

Neurally Mediated Cardiac Syncope: Autonomic Modulation After Normal Saline Infusion

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- OBJECTIVES** This study assessed the heart variability response to orthostatic stress during tilt table testing before and after normal saline administration.
- BACKGROUND** The efficacy of sodium chloride and mineralocorticoid in the treatment of neurally mediated cardiac syncope is attributed to intravascular volume expansion; however, their modulation of autonomic nervous system activity has not been evaluated.
- METHODS** Heart rate variability analysis was performed on 12 adolescents with a history of syncope or presyncope (mean age 15.2 ± 0.7 years) during tilt table testing. Subjects were upright 80° for 30 min or until syncope. After normal saline administration, the patient was returned upright for 30 min. Heart rate variability analysis data were analyzed by an autoregression model (Burg method).
- RESULTS** All subjects reproducibly developed syncope during control tilt table testing; median time to syncope was 9.4 ± 2.1 min. After normal saline infusion, none of the subjects developed syncope after 30 min upright. In the control tilt, there was an initial increase followed by a progressive decrease in low frequency power until syncope. Repeat tilt after normal saline administration demonstrates that low frequency power increased but the magnitude of initial change was blunted when compared with control. In addition, low frequency power increased during normal saline tilt sequence compared with the control tilt, during which it decreased.
- CONCLUSIONS** Normal saline blunted low frequency power stimulation and prevented paradoxical low frequency power (sympathetic) withdrawal. Increasing intravascular volume with normal saline alters autonomic responses that may trigger neurally mediated syncope reflexes. (J Am Coll Cardiol 1999;33:2059–66) © 1999 by the American College of Cardiology
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Recurrent unexplained syncope is a common disorder affecting children and adolescents, with up to 15% to 25% of children experiencing at least one episode of syncope (1,2). The most commonly accepted hypothesized mechanism for neurally mediated cardiac syncope invokes dependent pooling during orthostatic stress to produce effective hypovolemia, thereby activating the Bezold-Jarisch reflex and paradoxically reducing sympathetic tone; the result is vasodilation or bradycardia (3–5). Conversely, studies of cardiac transplant patients suggest that ventricular receptor activation may not be the exclusive cause of vasovagal syncope (6–9). Nevertheless, in young patients with recur-

rent syncope, the passive head-up tilt (HUT) may be very useful in suggesting a neurally mediated etiology and for determining the efficacy of varied therapeutic interventions (4). Indeed, HUT and other methods of orthostatic stress (standing, lower body negative pressure) have been used extensively in younger subjects in an attempt to understand the pathophysiology of syncope (10–18).

The mechanism by which normal saline prevents syncope is also not well elucidated. Although its efficacy has been attributed to intravascular volume expansion, its effect upon autonomic nervous system modulation during orthostatic stress has not been evaluated. One hypothesis is that restoration of intravascular volume blunts the sympathetic stimulation responsible for increasing contractility and reduction in left ventricular cavity dimension, thereby obviating the elicitation of the Bezold-Jarisch reflex. However, it is not clear the extent to which syncope is a function of neural activity and the degree to which other factors—humoral or paracrine—are involved (5).

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Abbreviations and Acronyms

HF = high frequency
HRV = heart rate variability
HUT = head-up tilt
LF = low frequency

Spectral analysis of heart rate variability (HRV) provides a simple noninvasive means for quantitative analysis of cardiac sympathovagal tone (19-23). We wished to address the following questions: How do changes in heart period oscillations relate to clinical status—namely: 1) What are the serial changes seen in low and high frequency power during a HUT test terminating syncope? and 2) How does administration of normal saline affect clinical status and the resulting power-frequency distribution?

METHODS

Study group. Of 65 adolescents evaluated with a history of at least one episode of syncope or presyncope, 12 (mean 15.2 ± 0.7 years) had reproducible syncope by HUT, without isoproterenol infusion, and formed our study group (Table 1). Reproducible syncope for the purpose of this study was defined as two consecutive HUT tests that resulted in significant hypotension with/without bradycardia. None displayed an cardioinhibitory form of neurally mediated cardiac syncope. Except for two subjects, one with mild aortic valvular insufficiency and the second with mild mitral regurgitation, all others had normal heart structure by two-dimensional echocardiography with Doppler interrogation. Electrocardiograms for all subjects were normal, with the corrected QT intervals ranging from 0.38 to 0.44. No conduction abnormalities were demonstrated. Twenty-four-hour Holter monitoring revealed no significant conduction or rhythm abnormalities. Two subjects had slightly

blunted blood pressure responses to graded exercise stress testing, and two demonstrated poor aerobic capacities, but otherwise had normal heart rate and blood pressure responses. The remainder of the subjects had normal tests. Informed consent was obtained from all subjects before HUT testing.

Head-up tilt protocol. The subjects received nothing per os for 6 to 8 h before the study. An intravenous line was placed for fluid administration. Under sterile conditions with 1% lidocaine for local anesthesia, a 22-ga radial arterial line was placed by the Seldinger technique in the left or right radial artery for continuous blood pressure monitoring. Electrocardiographic and blood pressure data were collected with the Arrhythmia Research Technologies Cardio-Lab computer system and stored on optical disk. After a 30-min recovery period after vascular line placement, the patient was elevated to 80° on an electrically driven tilt table with a foot board for weight-bearing for 30 min or until syncope occurred, after which the table was returned to the supine position (24). After recovery in the supine position to baseline heart rate and blood pressure, a second HUT was performed. Then after a second recovery period in the supine position, 1 liter of normal saline was administered intravenously over 20 min. After completion of the saline infusion, a third HUT test was conducted.

Heart rate variability analysis. Electrocardiographic data were acquired and stored on analog cassette tape using a Marquette Holter Recorder system, model 8500. The electrocardiographic data were digitized on a SpaceLab FT2000A Holter Analysis Workstation, transferred to a Sun Workstation and analyzed using the MATLAB analysis software package. Operator-selected epochs, 1 to 5 min in length, were selected for analysis to represent the following five states: 1) supine baseline; 2) early upright tilt (within the first few minutes); 3) midtilt (a few minutes preceding syncope or severe symptoms or if no symptoms

Table 1. Clinical Characteristics of Patients With Neurally Mediated Syncope

Patient	Age (yr/mo)	Gender	History of		Echocardiogram	Exercise Stress Test	ECG	Time to Syncope
			Dizziness	Syncope				
1	14/1	F	+	0	Normal	Normal	Normal QTc 0.44	4 min
2	13/9	M	+	+	Mild AR	Normal	Normal QTc 0.38	2 min
3	17/4	F	+	0	Normal	Normal	Normal QTc 0.41	21 min
4	17/7	M	+	+	Mild MR/PR/TR	Normal	Normal QTc 0.41	20 min
5	16/8	F	+	+	Normal	Normal	Normal QTc 0.43	6 min
6	14/5	F	+	+	Normal	Normal	Normal QTc 0.41	18 min
7	14/9	F	+	+	Normal	Normal	Normal QTc 0.42	6 min
8	15/10	M	+	+	Normal	Normal	Normal QTc 0.41	3 min
9	9/3	M	+	+	Normal	Normal	Normal QTc 0.42	4 min
10	14/10	M	+	+	Normal	Not performed	Normal QTc 0.40	4 min
11	16/2	M	+	+	Normal	Normal	Normal QTc 0.38	17 min
12	18/1	F	+	+	Normal	Normal	Normal QTc 0.41	8 min

AR = aortic regurgitation; ECG = electrocardiogram; F = female; M = male; MR = mitral regurgitation; PR = pulmonary regurgitation; QTc = corrected QT interval; TR = tricuspid regurgitation; + = present; 0 = absent.

Table 2. Heart Rate Variability Analysis

Control Studies		Saline Studies	
Low frequency power			
Supine	45.2 ± 5.6	Supine	47.3 ± 4.5
Early tilt	77 ± 1.8*	Early tilt	68.8 ± 2.6*
Midtilt	72.1 ± 2.4	Midtilt	71.8 ± 1.4
Faint/late tilt	51.6 ± 5.3†‡	Late tilt	71.3 ± 2.8
Recovery	41.4 ± 3.7	Recovery	43 ± 4.3
Peak LF density			
Supine	0.89 ± 0.18	Supine	0.83 ± 0.1
Early tilt	2.19 ± 0.16*	Early tilt	1.56 ± 0.12*
Midtilt	1.95 ± 0.21	Midtilt	1.70 ± 0.09
Faint/late tilt	1.11 ± 0.15†‡	Late tilt	1.77 ± 0.16
Recovery	0.72 ± 0.11	Recovery	0.74 ± 0.11
LF/HF ratio			
Supine	1.87 ± 0.57	Supine	1.57 ± 0.34
Early tilt	9.84 ± 1.32*	Early tilt	5.49 ± 1.17*
Midtilt	8.21 ± 1.09	Midtilt	6.18 ± 0.8
Faint/late tilt	2.77 ± 0.93†‡	Late tilt	7.28 ± 1.06
Recovery	1.25 ± 0.3	Recovery	1.38 ± 0.4
High frequency power			
Supine	40.2 ± 6.1	Supine	39.9 ± 4.6
Early tilt	9.7 ± 1.3*	Early tilt	17.5 ± 2.6*
Midtilt	10.2 ± 1.2	Midtilt	13.8 ± 1.7
Faint/late tilt	31.8 ± 5.5†‡	Late tilt	11.5 ± 1.3
Recovery	45 ± 4.7	Recovery	44.1 ± 4.3

*p < 0.05, early tilt vs. supine; †p < 0.05, late tilt vs. early tilt; ‡p < 0.05, faint/late tilt vs. midtilt.

HF = high frequency; LF = low frequency.

developed, at about 15 min); 4) syncope, that is, during severe symptoms or the last 5 min of a 30-min tilt, and 5) supine recovery.

The program used operator-supplied parameters to automatically detect QRS complexes; rarely occurring detection failures could be corrected with overview and editing by previously described methods (25). Histograms of RR intervals for sinus beats were computed and pseudodigitized at 10 samples/s for processing by conventional signal analysis algorithms. Autoregressive modeling (Burg method) was used to construct frequency domain spectrograms of the HRV (26). Heart rate period parameters extracted were low frequency (LF) power (0.03 to 0.15 Hz), peak LF power, high frequency (HF) power (0.16 to 0.50 Hz) and the ratio of LF to HF power.

Statistics. Mean and standard error of the mean for the parameters in each epoch are given in Table 2. A two-way repeated measures analysis of variance (Proc GLM on PC-SAS) (27) was used to identify significant treatment and between-treatment effects. P values were adjusted by the Huynh-Feldt criteria to account for asphericity. If identified as significant, a Student-Newman-Keuls test was applied to identify within-treatment significance. Significance was defined at the 0.05 level.

RESULTS

Hemodynamic changes during HUT testing. During both control studies, all 12 subjects experienced syncope, associated with hemodynamic instability manifested primarily as hypotension (systolic blood pressure 56 mm Hg ± 13). The mean time to syncope was 9.4 ± 2.1 min (range 2 to 21 min). Figure 1 shows mean values and standard error of the mean for heart rate and blood pressure for each stage of the second control tilt sequence. Syncope was presaged by a marked decrease in blood pressure (−35.8 ± 7.9 mm Hg, p < 0.05) and accompanied by a decrease in heart rate (−31.2 ± 5.5 beats/min, p < 0.05).

After saline infusion and 80° HUT, there was a small decrease in blood pressure (early tilt to late tilt = −16.5 ± 6.2, p < 0.05) and a small increase in heart rate (early tilt to late tilt = +16.2 ± 2.6 beats/min, p < 0.05). Despite maintenance of the upright position for 30 min, all patients remained without syncope (see Fig. 1, B). The initial increase in heart rate during the transition from supine to early tilt was significantly blunted. The heart rate increase first became significant at the midtilt point (+13.6 ± 2.9 beats/min, p < 0.05) and continued to increase despite maintenance of the upright position. Saline infusion modified the amplitude of the blood pressure response to tilt, as well as the phase response of heart rate to tilt significantly (p < 0.05).

Heart rate variability analysis. CONTROL STUDIES. A typical HRV sequence for a control tilt study is depicted as a graph of power spectral density in Figure 2A. Initially during early tilt there was a marked increase in the LF power. Subsequently LF power decreased progressively, as the upright position was maintained, until syncope occurred. High frequency power changed in a reciprocal manner.

In transition from the baseline supine position to early tilt, LF power (+34.3 ± 6.6, p < 0.05), peak LF density (+1.30 ± 0.25, p < 0.05) and LF/HF ratio (+7.98 ± 1.35, p < 0.05) increased significantly, whereas from early tilt to syncope, LF power (−25.4 ± 5.0, p < 0.05), peak LF density (−1.08 ± 0.21, p < 0.05) and LF/HF ratio (−7.07 ± 1.24, p < 0.05) decreased significantly. After recovery in the supine position, these parameters returned to their baseline values. Figure 3 depicts the tilt sequence for these LF parameters.

Initial decreases upon tilt in HF (−30.4 ± 5.5, p < 0.05) were significant. High frequency power increased significantly (HF, +22.1 ± 5.5, p < 0.05) from early tilt to syncope.

SALINE INFUSION STUDIES. Figure 2B shows the HRV sequence in a saline tilt study for the same patient as Figure 2, A. The moderate increase in LF power tended to be maintained at about the same level throughout the upright position.

In the saline studies, LF parameters initially increased

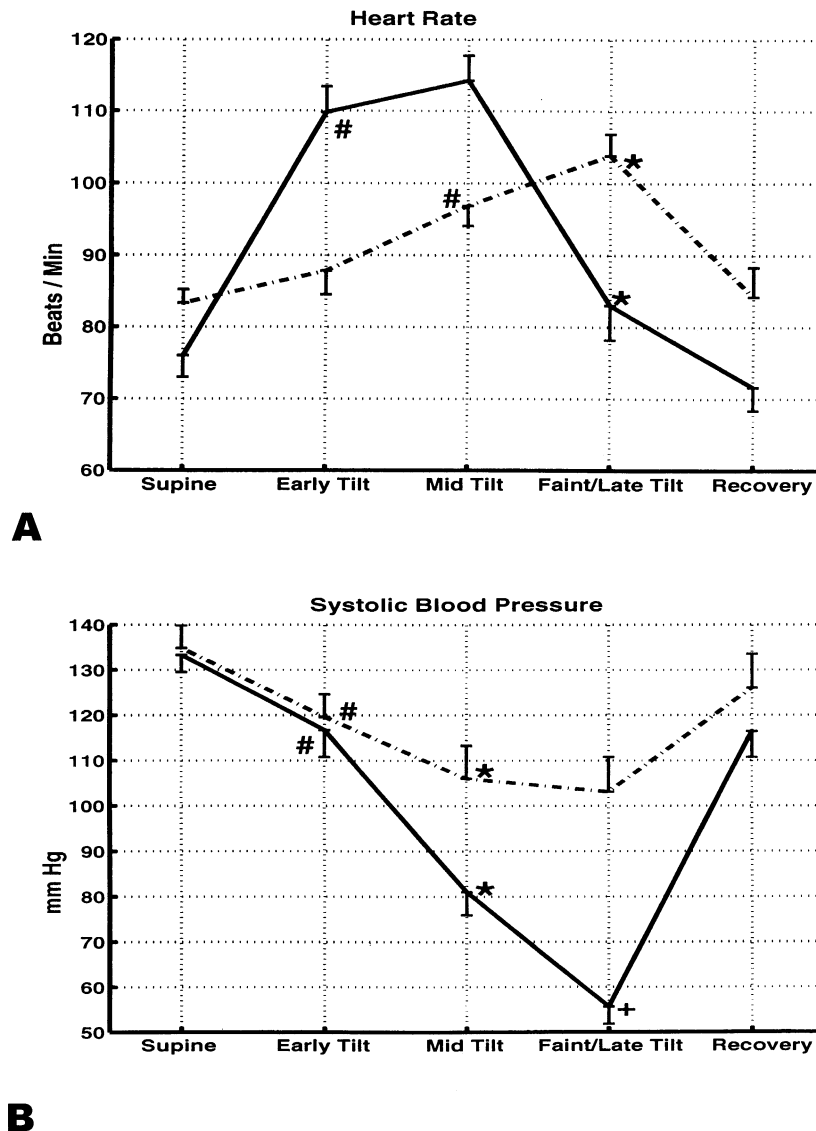


Figure 1. Heart rate and blood pressure changes during the control and saline tilt sequences. Heart rate increased markedly (A) and blood pressure (B) decreased early during the control tilt. A significant decrease in blood pressure presaged syncope; this occurred first and was subsequently accompanied by a significant decrease in heart rate. The hemodynamic changes were comparatively attenuated during the saline tilt. A small increase in heart rate between the early tilt and late tilt period was observed. [#]*p* < 0.05, early tilt or midtilt vs. supine. ^{*}*p* < 0.05, midtilt or late tilt vs. early tilt. ⁺*p* < 0.05 faint/late tilt vs. midtilt.

from the supine to the early tilt state, that is, LF (+22.5 ± 4.4, *p* < 0.05), peak LF (+0.73 ± 0.11, *p* < 0.05) and LF/HF (+3.9 ± 1.16, *p* < 0.05) (Fig. 3). After 30 min of upright position further increases in LF parameters were not significant.

The initial decrease in HF power (−22.4 ± 4.2, *p* < 0.05) was significant. High frequency power remained low during the upright position for 30 min and increased again after recovery in the supine state.

COMPARISON OF CONTROL VERSUS SALINE INFUSION STUDIES. Figure 1 reveals differences in the hemodynamic changes between the control and saline studies. This difference was also reflected in corresponding changes in HRV

parameters. Figures 2A and B depict a typical example of the differences observed in the HRV sequences between a control and a saline study on the same patient, particularly in the initial increase in LF. The same contrast of control versus saline studies is apparent in Figure 3. Saline was found to have a significant moderating effect on the response of heart rate, blood pressure, LF power and HF power during HUT (two-way analysis of variance, *p* < 0.01).

We emphasize one other important observation. The initial increase in LF parameters during the control studies was greater than their initial increase in the saline studies, for example, LF power (control = 20.9 ± 6.0 vs. saline =

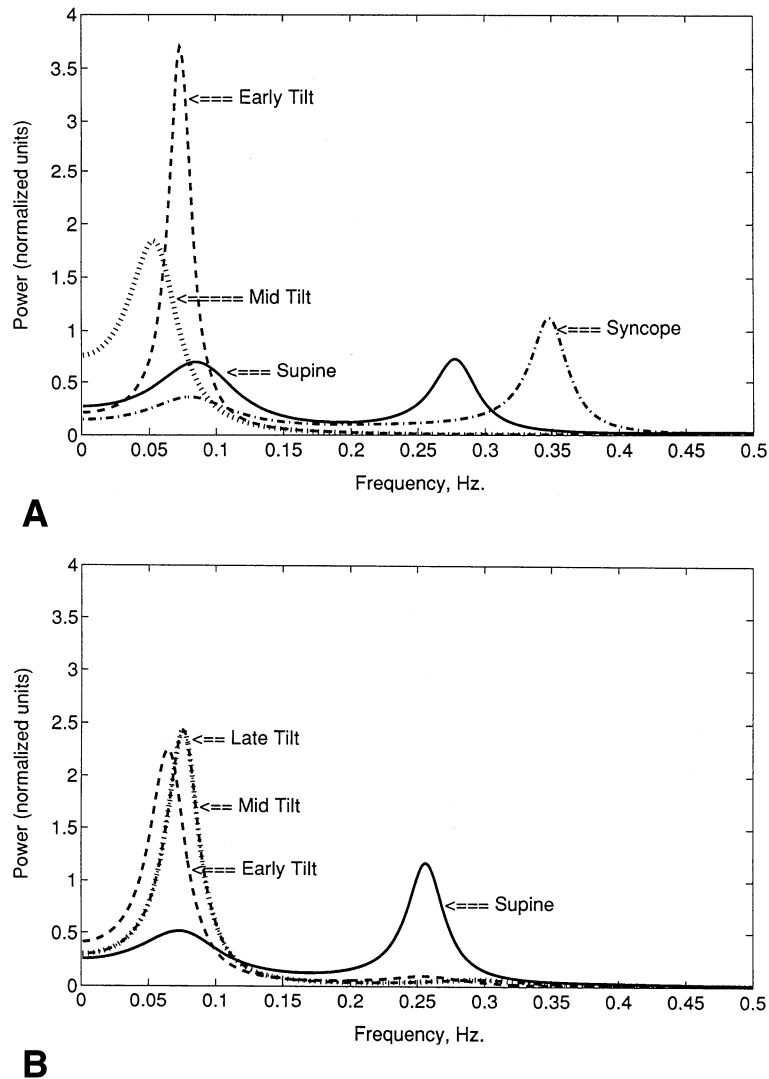


Figure 2. Power spectral density during control tilt (A) and saline tilt (B). During the control tilt, upon assumption of the upright position, there was a significant increase in low frequency power (0.03 to 0.15 Hz) with a decrease in high frequency power (0.16 to 0.50 Hz). Despite continued upright positioning, there was a progressive decline in low frequency power. After the administration of normal saline, low frequency power progressively increased during the remainder of upright positioning.

$15.2 \pm 4.4\%$, $p = \text{NS}$), peak LF density (control = 1.3 ± 0.25 vs. saline = 0.73 ± 0.11 normalized units, $p < 0.05$) and LF/HF ratio (control = 7.98 ± 1.35 vs. saline = 3.92 ± 1.16 , $p < 0.05$).

DISCUSSION

This study provides insight into the mechanism(s) by which the autonomic nervous system modulates hemodynamic responses to HUT testing in young patients who are susceptible to recurrent vasodepressor syncope. Our methodology allowed serial measurement of the changes in low and high frequency power, reflective of sympathetic and parasympathetic activity, respectively, during a tilt table study.

In control tilt studies, serial HRV analysis revealed that after an initial marked increase, LF power progressively decreased. At the time of syncope, LF power further diminished accompanied by a marked decrease in systolic blood pressure, suggesting a paradoxical withdrawal of sympathetic tone. After normal saline administration, autonomic responses to tilt table testing were altered in two important ways. First, the initial activation of LF power was attenuated when compared with the control tilt table sequence. In addition, after normal saline administration, LF power progressively increased during prolonged orthostatic stress, as opposed to the decrease noted during control studies.

Autoregressive modeling for HRV spectra. Autoregressive methods have been shown to produce better resolution

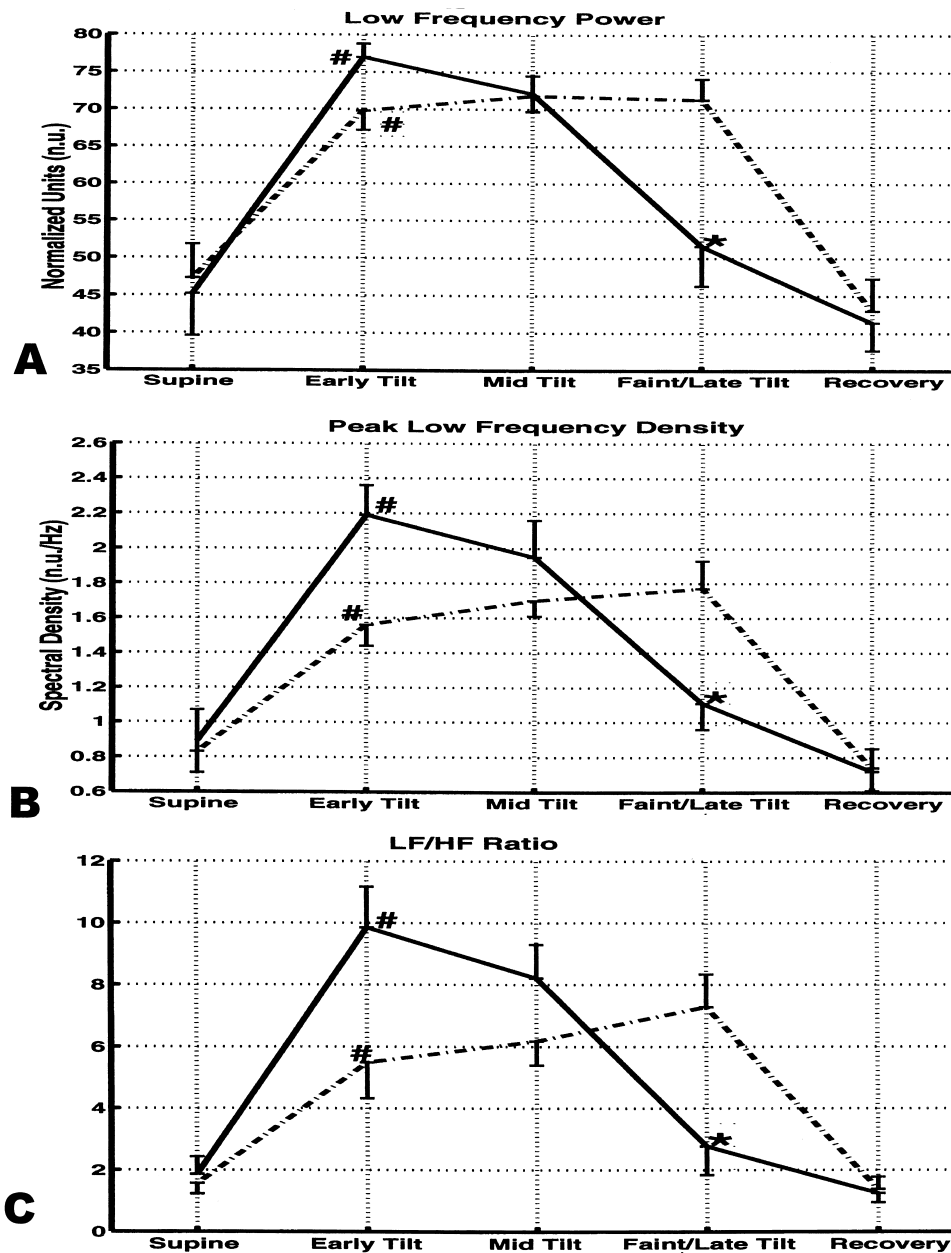


Figure 3. Low frequency (LF) power during control and saline tilt: **A**, LF power, **B**, peak LF power, and **C**, LF/high frequency (HF) ratio. With upright tilt during the control state, there was a rapid and early peak in LF power. With continued upright positioning, a progressive decrease in LF power was observed. However, after saline administration, LF power remained constant throughout the duration of upright tilt. **Solid line** = control tilt; **dashed line** = saline tilt. #*p* < 0.05, early tilt vs. supine. **p* < 0.05, faint/late tilt vs. early tilt.

of sharp peaks in HRV spectra than the fast Fourier transform; to make smoother, more interpretable curves, and to illustrate the reciprocal nature of sympathovagal balance (17,18,28). Moreover, shorter sampling periods of heart rate data could be analyzed using the autoregression algorithm compared to the fast Fourier transformation method (29,30). This allowed selection of discrete time epochs representing distinct physiologic states, preceding and during syncope, and demonstration of dynamic changes

in autonomic nervous system activity with and without therapeutic intervention in our study.

Heart rate variability and autonomic nervous activity. Heart rate variability analysis provides a quantitative measure of sympathetic and parasympathetic autonomic nervous activity; the relative contribution of each component to the frequency spectra of heart rate variability has been the subject of debate. The HF oscillations (0.15 to 0.50 Hz)

represent parasympathetic vagal influences, closely related to respiratory frequency, upon cardiac rhythmicity (19-23). Akselrod et al. showed that animals undergoing parasympathetic blockade with glycopyrrolate, a vagolytic agent, experienced elimination of the HF component of HRV (19).

Low frequency power (0.03 to 0.15 Hz) may represent both sympathetic and parasympathetic autonomic influences (19,31). Moderate exercise, mental stress, transient coronary artery occlusion and hemorrhage are associated with increases in LF power (32-35). Hayoz et al. showed a progressive withdrawal of muscle nerve sympathetic activity, which was accompanied by a concomitant decrease in LF power (36). Thus, it can be inferred that alterations in LF power are principally dominated by changes in sympathetic tone.

Previous studies of HRV and syncope. Previous studies of syncope in young subjects using HRV spectra have shown a shift from HF to LF power upon initial HUT, suggesting a shift from parasympathetic to sympathetic chronotropic control of the heart (17,18,23,37,38). In our study, the decrease of HF power similarly suggested a shift from parasympathetic control in the first few minutes of HUT. Similar to two earlier studies, syncope or presyncope was related to progressive withdrawal of LF power and a marked decrease in blood pressure during prolonged orthostasis (18,38). In our control studies, values for LF/HF ratio during supine and HUT stages were very similar to those found by Lagi et al. (18). High frequency power began to increase again during syncope. Serial HRV analysis in our study revealed that after an initial increase, all LF indexes (LF power, peak LF power density, LF/HF ratio) progressively decreased, accompanied by a marked decrease in systolic blood pressure, presaging syncope. At the time of syncope, LF indexes further diminished accompanied by a moderate decrease in heart rate. These data indicate the important role played by neural activity changes, but do not obviate other possible factors such as humoral or paracrine effects.

Some prior reports on neurally mediated syncope have shown different results than ours for several reasons (36-39). First, there is no standard procedure used to sequester blood volume and elicit syncope (24); some studies have used standing or lower body negative pressure, and others have incorporated protocols using lesser degrees of HUT maintained for longer times or isoproterenol administration (24). Second, our population was adolescent, and their physiology may not necessarily behave the same as older adults (12,16,39). Third, some reports fail to distinguish between vasodepressor and cardioinhibitory responses to HUT; the respective mechanism underlying each may not be quite the same (40). Last, our methodology allowed serial measurement of the changes in LF and HF power, reflective of distinct changes in sympathetic/parasympathetic activity during a tilt table study.

Therapeutic considerations. Strategies to treat neurally mediated syncope have included the following: administration of beta-adrenergic blocking agents such as esmolol and metoprolol; administration of alpha-adrenergic agents such as pseudoephedrine and midodrine, and administration of mineralocorticoids with increased fluid and salt intake (41).

In this study, intravenous administration of normal saline resulted in immediate volume expansion with amelioration of syncope during repeat HUT. Previous studies by Fouad et al. have demonstrated hypovolemia in this patient subset (42). Long-term oral administration of sodium chloride also has been shown to increase blood volume with concomitant improvement in tolerance of orthostasis (14,43). Mangru et al. have shown that saline infusion mitigated the hemodynamic effects of neurocardiogenic syncope in 84% of their cases and that those patients responding to saline infusion did well with a high salt diet with/without oral mineralocorticoids (44).

Future research. The tenuous state of syncope-prone individuals, which apparently does not allow them to compensate for normal postural changes, requires explanation. The efficacy of sodium chloride supplementation and mineralocorticoid administration in preventing further episodes of syncope suggests the possibility of defects in normal water and sodium homeostasis of the body or in autonomic vascular tone regulation. Hypoaldosteronism or aldosterone-resistant conditions may exist which alter the homeostatic state, preventing the body from adequately compensating for orthostatic stress. Increased understanding of these processes may allow for more directed therapies. Investigation of sodium and water regulation should be included in future research.

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