

An Increased Endothelial-Independent Vasodilation Is the Hallmark of the Neurally Mediated Syncope

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ABSTRACT

Background: The neurally mediated syncope (NMS) is sustained by complex cardiac and vascular reflexes, acting on and amplified by central autonomic loops, resulting in bradycardia and hypotension.

Hypothesis: Our aim was to assess whether the pathophysiology of NMS is also related to an abnormal peripheral vasoreactivity.

Methods: We evaluated by ultrasound the flow-mediated vasodilation (FMD) and the nitrate-mediated dilation (NMD) in 17 patients with NMS, induced by drug-free tilt test in 6 subjects and by nitrate-potentiated tilt test in the other 11 cases; the syncope was classified as vasodepressive (VD) in 8 cases, cardioinhibitory (CI) in 7, and mixed in 2.

Results: The FMD was not different from controls (10.2 ± 4.5 vs 11.4 ± 3.9 , $P = \text{ns}$), with normal recovery times; the NMD was greater in fainting subjects than in controls (26.7 ± 7.3 vs 19.0 ± 3.6 , $P < 0.05$), with higher values in VD than in CI syncope (31.1 ± 7.0 vs 23.1 ± 5.0 , $P = \text{ns}$); compared to controls, subjects with NMS showed normal recovery times after FMD but longer recovery times after nitrate administration (13.0 ± 5.6 vs 6.3 ± 0.7 minutes, $P < 0.05$).

Conclusions: The evaluation of endothelial function supports evidence that NMS is characterized by a marked and sustained endothelial-independent vasodilation, in the presence of a normal FMD; vascular hyperreactivity in response to nitrate administration is particularly overt in vasodepressive syncope and can explain the high rate of responses to nitrate administration during tilt test.

Introduction

The pathophysiologic mechanisms of the neurally mediated syncope (NMS), consisting of a transient loss of consciousness and postural tone, are complex and seem to involve changes in the autonomic and vascular tone, resulting in a reflex bradycardia with a marked hypotension, debated to be active or passive in origin.^{1–4}

Head-up tilt test is a powerful, low-risk method able to identify patients affected by an NMS; a positive response to the tilt test, reproducing the syncope, may explain the pathophysiologic cardiovascular mechanism specific for each patient. Patients experiencing a syncope driven by a deep reflex bradycardia or asystolia may be treated by cardiac pacing, which seems to be more effective than β -blockade for the prevention of syncopal recurrences in

highly symptomatic vasovagal fainters with relative bradycardia during tilt-induced syncope.⁵ On the other hand, pharmacologic therapy was shown to be disappointing in subjects with vasodepressive (VD) syncope, providing only a poor reduction of the recurrence of clinical events.^{6,7}

Recent studies have focused on mechanisms of the peripheral circulatory regulation in subjects affected by NMS. Both invasive and noninvasive methods have been used to identify an active or passive mechanism driving to the peripheral vasodilation^{8–11}; several articles have underlined the central role played by the endothelium for the regulation of the vascular tone, justifying the study of endothelial function in subjects with a history of syncope using a direct, noninvasive method.^{12–15} We tested the hypothesis that subjects with a tilt-induced syncope, especially if occurring after nitrate administration, may present an abnormal vascular reaction, independently of the response to the flow-mediated vasodilation (FMD); furthermore, we evaluated the clinical implication of the endothelial function at 2-year follow-up in these subjects.

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Methods

We evaluated 17 consecutive outpatient subjects, age 35.8 ± 16.0 years (8 men and 9 women), referred to our Department of Cardiology for a recent recurrent syncopal spell and with a positive response to the tilt table test. No patient was receiving pharmacologic therapy. All patients were nonsmokers and free from cardiovascular, immunologic, and neurologic diseases, as assessed at the clinical investigation, standard 12-lead electrocardiogram (ECG) and 24-hour ambulatory ECG, Doppler echocardiogram, and electroencephalogram. The results obtained by the study of the endothelial function in these patients have been compared with those coming from the same study performed in a control group consisting of 15 healthy subjects (9 men and 6 women) free from syncopal attacks, age 39.9 ± 12.5 years.

Head-up Tilt Test

The subjects underwent tilt testing in the morning in a quiet room, after overnight fasting, at a room temperature of 22°C , recording the systodiastolic blood pressure with a sphygmomanometer at 5-minute intervals and monitoring the cardiac rhythm with a 12-lead ECG device (Esa Ote P80 Power; Esa Ote Biomedica, Castenaso, Italy); the procedure was carried out using an electronically controlled tilt table, with a footboard support (VDE 0551; Ferro C.I.A.R., Codogné [TV], Italy), upright at 60 degrees for 30 minutes; if the passive tilt test phase was negative, each subject received $300\ \mu\text{g}$ of sublingual nitroglycerine spray (Natispray; Teofarma, Pavia, Italy), continuing the test for 15 more minutes; head-up tilt test was stopped at the induction of the syncope, and the observed responses were classified using the Vasovagal Syncope International Study (VASIS) criteria, as mixed (VASIS-1), cardioinhibition (VASIS-2A), severe cardioinhibition/asystole (VASIS 2-B) or pure vasodepression (VASIS-3).^{16–19}

Endothelial Function Study

Endothelial function was studied using ultrasound technique according to current guidelines, and the evaluation was performed 2 days after the head-up tilt test. The brachial artery reactivity was assessed in the morning, in a fasting, resting, and supine state; patients maintained clinostatic position for 20 minutes, at a room temperature of 22°C . The imaging of the brachial artery, 2 to 5 cm above the antecubital fossa, was obtained with a high-resolution ultrasonographic device equipped with a 10-MHz linear-array transducer (Agilent ImagePoint Hx; Agilent Technologies, MA). The left brachial artery was scanned over a longitudinal section, obtaining good-quality frames synchronized on the R wave of the ECG. The blood flow velocity of the brachial artery was measured by pulsed-wave Doppler signal, placing the sample volume in the center of the artery; peak flow rate echo-Doppler measurements were performed on the brachial artery at rest, during reactive hyperemia, and after sublingual nitrate administration. Measurements of the artery internal diameter were taken from the anterior to the posterior wall at the interface between media and intima or to the hardest echo ("M" line), at end diastole; the ultrasound transducer was maintained on the brachial

artery by a dedicated stereotactic probe-holding device. In our laboratory, the inter- and intraobserver variability of diameter measurements was $<3\%$.

The endothelium-dependent FMD was assessed by measuring the maximal increase in the internal diameter of the brachial artery during reactive hyperemia evoked by the release of a cuff inflated to 250 mm Hg for 5 minutes on the upper arm, distal to the measurement site. After cuff deflation, the maximal peak flow rate was measured at 15" and 30"; the changes in brachial artery diameter were continuously recorded and were measured each 30" for 6 minutes until each patient recovered the basal values and were reported as a percentage of the baseline. Reference normal values for FMD were $\geq 5\%$.^{14,15}

After a rest period of 15 minutes, baseline measurements (diameter and flow velocity) of the brachial artery were repeated, and the endothelium-independent vasodilatation was evaluated by sublingual administration of $300\ \mu\text{g}$ of nitroglycerine (Natispray); thereafter, the diameter of the brachial artery was measured every 30 seconds until each patient recovered the basal values; the changes in brachial artery diameter were reported as percentage of basal values. Reference normal values for nitrate-mediated dilation (NMD) were $\geq 10\%$.^{15,16} Investigations were in accordance with the Declaration of Helsinki.

Statistical Analysis

Data are expressed as mean \pm standard deviation if not otherwise stated. Obtained variables were tested for normal distribution by the Kolmogorov-Smirnov test. The values obtained in each group and the differences between measurements were analyzed by paired or unpaired Student *t* test or by analysis of variance for repeated measurements, followed by the Bonferroni test; the Wilcoxon test was used when otherwise appropriate. Linear regression analysis with Pearson correlation coefficient was used to investigate the relationship between variables of interest. Results were considered statistically significant if $P < 0.05$; differences between fainting subjects and controls were calculated with the unpaired *t* test; differences within each group, in different conditions, were calculated with paired *t* test. In all tests, statistical significance was defined as $P < 0.05$.

Results

The NMS, induced by tilt test, in our 15 patients, was classified as cardioinhibitory (CI) in 7 cases (VASIS-2A in 4 and VASIS-2B in 3), VD in 8 (VASIS-3), and mixed in 2 cases (VASIS-1); all but 1 of the subjects with VD syncope were women and were significantly younger than CI patients, (21.9 ± 4.6 vs 49.7 ± 11.8 years, $P < 0.05$).

Compared to the controls, patients showed lower basal values of systolic blood pressure (113.2 ± 14.8 vs 125.7 ± 7.3 mm Hg, $P < 0.05$), diastolic blood pressure (60.0 ± 8.8 vs 78.7 ± 3.2 mm Hg, $P < 0.05$), with similar heart rate values (66.4 ± 9.2 vs 68.2 ± 9.8 bpm, $P = \text{ns}$).

The drug-free tilt test phase induced the syncope in 6 subjects, at 19.5 ± 7.3 minutes of passive standing (CI in 3 cases and VD in 3); the other 11 patients developed syncope during the nitroglycerine-potentiated phase, at

Table 1. Results of Endothelial Function Study in Population and Controls

	No.	Resting Brachial Artery Diameter	FMD, %	NMD, %	FMD Recovery Times, min	NMD Recovery Times, min
NMD	17	3.4 ± 0.6 ^a	10.2 ± 4.5	26.7 ± 7.3 ^a	4.1 ± 2.5	13.0 ± 5.6 ^a
VD syncope	8	3.0 ± 0.4 ^a	11.3 ± 5.7	31.1 ± 7.0 ^a	3.7 ± 3.5	13.6 ± 6.2 ^a
CI syncope	7	3.8 ± 0.6	10.3 ± 2.1	23.1 ± 5.0	4.7 ± 1.8	15.0 ± 5.0 ^a
Mixed	2	3.4 ± 0.1	5.7 ± 5.1	20.4 ± 5.3	3.5 ± 0.7	7.5 ± 0.7 ^a
Controls	15	4.0 ± 0.8	11.4 ± 3.9	19.0 ± 3.6	3.3 ± 0.7	6.3 ± 0.7

Abbreviations: CI, cardioinhibitory; FMD, flow-mediated vasodilation; NMD, nitrate-mediated dilation; VD, vasodepressive. ^a*P* < 0.05.

11.6 ± 3.6 minutes after drug administration, classified as VD in 5 cases, CI in 4, and mixed in 2.

The ultrasound assessment of the endothelial function showed resting values of brachial artery diameter lower in syncope patients than in controls (3.4 ± 0.6 vs 4.0 ± 0.8 mm, *P* < 0.05); lower values of the brachial artery diameter were recorded in VD than in CI (3.0 ± 0.4 vs 3.8 ± 0.6 mm, *P* < 0.01) and mixed syncope (3.0 ± 0.4 vs 3.4 ± 0.1, *P* = ns); subjects with CI syncope had similar values of the brachial artery diameter compared to the controls (3.8 ± 0.6 vs 4.0 ± 0.8 mm, *P* = ns) (Table 1).

The FMD was within the normal range in NMS subjects, with poor and not significant differences compared to the controls (FMD = 10.2 ± 4.5 vs 11.4 ± 3.9, *P* = ns), as well as between patients with CI and VD syncope (10.3 ± 2.1 vs 11.3 ± 5.7, *P* = ns); the poorer FMD (5.7 ± 5.1) was recorded in the mixed NMS, and 1 of these subjects had increased low-density lipoprotein cholesterol with overt endothelial dysfunction, characterized by an FMD <5%.

In the subjects with NMS, the normal FMD values were paired to a poor increase of the recovery time after reactive hyperemia, compared to controls (4.1 ± 2.5 vs 3.3 ± 0.7 minutes, *P* = ns) (Table 1).

The endothelial independent vasodilation, assessed with the NMD, was significantly higher in fainting subjects than in controls (26.7 ± 7.3 vs 19.0 ± 3.6, *P* < 0.05), with a higher vasodilation in VD patients than in CI (31.1 ± 7.0 vs 23.1 ± 5.0, *P* = ns), as well as in VD vs mixed NMS (31.1 ± 7.0 vs 20.4 ± 5.3, *P* < 0.05); furthermore, the NMS patients showed a long-lasting passive vasodilation after nitroglycerine administration, with higher recovery times that were significantly longer in NMD than in controls (13.0 ± 5.6 vs 6.3 ± 0.7 minutes, *P* < 0.05), irrespective of the VASIS classification (Table 1).

Statistical analysis showed a correlation between resting brachial artery diameter and age (*r* = 0.705, *P* < 0.01), but we did not find a correlation between age of the fainting patient and his or her FMD (*r* = 0.364, *P* = ns) or between FMD and NMD values (*r* = 0.049, *P* = ns).

We implanted a permanent dual-chamber pacemaker in 2 of the 3 subjects, who were both more than 40 years old, with a head-up tilt test positive for a VASIS-2B CI syncope, according to the recommendations for the prevention of syncopal recurrences in highly symptomatic vasovagal fainters with a marked CI response during tilt-induced syncope.⁶ At the 2-year follow-up, both of them were free from new episodes of syncope and reported improvement

in quality of life. The other 15 patients followed a usual conservative treatment; the 2-year follow-up was obtained in 11 patients, and 3 of these reported a recurrence of syncope, without other significant cardiovascular events; the other 4 patients were lost to follow-up, including the women with an impaired response to the FMD.

Discussion

We found that the hallmark of patients with NMS is a marked and sustained endothelial-independent vasodilation, in the presence of a normal FMD; the vascular hyperreactivity that characterizes the response to the nitrate administration is particularly overt in subjects with a VD syncope and can partially explain the high rate of responses to the nitrate administration during the tilt test. Furthermore, all the syncopal subjects show a greater and longer than normal response to the nitrate administration, irrespective of the type of tilt-induced events, stated according to the VASIS classification, and unrelated to the basal brachial artery diameter, age, and levels of the FMD; we found an abnormal FMD, indicative for endothelial dysfunction, only in 1 hypercholesterolemic women, with a head-up tilt test positive for a mixed syncope.

The head-up tilt test is currently used to induce the syncope, allowing the identification of the pathophysiologic underlying mechanism. The syncope represents the diagnostic end point of the tilt test, but it may not always be induced by the drug-free test; to increase the sensitivity of this test, current protocols recommend pharmacologic stimulation with nitroglycerine or isoproterenol.^{17–19}

The cardiovascular response observed during this provocative test is characterized by the presence of a marked hypotension, typical of these patients, spontaneously occurring and amplified by nitroglycerine administration, which could be similar to the ultrasound pattern found at the evaluation of the endothelial dysfunction.^{12,13}

We found that the nitrate administration induced in all patients a higher endothelium-independent vasodilation, regardless of the type of neuromediated syncope induced by the tilt test; the vascular response to the nitrate administration was more pronounced, but without any statistically significant difference, in subjects with VD syncope.

Our patients showed a marked hypersensitivity to the sublingual nitrate administration that seems to be typical of these subjects and is further expressed by a longstanding endothelial-independent vasodilation, with prolonged

recovery time compared to the controls and without any correlation with the VD or CI mechanism observed at the head-up tilt test.

The deep vasodilator response to the nitrate administration, reported to occur in skeletal muscle district during the vasovagal syncope, seems to be typical of the NMS and likely is a dose-independent phenomenon^{20,21}; this phenomenon indeed seems to suggest an abnormal vascular reactivity that could explain the poor efficacy of the pharmacologic therapy in this setting of patients. All the drugs tested, even using several targets to counteract the reflex response or to enhance the vasoconstriction, were usually reported to be poorly effective.^{1,2,22,23}

The lower basal values of brachial artery diameter recorded in the subjects with a VD syncope seem to be due to the prevalence of young women, as compared to those patients with a CI syncope^{15,24}; moreover, we cannot exclude the possibility that some of our patients have a marked vasoconstrictive tone at rest, followed by a deep vasodilation after the nitrate administration.

The finding of nitrate overactivity, recorded in most of the fainting subjects, may also suggest the possible action of some still poorly assessed nitrergic mechanisms in the pathogenic pathway of NMS, with complex and poorly known interactions between the endothelial function and the autonomic nervous system.^{25–27}

Conclusion

The evaluation of endothelial function supports evidence that the NMS is characterized by a marked and sustained endothelial-independent vasodilation, in the presence of a normal FMD; the vascular hyperreactivity in response to the nitrate administration is particularly overt in the VD syncope and can explain the high rate of responses to the nitrate administration during the head-up tilt test. The small number of observed patients does not allow to draw a conclusion regarding the role of the endothelial-dependent and independent vasodilation in the NMS. Further studies, involving a greater number of patients, will clarify if an overt peripheral vascular hyperreactivity to the nitrate administration could be used as a marker to detect patients likely to experience an NMS but unable or not capable to perform the head-up tilt test, so that the evaluation of the endothelial function could be used also to integrate the noninvasive diagnostic procedures.

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