Spontaneous vs nitroglycerin-induced vasovagal reflex on head-up tilt: Are there neuroendocrine differences?

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BACKGROUND Head-up tilt test (HUT) has been used for nearly 30 years for diagnosing vasovagal syncope (VVS) and was enhanced by sublingual nitroglycerin (glyceryl trinitrate [GTN]) challenge in the 1990s.

OBJECTIVE The purpose of this study was to explore neuroendocrine differences between spontaneous and drug-induced HUT positivity.

METHODS Two hundred eighty-eight patients (41.3% male, age 49 ± 21 years) with either positive passive (n = 60 [20.8%], age 38 ± 17 years) or GTN-enhanced HUT (n = 228, age 51 ± 21 years) were assessed. Beat-to-beat hemodynamic data, plasma epinephrine, plasma norepinephrine, plasma renin, C-terminal pro-arginine vasopressin (CT-proAVP), C-terminal endothelin-1, and mid-regional fragment of pro–atrial natriuretic peptide were measured resting supine and after 3 minutes of HUT. In multivariate–adjusted regression analyses controlling for age and gender, clinical, neuroendocrine, and hemodynamic parameters were compared between spontaneous and GTN-mediated positive tests.

RESULTS Patients with spontaneous VVS reported more syncope compared to those with GTN-mediated VVS (median interquartile range 6 [17] vs 4 [6], $P = .002$). There was no difference in resting concentrations of neurohormones between the 2 groups. However, after 3 minutes of HUT, those who later developed spontaneous VVS demonstrated higher levels of CT-proAVP (59.5 ± 137 vs 6.9 ± 4.6, $P < 0.001$) and epinephrine (0.57 ± 1.43 vs 0.23 ± 0.19, $P = .003$), and lower blood pressure (119/73 vs 139/81 mm Hg, $P < .001$). Asystole during VVS was more common in the spontaneous VVS group (35% vs 17.5%, $P = .016$).

CONCLUSION Patients with spontaneous VVS on HUT reported more syncopal events than those with drug-potentiated positive HUT, but both groups shared similar supine neuroendocrine profiles. However, spontaneous VVS during HUT is characterized by lower blood pressure, pronounced increases in epinephrine and vasopressin during early HUT phase, and higher frequency of reflex asystole.

KEYWORDS Vasovagal syncope; Head-up tilt test; Neurohormone; Catecholamine; vasopressin

(Heart Rhythm 2016;13:1674–1678)

Introduction

Head-up tilt (HUT) has been identifying vasovagal reflex susceptibility since 1986.[1] The passive HUT proved to be time-consuming, prompting attempts to accelerate a positive result without generating excessive numbers of false positives by addition of pharmacologic challenges. Notably, these were two. First, nitrates in the form of intravenous and subsequently sublingual nitroglycerin (glyceryl trinitrate [GTN]) used by Raviele et al,[2,3] although nitrites/nitrates were used very early by Weiss et al[4] and by Weissler et al[5] in their physiologic experiments to try to understand vasovagal syncope (VVS). Second, intravenous isoproterenol was introduced for clinical testing by Almquist et al.[6]

This study was supported by grants from the European Research Council (StG 282225), Swedish Medical Research Council, Swedish Heart and Lung Foundation, Medical Faculty of Lund University, Malmö University Hospital, Albert Påhlsson Research Foundation, Crafoord Foundation, Ernhold Lundströms Research Foundation, Region Skåne, Hulda and Conrad Mossfelt Foundation, King Gustaf V and Queen Victoria Foundation, Wallenberg Foundation, Lennart Hanssons Memorial Foundation, and Anna Lisa and Sven-Erik Lundgrens Foundation. AF and OM are listed as co-inventors on a patent application "Biomarkers for the diagnosis, prognosis, assessment and therapy stratification of syncope" (PCT/EP2013/001081) for the use of BRAHMS CT-proAVP, CT-proET-1, and MR-proANP for diagnosis of syncope. **Address reprint requests and correspondence:** Dr. Artur Fedorowski, Department of Cardiology, Inga Marie Nilssons gata 46, Skåne University Hospital, 205 02 Malmö, Sweden. E-mail address: Artur.fedorowski@med.lu.se.

We previously characterized the potential role of neurohormones in cardiovascular dysautonomia, that is, in orthostatic hypotension and postural tachycardia syndrome.[7] However, little is known about possible differences in neuroendocrine responses between patients with spontaneous syncope during HUT and those with GTN-induced VVS, none of whom show signs of overt dysautonomia. Consequently, we aimed to study changes in catecholamines, renin, atrial natriuretic peptide (ANP), endothelin-1 (ET-1), and vasopressin in presumed autonomically intact patients (i.e., without signs of orthostatic hypotension or postural tachycardia syndrome) who demonstrated susceptibility to either spontaneous or GTN-induced VVS during tilt testing. Recently developed laboratory assays that allow detection of stable fragments generated during biosynthesis of ANP, ET-1, and vasopressin were applied along with standard catecholamine and renin assays.[8–10] We hypothesized that neuroendocrine and hemodynamic profiles in supine and during early orthostasis might identify patients with pronounced VVS susceptibility who developed syncopal reflex during passive HUT.

Methods

Study population and examination protocol

Two hundred eighty-eight patients (41.3% male, age 49 ± 21 years) with either positive passive (n = 60, 50% male, age 38 ± 17 years) or GTN-challenge HUT (n = 228 [79.2%], 39.0% male, age 51 ± 21 years) were assessed. The patients were selected from the Syncope Study of Unselected Population in Malmö (SYSTEMA) cohort, which was previously reported.[7,11] In brief, patients with unexplained syncope were recruited through referrals from primary care and hospitals in the Skåne region of Sweden, excluding those with cardiac syncope and neurologic, metabolic, and toxic causes of transient loss of consciousness and those with signs of advanced dementia and physical disability.

The examination protocol, previously reported,[7] included antecubital vein cannulation, supine rest for 10 minutes, and blood sampling both at supine rest and in the upright position 3 minutes after elevation of the table to an angle of 60–70° (i.e., after the expected hemodynamic stabilization has been achieved).[12] If diagnosis was not made after 20 minutes in the standing position (passive orthostasis), sublingual nitroglycerin (400 μg) was delivered according to the Italian protocol,[13] and the patient was observed for 15 minutes or until syncope occurred. Beat-to-beat blood pressure (BP) and ECG were continuously monitored using a noninvasive validated method (Nexfin monitor, BMEYE, Amsterdam, The Netherlands).[14,15] Mean BP and heart rate in the supine position and after 3 minutes of HUT were calculated using 30-second averaging. The Regional Ethical Review Board in Lund, Sweden, accepted the study protocol (Reference no. 82/2008), and all study participants gave written informed consent.

Inclusion criteria of VVS

The diagnostic criteria of VVS were met if reproduction of a previously experienced syncope occurred and was associated with an abrupt change in hemodynamic parameters, pronounced hypotension with or without intense bradycardia, or asystole during passive orthostasis or following nitroglycerin challenge.[16] Patients who showed evidence of orthostatic hypotension or postural tachycardia syndrome during passive HUT and those with carotid sinus syndrome were excluded according to the current European syncope guidelines.[16]Cardioinhibitory asystolic response and vasodepressor type were defined according to the modified Vasovagal Syncope International Study (VASIS) classification as either type 2B (asystole) or 3 (hypotension with no or minimal heart rate slowing), respectively.[17]

Assessment of neurohormones

The six cardiovascular neurohormones—plasma epinephrine, plasma norepinephrine, plasma renin, C-terminal pro–arginine vasopressin (CT-proAVP), C-terminal endothelin-1 (CT–proET-1), and mid-regional fragment of pro–atrial natriuretic peptide (MR-proANP)—were collected in resting supine and after 3 minutes of HUT. Plasma biomarkers were measured from blood samples (16 × 250-μL aliquots of EDTA plasma in plastic thermotubes) that had been frozen at –80°C after collection. CT-proAVP, CT–proET-1, and MR-proANP were measured using the following assays according to the manufacturer's instructions: Thermo Scientific BRAHMS CT-proAVP KRYPTOR, Thermo Scientific BRAHMS CT-proET-1 KRYPTOR, and Thermo Scientific BRAHMS MR-proANP KRYPTOR (BRAHMS GmbH, part of ThermoFisher Scientific, Hennigsdorf, Germany). Concentrations of epinephrine and norepinephrine were determined by high-performance liquid chromatography with fluorescence detection.[18] Plasma renin concentrations were analyzed using an immunoradiometric assay (Renin III Generation, Cisbio Bioassays International, Codolet, France).

Statistical analysis

The main characteristics of the study population are presented as mean ± SD for continuous variables and as percentages for categorical variables. Variables that were not normally distributed are presented as median and interquartile range, and were log-transformed before analysis. Group differences in continuous variables were compared using analysis of variance, and dichotomous variables were compared using the Pearson χ^2 test. Thereafter, we performed a multivariable linear/logistic regression analysis, as appropriate, entering the studied parameters (clinical and neuroendocrine) as the dependent variables, and age, gender, and spontaneous VVS during HUT as independent variables. These results are reported as the independent relationship between the clinical parameters, neurohormone concentrations, and spontaneous VVS. All analyses were performed