Comparing two different protocols for tilt table testing: sublingual glyceryl trinitrate versus isoprenaline infusion

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Abstract

***Objective*—To assess the diagnostic value and safety of sublingual glyceryl trinitrate tilt testing compared with isoprenaline infusion in patients with unexplained syncope.**

***Design*—Glyceryl trinitrate and isoprenaline tilt tests were performed in two successive days on a random basis in cases and controls.**

***Setting*—Outpatient cases with syncope referred to Shahid Rajaii Heart Hospital.**

***Subjects*—65 consecutive patients with unexplained syncope after thorough work up; 20 healthy volunteers.**

***Results*—Positive responses were observed in 20 patients during the passive phase. Of the other 45 patients, positive responses occurred in 25 cases during the glyceryl trinitrate phase and in 26 cases during the isoprenaline phase. In the control group, positive responses during the passive, glyceryl trinitrate, and isoprenaline phases occurred in one, one, and two cases, respectively. The sensitivity and specificity of the protocols were 55% and 94.7%, respectively, for glyceryl trinitrate *v* 58% and 89.4% for isoprenaline. Owing to discordant responses in 75% of the cases, the sequential use of the tests (if one was negative) would increase the sensitivity to 84% while decreasing the specificity slightly (to 84%). Side effects were less frequent with glyceryl trinitrate.**

***Conclusions*—Sublingual glyceryl trinitrate tilt testing is an effective and safe alternative to the isoprenaline infusion test and can be used as a complementary test.**

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Keywords: syncope; tilt table test; isoprenaline; glyceryl trinitrate

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Tilt table testing is a widely accepted tool for confirming the clinical diagnosis of neurocardiogenic or vasovagal syncope.[1] Several adjunctive pharmacological agents have been proposed to increase the sensitivity of the test,[2–5] with varying results,[6 7] but isoprenaline infusion has remained the most popular.[1 8 9] Isoprenaline infusion however, is rather cumbersome, undesirable in many patients with organic heart disease,[10] and relatively often has side effects.[11] This study was designed to compare the diagnostic value and tolerance of sublingual glyceryl trinitrate and isoprenaline infusion during tilt testing in the same group of patients.

Methods

PATIENTS

We studied 65 consecutive patients with unexplained syncope (26 men, 39 women; age 17 to 56 years, mean (SD), 34 (11.2) years). The number of episodes of syncope varied from one to 20 (mean (SD), 3.3 (3.8)). No abnormalities were found after a careful physical examination (including orthostatic blood pressure measurements and carotid sinus massage), routine laboratory tests, 12 lead electrocardiography, echocardiography, and 24 hour Holter recording. Other investigations, including stress tests, electrophysiological studies, angiography or computed tomography of the brain, were performed if clinically indicated.

CONTROL GROUP

Control subjects were 20 healthy volunteers (10 men, 10 women; age 17 to 56 years, mean (SD), 29 (9.5)). They had no history of syncope or presyncope and no evidence of any abnormalities on physical examination, electrocardiography, and echocardiography.

TILT TABLE TEST PROTOCOL

Informed consent was obtained from all patients and control subjects. Both isoprenaline and glyceryl trinitrate protocols were performed in each patient and each control subject on two successive days, in random order. Tests were performed in the morning after an overnight fast. An intravenous cannula was inserted at least one hour before the start of both protocols. No subject was taking any drugs. The room was quiet with dim lights. An electronically controlled table with footboard support and restraining belts at chest level was used. The ECG was continuously recorded and blood pressure was recorded by non-invasive sphygmomanometer every three minutes or less if necessary.

Passive phase

After 15 minutes of rest in the supine position, the table was tilted to 70° and the tilt was continued for up to 45 minutes. Pharmacological provocation was then started as described below if a positive response was not encountered.

Glyceryl trinitrate phase

Patients received 400 µg of sublingual glyceryl trinitrate and continued to be tilted at 70° for a maximum of 20 minutes.

Table 1 Summary of positive responses

	Passive phase	*ISO phase*	*GTN phase*
Cases			
Positive responses	20/65 (31%)	26/45 (58%)	25/45 (55%)
Time to response (mins)	15.5 (7.3)	11.0 (3.9)	11.2 (3.7)
Controls			
Positive responses	1/20 (5%)	2/19 (10.5%)	1/19 (5.2%)
Time to response (mins)	12.0	15.4 (2.5)	10.0

Values are mean (SD).
ISO, isoprenaline; GTN, glyceryl trinitrate.

Table 2 Types of response

	Type I	*Type II*	*Type III*
Passive phase	13 (65%)	6 (30%)	1 (5%)
ISO phase	20 (77%)	4 (15%)	2 (8%)
GTN phase	13 (52%)	9 (36%)	3 (12%)

Types of response described in the text.
ISO, isoprenaline; GTN, glyceryl trinitrate.

Isoprenaline phase

Isoprenaline infusion was started at 1 μg/min in the supine position and the patient was tilted to 70° for 10 minutes. If a positive response was not seen, the dose was increased by 1 μg/min at 10 minute stages, up to a maximum of 4 μg/min or until the heart rate rose over 150 beats/min.

DEFINITIONS

Syncope—Transient loss of consciousness with spontaneous recovery.

Presyncope—A state of intense dizziness associated with one or more of the following symptoms: decreased vision, slow response to verbal stimuli, partial loss of tone, nausea, or vomiting.

Positive response—Development of symptoms of presyncope or syncope accompanied by a rapid (within five minutes) fall in systolic blood pressure by more than 50% of the baseline or to less than 60 mm Hg, and/or a fall in heart rate by more than 30% from the peak rate or to less than 50 beats/min.

TYPES OF RESPONSE

Responses were classified as type I or mixed (hypotension or bradycardia develops but ventricular rate does not fall to less than 40 beats/min for more than 10 seconds and without asystole for more than three seconds); type II or cardioinhibitory (hypotension with ventricular rate of less than 40 beats/min for more than 10 seconds or asystole for more than three seconds); and type III or vasodepressor (hypotension develops but rate does not fall more than 10% from the peak).

Results

Positive responses are summarised in table 1. During the initial passive phase, 20 patients (31%) showed positive responses. With pharmacological provocation in the other 45 patients, positive responses to glyceryl trinitrate and isoprenaline occurred in another 25 (55%) and 26 (58%) patients, respectively. Types of response are summarised in table 2. In the control group, positive responses occurred during the passive phase in one case, during isoprenaline phase in two cases, and during the glyceryl trinitrate phase in one case.

A concordant response to isoprenaline and glyceryl trinitrate tests was observed in 13 cases only, while 38 cases (75%) showed positive responses with one or other test.

The mean (SD) times to positive response were not significantly different between glyceryl trinitrate and isoprenaline phases (11.2 (3.7) *v* 11.0 (3.9) min, respectively), but they were shorter than for the passive phase (15.5 (7.3) min).

SIDE EFFECTS

Few significant side effects were encountered with either protocol. With isoprenaline, they included self terminating episodes of supraventricular tachycardia (two patients, one control), chest pain (one patient), headache (two patients, one control), and nausea (three patients, two controls). With glyceryl trinitrate, one patient and one control subject suffered from headache. The tilt test was interrupted because of side effects in two patients during isoprenaline infusion but no patient during glyceryl trinitrate testing. Many patients felt an unpleasant sensation with isoprenaline, though continuing the test, but tolerated glyceryl trinitrate well.

Discussion

Vasovagal syncope is thought to be the most common identifiable cause of syncope, but the clinical history may be unreliable owing to the possible absence of typical precipitating factors and prodromal symptoms.[12]

The sensitivity of passive tilt table testing has been variously reported as 19% to 69%[4 13 14] but is mostly poor. Isoprenaline is known to increase the sensitivity while decreasing the specificity of the test,[14 15] but it requires an infusion system and is unpleasant to many patients, with relatively frequent side effects.[11]

The use of glyceryl trinitrate in the tilt test, first introduced by Raviele *et al*,[16] is promising because the agent does not have to be infused and seems to be safer than isoprenaline. In this study we attempted to compare the two tests in the same patients and we showed comparable sensitivities for glyceryl trinitrate and isoprenaline protocols (55% *v* 58%, respectively), with a somewhat better specificity for the glyceryl trinitrate protocol (94.7% *v* 89.4%). As a typical pharmacological tilt test is routinely started with a passive phase, it is reasonable to sum the results of the passive and pharmacological phases when determining sensitivity and specificity. When this was done, the sensitivity and specificity of the tests were 71% and 85% for isoprenaline and 69% and 90% for glyceryl trinitrate, respectively. Owing to discordant responses, if the two tests are used sequentially (when one is negative), the sensitivity would rise to 84%, while the specificity would decrease slightly to 84%.

Our rate of positive responses during all three phases was lower than in some earlier studies. The rate of positivity of tilt table testing has been reported to be higher with more aggressive protocols, increasing severity of syncopal attacks, shorter interval between the last episode and the test, younger age, and female

sex.[14 15 17] We could not identify any differences in these variables between our study and those with a higher rate of positive responses.

As noted previously,[18 19] discordant responses were seen in three quarters of the patients. This discrepancy suggests the presence of different pathophysiological subsets of patients with vasovagal syncope, provoked by different triggers. Alternatively, the reproducibility of the test may not be consistent, and this needs to be studied further. Nevertheless, when one test is negative, the positive response rate can be increased by performing the other test without significant loss of specificity.

LIMITATIONS

As noted by others,[8] the definition of neurocardiogenic syncope is a clinical one and no gold standard exists. Thus the definitions of sensitivity and specificity are arbitrary. Day to day variability in response cannot be ruled out, though the order of performing the tests was selected randomly. Our control subjects were younger on average, but this is likely to decrease the specificity rather than to increase it, as positive responses are more prevalent in younger people.[13]

CONCLUSION

The glyceryl trinitrate tilt test is a better tolerated and equally sensitive alternative to isoprenaline tilt testing. It can be used as the first line provocative agent in tilt table testing, as a complementary test in patients with a negative isoprenaline tilt, or as an alternative to isoprenaline where there is a contraindication to catecholaminergic drugs.

1 Benditt DG, Ferguson DW, Grubb BP, *et al.* Tilt table testing for assessing syncope. *J Am Coll Cardiol* 1996;**28**:263–75.

2 Almquist A, Goldenberg IF, Milstein S, *et al.* Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. *N Engl J Med* 1989;**320**:346–51.

3 Raviele A, Menozzi C, Brignole M, *et al.* Value of head-up tilt testing potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. *Am J Cardiol* 1995;**76**:267–72.

4 Calkins H, Kadish A, Sousa J, *et al.* Comparison of responses to isoproterenol and epinephrine during head-up tilt in suspected vasodepressor syncope. *Am J Cardiol* 1991;**67**:207–9.

5 Lurie KG, Dutton J, Mangat R, *et al.* Evaluation of edrophonium as a provocative agent for vasovagal syncope during head-up tilt testing. *Am J Cardiol* 1993;**72**:1286–90.

6 Kenny RA, Bayliss J, Ingram A, *et al.* Head-up tilt: a useful test for investigating unexplained syncope. *Lancet* 1986;i: 1352–4.

7 Sra JS, Anderson AJ, Sheikh SH, *et al.* Unexplained syncope evaluated by electrophysiologic studies and head-up tilt testing. *Ann Intern Med* 1991;**114**:1013–19.

8 Abi-Sarma F, Maloney JD, Fouad-Tarazi FM, *et al.* The usefulness of head-up tilt testing and hemodynamic investigations in the work-up of syncope of unknown origin. *PACE* 1998;**11**:1206–14.

9 Grub BP, Temesy-Armos P, Hahn H, *et al.* Utility of upright tilt table testing in the evaluation and management of syncope of unknown origin. *Am J Med* 1991;**90**:6–10.

10 Sheldon R, Rose S, Koshman ML. Isoproterenol tilt table testing in patients with syncope and structural heart disease. *Am J Cardiol* 1996;**78**:700–2.

11 Brignole M, Menozzi C, Gianfranchi L, *et al.* Carotid sinus massage, eyeball compression and head-up tilt test in patients with syncope of uncertain origin and in healthy control subjects. *Am Heart J* 1991;**122**:1644–51.

12 Sra JS, Anderson AJ, Sheikh SH, *et al.* Unexplained syncope evaluated by electrophysiologic studies and head-up tilt testing. *Ann Intern Med* 1991;**114**:1013–21.

13 Pongiglione G, Fish F, Starsburger JF, *et al.* Heart rate and blood pressure response to upright tilt in young patients with unexplained syncope. *J Am Coll Cardiol* 1990;**16**:165–70.

14 Fitzpatrick AP, Epstein LM, Lesh MD, *et al.* Effect of patient characteristics on the yield of prolonged baseline head-up tilt testing and the additional yield of drug provocation. *Heart* 1996;**76**:406–11.

15 Cardlioz R, Graux P, Haye J, *et al.* Prospective evaluation of high or low dose isoproterenol upright tilt protocol for unexplained syncope in young adults. *Am Heart J* 1997;**133**:346–52.

16 Raviele A, Gasparini G, Dipede F, *et al.* Nitroglycerin infusion during upright tilt: a new test for the diagnosis of vasovagal syncope. *Am Heart J* 1994;**127**:103–11.

17 Blank J, Victor J, Mansourati J, *et al.* Accuracy and mean duration of different protocols of head-up tilt testing. *Am J Cardiol* 1996;**77**:310–13.

18 Benditt DG, Lurie KG, Adler SW, *et al.* Rationale and methodology of head-up tilt table testing for evaluation of neurally-mediated (cardioneurogenic) syncope. In: Zipes DP, Jalife J, eds. *Cardiac electrophysiology: from cell to bedside*. Philadelphia: WB Saunders 1995:1115–28.

19 Janosik DL, Genovely H, Ferdman C, *et al.* Discrepancy between head-up tilt test results utilizing different protocols in the same patient. *Am Heart J* 1995;**123**:538–41.