Does a Role Exist for Tilting-Guided Therapy in the Management of Neurocardiogenic Syncope?

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Purpose - Upright tilt-table testing (UTT) is a useful method for identifying patients with neurocardiogenic syncope, but its role in the evaluation of therapeutic efficacy is controversial. The aim of this study was to determine the correlation between negative UTT after therapy introduction (acute efficacy) and symptom recurrence during follow-up (chronic efficacy).

Methods - We studied 56 severely symptomatic patients (age 27±19 years) with recurrent (7±12 episodes) neurocardiogenic syncope (positive UTT). Once empirical pharmacological therapy was initiated, all patients underwent another UTT (therapeutic evaluation test - TET). Therapy was not modified after TET results. The probability of symptom recurrence was analyzed with the Kaplan-Meier method and compared by log-rank test in patients with negative and positive TET.

Results - Negative UTT after therapy was related to a significantly lower probability of recurrence during follow-up (4.9 versus 52.4% in 12 months, P<0.0001).

Conclusion - A good correlation exists between acute and long-term efficacy of pharmacological therapy for neurocardiogenic syncope, so that serial UTT may be considered a good method for identifying an effective therapeutic strategy.

Keywords: tilt-table test, therapy, neurocardiogenic syncope

Clinical features of neurocardiogenic syncope are highly variable. A relevant aspect of this disorder is that syncope may be sporadic with long asymptomatic periods between episodes. Multiple recurrences are not uncommon, however, they have a great impact on lifestyle, and social and professional life.

Management of neurocardiogenic syncope can be accomplished both pharmacologically and nonpharmacologically. A specific treatment is usually recommended for patients with frequent recurrences. In case of a short prodromic period, high-risk professional activities or physical injury, treatment is recommended even after an isolated event. One of the main problems in managing neurocardiogenic syncope is establishing the real efficacy of medical treatment. Although the usefulness of upright tilt-table testing (UTT) in evaluating syncope is well established, its value as a predictor of therapeutic efficacy is still controversial.

Some authors consider a negative UTT after drug therapy as a mark of the acute efficacy of treatment. However, clinical studies assessing short- and long-term outcome in these patients are limited and have conflicting results. Studies evaluating immediate and long-term reproducibility of the test have demonstrated that concordance between 2 positive tests is lower than between 2 negative tests.

The objective of this study was to assess the correlation between UTT results performed after the introduction of therapy (acute efficacy) and symptom recurrence during follow-up (chronic efficacy) in patients with recurrent neurocardiogenic syncope.

Methods

From August 1991 to November 1997, we prospectively studied 56 patients diagnosed with recurrent neurocardiogenic syncope (positive UTT). The criteria for inclusion in the study was a clinical history of 2 or more episodes of syncope or 1 syncope plus 3 or more near-syncope episodes during the year prior to UTT. Near-syncope was defined as the imminent sensation of loss of consciousness and loss of postural tone.
The physical examination and noninvasive tests, such as 12-lead electrocardiography, 24-hour ambulatory Holter monitoring, and echocardiography disclosed negative findings.

Patients’ mean age was 27±19 years (ranging from 6 to 70 years) and 30 were female. Time elapsed from the first episode of syncope and UTT was 32±45 months (ranging from 1 week to 22 years, median 12 months). Mean number of total episodes of syncope was 7±12 (median of 4 episodes) with a mean of 4±3 occurring during the year prior to admission (median of 3 episodes).

Upright tilt-table testing protocol - UTT - was performed in the morning, with patients in a fasting state. Patients were placed into a supine position on a tilt-table (Carci Industry, SP, Brazil). Blood pressure (BP) was continuously and noninvasively measured with a digital monitor (Finapress 2300 - Ohmeda) and a continuous electrocardiogram (ECG) was acquired by an ECG system (Hewlett-Packard) connected to the BP monitor. After the patients had been lying in a supine position for 20 minutes, they were tilted upright at a 60-degree angle and observed for 40 minutes or until syncope or near-syncope occurred. In that case, the table was replaced in the supine position (or Trendelenburg, if recovery was not achieved). No other intervention was necessary to control symptoms.

According to BP and HR changes, positive UTT responses were defined as: (1) vasodepressor response: decrease in systolic blood pressure of at least 30mmHg without significant changes in heart rate; (2) cardioinhibitory response: sudden asystolic periods of more than 3 seconds associated with hypotension; (3) mixed response: decrease in systolic blood pressure of 30mmHg or more, associated with bradycardia.

Study design: all patients were empirically and in a nonrandomized way treated with b-blocker (propranolol -1 mg/kg daily) or fludrocortisone (Florinef - 1 µg/kg daily, up to a maximum of 200 µg daily for adults).

Between 15 days and 1 month after drug therapy introduction, another UTT was performed (therapeutic evaluation test – TET). In case of recurrence, patients were asked to return for clinical evaluation without delay. Drugs were not modified according to the result of the TET. This was only done in case of recurrence of symptoms or drug intolerance, when therapy was empirically modified by increasing the dosage, replacing it, or adding another drug, such as disopyramide (2000 to 400mg daily), theophylline (0.2 or 0.4g daily) or sertraline hydrochloride (50 mg daily) to the initially assigned therapy. After therapy modification, 26 tests were performed again (TET2 and TET3), and their data were included for another analysis of recurrence. In those patients whose therapy was modified but no other TET performed, the event occurring before drug therapy modification was regarded as the final one (Fig. 1).

The mean follow-up period was 19±15 months (median 17 months).

Data analysis: in patients with a negative TET and in those with a persistently positive test, the correlation between drug efficacy and negative UTT was assessed by analysis of probability of recurrence using the Kaplan-Meier actuarial method.

Results were compared with the log-rank test. A P value <0.05 was considered statistically significant.

Results

Negative UTTs were observed in 37 (66%) patients after the initial therapy (TET1), whereas the test remained positive in 19 (34%).

When all 82 TET results were collectively analyzed (TET1, TET2, TET3), 43 (52%) were negative and 31 (38%) remained positive. In 8 (10%) patients, postural orthostatic tachycardia syndrome (POTS - defined as an increase in heart rate of more than 30 bpm in the upright position when compared with baseline values, associated with symptoms of orthostatic intolerance) was observed.

The correlation between symptom recurrence and UTT results obtained by Kaplan-Meier actuarial analysis is shown in Figure 2. Table I demonstrates that after a 6-month follow-up, the probability of symptom recurrence was 2% for patients with a negative TET and 36% for those with positive tests. After a 1-year follow-up, 52% of the patients showing positive tests experienced a recurrence of symptoms, whereas 95% of the negative UTT patients were asymptomatic. All patients with POTS had a recurrence of symptoms.

Only 13 patients (16%) experienced syncope spells (1.6±0.93 episodes, median of 1 episode) after starting drug therapy. Most patients that remained symptomatic experienced near-syncope.

Discussion

The present study consists of severely symptomatic patients with neurocardiogenic syncope who received specific drug therapy. Although this disorder is generally associated with a very good prognosis, all patients included in this study had many recurrences and severe social and psychological limitations affecting their quality of life and warranting specific pharmacological therapy.

We have demonstrated a significantly lower probability of recurrence related to a negative UTT. These data suggest that in patients with severely symptomatic neurocardiogenic syncope, UTT may be an acceptable method for assessing drug therapy efficacy during a short-term follow-up.

Cox et al25, studying the correlation between treatment efficacy and UTT results in patients with neurocardiogenic syncope, observed a recurrence of symptoms in 10% of the patients with tilting-guided therapy and in 23% of empirically treated patients. When the presumably effective therapy (negative UTT) was discontinued, 42% of the patients had syncope recurrences (P<0.0009). Although the authors have not mentioned the time elapsed from the onset of drug therapy to the recurrence of symptoms, their results also suggest that negative UTT may be considered a predictor of treatment efficacy.

Natale et al26 investigated potential variables related
Fig. 1 - Study design.
to efficacy of treatment with β-blocking agents in patients with neurocardiogenic syncope. They concluded that negative UTT after esmolol was a good predictor of oral metoprolol efficacy (P < 0.0001). In another study, to assess the efficacy of different drugs for neurocardiogenic syncope, Natale et al. observed that 6% of the patients who received tilting-guided therapy experienced a recurrence. Thirty-six percent of the patients in the empirical therapy group had recurrences, whereas 67% of the patients without treatment persisted over time, independently of the use of placebo or tilting-guided therapy. They reported that, although a marked difference occurred in the frequency of negative tests between the placebo group and those assigned to medical therapy, clinical behavior during the follow-up was similar in both groups. The explanation for that is the well-known placebo effect observed in patients with neurocardiogenic syncope, a disorder clearly related to anxiety states. Recognizing precipitating factors and prodromic symptoms to take clinical preventive measures certainly influences patient outcome. However, in that study, recurrences were observed earlier in the placebo group.

In our study, after 48 months of follow-up, all patients with positive TET had recurrences, 52% occurring during the first year. However, a large long-term recurrence rate occurred in patients with a negative TET. A marked difference between the probability of recurrence in patients with a negative and positive TET persisted over time, but a significant increase occurred in recurrence rates in both groups during long-term follow-up.

Because the prognosis of neurocardiogenic syncope is highly favorable, medical therapy is mainly recommended to improve quality of life. However, frequent recurrences carry a risk of physical trauma, car accidents, and social and psychological distress, along with the need for health assistance.

Concluding, the present study demonstrated a good correlation between the acute (negative UTT) and chronic efficacy (symptom-free) of drug therapy for neurocardiogenic syncope, so that serial UTT should be indicated for severely symptomatic patients with neurocardiogenic syncope, in order to guide therapy.

Table I - Probability of recurrence and the upright-tilt testing result after therapy.

<table>
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<th>Follow-up(months)</th>
<th>Probability of recurrence</th>
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<th>Probability of recurrence and negative TET</th>
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P < 0.0001; TET - therapeutic evaluation test.

References