Usefulness and Safety of Shortened Head-Up Tilt Testing Potentiated with Sublingual Glyceryl Trinitrate in Older Patients with Recurrent Unexplained Syncope

Attilio Del Rosso, MD, Andrea Ungar, MD,† Paolo Bartoli, MD,* Tommaso Cellai, MD,† Chiara Mussi, MD,‡ Niccolò Marchionni, MD,† Giulio Masotti, MD† and The Gruppo Italiano di Studio della sincope dell'anziano*

OBJECTIVES: To evaluate the sensitivity and tolerability of shortened, glyceryl trinitrate (GTN)-potentiated, head-up tilt test (HUT) in patients older and younger than 65 with unexplained syncope and to compare the specificity of GTN-potentiated HUT (GTN-HUT) in older and younger controls.

DESIGN: Methodological study.

SETTING: Syncope units in secondary and tertiary hospitals.

PARTICIPANTS: Three hundred twenty-four consecutive patients with unexplained syncope (100 aged ≥65 (mean age ± standard deviation 73 ± 6; 35 men) and 224 aged <65 (41 ± 15; 111 men)) and 64 controls (29 aged ≥65 (73 ± 6; 13 men) and 35 aged <65 (42 ± 13; 16 men)).

INTERVENTION: Patients and controls were tilted upright to 60° for 20 minutes. If syncope did not occur, sublingual GTN (400 μg) was administered and 60° HUT was continued for 15 minutes. Responses were classified as positive, negative, or exaggerated (slow decrease in blood pressure with a slight decrease in heart rate after GTN).

MEASUREMENTS: Electrocardiogram and arterial pressure were monitored continuously.

RESULTS: GTN-HUT was positive in 60% and 66% (NS), negative in 29% and 33% (NS), and exaggerated in 11% and 1% ($P < .001$) of older and younger patients, respectively. In older and younger controls, the GTN-HUT was negative in 70% and 86% and exaggerated in 28% and 9% of cases, respectively, ($P < .05$). The overall specificity (considering as negative also the exaggerated responses) was 97% in older and 94% in younger subjects. No patient or control experienced serious side effects.

CONCLUSION: The shortened GTN-HUT provides satisfactory positivity rate and specificity in older patients. This test may be considered as a diagnostic tool in assessing recurrent unexplained syncope in older patients. **J Am Geriatr Soc 50:1324–1328, 2002.**

Key words: syncope; head-up tilt testing; older; glyceryl trinitrate

Syncope is a common syndrome in older people, and its prevalence increases with advancing age.[1] Even when it is indicative of benign conditions, syncope is associated with increased morbidity.[2] Neurally mediated syncope was thought to be a rare cause of loss of consciousness in older people when the diagnosis relied on only clinical data.[3,4] Over the past decade, with expanded use of the head-up tilt test (HUT), a neurally mediated mechanism has emerged as a frequent cause of fainting, even at older ages.[5] Despite its increasing popularity, this test is still not well standardized. The low positivity rate of the unmedicated Westminster protocol in an unselected population[6] has prompted the use of drugs as provocative agents to increase the sensitivity of HUT.[7,8] Shortened HUT potentiated with sublingual glyceryl trinitrate (GTN) provides an adequate test with good specificity and positivity rate in young patients[9] and has recently been proposed as the standard protocol for the diagnosis of neurally mediated syncope.[10] Nevertheless, its use in older patients with unexplained syncope has not been validated.

The aims of this study were to evaluate the sensitivity, specificity, and tolerability of shortened GTN-potentiated HUT (GTN-HUT) in patients with unexplained syncope aged 65 and older and to compare the positivity rate and specificity of shortened GTN-HUT of this group with that of a group of younger patients.

From the *Division of Cardiology, Ospedale San Pietro Igneo, Fucecchio, Florence, Italy; †Department of Medical and Surgical Critical Care, Section of Gerontology and Geriatrics, University of Florence and Azienda Ospedaliera Careggi, Florence, Italy; and ‡Geriatric and Gerontology Institute, University of Modena, Modena, Italy.

This research was submitted as an oral presentation at the Congresso Nazionale di Cardiologia, Florence, Italy, May 24, 2000.

Address correspondence to Attilio Del Rosso, MD, Via Francesca 221, 50050, Cerreto Guidi, Italy. E-mail: cardiofu@leonet.it

0002-8614/02/$15.00

METHODS

Patient Population

One hundred consecutive patients aged 65 and older and 224 patients younger than 65 with a syncope of unknown origin were studied to determine the positivity rate of GTN-HUT. All patients were referred from the emergency room or from outpatient clinics to the "Syncope unit" of the cardiology or geriatric medicine divisions at three hospitals (Fucecchio, Florence, and Modena). The demographic and clinical characteristics of the two groups are presented in Table 1.

Patients who were on antihypertensive treatment were considered hypertensive. Syncope was categorized as unexplained if no plausible cause was detected after a clinical history was taken and a physical examination that included supine and orthostatic blood pressure measurements, basal electrocardiogram (ECG), and bilateral carotid sinus massage in supine and upright positions was performed. Other cardiac (ambulatory 24-hour ECG monitoring, echocardiogram, electrophysiologic study) and neurological (electroencephalogram, computed tomographic scan) diagnostic tests were performed when necessary. Patients with carotid sinus syndrome, organic heart disease, sick-sinus syndrome, intraventricular conduction defects, orthostatic hypotension, chronic and paroxysmal atrial fibrillation, or permanent pacemaker were excluded from the study.

To assess the specificity of the GTN-HUT protocol, 29 control subjects aged 65 and older (mean age ± standard deviation 73 ± 6; 13 men) and 35 control subjects younger than 65 (42 ± 13; 16 men) were also included in the study. All control subjects were considered healthy on the basis of medical history, physical examination, and standard ECG. In particular, they had no history of syncopal or presyncopal episodes. No control subject was taking any medications. All patients and control subjects gave informed consent to the diagnostic procedure.

Drug

Sublingual spray GTN (400 μg Natispray, Teofarma srl, Pavia Italy) was used in this study as the provocative test. The spray was preferred to sublingual tablets, which, before absorption, require a prolonged dissolution process.

Recordings

ECG leads I, II, and III were monitored on a multichannel oscilloscope. When symptoms developed, the ECG was recorded at a speed of 25 mm/sec with a Mingograph 7 (Siemens Elema, Stockholm Sweden). Arterial pressure was continuously monitored by the Penaz volume-clamp method[11] using a finger cuff (Finapres Ohmeda 2300, Louisville, CO). An appropriate-size finger cuff was used, and the hand was supported with a sling to keep the finger at heart level while the patient was in a supine and upright position. No invasive instrumentation was used during the test.

Experimental Procedure

To avoid interference of diurnal autonomic variability,[12] HUT was performed between 8:30 and 10:30 a.m. All cardiovascular drugs were withdrawn at least 2 weeks before the study, with the exception of drugs that patients were taking at the time of their syncopal episode for reproducing the clinical setting of spontaneous syncopal episodes. Ten minutes was allowed for stabilization in the supine position before HUT. Patients were tilted upright to 60° for 20 minutes on a motorized tilt-table with footplate support. If syncope or presyncope did not occur within 20 minutes, sublingual GTN (400 μg) was administered and observation was continued at the same angle for an additional 15 minutes. If syncope occurred during the test, the patient was returned to the supine position, and the test was interrupted. The angle of 60° was chosen because, in a previous report, the adoption of this angle[13] guaranteed a high specificity without increasing the proportion of false positive tests.

Definitions

Syncope was defined as a sudden loss of consciousness with inability to maintain postural tone and spontaneous recovery. HUT was considered positive when syncope was reproduced in association with hypotension (decrease in systolic blood pressure >60% of the maximal value in upright position), bradycardia (decrease in heart rate >30%

Table 1. Demographic and Clinical Features of Patients

Variable	Age ≥65 (n = 100)	Age <65 (n = 224)
Age, (mean ± SD)	73 ± 6	41 ± 15
Age range	65–87	8–64
Men/women	35/65	111/113
Number of syncopal episodes, mean ± SD	4 ± 5	4 ± 5
Mean duration of symptoms, months, mean ± SD	95 ± 195	82 ± 136
Patients with recurrent syncope, n (%)	56 (56)	136 (61)
Total traumas, n (%)	23 (23)	70 (31)
Major traumas (fractures), n (%)	6 (6)	13 (6)
Patients with arterial hypertension, n (%)	30 (30)	5 (2)

SD = standard deviation.

of the maximal value in upright position), or both. According to Vasovagal Syncope International Study (VASIS),[14] positive responses were classified as type 1 (mixed), types 2A and 2B (cardioinhibitory), type 3 (vasodepressive), exception 1 (chronotropic incompetence), and exception 2 (excessive rise in heart rate). A positive cardioinhibitory response was considered present only when bradycardia or asystole occurred immediately before or at the moment of the loss of consciousness and not when they occurred after syncope. According to Raviele et al.,[7] we defined as an exaggerated response the gradual development of symptoms (usually minor and different from the spontaneous ones) associated with a slow (>5 minutes) decrease in blood pressure alone and only a slight (<30%) reduction in heart rate during the pharmacological phase. Time to syncope was defined as the interval from the beginning of HUT to the loss of consciousness.

Statistics

Statistical analysis was performed with StatSoft 5.1 software (Tulsa, OK). All data are reported as mean ± standard deviation. The Student's *t* test for unpaired data was used to compare continuous variables between groups. The chi-square method was used to compare categorical variables. $P \leq .05$ was considered statistically significant.

RESULTS

Patients with Syncope

Positivity rate and specificity of the GTN-HUT are illustrated in Figure 1. The test was positive in 60 (60%) older patients. Five patients had syncope during the unmedicated phase, 55 after GTN administration. The mean time to syncope was 11 ± 1 minutes during the drug-free phase and 4 ± 2 minutes during the GTN-potentiated phase of HUT. The different hemodynamic patterns of positive responses are reported in Table 2. We observed an asystole of longer than 3 seconds in three patients during the syncopal phase. A negative response was observed in 29% and an exaggerated response in 11% of older patients. The positivity rate of HUT was 43% in older patients with a history of a single syncope and 57% in those with three or more syncopal attacks. GTN-HUT was positive in 147 (66%) younger patients: 28 during the unmedicated phase and 119 after GTN (Figure 1). The mean time to syncope was 13 ± 5 minutes during the first phase and 4 ± 3 minutes during the second one. The hemodynamic pattern of positive responses is reported in Table 2. An asystole of longer than 3 seconds was observed in 46 patients during the syncopal phase. A negative response was observed in 33% and an exaggerated response in 1% of younger patients ($P < .001$, older vs younger group). The positivity rate of HUT was 54% in younger patients with a history of a single episode of syncope and 74% in those with three or more syncopal attacks. The hemodynamic changes during HUT in patients with a positive response are reported in Table 3. Two patients each in the younger and older groups developed a sustained atrial fibrillation after a prolonged asystole occurring during the test. No other serious side effects were observed during the study, and HUT was completed in all cases.

Table 2. Distribution of Positive Responses During Head-Up Tilt Test in Older and Younger Patients According to Vasovagal Syncope International Study Classification[14]

	Age		
	≥65	<65	
Type of Response	n (%)		*P*-value
Type 1	37 (62)	55 (37)	<.001
Type 2A	5 (8)	38 (26)	<.001
Type 2B	3 (5)	18 (12)	.159
Type 3	10 (17)	8 (5)	<.001
Exception 1	3 (5)	7 (5)	.926
Exception 2	2 (3)	21 (14)	<.03

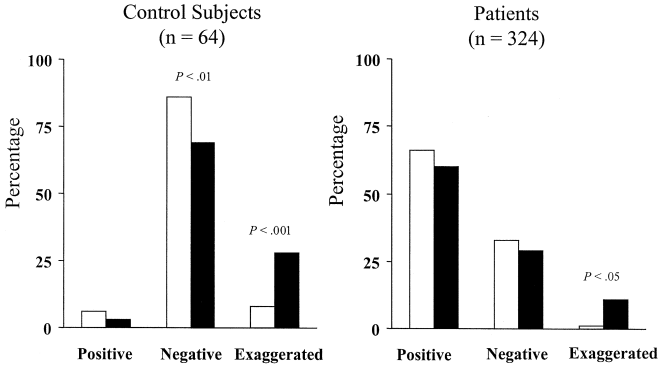

Figure 1. Distribution of responses to head-up tilt test potentiated with sublingual glyceryl trinitrate in control subjects (left panel) and syncope patients (right panel) (□ <65 years, ■ ≥65 years).

Control Subjects

In 20 of 29 older controls, the GTN-HUT was negative. One subject had a positive response after GTN administration, and eight others had an exaggerated response. In 30 of 35 younger controls, the GTN-HUT was negative. Two subjects had a positive response after GTN, and three others had an exaggerated response ($P < .05$, older vs younger controls). No subject with a positive HUT had a cardioinhibitory response in either control group. The specificity was 69% in older and 86% in younger controls. If one categorizes the exaggerated responses as negative responses, the overall specificity of the protocol is increased to 97% in older and 94% in younger individuals.

DISCUSSION

HUT is commonly used to evaluate patients with unexplained syncope. In the recent Guidelines of the European Society of Cardiology,[15] HUT is indicated in recurrent unexplained syncopal episodes in the absence of organic heart diseases, the presence of single syncope in high-risk settings (e.g., occurrence of or potential risk of physical injury, particularly relevant in an older population), and the presence of organic heart disease after a cardiac cause of syncope has been excluded. The usefulness of HUT has

Table 3. Changes in Heart Rate and Blood Pressure During Head-Up Tilt Test in Older and Younger Patients with a Positive Response

	Age		
	≥65	<65	
Hemodynamic Parameter	mean ± standard deviation		*P*-value
HR1	65 ± 10	69 ± 12	<.05
SBP1	133 ± 27	130 ± 19	.344
DBP1	74 ± 16	76 ± 13	.522
HR2	74 ± 13	84 ± 14	<.001
SBP2	125 ± 24	118 ± 17	<.05
DBP2	75 ± 14	74 ± 12	.848
HR3	97 ± 17	109 ± 22	<.001
SBP3	100 ± 28	111 ± 19	.0826
DBP3	66 ± 17	69 ± 13	.120
HR4	50 ± 27	36 ± 32	<.003
SBP4	31 ± 20	23 ± 24	<.023
DBP4	22 ± 16	15 ± 16	<.006

HR = heart rate (beats per minute); SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); 1 = at baseline; 2 = at the end of unmedicated head-up tilt test; 3 = at the time of maximal heart rate; 4 = at the time of syncope.

been demonstrated also in older people.[5] In the past, the diagnosis of vasovagal syncope was based on clinical history, but the frequent absence of prodromic symptoms in older people reduces the "diagnostic yield" of clinical evaluation. Indeed, after widespread introduction of HUT in clinical practice, the diagnosis of syncopal attacks of vasovagal origin increased, so that unexplained syncope in the older population has dropped from 40% to 15%.[5] Recently, pharmacological stimulation has been introduced to increase the diagnostic accuracy of HUT, but isoproterenol, the most widely used drug in the United States, cannot be used in approximately 10% of patients because of contraindications[16] and because, in as many as 16% to 24% of subjects,[17] particularly at older ages, onset of side effects imposes an early withdrawal. Furthermore, the positive chronotropic effect of isoproterenol may mask the chronotropic-incompetence response, which is frequently observed in older patients. GTN-potentiated HUT as proposed by Raviele et al.[7] is a promising tool for evaluating older patients with unexplained syncope because it has been proven substantially safe and well tolerated. Recently, comparable positivity rates and specificity have been reported for the shortened GTN-HUT, which differs from the original Raviele protocol in that its unmedicated phase is shorter.[9]

Our study demonstrated that the shortened GTN-HUT had a similar positivity rate in older and younger patients with unexplained syncope, whereas several previous studies of low- and high-dose isoproterenol HUT have reported that the positivity rate decreases with aging.[18,19] A possible explanation for this difference may be identified in the age-related decline in the responsiveness to catecholamines,[20] but Marchionni et al. have demonstrated that, despite similar pharmacokinetics, the pharmacodynamic response to the vasodilating effect of GTN is greater in older individuals, probably because of the diminished plasma volume typical of this population.[21] This might result in a higher proportion of false-positive responses to the GTN-potentiated HUT in older individuals.

In our study, we distinguished between a positive response (expressive of activation of a neural reflex) and an exaggerated response (considered the result of excessive vasodilatation).[7] The clinical significance of the latter is uncertain, and it is frequently observed in older patients who are more susceptible to the vasodilator effect of GTN. If we consider such responses as negative, at least in terms of lacking demonstration of a neuromediated origin of syncope, the specificity of our protocol becomes quite satisfactory and similar in younger and older individuals. As a consequence, we observed a lower positivity rate in the older population than did Natale et al.,[19] who did not classify separately this pattern of response.

According to previous studies,[6–9] the rate of mixed or vasodepressive responses (types 1 and 3) was higher in older patients, whereas the cardioinhibitory responses (types 2A and 2B) prevailed in the younger ones. Such a difference may be caused by an age-related decline in the parasympathetic drive to the heart.[22] In a study by Kurbaan et al.,[6] exception 1 response (chronotropic-incompetence) was associated with older age. In this regard, we did not observe a statistically significant difference between the two age groups. This response is mostly seen in older patients with structural heart disease and may be due to an impaired reflex response or to intracardiac conduction defects. Our patient selection, with the exclusion of those with structural heart disease and suspected sick sinus syndrome, may account for the differences between our findings and Kurbaan's results.[6] The VASIS classification is based on the different behavior of blood pressure and heart rate observed when symptoms and vasovagal reaction occur. Recently, an analysis of the presyncopal phase has identified a dysautonomic pattern, characterized by a gradual and progressive decrease in blood pressure with a small change in heart rate.[23] The original VASIS classification does not take into account this pattern of response, whose pathophysiological mechanism, in contrast to that of vasovagal syncope, may consist of an inability of the cardiovascular system to adapt to the HUT-related hemodynamic stress. The prevalence of this response in our study was similar in older and younger patients (12% vs 9%, $P = .573$). This is probably because this response is observed preferentially in older patients with coexistent carotid sinus hypersensitivity,[23] who were excluded from our study. The shortened GTN-HUT has been well tolerated in all older patients. This represents an advantage over the standard GTN protocol. Indeed, in the study of Kurbaan et al.,[6] 28% of patients aged 75 and older could not tolerate the longer GTN-HUT. No serious adverse events were observed in younger or older patients during HUT. Incidence of atrial fibrillation after asystole was similar in both groups and in all cases was self-limited.

Therapeutic Implications

GTN-HUT allows for identification of the cardioinhibitory and vasodepressive components of syncope and may be a guide to the selection of the most-appropriate thera-

peutic approach (permanent cardiac pacing in patients with frequent cardioinhibitory syncope despite education and drug therapy[24] or fludrocortisone or midodrine[25] in those with a vasodepressive response). This therapeutic approach should be validated in additional prospective randomized studies.

Nevertheless, after a negative HUT in cases with an isolated syncope, the diagnostic process can be stopped when a cardiac cause of syncope can be excluded, whereas, in cases of recurrent, unexplained syncope, an implantable loop recorder can be the next recommendable diagnostic step.[15]

Limitations of the Study

In this study, we excluded patients with intracardiac conduction defects, orthostatic hypotension, organic heart diseases, or carotid sinus hypersensitivity. These selection criteria may have affected our results. Further study is needed to assess the clinical value of GTN-HUT in patients with these conditions. The exact sensitivity of HUT is difficult to ascertain because there is no real reference criterion standard, but the "diagnostic yield" of GTN-HUT is substantially higher than any other diagnostic test used to evaluate unexplained syncope.[26] Nevertheless, HUT, when properly used, can be useful in suggesting a diagnosis where history, physical examination, and other tests have failed. In this study, 400 μg of GTN were used because this is the only dose available as a sublingual spray preparation. Ammirati et al., using a reduced dose of isosorbide dinitrate (1.25 mg, one-quarter of the dose used for clinical purposes), had a higher specificity in normal subjects.[27] In our opinion, the diagnostic power of a low dose of sublingual GTN should be investigated. The main concern about the use of GTN-HUT in older patients is the difficulty of interpreting the nonspecific responses to GTN. During unmedicated HUT, a different hemodynamic and neurohumoral profile has been demonstrated in controls and patients with vasovagal syncope.[28] Further studies are necessary to confirm the meaning of the exaggerated responses to GTN. Another possible limitation may be the different proportion of male/female and normotensive/hypertensive subjects in the two groups of patients. In previous studies, no difference were observed in the HUT responses on the basis of the gender.[29] The effect of arterial hypertension per se on HUT response is unclear and is the object of ongoing work by our group.

CONCLUSIONS

The shortened GTN-HUT, one of the tests that can be used in the diagnostic assessment of patients with recurrent unexplained syncope,[10,17,26,30] provides a highly satisfactory positivity rate and highly satisfactory specificity even in older patients. Because of its safety and tolerability, this test should be preferred in the evaluation of such patients.

REFERENCES

1. Savage DD, Corwin L, McGee DL et al. Epidemiological features of isolated syncope: The Framingham Study. Stroke 1985;16:626–629.
2. Linzer M, Pontinen M, Gold DT et al. Impairment of physical and psychosocial function in recurrent syncope. J Clin Epidemiol 1991;44:1037–1043.
3. Lipsitz LA, Wei JY, Rowe JW. Syncope in an elderly, institutionalized population: Prevalence, incidence and associated risk. Q J Med 1985;55:45–54.
4. Kapoor WN, Snustad D, Peterson J et al. Syncope in the elderly. Am J Med 1986;80:419–428.
5. Dougnac A, Gonzales R, Kychenthal A et al. Syncope: Etiology, prognosis and relationship to age. Aging 1991;3:63–72.
6. Kurbaan AS, Franzen AC, Bowker TJ et al. Usefulness of tilt test-induced patterns of heart rate and blood pressure using a two-stage protocol with glyceryl trinitrate provocation in patients with syncope of unknown origin. Am J Cardiol 1999;84:665–670.
7. 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;76:267–272.
8. Kapoor WN, Brant N. Evaluation of syncope by upright tilt testing with isoproterenol. Ann Intern Med 1992;116:358–363.
9. Del Rosso A, Bartoli P, Bartoletti A et al. Shortened head-up tilt testing potentiated with sublingual nitroglycerin in patients with unexplained syncope. Am Heart J 1998;135:564–570.
10. Bartoletti LA, Alboni P, Ammirati F et al. "The Italian Protocol": A simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. Europace 2000;2:339–342.
11. Friedman DB, Jensen FB, Matzen S et al. Non-invasive blood pressure monitoring during head-up tilt using the Penaz principle. Acta Anesthesiol Scand 1990;34:519–522.
12. Malik M, Farrel TG, Camm AJ. Evaluation of receiver operator characteristics: Optimal time of day for assessment of heart rate variability after acute myocardial infarction. Int J Biomed Comput 1991;27:175–192.
13. Natale A, Akhtar M, Jazayeri M et al. Provocation of hypotension during head-up tilt testing in subjects with no history of syncope or presyncope. Circulation 1995;92:54–58.
14. Sutton R, Petersen M, Brignole M et al. Proposed classification for tilt induced vasovagal syncope. Eur J Cardiac Pacing Electrophysiol 1992;3:180–183.
15. Brignole M, Alboni P, Benditt D et al. Guidelines on management (diagnosis and treatment) of syncope. Eur Heart J 2001;22:1256–1306.
16. 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;122:1644–1651.
17. Kenny RA, O'Shea D, Parry SW. The Newcastle protocols for head-up tilt table testing in the diagnosis of vasovagal syncope, carotid sinus hypersensitivity, and related disorders. Heart 2000;83:564–569.
18. Sheldon R. Effects of aging on responses to isoproterenol tilt-table testing in patients with syncope. Am J Cardiol 1994;74:459–463.
19. Natale A, Sra J, Akhtar M et al. Use of sublingual nitroglycerin during head-up tilt-table testing in patients > 60 years of age. Am J Cardiol 1998;82:1210–1213.
20. Lipsitz LA, Mietus J, Moody BG et al. Spectral characteristics of heart rate variability before and during postural tilt. Circulation 1990;81:1803–1810.
21. Marchionni N, Schneeweiss A, Di Bari M et al. Age-related hemodynamic effects of intravenous nitroglycerin for acute myocardial infarction and left ventricular failure. Am J Cardiol 1988;61:81E–83E.
22. Pfeifer MA, Weinberg CR, Cook D et al. Differential changes of autonomic nervous system function with age in man. Am J Med 1983;75:249–258.
23. Brignole M, Menozzi C, Del Rosso A et al. New classification of haemodynamics of vasovagal syncope: Beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. Europace 2000;2:66–76.
24. Sutton R, Brignole M, Menozzi C et al. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: Pacemaker versus no therapy: A multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators. Circulation 2000;102:294–299.
25. Bloomfield D, Sheldon R, Grubb B et al. Panel Consensus. Putting it together: A new treatment algorithm for vasovagal syncope and related disorders. Am J Cardiol 1999;84:33–39.
26. Linzer M, Yang EH, Estes NAM et al. Clinical guideline. Diagnosis Syncope. Part 2. Unexplained syncope. Ann Intern Med 1997;127:76–86.
27. Ammirati F, Colivicchi F, Biffi A et al. Head-up tilt testing potentiated with low-dose sublingual isosorbide dinitrate: A simplified time-saving approach for the evaluation of unexplained syncope. Am Heart J 1998;135:671–676.
28. Leonelli FM, Wang K, Evans JM et al. False positive head-up tilt: Hemodynamic and neurohumoral profile. J Am Coll Cardiol 2000;35:188–193.
29. Mc Gavinan AD, Hood S. The influence of sex and age on response to head-up tilt-table testing in patients with recurrent syncope. Age Ageing 2001;30:295–298.
30. Krahn AD, Klein GJ, Yee R et al. Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators. Circulation 1999;99:406–410.