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Sublingual Nitroglycerin Used in Routine Tilt Testing Provokes a Cardiac Output-Mediated Vasovagal Response

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OBJECTIVES We set out to determine the effect of sublingual nitroglycerin (NTG), as used during routine tilt testing in patients with unexplained syncope, on hemodynamic characteristics and baroreflex control of heart rate (HR) and systemic vascular resistance (SVR).

BACKGROUND Nitroglycerin is used in tilt testing to elicit a vasovagal response. It is known to induce venous dilation and enhance pooling. Also, NTG is lipophilic and readily passes cell membranes, and animal studies suggest a sympatho-inhibitory effect of NTG on circulatory control.

METHODS Routine tilt testing was conducted in 39 patients with suspected vasovagal syncope (age 36 ± 16 years, 18 females). Patients were otherwise healthy and free of medication. Before a loss of consciousness set in, oncoming syncope was cut short by tilt-back or counter-maneuvers. Finger arterial pressure was monitored continuously (Finapres). Left ventricular stroke volume (SV) was computed from the pressure pulsations (Modelflow). Spontaneous baroreflex control of HR was estimated in the time and frequency domains.

RESULTS During tilt testing, 22 patients developed presyncope. After NTG administration but before presyncope, SV and cardiac output (CO) decreased ($p < 0.001$), whereas SVR and HR increased ($p < 0.001$) in all patients. Arterial pressure was initially maintained. Baroreflex sensitivity decreased after NTG. On Cox regression analysis, the occurrence of a vasovagal response was related to a drop in SV after NTG (hazard ratio 0.86, $p = 0.005$).

CONCLUSIONS The cardiovascular response to NTG is similar in vasovagal and non-vasovagal patients, but more pronounced in those with tilt-positive results. The NTG-facilitated presyncope appears to be CO-mediated, and there is no evidence of NTG-induced sympathetic inhibition. (J Am Coll Cardiol 2004;44:588–93) © 2004 by the American College of Cardiology Foundation

Recurrent syncope is a common medical problem. Head-up tilt testing with or without pharmacologic intervention has been shown to be a useful diagnostic test to document a tendency toward vasovagal fainting (1–7). Nitroglycerin (NTG) is commonly administered to increase the diagnostic yield of the procedure (8–10), because as potent venodilators (11), nitrates might facilitate vasovagal syncope (VVS) by enhancing venous pooling in the upright posture. Nitroglycerin has been proposed to enter smooth muscle cells where it undergoes metabolic activation to nitric oxide (NO) (12,13). There is mounting evidence that NO donors have pronounced central effects (14). Nitroglycerin is lipid-soluble and readily crosses cell membranes. Animal studies suggest a direct effect of NTG on the central nervous system, resulting in sympathetic inhibition (15). We therefore hypothesized that NTG facilitates a vasovagal reaction in routine head-up tilt testing not only via venous vasodilation, but also by acting centrally on circulatory control and inhibiting the baroreflex control of heart rate (HR) and arterial peripheral resistance, thus leading to syncope by dual pathways. The purpose of this study was to investigate the effect of NTG, as used in routine tilt testing in otherwise healthy patients with a history of VVS, on hemodynamic characteristics and baroreflex control of HR and systemic vascular resistance (SRV). We further sought to assess whether an immediate cardiovascular response to NTG was related to the test outcome.

METHODS

Study population. The study group consisted of patients with suspected VVS, referred for routine tilt-table testing to the Syncope Unit of the Academic Medical Center in the period of June 2002 to July 2003. Excluded were patients with a history of cardiovascular disease, carotid sinus syndrome, or any disease that might affect the autonomic nervous system, as well as patients using medication that might affect the circulation or circulatory control. Subsequently, we excluded patients who experienced a vasovagal episode before administration of NTG (n = 2). A total of 39 patients (18 females) were included in the study.

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Abbreviations and Acronyms

BRS = baroreflex sensitivity
CO = cardiac output
DAP = diastolic arterial pressure
HR = heart rate
IBI = interbeat interval
MAP = mean arterial pressure
NO = nitric oxide
NTG = nitroglycerin
SAP = systolic arterial pressure
SNP = sodium nitroprusside
SV = stroke volume
SVR = systemic vascular resistance
VVS = vasovagal syncope

Tilt-test protocol and measurements. The tests were done between 9:00 AM and 1:00 PM in a temperature-controlled room (23°C). A manually operated tilt table with a footboard was used. Blood pressure was measured continuously and non-invasively using the Finapres Model 5 (TNO Biomedical Instrumentation, Amsterdam, the Netherlands). Beat-to-beat changes in stroke volume (SV) were estimated by modeling flow from arterial pressure (Modelflow, TNO Biomedical Instrumentation) (16–18). The tilt-table test started with 5 min of supine rest, followed by 20 min head-up tilt (60°). If no VVS developed, NTG was administered sublingually (0.4 mg) for an additional 15-min tilt duration (19). Oncoming syncope was aborted by means of tilt-back or counter-maneuvers, such as leg crossing (20), before a loss of consciousness set in. The study was approved by the Medical Ethical Committee of the Academic Medical Center, University of Amsterdam, the Netherlands.

Data acquisition and analysis. The Finapres arterial pressure signal was analog to digital converted at 100 Hz and stored on hard disk for off-line analysis. Mean arterial pressure (MAP) was the true integral of the arterial pressure wave over one beat divided by the corresponding beat interval. Heart rate was computed as the inverse of the interbeat interval (IBI) and expressed as beats per minute. Cardiac output (CO) was the product of SV and HR, and SVR was MAP at the heart level divided by CO. Beat-to-beat values were computed and averaged per minute. Stroke volume, CO, and SVR were set at 100% (baseline) in the upright posture, 5 min before NTG administration, and variations were expressed as percentages of this baseline. Slopes were computed for the minute averages of HR, systolic and diastolic arterial pressure (SAP and DAP, respectively), MAP, SV, CO, and SVR over a 4-min time frame starting at NTG administration in all patients.

Of those patients who developed VVS during the tilt test, minute averages were calculated for beat-to-beat data up to a point where a drop in HR and/or arterial blood pressure preceding the vasovagal episode was detected. To analyze the hypotensive, presyncopal episode in tilt-positive patients, the last 15 s before the intervention, such as tilt-back, was analyzed.

Baroreflex sensitivity (BRS). Beat-to-beat SAP and IBI time series were detrended and Hanning windowed. Power spectral density and cross-spectra of SAP and IBI in the low-frequency band (0.06 to 0.15 Hz) were computed using discrete Fourier transform, as described elsewhere (21). For time-domain analysis of spontaneous BRS, we used the cross-correlation method PRVXBRS (22), which is now a standard part of the software packages delivered with Portapres and Finometer products (FMS, Amsterdam, the Netherlands). The SAP and IBI time series were resampled at 1 Hz. In a 10-s window, the correlation and regression slope between SAP and IBI were computed. Delays of 0- to 5-s increments in IBI were computed, and the delay with the highest positive coefficient of correlation was selected. The slope between SAP and IBI was recorded as a BRS estimate if the correlation was significant at $p = 0.01$.

Statistical analysis. Variables were tested for normality using the Kolmogorov-Smirnov test and expressed as the mean value ± SD, unless stated otherwise. Responses to sublingual NTG were analyzed using the non-parametric test for two related samples (Wilcoxon signed rank test) or the paired *t* test, where appropriate. Differences between groups were analyzed using the non-parametric test for two independent samples (Mann-Whitney *U* test) or the *t* test, where appropriate. Pearson's correlation coefficient was computed for the correlation between the BRS results in the time-frequency domain. The association between data (computed slopes) and test outcome (time to faint), including censored data on those patients without VVS during the test, was assessed using Cox regression analysis (SPSS for Windows, release 11.5.2). Significance of the Walt statistic was computed.

RESULTS

Subjects. Nitroglycerin-induced presyncope in 22 (56%) of the 39 otherwise healthy patients included in the study. The average age (36 ± 16 years), height (175 ± 10 cm), weight (73 ± 15 kg), and distribution of gender did not differ between the patients who experienced near syncope during the tilt test and those who did not. The time from administration of NTG to presyncope in the tilt-positive patients ranged from 2 min, 50 s to 14 min, 50 s. All vasovagal patients indicated prodromal symptoms such as light-headedness or nausea. Data recording was stopped in two tilt-negative patients (in the fourth and tenth minute after NTG administration) because of technical reasons.

Cardiovascular response to NTG. Hemodynamics during 4 to 1 min preceding and 1 to 4 min following NTG administration in all patients are summarized in Table 1. Before NTG, patients were asymptomatic, and the average MAP was 87 mm Hg (range 67 to 101 mm Hg). One patient became symptomatic in the third minute after NTG, another in the fourth minute. Systolic and mean Finapres blood pressures were well maintained after NTG, whereas DAP increased. There was a reduction in SV, and

Table 1. Cardiovascular Characteristics of All Patients During Periods of 3 Minutes Before and After Nitroglycerin Administration While Tilted to 60° Head-Up Tilt

	4 to 1 min Before NTG	1 to 4 min After NTG	p Value
Hemodynamic data			
SAP (mm Hg)	118 ± 12	117 ± 12	NS†
MAP (mm Hg)	87 ± 10	87 ± 10	NS†
DAP (mm Hg)	72 ± 10	75 ± 9	0.001†
HR (beats/min)	85 ± 14	95 ± 17	0.001‡
SV (%)	98 ± 6	84 ± 10	0.001‡
CO (%)	99 ± 5	93 ± 8	0.001†
SVR (%)	103 ± 8	111 ± 11	0.001‡
Frequency-domain analysis			
SAP LF power (mm Hg^2)*	18 ± 15	24 ± 21	NS‡
IBI LF power (ms^2)*	819 ± 673	1,095 ± 866	0.05‡
BRS LF gain (ms/mm Hg)*	4.9 ± 2.5	3.8 ± 2.4	0.01‡
Coherence*	0.66 ± 0.16	0.65 ± 0.16	NS‡
Time-domain analysis			
BRS (ms/mm Hg)*	8.0 ± 3.1	6.1 ± 2.8	0.001‡

*Results on 38 of 39 patients. †Paired samples *t* test. ‡Wilcoxon signed rank test. Data are presented as the mean value ± SD.
BRS = baroreflex sensitivity; CO = cardiac output; DAP = diastolic arterial pressure; HR = heart rate; IBI = interbeat interval; LF = low-frequency; MAP = mean arterial pressure; NTG = nitroglycerin; SAP = systolic arterial pressure; SV = stroke volume; SVR = systemic vascular resistance.

although HR increased, CO diminished. Furthermore, SVR increased after NTG ($p < 0.001$) (Fig. 1). During these periods, there were no significant differences in hemodynamic characteristics between tilt-positive and tilt-negative patients.

Power spectral density and BRS. After excluding one tilt-positive patient from spectral analysis because of frequent extrasystolic beats, for the remaining 38 of the 39 patients, the IBI low-frequency power density increased after NTG ($p < 0.05$). The SAP low-frequency power also tended to increase ($p = 0.12$). The spectral power and BRS estimates are given in Table 1. The BRS low-frequency gain decreased after the hemodynamic changes induced by NTG, as did the spontaneous BRS calculated in the time domain (Fig. 1F). There were no differences in BRS or power spectral density between the patients with a negative versus positive test outcome in the selected periods. Although the BRS low-frequency gain results were lower than the time-domain BRS estimates, the methods correlated well (Pearson's $r = 0.79$, $p < 0.001$).

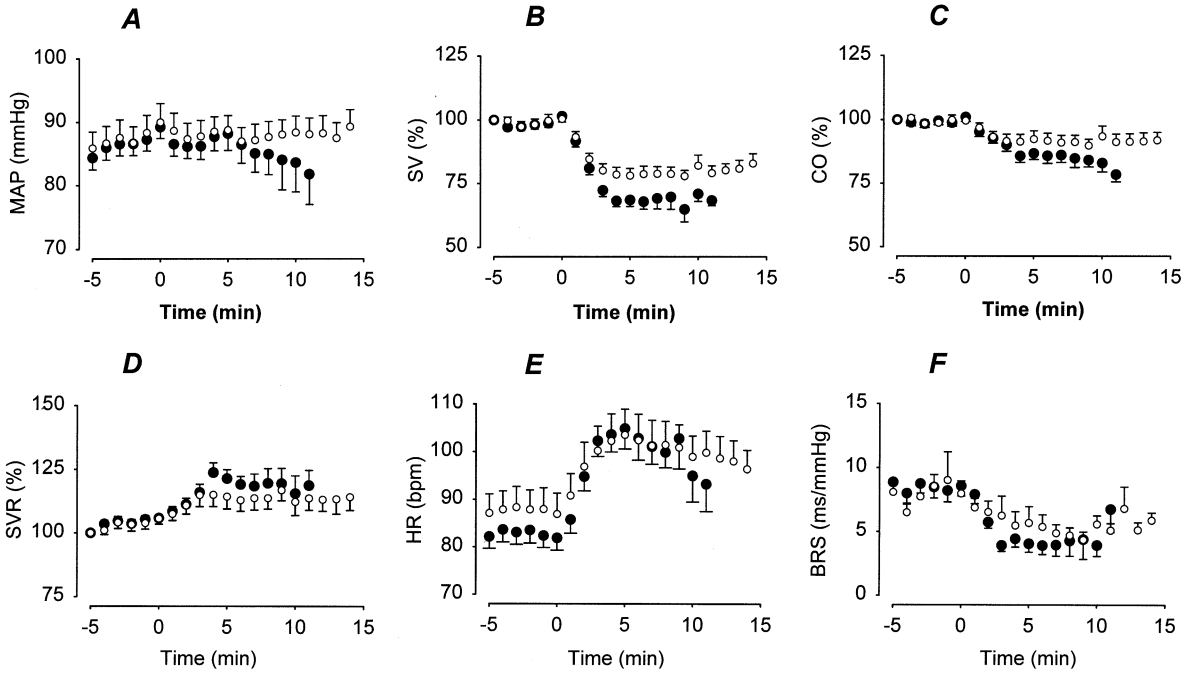

Figure 1. Hemodynamic response to NTG during the 60° tilt test. At 0 min, nitroglycerine is administered. **(A)** mean arterial pressure (MAP); **(B)** stroke volume (SV); **(C)** cardiac output (CO); **(D)** systemic vascular resistance (SVR); **(E)** heart rate (HR); **(F)** baroreflex sensitivity (BRS). **Circles** = minute averages and SEM. **Open circles** = negative tilt test; **solid circles** = positive tilt test.

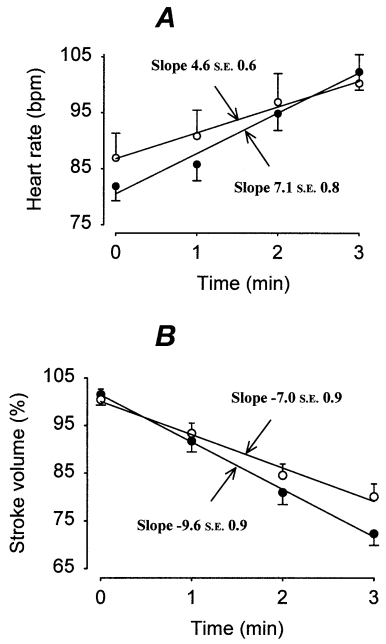

Figure 2. Computed trends of minute averages over 4 min immediately after nitroglycerine administration during 60° tilt test. **(A)** Slope of heart rate; **(B)** Slope of stroke volume. **Open circles** = negative tilt test; **solid circles** = positive tilt test. Bars indicate SEM.

Computed trends after NTG administration. Cardiovascular trends in patients who experienced presyncope and those who did not are shown in Figure 1. The tilt-positive patients demonstrated a greater drop in SV, CO, and arterial blood pressure. The HR in the period preceding NTG appears higher in the tilt-negative group; however, this difference is not significant (88 ± 17 beats/min vs. 83 ± 12 beats/min, $p = 0.3$). To avoid statistical testing of episodes where the number of tilt-positive patients was greatly reduced, trends were analyzed by calculation of the slope during the first 4 min after NTG administration (Fig. 2). The tilt-positive patients had a steeper drop in SV compared with the tilt-negative patients ($p < 0.05$). The concomitant rise in HR was also steeper in the tilt-positive patients ($p < 0.05$).

Vasovagal episode. During the last 15 s before tilt-back or counter-maneuver, the tilt-positive patients showed marked hypotension with SAP of 81 ± 11 mm Hg and DAP of 54 ± 10 mm Hg. Heart rate ranged from 45 to 111 beats/min during this period (mean 78 ± 23 mm Hg). Five of the 22 tilt-positive patients had a HR >100 beats/min, whereas seven had a HR <60 beats/min. Stroke volume was 68 ± 12% of baseline, CO was 63 ± 14%, and SVR was 126 ±44%. Both SV and CO during the vasovagal episode were lower than those of tilt-negative patients in their last minute of tilt, who had an average SV of 83 ± 15% ($p = 0.002$) and CO of 92 ± 12% ($p < 0.001$) (Figs. 1B and 1C). During near syncope, in 18 of the 22 tilt-positive patients, SVR was increased compared with baseline. The SVR and HR responses were not related to age.

Table 2. Cox Regression Analysis for Time to Presyncope Computed Slopes

	Wald Chi-Square	Hazard Ratio (95% CI)	p Value
Model A: slope of HR (beats/min)	5.66	1.12 (1.02–1.22)	0.017
Model B: slope of SV (%/min)	7.91	0.86 (0.77–0.95)	0.005

CI = confidence interval; other abbreviations as in Table 1.

Cox regression model. Using the calculated slopes to model the tilt-test outcome (time to presyncope), Cox regression showed that a rise in HR was related to the occurrence of a vasovagal response during tilt testing (Fig. 2A, Table 2). The drop in SV was also related to the test outcome; a steep drop in SV was associated with an increased hazard of a vasovagal response (Fig. 2B, Table 2). Modeling both slopes of SV and HR together does not improve the model, as these variables are correlated ($r = -0.54$, $p < 0.01$).

DISCUSSION

The present findings demonstrate that administration of NTG during routine tilt testing of otherwise healthy patients suspected of VVS leads to a rapid drop in SV, a rise in SVR and HR, and initially a maintained arterial blood pressure in patients with a positive test outcome, as well as in those with a negative test outcome. This implies an adequate arterial resistance response to NTG-induced venous dilation and pooling, rendering impaired circulatory control due to NTG unlikely. The cardiovascular response to NTG was similar in vasovagal and non-vasovagal patients, but the response was more pronounced in tilt-positive patients; the reduction in SV after NTG administration was related to the tilt-test outcome. Despite an increase in HR, there was a reduction in CO. A NTG-induced vasovagal response, therefore, appears CO-mediated and is not preceded by a decrease in SVR.

Effect of NTG on circulatory control. Baroreflex sensitivity was decreased in the period after NTG, which, together with the rise in HR and SVR, suggests sympathetic activation. Interestingly, the rises in HR and SVR after NTG were not preceded by a reduction in arterial pressure. Possible explanations for this are, first, that arterial baroreceptors respond to mechanical deformation and not pressure, and small reductions in effective blood volume are known to trigger baroreflex adjustments of arterial pressure (23); and second, another pathway leading to an increase in SVR is via the cardiopulmonary reflex (24), which is sensitive to changes in venous pressure. Activation of the cardiopulmonary reflex is likely after NTG administration, which is known to result in venodilation and pooling of blood (11).

We found no difference in BRS between tilt-positive and tilt-negative patients before or after NTG administration. This seems at odds with a recent report by Samniah et al. (25) of modification of BRS during VVS. Their results are

not comparable, however, as they studied the BRS during tilt-back immediately after full syncope, whereas we computed BRS in the lead-up to presyncope.

The present findings indicate an increase in SVR after NTG administration in all patients and a sustained increase in SVR at the onset of presyncope. This seems at odds with previous reports of an early progressive decrease in SVR leading to syncope in healthy young subjects without use of NTG (26). The supine recording is commonly used as a control period for expressing SVR as percentage of baseline. In the present study, however, we explicitly omitted the supine recording as baseline and used the upright tilt recording before NTG administration as baseline to avoid SV estimations during posture change (27). After 20-min upright tilt with corresponding cardiovascular adjustments to orthostatic stress, NTG was administered. We have not analyzed the changes in SV, CO, and SVR from the supine to the upright tilt position, and we therefore limit our conclusions to the effect of NTG administration during routine tilt testing in otherwise healthy, medication-free patients.

Central effects of NTG. Since the discovery that NO is not only a regulator of smooth muscle tone but also a neuromodulator within the central and peripheral nervous system (28,29), it is likely that the cardiovascular actions of NO are not confined to its direct effects on blood vessels, but rather include effects on the central and peripheral nervous system (14). In humans, the effect of NO donors on cardiovascular autonomic control has been investigated using infusions of sodium nitroprusside (SNP), and the results suggest that SNP had no effects on the cardiac/vagal limb of the baroreflex (30). However, SNP is hydrophilic, and the compound has difficulty crossing membranes. Nitroglycerin, on the other hand, is lipophilic, and the compounds readily enter cells to form NO. The results of animal studies suggest that within the central nervous system there are sites that modulate the cardiovascular effects of NTG, and the hypotensive effects of NTG may be modified by central noradrenergic activity controlling the circulation (15). In the present study, we demonstrate that BRS, established using time and frequency domain methods, became diminished after sublingual NTG. The increase in DAP and SVR, however, together with the increase in HR and IBI low-frequency spectral power, provides strong circumstantial evidence of increased sympathetic outflow (31). We therefore consider sympathico-inhibition due to a central effect of NTG, as used during routine clinical tilt testing, unlikely.

Study limitations. The present results were obtained in patients with no cardiovascular or neurologic diseases and no medication. The patient group has thus been selected, resulting in a group that is relatively younger and healthier than the total of patients referred for unexplained syncope. Included were only those patients who did not have a vasovagal episode before NTG, thus excluding the most outspoken cases. A vasovagal response was aborted before a loss of consciousness set in, and we therefore limited our analysis and our conclusions to the prodromal phase and the onset of a vasovagal response.

We used a new method of BRS computation (time-domain cross correlations) and an established method (frequency-domain cross-spectral calculations). Although these methods correlated well, the frequency-domain BRS gain was lower than the time-domain BRS. Considering that both methods calculated the correlation between spontaneous variations in SAP and IBI, we would ideally expect identical results. However, with the frequency-domain method, we made a frequency-band selection (i.e., the low-frequency band), whereas the time-domain method, in principle, includes all frequencies, which might explain the greater BRS estimates we found using the latter method.

Conclusions. Our study of otherwise healthy patients suspected of VVS demonstrates a rapid decrease in SV and an increase in SVR and HR after NTG administration during tilt testing. We found strong indications that sublingual NTG induces an increase in sympathetic outflow, resulting in initially maintained arterial pressure. The NTG-triggered syncopal episode is not preceded by a decrease in SVR, but appears CO-mediated. Our finding that the decrease in SV after NTG administration is related to the time to presyncope supports this.

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