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Abnormal Reflex Venous Function in Patients With Neuromediated Syncope

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Objectives. **We sought to compare the forearm reflex venous response to mental arithmetic stress in patients with neuromediated syncope and in normal subjects.**

Background. **Patients with neuromediated syncope have a paradoxic arterial vasodilation in response to stressors that usually provoke vasoconstriction. Given the postulated role of diminished preload in provoking the reflex responses resulting in syncope, we hypothesized that mental stress might provoke paradoxic reflex venodilation in patients with neuromediated syncope.**

Methods. **Twelve normal subjects (mean age [±SD] 47 ± 9 years) and 27 patients with neuromediated syncope (mean age 42 ± 13 years) were studied before and during a mental arithmetic stress test. Forearm venous pressure-volume relations were determined by using radionuclide plethysmography.**

Results. **During mental arithmetic stress, heart rate and systolic and diastolic blood pressure increased significantly and similarly both in normal subjects and in patients with neuromediated syncope. The heart rate and blood pressure changes were qualitatively similar in both groups. However, with mental arithmetic stress, forearm venoconstriction of 13 ± 2% (mean ± SEM) was noted in normal subjects ($p < 0.001$) but not in patients with neuromediated syncope (mean 2%, p = NS). This group response of patients with neuromediated syncope did not result from a lack of individual responses but occurred because these patients had a wide range of responses. The normal physiologic and methodologic variability of the method was ±4%. Thirteen of the 27 patients with neuromediated syncope had forearm venoconstriction of 14.5 ± 6.8% during mental arithmetic stress, whereas 7 had paradoxic forearm venodilation of 14.6 ± 8.8%, and 7 were considered nonresponders (−1.3 ± 3.4%). Thus, 14 (52%) of the 27 patients with syncope did not have normal vasoconstriction in response to mental stress.**

Conclusions. **Patients with neuromediated syncope have an abnormal range of forearm venomotor responses to mental arithmetic stress. Reflex control of the veins may play an important role in the pathogenesis of neuromediated syncope.**

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The pathophysiology of neuromediated syncope is poorly understood. It has been postulated (1–4) that an initial reduction in preload is followed by an exaggerated sympathetic response, causing excessive stimulation of left ventricular mechanoreceptors. This in turn triggers an inappropriate decrease in vasomotor tone and heart rate (4–7). Although the role of ventricular mechanoreceptors in the pathophysiology of this syndrome is unclear (8–10), patients with neuromediated syncope do demonstrate abnormal peripheral arterial dilation at the time of syncope or presyncope (4–7). Furthermore, abnormal reflex vascular resistance responses to stimuli that do not induce syncope or presyncope have been observed (11,12).

The cause or causes of individual susceptibility to vasovagal reactions in response to modest degrees of orthostatic stress during everyday life or diagnostic head-up tilt testing remain to be explained. Given that syncope due to the mental stress of fear of blood or injury is widely acknowledged, we postulated that patients with neuromediated syncope might exhibit abnormal reflex venous responses to mental stress. We (13,14) have described a method that uses radionuclide plethysmography to measure reflex changes in forearm venous tone. The purpose of this study was to assess forearm reflex venous function in patients with neuromediated syncope by assessing changes in the forearm venous pressure-volume relation in response to mental arithmetic stress (15).

Methods

Study patients. Thirty-nine patients were studied. The test group included 27 patients, 15 women and 12 men, with neuromediated syncope and a mean age ± SD of 42 ± 13 years (range 19 to 71). All had a history of recurrent syncope in the absence of organic heart disease; only three had a history of possible provocation of presyncope or syncope by mental stress. They were included in the study if they developed presyncope or syncope on a head-up tilt table test, which was

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carried out as previously described (16). The comparison group comprised 12 normal subjects, 8 men and 4 women, with an average age of 47 ± 9 years (range 33 to 72). These 12 subjects were selected from consecutive patients referred to the nuclear cardiology laboratory for rest-exercise radionuclide ventriculography to rule out coronary artery disease because of atypical chest pain. They were invited to participate if their posttest likelihood of coronary artery disease was <10% and if they had normal findings on a rest-exercise radionuclide ventriculogram. No subject in either group was taking medication at the time of the study. All 39 participants provided informed written consent. The study was approved by the University of Calgary Conjoint Medical Ethics Committee.

Mental arithmetic stress test. One investigator, not previously known to the participants, administered a standard mental arithmetic stress test (15) to all study subjects. The test required subtraction of serial 17s from a 4-digit number or serial 7s and 3s from a 3-digit number. We began the arithmetic test with serial subtraction of 7s, then adjusted the difficulty to obtain optimal effort without causing the patient to stop because of frustration. The only interaction with the subjects during administration of the test was frequent prompting to concentrate or to accelerate if they appeared to be relaxing during the task. Individual perception of the stress level varied widely and did not relate to how well or how poorly each person performed. The Borg scale was used to quantitate the degree of difficulty during the test.

Radionuclide plethysmography. Forearm venous pressure-volume relations were determined with radionuclide plethysmography, a previously described and validated technique (13,14). Briefly, forearm venous volume was measured by using blood pool scintigraphy. After in vivo labeling of the red blood cells with 740 mBq (20 mCi) of technetium-99m, 30-s static forearm images were acquired with a standard gamma camera (Siemens Mobile LEM+ZLC Digitract) equipped with a high sensitivity parallel-hole collimator and interfaced to a dedicated nuclear medicine computer system (ADAC model 3000). Imaging was started ≥30 min after initial labeling to minimize measurement error due to unbound technetium-99m (17). Forearm images were recorded before and 30 s after inflation of a blood pressure cuff placed on the arm being imaged. Thirty seconds was deemed appropriate to allow for hemodynamic stabilization.

The count rate in a region of interest of the mid-forearm obtained with no occluding pressure or mental arithmetic stress was arbitrarily taken to represent 100% forearm vascular (venous) volume. All subsequent readings, corrected for physical decay, were expressed as a percent of this value. Measures of scintigraphic forearm vascular volumes (in percent units) at occluding cuff pressures of 0, 10, 20 and 30 mm Hg were used to construct forearm venous pressure-volume relations (13).

Study design. All studies were performed in the morning after an overnight fast. With subjects in the sitting position, the forearm was placed prone on the surface of the gamma camera, which was positioned in front of the patient with its surface facing up at a level 4 cm below the sternal angle.

Control data were recorded first. Thirty-second scintigrams were taken at 0, 10, 20 and 30 mm Hg arm occluding pressures, starting at 0 and increasing stepwise at 1-min intervals to 30 mm Hg. After data at 30-mm Hg occluding pressure were recorded, cuff pressure was reduced to 0. Four minutes later, duplicate control data were recorded at the same four venous arm occluding pressures. Two minutes after this duplicate recording, mental arithmetic stress was begun. Scintigrams of the forearm were recorded at the four occluding pressures in duplicate, with the first run beginning at 2 min and the second run starting at 8 min after initiation of mental stress. Thus, mental stress testing was performed for 12 min in this study and was always administered by the same operator. The last scintigraphic run (post-stress stage) was recorded 10 min after termination of mental arithmetic stress. Heart rate (by 15-s electrocardiographic rhythm strip recording) and blood pressure (by sphygmomanometer cuff on the opposite arm) were recorded at 2-min intervals during the control, mental arithmetic stress and post-stress stages.

Statistical analysis. For purposes of analysis, for each participant, we averaged the duplicate control values of the forearm volumes at the respective occluding pressures to obtain a single control value for forearm vascular pressure-volume relation before the performance of any intervention. The relative forearm regional blood pressure volume changes produced by mental arithmetic stress were analyzed by using analysis of variance (ANOVA) with repeated measures. Orthogonal contrasts (18) were defined to examine the pressure-volume curves for evidence of nonlinearity and nonzero slope, the changes between the curves in the control period and during mental arithmetic stress and the interaction between them. A significant interaction would indicate a lack of parallelism of the curves. We used linear regression analysis and defined dummy variables for each participant so that we could examine the estimates for each participant's curve and the changes between the curves for each participant, together with the SEE and the corresponding p value. The results showed that the pressure-volume curves in the range of the venous occluding pressure used were linear and that the control and mental arithmetic stress curves were parallel. The ANOVA with repeated measures showed no evidence of a lack of parallelism of the curves ($p = 0.94$). The nonsignificant F value ($p = 0.21$) obtained for the nonlinear fit indicated that adoption of a straight line model would be appropriate. There was evidence of nonzero slopes ($p < 0.001$). We therefore adopted a parallel straight line model as in previous studies (18). The ANOVA with Newman-Keuls and Tukey tests was used to establish the significance of the changes in blood pressure and heart rate among control, mental arithmetic stress testing and post-stress data. Statistical significance was accepted at the 95% confidence level ($p < 0.05$). Data are presented as mean value ± SD unless otherwise noted.

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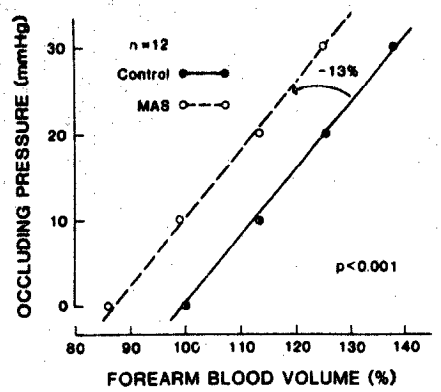

Figure 1. Mean forearm vascular (venous) pressure-volume relation before (Control) and during mental arithmetic stress (MAS) in 12 normal subjects. Mental arithmetic stress produced significant venoconstriction. There was no loss of linearity of parallelism.

Table 1. Distribution of Estimates of Displacement in Pressure-Volume Relations on the Volume Axis Due to Mental Arithmetic Stress

	Subjects (no.)	Percent Volume Displacement*		
		Mean ± SD	Median	Range
Group 1 (venodilation)	7	14.6 ± 8.8	9.7	8.8 to 30.8
Group 2 (venoconstriction)	13	−14.5 ± 6.8	−9.1	−26.9 to −5.8
Group 3 (nonresponders)	7	−1.3 ± 3.4	−3.1	−4.6 to 4.8

*Positive estimates indicate displacement away from the pressure axis (venodilation); negative estimates indicate displacement toward the pressure axis (venoconstriction). The statistical significance is $p < 0.001$.

Results

All subjects completed the study protocol without incident. Perception of the level of stress was similar in both groups. The mean Borg scale grading was 6.4 ± 2.6 for normal subjects and 6.2 ± 2.1 for patients with neuromediated syncope (p = NS). During mental arithmetic stress, blood pressure and heart rate increased significantly in both groups. There were no significant differences between normal subjects and patients in the changes produced by mental arithmetic stress testing in systolic blood pressure (+21 vs. +20 mm Hg), diastolic blood pressure (+9 vs. +9 mm Hg) or heart rate (+12 vs. +13 beats/min).

For example, heart rate increased in normal subjects from 75 ± 15 to 87 ± 17 beats/min and in patients with syncope from 72 ± 11 to 85 ± 16 beats/min. Similarly, systolic pressure increased in normal subjects from 130 ± 14 to 151 ± 21 mm Hg and in patients with syncope from 123 ± 18 to 143 ± 20 mm Hg. Diastolic pressure increased in normal subjects from 82 ± 11 to 91 ± 16 mm Hg and in patients with syncope from 76 ± 17 to 85 ± 17 mm Hg ($p < 0.001$, ANOVA with repeated measures).

During mental arithmetic stress, the forearm vascular pressure-volume relation in normal subjects was displaced toward the pressure axis by 13% ($p < 0.001$), implying venoconstriction (Fig. 1). The F value for the mean change in the forearm vascular pressure-volume relation due to mental arithmetic stress in the patients with syncope did not show the same degree of significance ($p < 0.05$). Examination of the estimates of the individual pressure-volume curves from the regression analysis indicated that the patients with neuromediated syncope responded with a wide range of venous volume changes, with some patients showing forearm venoconstriction, some showing venodilation and some showing no response.

To determine the significance of this wide range of venous responses, we first defined the normal variability of the forearm vascular pressure-volume curves between the two sets of control unstressed data in all 39 study participants. The pressure-volume curves of both control stages for the entire group were very similar. The SEE values were <2% at all levels of arm cuff occluding pressures. Because twice the SEE will include 95% of all repeated measurements, we defined the normal variability of forearm vascular pressure-volume measurements to be ±4% volume units. We then grouped the patients with syncope and normal subjects by their response to mental arithmetic stress according to whether they showed forearm venoconstriction (displacement of the pressure-volume relation toward the pressure axis by ≥5% volume units), venodilation (displacement of the forearm pressure-volume relation away from the pressure axis by ≥5% volume units) or no response (displacement of the pressure-volume curve toward or away from the pressure axis by ≤4% volume units). Venoconstriction of 13 ± 2% (mean ± SEM) was present during mental stress in the normal group (Fig. 1); 11 of these 12 subjects exhibited forearm venoconstriction ≥5% during mental arithmetic stress, and the 12th subject also showed leftward displacement of the forearm vascular pressure-volume relation but of only 3% volume units. No subject in the normal group showed forearm venodilation during mental arithmetic stress.

The patients with neuromediated syncope were classified into three groups according to their response to mental arithmetic stress (Table 1). Figure 2 shows representative curves from two patients from each of these three groups. Group 1 (seven patients) showed significant ($p < 0.05$) displacement of the forearm pressure-volume relation away from the pressure axis, suggesting forearm venodilation; they had a mean forearm venodilation of 14.6% (range 8.8% to 30.8%). Group 2 (13 patients) showed significant ($p < 0.05$) displacement of the forearm pressure-volume relation toward the pressure axis, suggesting venoconstriction; they had a mean displacement of the forearm venous pressure-volume toward

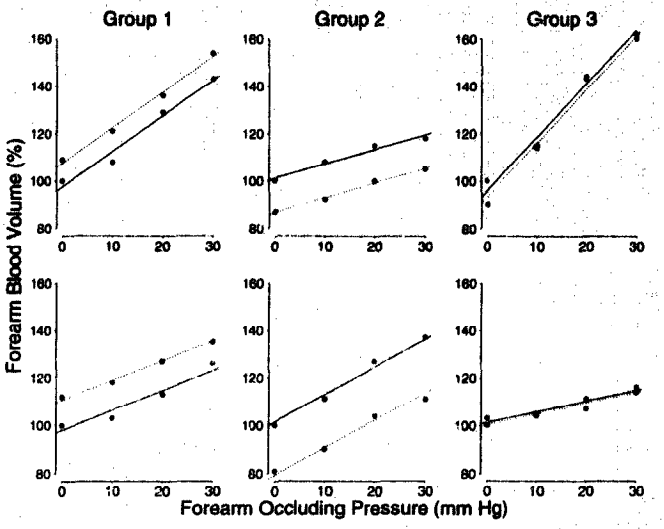

Figure 2. Forearm vascular (venous) pressure-volume relations before (control **[solid lines]**) and during mental arithmetic stress **(dotted lines)** in three subgroups of patients with neuromediated syncope. The relations are from two patients with venoconstriction (Group 1, **left panels**), two patients with venodilation (Group 2, **center panels**) and two patients with no significant response to mental stress (Group 3, **right panels**).

the pressure axis of 14.5% (range 5.8% to 26.9%). In both groups 1 and 2, forearm venoconstriction or venodilation, respectively, was statistically highly significant ($p < 0.001$) compared with the respective control value. In group 3 (seven patients) displacement of the forearm pressure-volume relation was not significantly different from 0; the mean displacement of the forearm venous pressure-volume toward the pressure axis was only 1.3%. The difference in the distributions of patients and control subjects in these three groups was highly significant ($p < 0.001$, chi-square). No differences were found between these three subgroups in age, gender, clinical characteristics, tilt table test results or hemodynamic responses to mental arithmetic stress testing.

Discussion

Patients with neuromediated syncope have a paradoxic arterial vasodilation in response to stressors that usually provoke vasoconstriction. The principal new finding from this study is that patients with syncope have an abnormal range of forearm venomotor responses to mental arithmetic stress. At least 14 of the 27 patients did not have normal venoconstriction in response to such stress.

Vasomotor tone and syncope. Abnormal arterial vasomotor responses have been noted during spontaneous or provoked episodes of hypotension in patients with neuromediated syncope (2,19,20). Moreover, abnormal arterial dilation also occurs in the presence of nonhypotensive stimuli (11,12) such as orthostatic stress and graded lower body negative pressure. More recently, patients with neuromediated syncope have been reported (21) to show impaired constriction or paradoxic vasodilation during isotonic exercise instead of the normal reflex vasoconstrictor response of resistance vessels in nonexercising limbs. Thus, patients with neuromediated syncope might not have appropriate vasoconstriction in response to a variety of physiologic stressors.

Patients with syncope also might have abnormal autonomic control of the veins. During head-up tilt testing, such patients had greater venous pooling and less variability in calf venous volume during syncope (22). This loss of variability might represent the loss of venous responsiveness to sympathetic stimulation. Shalev et al. (3) showed that cardiac volumes were diminished during syncope induced by tilt table testing in patients with neuromediated syncope. This might have been caused by loss of preload due to paradoxic venodilation, in a setting that might be expected to produce venoconstriction as it also increases catecholamine levels (1).

Mental arithmetic is a well established technique for evoking physiologic stress. We (14) recently showed that mental arithmetic stress produced significant forearm venoconstriction in a group of normal subjects. Venoconstriction, as well as an increase in heart rate and blood pressure, is believed (23,24) to result from stimulation of the sympathetic nervous system and release of adrenomedullary catecholamines induced by mental stress. In this study we have shown that patients with syncope exhibit a range of forearm venomotor responses, with 7 of the 27 patients exhibiting a paradoxic venodilation, 13 exhibiting venoconstriction and 7 patients showing no significant venomotor response to mental stress.

Sympathoinhibition and syncope. Thus, many subjects with neuromediated syncope have abnormal forearm venomotor responses to mental arithmetic stress. They also exhibit paradoxic vasodilation in response to orthostatic stress (11),

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graded lower body negative pressure (12) and isotonic exercise (21). Each of these stresses might be expected to produce sympathoexcitation yet produce vasodilation and venomotor abnormalities consistent with sympathoinhibition. We speculate that the common feature of these pathophysiologic findings is an abnormal stimulation by efferent sympathetic nerves of one or more groups of sinoaortic or cardiopulmonary baroreceptors. Local catecholamines stimulate canine ventricular baroreceptors (25) and rat carotid sinus baroreceptors (26). Baroreceptor activation causes sympathoinhibition; therefore, the sympathetic excitation caused by orthostatic stress, mental stress and isotonic exercise might cause paradoxic sympathetic withdrawal from peripheral vasculature, manifested in vasodilation and venodilation. It is tempting to conjecture that the sympathetic withdrawal seen during neuromediated syncope shares this pathophysiology (27).

Limitations of the study. Although all patients had a clinical diagnosis of neuromediated syncope and had had a positive tilt table test, they were not a homogeneous group selected on the basis of their clinical response to mental stress. In fact, only 3 of the 27 patients thought that intellectual or emotional stress provoked their syncope (28). Although a selected population of these patients with fear of blood or injury might have had a more homogeneous response, we have not routinely studied them because our clinical program is aimed toward patients with syncope of unexplained etiology. Similarly, our normal subjects were not completely asymptomatic volunteers, although none had cardiovascular disease. It is conceivable that they had occult autonomic disturbances that were responsible for their atypical chest pain, although such a link is speculative.

However, both cold pressor stimulus (29) and infused catecholamines (30) alter forearm venous volume and tone measured by strain gauge plethysmography, and we (13) have shown that results of radionuclide plethysmography correlate well with those of strain gauge plethysmography. We cannot directly distinguish venomotor from arteriolar changes. Thus, some of the decrease in forearm blood volume during mental arithmetic stress may have resulted from arterial vasoconstriction, decreased blood flow and, therefore, less distending pressure in the veins and venules. However, mental stress caused an increase, not a decrease, in blood flow in three separate studies (24,29,31), suggesting that our findings reflect changes in venomotor tone. Only forearm venomotor tone was studied, and although we have extrapolated from the forearm data, it is conceivable that other venous beds respond differently to mental stress.

Finally, the present study was not designed to elucidate the mechanism or mechanisms of the venomotor changes produced by mental arithmetic stress. Although (forearm) muscle veins are sparsely innervated by sympathetic nerves (32), the stimulus of mental stress raises plasma catecholamine levels (23,24) and might constrict noninnervated forearm veins (32,33). We cannot exclude the participation of forearm muscle veins or the cutaneous veins in the response to mental arithmetic stress.

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