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Original Article

Reduced systemic vascular resistance is the underlying hemodynamic mechanism in nitrate-stimulated vasovagal syncope during head-up tilt-table test

Byung Gyu Kim, MD[a], Sung Woo Cho, MD[a,b], Hye Young Lee, MD[a], Deok Hee Kim, MD[a], Young Sup Byun, MD[a], Choong Won Goh, MD[a], Kun Joo Rhee, MD[a], Byung Ok Kim, MD[a,*]

[a] Division of Cardiology, Department of Internal Medicine, Sanggye Paik hospital, Inje University College of Medicine, Seoul 139-707, Republic of Korea
[b] Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea

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ABSTRACT

Background: Nitroglycerin (NTG) challenge during head-up tilt-table testing (HUTT) is often utilized to determine the etiology of unexplained vascular syncope. However, conflicting results concerning nitrate-induced hemodynamic changes during HUTT have been reported. The purpose of this study was to assess the determinants of presyncopal symptoms during NTG-stimulated HUTT.
Methods: We evaluated 40 patients with suspected vasovagal syncope. Beat-to-beat changes in blood pressure, heart rate (HR), cardiac index (CI), and systemic vascular resistance (SVR) during HUTT were measured with thoracic impedance cardiography and a plethysmographic finger arterial pressure monitoring device.
Results: None of the 40 patients complained of presyncopal symptoms during passive HUTT. However, after the administration of NTG 28 patients showed presyncopal symptoms (NTG+ group) and the remaining 12 patients did not (NTG– group). HR, CI, and the stroke index did not significantly differ between the two groups, whereas mean arterial pressure and SVR were significantly lower in the NTG+ group.
Conclusions: Presyncopal symptoms during NTG-stimulated HUTT are SVR mediated, not cardiac output mediated. This study challenges the conventional idea of a decrease in cardiac output mediated by NTG as the overriding cause of presyncopal symptoms during HUTT.

1. Introduction

Syncope is a syndrome in which a relatively short period of temporary and self-limited loss of consciousness is caused by a transient diminution of blood flow to the brain. The prevalence of syncope in the general population is reported to vary from 15% to 23% [1]. Vasovagal syncope is a transient loss of consciousness caused by systemic arterial hypotension resulting from reflex vasodilatation and/or bradycardia. It is the most common cause of syncope in the general population and is responsible for one-fifth of all syncope episodes [2].

The diagnosis of vasovagal syncope is usually based on a combination of careful history taking, clinical examination, and a surface electrocardiogram to exclude cardiac and non-cardiac causes of syncope [3,4]. When the etiology of syncope is uncertain, head-up tilt-table testing (HUTT) is commonly used to reproduce symptoms in patients with suspected vasovagal syncope [3,5]. Nitroglycerin (NTG) challenge during HUTT is often utilized to determine the etiology of unexplained syncope [5,6]. NTG may facilitate syncope through various pathways, but the precise mechanism of its contribution to syncope remains unclear [7].

Traditionally, venodilation and the venous pooling of blood into the low extremities and splanchnic and mesenteric vasculature along with the subsequent reduction of left ventricular preload have been regarded as the main hemodynamic effects of NTG, while arterial dilatation is thought to play a smaller role [8,9]. Some studies showed that sublingual NTG provokes a cardiac output-mediated vasovagal response that is not preceded by a fall in systemic vascular resistance (SVR) [10,11]. However, conflicting results concerning NTG-induced hemodynamic changes have been reported. Several studies revealed decreases in SVR without a

* Correspondence to: Division of Cardiology, Department of Internal Medicine, Sanggye Paik hospital, Inje University College of Medicine, 1342, Dongil-ro, Nowon-gu, Seoul 139- 707, Republic of Korea. Tel.: +82 2 950 1266; fax: +82 2 950 1248.
E-mail address: byungokim@paik.ac.kr (B.O. Kim).

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marked change in cardiac output (CO) or heart rate (HR) during NTG administration [12].

The purpose of this study was to assess the determinants of presyncopal symptoms and to compare hemodynamic patterns between patients with and without presyncopal symptoms during NTG-stimulated HUTT.

2. Materials and methods

2.1. Study population and head-up tilt-table test protocol

We evaluated 42 consecutive patients admitted to our hospital for syncope or presyncope between November 2012 and March 2013. All patient medical histories included at least one syncopal episode suspected to have been caused by vasovagal response in the last year. The exclusion criteria were an age of less than 18 years, a history of cardiovascular disease, carotid sinus syndrome, any disease that might affect the autonomic nervous system, and the use of medication that might affect the cardiovascular system.

HUTT was performed in accordance with current guidelines by a trained nurse [4]. Testing was performed between 9:00 AM and 1:00 PM in a quiet, temperature-controlled (23 °C) room [13].

Patients refrained from caffeine-containing products, smoking, and heavy meals for at least 6 h and from alcohol for at least 24 h prior to the test. After 10 min of supine rest, the table was tilted to 70° (passive tilt phase). If presyncopal symptoms did not occur during 20 min of passive tilt, 0.25 mg of NTG was administered sublingually and testing continued for another 20 min (NTG phase).

Presyncopal symptoms were defined as light-headedness, nausea, blurred vision, pallor, and sweating in association with hypotension and/or bradycardia. Impending syncope was halted by means of tilt-back. Patients were divided into two groups according to whether or not they experienced presyncopal symptoms after NTG administration.

2.2. Hemodynamic measurements

Hemodynamic parameters were determined with a thoracic bioimpedance cardiography (ICG) device (***Niccomo***™, Medis, Ilmenau, Germany), which records continuous changes in body electric impedance during the cardiac cycle. After rubbing and cleaning the skin with alcohol to achieve as low as possible skin-to-electrode impedance, two sensors with gel pads were carefully placed on each side of the thorax along the mid-axillary line and the two remaining sensors were placed on each side of the neck just above the clavicle. An alternating current of 1.5 mA (85 kHz) was applied, and the ICG signal was continuously displayed on the screen along with the electrocardiographic signal. Stroke volume (SV, mL) was computed every single heart beat and averaged over 15 heart beats to take physiological respiratory variations into account. The stroke index (SI, min/m^2) was calculated based on SV and body surface area. CO (L/min) was the product of the estimated SV and HR. The cardiac index (CI, L/min/m^2) was then calculated based on the SV, HR, and body surface area. Raw data were analyzed offline and all ICG measurements were performed with a single monitor using PC-version 1.9 of the *Niccomo* software. Beat-to-beat changes in systolic and diastolic arterial blood pressures were measured at every heart beat from the finger arterial pressure wave form by a plethysmographic method via the Finometer (***Finometer***® ***PRO***, Finapres Medical System, Netherlands) and averaged. mean arterial pressure (MAP) was the true integral of the arterial pressure wave over one beat divided by the corresponding beat interval. HR (bpm) was obtained continuously by five-lead electrocardiographic monitoring. SVR (dyn s/cm^5) was calculated as the MAP at heart level divided by the computed CO.

2.3. Study periods

1. Supine baseline: beat-to-beat data of the last 5 min in the supine position before head-up tilting were averaged.
2. After tilt: beat-to-beat data from the 5 min in the 70° head-up tilt position to the last minute before NTG administration were averaged (early steady-state circulatory adjustment). The first 5 min after head-up tilting were not included in order to avoid transition phenomena.
3. After NTG administration: beat-to-beat data of the last 5 min after NTG administration were averaged. If presyncopal symptoms occurred, the last 5 min before tilt back or countermaneuvers were averaged.

2.4. Statistical analysis

Data were reported as mean and standard deviation for continuous variables and as percentages for categorical variables. For the testing of significance, between-group comparisons of continuous variables were analyzed by independent *t*-tests. Comparisons of categorical variables were generated by the Pearson χ^2 test. Statistical comparisons were performed using SPSS, version 15.0 software (SPSS Inc.). All tests were 2-sided, and the results were considered statistically significant at a p-value < 0.05.

3. Results

3.1. Study population

Of 42 patients, 2 were excluded because presyncopal symptoms were noted prior to the administration of NTG. The 28 (70%) patients who showed presyncopal symptoms after NTG administration were classified as the NTG+ group. Another 12 patients who had negative results were classified as the NTG− group. Table 1 lists comparative differences between the two groups. The NTG+ and NTG− groups did not differ significantly with regard to age, gender distribution, body mass index (BMI), smoking status, and history of hypertension or diabetes. The number of previous syncopal episodes was not different between the two groups (NTG+ vs. NTG−; 2.6 ± 2.2 vs. 2.2 ± 1.4; $p=0.5$). The presence of prodromal symptoms before syncope was similar between the two groups (NTG+ vs. NTG–; 70% vs. 75%; $p=1.0$) and nausea with sweating was the most frequently observed symptom. The occurrence of associated injury was similar in the NTG+ and NTG– groups (NTG+ vs. NTG–; 15% vs. 17%; $p=1.0$).

Table 1
Baseline characteristics of the study population.

Variables	NTG+ group ($n=28$)	NTG− group ($n=12$)	p-Value
Age (years)	38 ± 15	43 ± 18	0.17
Male (n, %)	11 (39%)	8 (66%)	0.21
Body mass index (kg/m^2)	23.8 ± 4	24.3 ± 3.7	0.18
Smoking (n, %)	4 (14.3%)	3 (25%)	0.13
Hypertension (n, %)	4 (14.3%)	2 (16.7%)	0.64
Diabetes (n, %)	1 (3.6%)	1 (8.3%)	0.51
Syncopal episodes (n)	2.6 ± 2.2	2.2 ± 1.4	0.5
Presence of prodromal symptoms (n, %)	19 (70.4%)	9 (75%)	1.0
Presence of associated injury (n, %)	4 (14.8%)	2 (16.7%)	1.0

Data are expressed as the mean ± SD or number (percentage).
Body mass index (BMI)=Weight (kg)/Length^2 (m^2).