



Europace (2008) 10, 1091–1094  
doi:10.1093/europace/eun196

# Head-up tilt testing with different nitroglycerin dosages: experience in elderly patients with unexplained syncope

Ana Teresa Timoteo\*, Mario Martins Oliveira, Joana Feliciano, Eduardo Antunes, Manuel Nogueira da Silva, Sofia Silva, Sofia Santos, and Rui Ferreira

Cardiology Department, Santa Marta Hospital, R. Santa Marta, 1169-024 Lisboa, Portugal

Received 8 May 2008; accepted after revision 10 July 2008; online publish-ahead-of-print 6 August 2008

## KEYWORDS

Head-up tilt testing;  
Nitroglycerin dosages;  
Elderly

**Aims** Protocols using sublingual nitrates have been increasingly used to improve diagnostic accuracy of head-up tilt testing (HUT). Nevertheless, exaggerated responses to nitrates have been frequently described, particularly in elderly patients. The aim of this article is to evaluate, in an elderly population with unexplained syncope, whether the impact of sublingual nitroglycerin (NTG) used as a provocative agent is dose-dependent.

**Methods and results** One hundred and twenty consecutive elderly patients submitted to HUT using NTG after an asymptomatic drug-free phase were studied. Patients were divided into three groups according to the NTG dosage: 500, 375 and 250 µg. The test was considered positive when there was reproduction of symptoms with bradycardia and/or arterial hypotension. A gradual decrease in the blood pressure after NTG was considered an exaggerated response to nitrates. There were no differences in the clinical characteristics of the different subgroups. A positive test was obtained in 50% of the patients in each group. The rate of exaggerated responses was identical in all groups and ranged between 15 and 17%.

**Conclusion** In an elderly population with syncope of unknown origin submitted to HUT, the response to NTG is not dose-dependent, and no difference was found in the rate of exaggerated responses to nitrates with different NTG dosages.

## Introduction

Since its first description by Raviele *et al.*<sup>1</sup> in 1994, head-up tilt testing (HUT) using nitrates as a provocative agent has been increasingly used. Its main advantage is the fact that it can be well tolerated (compared with isoproterenol), and the protocol is more simplified than the use of isoproterenol. It can also be more safely used in elderly patients, as, in this population, there is a contraindication to the use of isoproterenol in up to 10% of the patients.<sup>2</sup> It also allows us to identify exaggerated response to nitrates. In previous studies that compared younger with elderly patients, an increased prevalence of exaggerated responses to nitrates has been described in the elderly group.<sup>3</sup> However, in our own experience, the incidence of exaggerated responses to nitrates was similar in both elderly and younger patients.<sup>4</sup>

Several protocols are being used, with different nitrate formulations, preparations, and dosages, making them difficult to compare the results between centres.<sup>5–7</sup> The results are considered good for most of the protocols proposed, but slightly different from each other. Additionally, there is lack of data if responses are dose-dependent.

It was our objective to analyse, in a population of elderly patients with syncope of unknown aetiology, whether the impact of sublingual nitroglycerin (NTG), as a provocative agent in HUT, is dose-dependent.

## Patients and methods

The prospective study includes 120 consecutive elderly patients ( $\geq 65$  years), submitted to HUT using sublingual NTG. Only patients with an asymptomatic drug-free phase of the test were included in the study (81%) out of a total of 149 elderly patients submitted to HUT in the same period. Patients with very typical precipitating factors or prodromal symptoms for syncope were not included in this study.

\* Corresponding author: Av. Miguel Torga, No. 27, Edifício C, 9<sup>o</sup>A, 1070-183 Lisboa, Portugal. Tel: +351 21 3594311.

E-mail address: ana\_timoteo@yahoo.com

All patients underwent a standard evaluation to exclude other causes of syncope: clinical history and physical examination (including neurological evaluation), routine blood tests, 12-lead ECG, 24 h Holter monitoring, transthoracic echocardiography, stress testing, and carotid ultrasound. When this complete evaluation was negative and the aetiology for the syncope remained unknown, the patient was referred for HUT. Patients underwent HUT in a fasting state (4–6 h) between 11 am and 2 pm. Beta-blockers and nitrates were stopped for at least 48 h. An automatic tilt table was used with continuous monitoring of heart rate and blood pressure with a Task Force Monitor (CNSystems™).

A modified Italian Protocol was used.<sup>6</sup> The first change was the use of intravenous cannulation. As this can influence the specificity of the test, the stabilization phase was prolonged to 30 min to achieve a stable condition of the patient. The other difference was the use of a 70° tilt angle. After the stabilization phase, carotid sinus massage was performed to test for carotid sinus hypersensitivity. Then, the patient was tilted to 70° and the carotid sinus massage was performed again in the upright position. Further, we moved on to the passive phase (20 min). When this phase was negative, the patient received sublingual NTG and underwent a provocative phase for another 20 min, followed by the recovery phase. The test was interrupted after the completion of the protocol in the absence of symptoms or if syncope occurred.

Syncope was defined as a sudden transient loss of consciousness with inability to maintain postural tone and with spontaneous recovery. A positive test was defined as reproduction of the spontaneous syncope in association with bradycardia (decrease in heart rate >30% of the maximum value observed in the upright position), hypotension (decrease in the systolic blood pressure >50% of the maximal value observed in the upright position), or both, with rapid onset (occurring within 5 min), and classified according to the classical VASIS classification of neurocardiogenic responses: cardioinhibitory, vasodepressive, or mixed.<sup>8</sup> An exaggerated response to nitrates was defined as a gradual development of symptoms, as a consequence of progressive and slow (occurring in >5 min) decrease in blood pressure along with only a slight reduction (<30%) or no change in the heart rate.<sup>1</sup>

To test our hypothesis, three different NTG dosages were tested. The first 20 consecutive elderly patients received 500 µg, followed by 20 patients receiving 250 µg and 20 patients receiving 375 µg. This process was repeated in the same sequence, until 40 patients were included in each group. Heart rate and blood pressure in the basal state (with tilting at 70°) and 5 min after sublingual NTG (time considered for the complete absorption of the sublingual NTG tablet) were also compared.

The study complies with the Declaration of Helsinki, and informed consent was obtained from all the patients.

## Statistical analysis

Continuous variables were expressed as mean  $\pm$  SD and categorical variables as frequencies and percentages. Continuous variables were compared with the two-tailed Student's *t*-test. Categorical variables were compared with the  $\chi^2$  test/Fisher's test, as appropriate, to compare all the groups. A *P*-value less than 0.05 was considered statistically significant.

## Results

Groups had an identical distribution for the clinical characteristics (Table 1). Most patients had no structural heart disease, and the distribution of hypertension and stable chronic ischaemic heart disease was identical. Most patients did not receive any previous cardiac medication. Some were on beta-blockers, ACE inhibitors, or nitrates, but there were no statistically significant differences between groups in the type of medication received.

**Table 1** Patients' clinical characteristics

(%)	500 µg (n = 40)	375 µg (n = 40)	250 µg (n = 40)	<i>P</i> -value
Age (years)	73 $\pm$ 6	75 $\pm$ 6	72 $\pm$ 8	NS
Female gender	55	50	60	NS
Without heart disease	59	66	60	NS
Hypertensive heart disease	27	28	30	NS
Ischaemic heart disease	14	6	10	NS
Previous medication				
Beta-blockers	19	11	17	NS
ACEI	18	17	10	NS
Nitrates	6	3	4	NS
No cardiac medication	57	55	60	NS

ACEI, angiotensin-converting enzyme inhibitor.

**Table 2** Responses obtained during head-up tilt testing

<i>n</i> (%)	500 µg (n = 40)	375 µg (n = 40)	250 µg (n = 40)	<i>P</i> -value
Negative test	13 (33)	14 (35)	13 (33)	NS
Exaggerated response	7 (17)	6 (15)	7 (17)	NS
Positive test	20 (50)	20 (50)	20 (50)	NS
Vasodepressive	12 (60)	9 (45)	10 (50)	NS
Cardioinhibitory	2 (10)	3 (15)	1 (5)	NS
Mixed	6 (30)	8 (40)	9 (45)	NS

The test was positive in 50% of the patients. Exaggerated responses to nitrates ranged between 15 and 17%. Vasodepressive neurocardiogenic type of response was more commonly observed (45–60%), followed by a mixed response (30–45%) and a cardioinhibitory response (5–15%) (Table 2). There were also no statistically significant differences between different age groups (Table 3).

When blood pressure and heart rate were compared at basal conditions and at the peak effect of NTG (5 min after sublingual administration), there were some differences in terms of systolic blood pressure between 500 and 375 µg and between 500 and 250 µg (Table 4). No differences were found in the diastolic blood pressure and heart rate. However, the average change in the systolic blood pressure and heart rate was significantly lower in the group that received 250 µg, suggesting that the effect of NTG on blood pressure and heart rate is dose-dependent.

## Discussion

After its introduction by Raviele *et al.*,<sup>1</sup> HUT protocols with nitrates have been replacing isoproterenol as a provocative agent with similar accuracy, better tolerance, and without serious side effects. In fact, isoproterenol is contraindicated in patients with coronary artery disease, aortic stenosis, and

**Table 3** Responses obtained during head-up tilt testing by age groups

Age groups (years)	500 µg		375 µg		250 µg	
	65–75 n = 24	>75 n = 16	65–75 n = 20	>75 n = 20	65–75 n = 24	>75 n = 16
Positive test, n (%)	13 (54)	7 (44)	10 (50)	10 (50)	13 (54)	7 (44)
Negative test, n (%)	7 (29)	6 (37)	7 (35)	7 (35)	8 (33)	13 (31)
Exaggerated response, n (%)	4 (17)	3 (19)	3 (15)	3 (15)	3 (13)	4 (25)

*P*-value=non-significant for all comparisons.

**Table 4** Blood pressure and heart rate obtained during head-up tilt testing

	500 µg (n = 40)	375 µg (n = 40)	250 µg (n = 40)
Basal SBP (mmHg) <sup>a,b</sup>	120 ± 10	133 ± 17	126 ± 16
Basal DBP (mmHg)	81 ± 10	81 ± 13	84 ± 12
Basal HR (bpm)	73 ± 14	72 ± 14	71 ± 14
Peak NTG SBP (mmHg) <sup>a,b</sup>	107 ± 16	118 ± 24	121 ± 28
Peak NTG DBP (mmHg)	72 ± 11	77 ± 16	76 ± 16
Peak NTG HR (bpm)	86 ± 16	84 ± 18	83 ± 18
ΔSBP (basal-peak) (mmHg) <sup>b,c</sup>	−13 ± 20	−15 ± 20	−5 ± 15
ΔDBP (basal-peak) (mmHg)	−9 ± 16	−4 ± 14	−8 ± 16
ΔHR (basal-peak) (bpm) <sup>b,c</sup>	+13 ± 12	+12 ± 20	+2 ± 12

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; Δ, average change; NTG, nitroglycerin.

<sup>a</sup>*P* < 0.05 (500 vs. 375 µg).

<sup>b</sup>*P* < 0.05 (500 vs. 250 µg).

<sup>c</sup>*P* < 0.05 (375 vs. 250 µg).

severe hypertension, compromising its use in almost 10% of the patients mainly in an elderly population.<sup>2</sup> Isoproterenol can cause ventricular arrhythmias and angina pectoris in up to 18% of the patients submitted to HUT.<sup>1,9</sup> With nitrates, the main side effect described is headache without serious complications. This makes nitrates the ideal provocative agent to be used in elderly patients.

Although intravenous NTG is well tolerated, it requires venous cannulation (with a prolonged stabilization phase) and it is more technically demanding. To simplify the test, Raviolo *et al.*<sup>10</sup> introduced sublingual NTG in 1995 as an alternative with similar accuracy for the diagnosis of syncope. This protocol was further simplified in subsequent studies, by shortening the passive phase.<sup>11,12</sup> Because each centre adopted different protocols, Bartoletti *et al.*,<sup>6</sup> in an attempt to standardize the test, described the 'Italian Protocol'. For the same purpose, the European Society of Cardiology described the recommended protocol in the 'Syncope Guidelines' updated in 2004.<sup>2</sup>

The first study comparing results in elderly and younger patients, obtained a positive rate of 66% in the elderly and 60% in the younger patients.<sup>3</sup> However, according to the same author, the exaggerated response was more commonly

observed in the elderly (11 vs. 1%) using 400 µg of sublingual NTG spray. Other studies showed a rate of exaggerated responses in the elderly similar to that described in younger patients.<sup>4,13–16</sup> However, results are difficult to compare because each centre uses not only different protocols (tilt angle, passive and stimulated phase duration) but also different nitrate formulations, preparations, and dosages.<sup>5,6</sup> These different dosages and types of administration are responsible for different rates of absorption and bioavailability of nitrates. In two recently published reviews, positive rates during HUT ranged from 51 to 78% and exaggerated responses from 4 to 21%.<sup>5,6</sup> This had implications in the range of sensitivity (35–87%), specificity (63–100%), and accuracy (56–81%) obtained with HUT. Although we believed that different nitrate dosages could influence the HUT results, it was not possible to obtain conclusive answers from the published data. In our country, the formulation available for NTG is 500 µg tablets. Our study was designed to study the influence of nitrate dosage on the results of the HUT. All patients underwent the same protocol, with changes only in the NTG dosage.

Because of its potent vasodilatory effect in the capacity vessels (by indirect stimulation of GMPc, causing relaxation of vascular smooth muscle), nitrates significantly increase venous pooling (in the lower limbs, viscera, and mesentery) already enhanced by the upright posture. The reduction in venous return, ventricular volume, and cardiac output induces a reflex increase in the sympathetic tone with consequent vigorous contraction of the heart. In predisposed patients, this leads to a paradoxical activation of the ventricular mechano-receptors with inhibitory afferents to cardiovascular brainstem centres, which are ultimately responsible for the triggering of Bezold–Jarish reflex with vasodilation, bradycardia, hypotension, and syncope.<sup>5</sup> However, the precise mechanism by which nitrates increase the sensitivity of the test may be more complex than the widely assumed venodilating phenomenon. In fact, in our study, the systolic blood pressure was slightly different between groups after NTG, with the lowest systolic blood pressure in the 500 µg group and the highest in the 250 µg group. The average change in the systolic blood pressure and heart rate was also significantly lower in the group that received 250 µg, suggesting that the effect of NTG on blood pressure and heart rate is dose-dependent. But according to our results, NTG dosage does not seem to influence the paradoxical activation of the Bezold–Jarish reflex. Nitrates are lipid soluble and readily cross the blood-to-brain barrier in humans, which potentially makes the central action an additional pathway of nitrate-induced syncope.<sup>5</sup> Other factors such as neurohumoral activation could also contribute either

directly or indirectly to the vaso-vagal cascade through the baro-reflex.<sup>5</sup> These hypotheses can suggest an explanation underlying different mechanisms associated with a response to nitrates that might not be dose-dependent.

Exaggerated responses to nitrates are usually considered as a manifestation of an excessive vasodilation produced by NTG and not as secondary to the triggering of neural reflex. In our work, the incidence of this type of response was identical in all three groups and does not seem to be dose-dependent also. We can hypothesize that other mechanisms of action of nitrates might be involved in this type of response. A detailed study of the autonomous nervous system changes by spectral analysis, neurohumoral behaviour, or other potential mechanisms in this particular population of patients could be performed to give some insight into this subject.

The overall rate of positive tests for neurocardiogenic responses was 50%, slightly lower than those reported by other authors.<sup>3,10–14</sup> However, in our study, we did not consider passive phase results, as patients with a diagnosis obtained in this phase were not included in the study. This represents ~10–20% of the HUT results in other studies, and it was 19% in our experience.<sup>3,7,14</sup>

In our population, most patients had a vasodepressive response followed by the mixed response, which is in accordance with other authors.<sup>3,13–16</sup> In fact, Kochiadakis *et al.*<sup>15</sup> performed a detailed study of autonomic activity during HUT and concluded that autonomic nervous system behaviour was similar in older and younger patients, suggesting that the mechanism responsible for vasovagal syncope is basically the same in both the groups. Nevertheless, although a reduction of sympathetic activity in response to tilting was observed in both groups, it was greater in elderly patients, which may explain the subsequent vasodilation in these patients. In contrast, parasympathetic system activation immediately prior to syncope occurred less in elderly than in younger patients, which may explain the low incidence of marked bradycardia in the elderly.

## Limitations

One limitation of the present study is the fact that the results cannot be generalized to formulations other than NTG tablets, because the spray has a different rate of absorption and bioavailability. Another limitation is the fact that we do not have a control group that could be used to evaluate sensitivity and specificity with different NTG dosages. However, our results are similar to other previously reported in terms of positivity rate of the HUT with nitrates.<sup>5,6</sup> Finally, it seems that the results are similar in different age groups (65–75 and >75 years) and NTG dosages. However, the small number of patients in each subgroup is a statistical limitation for an adequate statistical analysis.

## Conclusion

In a population of elderly patients with syncope of unknown origin submitted to HUT potentiated by sublingual NTG, the response to nitrates is not dose-dependent, and no

difference was found in terms of the rate of exaggerated responses to nitrates. Head-up tilt testing is a safe test, and using sublingual NTG as a provocative agent provides a significant contribution to the aetiological diagnosis of syncope in patients with a negative passive test.

## Acknowledgements

We gratefully thank Luisa Moura Branco and Duarte Cacula for their help in reviewing the manuscript.

**Conflict of interest:** none declared.

## References

1. Raviele A, Gasparini G, Di Pede F, Menozzi C, Brignole M, Dinelli M *et al.* Nitroglycerin infusion during upright tilt: a new test for the diagnosis of vaso-vagal syncope. *Am Heart J* 1994;127:103–11.
2. Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc JJ, Bloch PE *et al.* Guidelines on management (diagnosis and treatment) of syncope—update 2004. *Eur Heart J* 2004;25:2054–72.
3. Del Rosso A, Ungar A, Bartoli P, Cellai T, Mussi C, Marchionni N *et al.* Usefulness and safety of shortened head-up tilt testing potentiated with sublingual glyceryl trinitrate in older patients with recurrent unexplained syncope. *J Am Geriatr Soc* 2002;50:1324–8.
4. Timoteo AT, Oliveira M, Antunes E, Pelicano N, Feliciano J, Silva S *et al.* Use of nitroglycerin in the active phase of tilt testing. Is there a difference in elderly patients? *Rev Port Cardiol* 2007;26:325–30.
5. Aerts AJ, Dendale P. Nitrate stimulated tilt table testing: a review of the literature. *Pacing Clin Electrophysiol* 2003;26:1528–36.
6. Bartoletti A, Alboni P, Ammirati F, Brignole M, Del Rosso A, Foglia Manzillo G *et al.* 'The Italian Protocol', a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;2:339–42.
7. Timoteo AT, Oliveira MM, Antunes E, Vieira AP, Feliciano J, Fiarresga AJ *et al.* Tilt test in elderly patients with syncope of unknown etiology: experience with pharmacological stimulation with nitroglycerin. *Rev Port Cardiol* 2005;24:945–53.
8. Sutton R, Petersen M, Brignole M, Raviele A, Menozzi C, Giani P *et al.* Proposed classification for tilt induced vasovagal syncope. *Eur J Cardiol Pacing Electrophysiol* 1992;2:180–3.
9. Gatzoulis KA, Mamarelis IE, Apostolopoulos T, Dilaveris P, Gialafos J, Toutouzas P. Polymorphic ventricular tachycardia induced during tilt table testing in a patient with syncope and probable dysfunction of the sinus node. *Pacing Clin Electrophysiol* 1995;18:1075–9.
10. Raviele A, Menozzi C, Brignole M, Gasparini G, Alboni P, Musso G *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.
11. del Rosso A, Bartoli P, Bartoletti A, Brandinelli-Geri A, Bonechi F, Maioli M *et al.* Shortened head-up tilt testing potentiated with sublingual nitroglycerin in patients with unexplained syncope. *Am Heart J* 1998;135:564–70.
12. del Rosso A, Bartoletti A, Bartoli P, Ungar A, Bonechi F, Maioli M *et al.* Methodology of head-up tilt testing potentiated with sublingual nitroglycerin in unexplained syncope. *Am J Cardiol* 2000;85:1007–11.
13. Natale A, Sra J, Akhtar M, Kusmirek L, Tomassoni G, Leonelli F *et al.* Use of sublingual nitroglycerin during head-up tilt table testing in patients >60 years of age. *Am J Cardiol* 1998;82:1210–3.
14. Mussi C, Tolve I, Foroni M, Valli A, Ascari S, Salvioli G. Specificity and total positive rate of head-up tilt testing potentiated with sublingual nitroglycerin in older patients with unexplained syncope. *Aging* 2001;13:105–11.
15. Kochiadakis GE, Papadimitriou EA, Marketou ME, Chrysostomakis SI, Simantirakis EN, Vardes PE. Autonomic nervous system changes in vasovagal syncope: is there any difference between young and older patients? *Pacing Clin Electrophysiol* 2004;27:1371–7.
16. Kurbaan AS, Bowker TJ, Wijesekera N, Franzén AC, Heaven P, Itty S *et al.* Age and hemodynamic responses to tilt testing in those with syncope of unknown origin. *J Am Coll Cardiol* 2003;41:1004–7.