Age-dependence of relative change in circulating epinephrine and norepinephrine concentrations during tilt-induced vasovagal syncope

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BACKGROUND Although vasovagal syncope (VVS) is preceded by a surge of circulating catecholamines (epinephrine [Epi] and norepinephrine [NE]) of adrenal/renal and synaptic origin, prevention of VVS with β-adrenergic blockade has been ineffective except in "older" VVS patients.

OBJECTIVE We hypothesized that age-related differences of β-blocker effect may be due in part to differences in the relative magnitudes of Epi and NE release during an evolving faint, specifically, greater Epi/NE ratio in younger fainters compared to older patients. To assess this hypothesis, we measured changes in Epi/NE ratios in younger ($<$40 years) vs older ($\geq$40 years) patients during head-up tilt-table test–induced VVS.

METHODS The study comprised 29 patients (12 patients $\geq$40 years [mean 56 $\pm$ 10.7 years] and 17 patients $<$40 years mean 25 $\pm$ 5.7 years]) with recurrent suspected VVS in whom 70° head-up tilt testing reproduced symptoms. Arterial Epi and NE concentrations were measured at baseline (supine), 2 minutes of head-up tilt, and syncope.

RESULTS Baseline Epi and NE concentrations and the Epi/NE ratio did not differ in younger and older groups (Epi: 90 $\pm$ 65 pg/mL vs 70 $\pm$ 32 pg/mL; NE: 226 $\pm$ 122 pg/mL vs 244 $\pm$ 183 pg/mL). However, Epi/NE ratio increased to a greater extent in younger fainters during head-up tilt and tended to be greater in younger patients at both 2 minutes ($<$40: 1.02 $\pm$ 1.29 vs $\geq$40: 0.40 $\pm$ 0.27, P = .11) and at symptoms ($<$40: 2.6 $\pm$ 1.26 vs $\geq$40: 1.6 $\pm$ 0.71, P = .03). At symptoms, Epi/NE ratio $\geq$2.5 was observed in 9 of 17 younger patients vs 1 of 12 older patients (P = .02).

CONCLUSION Epi/NE ratios tend to be greater in younger fainters, a finding that may account in part for the observation that β-blocker therapy is less effective in reducing VVS susceptibility in younger individuals.

KEYWORDS Epinephrine; Norepinephrine; Vasodilation; Vasovagal syncope

ABBREVIATIONS **Epi** = epinephrine; **NE** = norepinephrine

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Introduction

The pathophysiology of vasovagal syncope remains incompletely understood. Nevertheless, one consistent observation is that evolving vasovagal episodes are preceded by an apparent transient period of increased sympathetic activity. This "hypersympathetic" phase typically is characterized by sinus tachycardia and a surge of sympathetic neurohumoral activity.[1–4] However, as pointed out previously,[3] there is a potentially important difference in the relative magnitudes of increase of circulating epinephrine (Epi) and norepinephrine (NE), with the Epi surge being substantially greater ("sympathoadrenal imbalance"[3]). Because the β_2-adrenergic agonist properties of Epi cause vasodilation through effects on vascular smooth muscle whereas NE (α-adrenergic action) tends to do the reverse, excess Epi release may be expected to increase the risk of hypotension and consequent cerebral hypoperfusion.

Whether sympathetic neural and hormonal activation plays a direct role in triggering subsequent hypotension (with or without marked bradycardia) in vasovagal patients remains unknown. Nevertheless, recognition of a premonitory period of increased sympathetic activity provided the rationale for assessing the possibility that β-adrenergic blockade might reduce vasovagal susceptibility. In this regard, despite positive findings in observational reports and one clinical trial,[5–8] when subjected to randomized controlled trials, β-adrenergic blockade therapy has generally proved to be ineffective.[9–14] On the other hand, several studies, including the randomized multicenter Prevention of Syncope Trial (POST),[14] observed an effect modification by age. Specifically, these reports suggested that β-adrenergic blockade may be beneficial in "older" vasovagal syncope patients but not in younger individuals.[6,14,15]

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In this study, we hypothesized that the relative magnitudes of excess catecholamine release during the premonitory "hypersympathetic" phase of an evolving vasovagal syncope favored greater Epi than NE release in younger individuals compared to older fainters. If true, it may be more difficult to achieve β-adrenergic blockade with consequent relative α-adrenergic predominance using conventional doses of β-adrenergic agents in younger individuals. To assess this hypothesis, we examined the relative magnitudes of circulating arterial Epi and NE concentrations at baseline and during head-up tilt-table test–induced vasovagal syncope in younger and older patients.

Methods

Patient population

Data used in this study were obtained prospectively during assessment of patients suspected of having recurrent (>2 in past 6 months) vasovagal syncope, but in whom head-up tilt study was deemed appropriate in order to help confirm the diagnosis. The patient population was divided into 2 tilt-test positive groups—a younger group <40 years of age and an older group ≥40 years of age—and 1 tilt-test negative group (Control). The age cutoffs (ie, <40 and ≥40 years) were based on the predetermined age cutoffs used in the POST design.[16] Data obtained in syncope patients were compared with analogous measurements from the Control group.

Patients and control subjects were included in this study based on the following clinical findings:

1. History of recurrent apparent syncope and presyncope symptoms suspected to be of vasovagal origin during initial clinical evaluation, but in whom the cause remained uncertain after a detailed medical history and physical examination, 12-lead ECG, and echocardiogram,
2. Absence of excessive obesity (body mass index <30), hematologic or biochemical abnormalities, or use of drugs known to predispose to orthostatic hypotension,
3. Absence of left ventricular systolic dysfunction (estimated ejection fraction >50% by echocardiogram or radionuclide evaluation), and
4. Withdrawal of all cardioactive medications for at least 5 half-lives prior to tilt-table study.

Written informed consent was obtained from all individuals prior to study.

Upright tilt-table testing protocol

A minimum 20-minute equilibration time, with the patients or control subjects resting in the supine position in a darkened quiet procedure room, was allowed prior to commencement of baseline recordings for the tilt-table testing procedure. During the equilibration period, each individual received approximately 500 mL of normal saline (approximately 100 mL for each "fasting hour" prior to the study in order to approximate a euvolemic state). Subsequently, each patient or control subject was maintained with a normal saline intravenous infusion of 50 mL/h.

The clinical laboratory methods used in this study have been described in detail previously.[4] In brief, arterial pressure was recorded using a femoral artery catheter (placed approximately 30 minutes prior to initiating the tilt-test procedure) and a fluid-filled system calibrated to the right atrial level. The patient was gently secured (using hook-and-loop straps) to the tilt table, ensuring appropriate positioning to permit use of a footboard for weight-bearing.

The protocol comprised a 70° head-up tilt for a maximum of 30 minutes' duration in the absence of any provocative drugs. Upright posture was maintained until either development of syncope or intolerable near-syncope symptoms, or completion of maximum tilt duration. If syncope occurred, the table was promptly returned to the supine position. Only patients who developed frank syncope or intolerable near-syncope were included in this study.

Catecholamine sampling and measurements

In all individuals, a standard sidearm vascular introducer was used to obtain femoral artery blood samples. The latter catheter was secured in position by a transparent adhesive dressing in order to prevent displacement during movement of the tilt table to the upright position.

Blood samples were obtained with the patient resting in the supine position (baseline), at approximately 2 minutes of upright tilt, and at development of symptoms of syncope or imminent syncope. Measurement of Epi and NE plasma concentrations was undertaken by high-pressure liquid chromatography technique. Because blood sampling required slow withdrawal and fluid reinfusion to minimize hemodynamic impact, the timing of samples is approximate

Table 1 Baseline data

Patient group	Age (y)	Gender (female/male)	Baseline blood pressure (mm Hg)	Epi/NE ratio
Younger (<40 y)	25 ± 5.7	9/8	Systolic: 135 ± 17.4 Diastolic: 71 ± 12.1 Mean: 90 ± 13	0.4 ± 0.22
Older (≥40 y)	56 ± 10.7	7/5	Systolic: 121 ± 11.5 Diastolic: 65 ± 4.6 Mean: 86 ± 7	0.3 ± 0.20

Values are given as number or mean ± SD.
Epi = epinephrine; NE = norepinephrine.