the syncope episodes even in these select groups of patients. In the study of Reybrouck, *et al*, daily tilt training resulted in a superior outcome during a follow-up period of 15 ± 7.3 months, with only 1 patient (2.4%) experiencing recurrent syncope and 4 (9.5%) patients episodes of presyncope without syncope. In their study, the remaining 36 patients (86%) were asymptomatic during the follow-up period. The study reported a compliance rate of 70%. Similarly, Girolamo, *et al* reported 0% recurrence of syncope in patients with good compliance to the program throughout an 18 month follow-up period. In their study, control tilt tests at one month were all negative in the training group, except in 1 patient (4.2%), and the control tilt test results were in concordance with their clinical status. Patient compliance at the end of 1 month was 100% in this study group.

These two studies evaluated the effectiveness of continued tilt training programs (continued home exercises) for preventing the recurrence of neurocardiogenic syncope. Patient compliance is essential for a continuous tilt training program and it may be difficult to achieve a high rate of patient compliance in every patient group. The social status of the patients and the symptomatic status of the patients before the training program may play a critical role in the maintenance of compliance. Girolamo and colleagues claim that a high therapeutic success rate for this modality (95.8%) maintains the clinical well-being of the patients, which in turn encourages the patient to continue the program. It should be kept in mind that the patients in these previous studies were severely symptomatic patients with resistance to various drug therapies. Maintenance of a syncope free life with this treatment modality in these select groups of patients may be the primary factor determining program compliance.

It may be argued that patients with a better symptomatic status before the program and patients who were not treated with any medication before may not be as eager as those in the previous studies to continue the program. The diary notes of our 6 patients in the first month confirms this argument as our patients stated that the tilt training program interfered with their daily activities and they were not eager to continue this program, even if requested, for more 2 months. A tilt training program with lower exercise loads or programs for a transient period

of time may be very useful in patients with poor compliance or in patients with busy daily activities. However, it is not clear whether or not a transient period of home exercises may be effective in the prevention of syncope recurrence in light of these previous trials. This study investigated the effectiveness of a tilt training program lasting for only 2 months at preventing recurrent syncope in the long-term (a mean period of more than a year). It has been found that at the end of the follow-up period the syncope recurrence rate was only 18%. In contrast, the rate of recurrent syncope was 56.5% in the control group in the Girolamo study.⁹⁾ Although our study reveals a lower success rate for preventing syncope prevention in comparison with the 2 previous studies, the effectiveness may be considered to be surprisingly high, most likely because of the transient methodology of tilt training performed in the current study.

An important issue at this point may be the mechanism of syncope recurrence prevention of a tilt training program. It has been recently reported by Takase and colleagues that increases in beta-endorphin and epinephrine levels during a head-up tilt test in patients with neurocardiogenic syncope may be pathophysiologically related with the occurrence of neurocardiogenic syncope.²¹⁾ These investigators revealed that patients with positive tilt test results have higher levels of beta-endorphin and epinephrine during head-up tilt than patients with negative tilt test results. Tilt training programs may alter the release pattern of endogenous opioids and epinephrine. This should be investigated in future studies.

An important issue at this point may be the mechanism of syncope recurrence prevention of a tilt training program lasting for 2 months. We believe that the primary mechanism in the prevention of syncope to transient tilt training may be related to patient education achieved with this program. Repeated tilt procedures performed in the hospital and home exercises may play a critical role in easy and early recognition of prodromal symptoms. This may be important in the prevention of syncope attacks in real life. Carvelatti and colleagues confirmed our argument regarding patient education.²²⁾ They have reported that patient education regarding the mechanism, prognosis, and symptomatology of neurocardiogenic syncope by a group of dedicated nurses and physicians effectively decreases the rate of syncope recurrence.

The present study has revealed that the syncope recurrence rate was not related to the control tilt test results at the end of the first and second months of home exercise. Surprisingly, failure to complete the in-hospital training program did not appear to be a great handicap since 2 of these 3 patients who failed were free of syncope in the follow-up. This can only be explained by the hypothesis of patient education rather than a real acquired orthostatic tolerance achieved with the tilt training program.

The patient groups in the two previous studies consisted mainly of patients with malignant neurocardiogenic syncope that was refractory to medical treatment. On the contrary, our patient group was composed of patients with no previous therapy or diagnostic evaluation. It is possible that a transient tilt training program for a group of patients with malignant neurocardiogenic syncope or for patients resistant to medical therapy may not be as effective.

In conclusion, continuous tilt training is an acceptable treatment modality for neurocardiogenic syncope in motivated patients who are eager to comply with the program. This study revealed that similar successful results can also be obtained with a transient tilt training program as a first line treatment strategy. Less interference with the daily activities of the patients is the major advantage of this strategy. The ease of performance and high effectiveness rate will probably result in more frequent utilization of this treatment modality. The major drawback of this study is the lack of a control group. Future studies with control groups investigating the effectiveness of transient tilt training in patients with various types of symptomatic status should help answer many questions in this field.

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