Simultaneous Heart Rate and Blood Pressure Variability Analysis: Insight Into Mechanisms Underlying Neurally Mediated Cardiac Syncope in Children

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OBJECTIVES The purpose of our investigation was to examine serial changes in autonomic nervous system activity along with measurements of hemodynamics and cardiac contractility, in assessing the mechanism(s) that underlie neurally mediated cardiac syncope (NMCS) in children.

BACKGROUND Previous research that used heart rate variability analysis alone to understand changes in autonomic activity that result in NMCS has provided conflicting results. We performed simultaneous heart rate and blood pressure variability analyses to characterize dynamic alterations in sympathetic and vagal tone during tilt-table testing in 23 children with a history of syncope or frequent dizziness.

METHODS Power spectra of heart rate and blood pressure variability were analyzed using autoregressive modeling. Maximum dP/dT of systolic blood pressure and the electrical-mechanical activation time were used to assess cardiac contractility.

RESULTS Tilt-table testing was positive in 12 children and negative in 11. Syncope was associated with decreased heart rate, blood pressure and low-frequency (LF) power. Before episodes of syncope, systolic blood pressure dP/dT decreased, and the electrical-mechanical activation time was prolonged. The decrease in blood pressure LF power exceeded and occurred before the decrease in heart rate LF power. Despite similar early increases in LF power to the initial stress of upright tilting, no significant decline in LF power (heart rate or blood pressure) was observed during negative tilt-table tests.

CONCLUSIONS All of these changes considered in total provide evidence supporting the hypothesis of sympathetic withdrawal/failure, resulting in a decrease in peripheral vascular tone and cardiac contractility, which result in profound hypotension in children with NMCS.

Up to 15% to 25% of children and adolescents experience at least one episode of unexplained syncope (1). The most common hypothesized mechanism for neurally mediated cardiac syncope (NMCS) invokes dependent pooling of venous blood during orthostatic stress. The resultant effective hypovolemia stimulates ventricular emptying and a compensatory increase in cardiac contraction, which ultimately activates the Bezold-Jarisch reflex. Activation of this reflex elicits a paradoxical reduction in sympathetic tone, which causes vasodilation and/or bradycardia (2). However, studies in cardiac transplant patients suggest that ventricular receptor activation may not be the exclusive cause of NMCS (3). Furthermore, the importance of neuro-endocrine and other humoral factors has been controversial (4,5).

In young patients with recurrent syncope, the passive head-up tilt test (HUT) may be very useful in determining NMCS as the etiology underlying syncope (6) and in understanding its pathophysiology.

Spectral analysis of heart rate variability (HRV), also known as heart period variability (HPV), has been used as a noninvasive means for quantitative analysis of cardiac symp-athovagal balance. However, HPV analysis alone has provided conflicting results regarding the mechanisms of NMCS (7–9). The purpose of this study was to examine the combined use of blood pressure (BP) and HRV, along with measures of cardiac contractility, in assessing serial changes in sympathovagal balance that result in NMCS in children during tilt-table testing.

METHODS

Study group. Twenty-three adolescents, ranging in age from 8.8 to 17 years, had a history of at least one episode of syncope or multiple presyncopal episodes and formed our study group (Table 1). Twelve patients (mean age 14.9 ± 0.6 years) had a positive tilt study (HUT+), all of them without isoproterenol provocation. Eleven subjects (mean age 14.6 ± 0.9 years) had a negative tilt study (HUT−) and formed the control group. No patient displayed a primary cardioinhibitory form of NMCS. Informed consent was obtained from all subjects before testing.

HUT protocol. The subjects received no oral intake 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-gauge radial arterial line was placed by the Seldinger technique in the left or right radial artery for continuous BP monitoring. Simultaneous
electrocardiographic (seven electrocardiogram [ECG] leads recorded) and arterial BP data were digitized at 1,000 samples per second, collected with the Prucka Cardio-Lab computer system (Sugarland, Texas) and stored on magneto-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 footboard for weight bearing for 30 min or until syncope occurred, after which the table was returned to the supine position.

**HPV and BPV analysis.** Operator-selected epochs that were 1 to 5 min in length were selected for analysis to represent the following five states: 1) supine position, or baseline; 2) early upright tilt (within the first few minutes); 3) mid-tilt (a few minutes preceding syncope or severe symptoms, or at about 15 min if no symptoms developed); 4) syncope, i.e., during severe symptoms or the last 5 min of a 30-min tilt; and 5) recovery, or supine position.

The ECG and BP data were reduced to 200 samples per second and were processed using locally developed analysis programs written in MATLAB language (10). The programs used operator-supplied parameters to automatically detect QRS complexes; detection failures, which occurred rarely, were corrected with overview and editing by previously described methods (11).

Occasional distortions of the BP data by noise or artifact were corrected using an operator-selected template pattern for each epoch. The programs automatically determined RR interval and systolic BP for each beat. Also computed on a beat-by-beat basis were maximum (max) BP dP/dT (mm Hg/s) and the electrical-mechanical activation time (ms). The electrical-mechanical activation time was derived by measuring the time interval from the peak of the QRS complex to the max positive dP/dT of the arterial BP waveform (12). This interval approximated the pre-ejection period. The first derivative of the arterial BP waveform was digitally derived to detect systolic BP max dP/dT (13–15).

Histograms of RR intervals and systolic BP values for sinus beats were computed and pseudodigitized at 10

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**Table 1.** A. Clinical Characteristics of Patients With Positive Tilt-Table Study

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<thead>
<tr>
<th>Patient</th>
<th>Age (yr/mo)</th>
<th>Gender</th>
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<th>Exercise</th>
<th>Time to Syncope (min)</th>
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**B. Clinical Characteristics of Patients With Negative Tilt-Table Study**

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<th>Exercise</th>
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<td>11</td>
<td>17/11</td>
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<td>+</td>
<td>Normal</td>
<td>0.39</td>
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abnl = abnormal; MV = mitral valve; MVP = mitral valve prolapse; – = absent; ND = not done; PAPVR = partial anomalous pulmonary venous return.; + = present; S/P = status post.
samples per second. Auto-regressive modeling (Burg method) was used to construct frequency domain spectrograms of the HPV and BPV (10,11). Parameters extracted from the variability spectra were low-frequency (LF) power (0.03 to 0.15 Hz) and high-frequency power (0.16 to 0.50 Hz), normalized to total power over the range from 0.01 to 0.50 Hz. LF HPV and LF BPV have previously been demonstrated to measure changes in sympathetic activity (16).

Statistics. The data were analyzed using repeated measures analysis of variance (Proc Mixed on PC SAS) with a compound symmetry covariance structure that is heterogeneous across treatment groups (responders and nonresponders). In the model, the values of the outcomes at early-tilt, mid-tilt, late-tilt/faint and recovery stages were the dependent variables. The predictors were the values of the outcomes in the supine position, the treatment groups, time and the interaction between the treatment groups and time. A p value <0.05 was adjusted in the Proc Mixed program using the Bonferroni formula. Results are reported in the text as mean and SEM.

RESULTS

Hemodynamic changes during HUT testing. Figure 1 shows the mean and SEM for heart rate (Fig. 1A) and BP (Fig. 1B) at each stage of the tilt sequence in the HUT+ and HUT− subjects. Heart rate and BP responses of the two groups to HUT differed significantly (p < 0.0001 for both changes). Twelve subjects responded to HUT with syncope manifested primarily as hypotension (systolic BP = 58 ± 7.6 mm Hg). Syncope was presaged by a decrease in BP (−20.4 ± 4.2 mm Hg, p = 0.0006) and accompanied by a decrease in heart rate (−21.3 ± 4.5 beats/min, p = 0.0002). In the 11 HUT− subjects, there was no statistically significant change noted in the BP response. There was a statistically insignificant increase in heart rate after the early tilt phase.

Figure 2 shows the mean and SEM of maximum systolic BP dP/dT (Fig. 2A) and the electrical-mechanical activation time (Fig. 2B) for the two groups of patients during HUT. The responses of dP/dT and activation time between the two groups (HUT+ and HUT−) were different (p = 0.0003 and p < 0.0001, respectively). In the HUT+ group, BP max dP/dT decreased significantly at the mild-tilt interval (p = 0.0171) and further at the time of fainting (p < 0.0001). A minor, nonsignificant change was observed in the HUT− group. The response of the electrical-mechanical activation time was discordant between the two groups. The electrical-mechanical activation interval increased in the 12 HUT+ subjects (p = 0.0016, mid-tilt to faint), whereas in the 11 HUT− subjects, there was a nonsignificant trend toward shortening.

BP waveform. Figure 3 shows characteristic serial changes in the radial artery pulse wave contour in a patient who was tilt positive. Similar qualitative changes were noted in all HUT+ patients. Evident are the following three findings: 1) a progressive decrease in systolic and diastolic BP; 2) a progressive decrease in the dicrotic notch (representing decreased pulse wave reflectance) and 3) the disappearance of the dicrotic notch at the time of syncope.

Cardiovascular autonomic variability analysis. HPV. Figure 4A graphically demonstrates the mean and SEM values of HPV in the HUT+ and HUT− groups. The difference in overall response between the two groups failed to reach statistical significance (p = 0.0575). The HUT+ and HUT− groups differed significantly only at the time period of faint/late-tilt (p = 0.0003). LF HPV for the HUT+ group decreased (p = 0.0186) while still in the upright position whereas it remained elevated for the HUT− group.
in the upright position. The initial response of the HUT+ group upon upright tilt was similar to the response of the HUT− group (p < 0.0001 for both).

BPV. Figure 4B shows the response of BPV to HUT. The response of LF BPV differed significantly between the HUT+ and HUT− groups (p < 0.0001). The early increase in LF BPV for both HUT+ and HUT− groups was equivalent (9.7 vs. 7.3 normalized units). However, LF BPV decreased significantly in the HUT+ group after the initial increase (p = 0.0001). LF BPV at the time of syncope was significantly less than the baseline supine value (p < 0.0001). In contrast, LF BPV remained elevated in the HUT− groups during the upright position.

SYNCOPE. Syncope was presaged by a decrease in LF BPV, (−21.4 ± 3.4 normalized unit, early-tilt to faint). At mid-tilt, LF BPV was significantly less in the HUT+ compared with the HUT− group (p < 0.0001). The decrease in LF BPV became significant at the faint (early-tilt compared with faint/late-tilt, p = 0.0001). Syncope was also accompanied by a decrease in LF HPV (−11.3 ± 4.1 normalized units, p < 0.0186, early-tilt to faint). Changes in LF BPV occurred earlier in the tilt sequence (mid-tilt) and were more marked than the changes in LF HPV. The max dP/dT of BP was observed to decrease in the mid-tilt time period. The electrical-mechanical activation time prolonged at the time of syncope.

DISCUSSION

Our study revealed that head up tilt-table testing resulted in significant serial changes in cardiac hemodynamics, systemic BP max dP/dT, pre-ejection period and heart period and BP variability. Marked differences were observed between the tilt positive and negative groups.

The population of patients chosen for our study could be characterized as having the mixed cardioinhibitory/vasodepressor form of NMCS. In our population, syncope was elicited without the use of any provocative agents, such as isoproterenol or nitroglycerin. We chose this population to study because they represented the closest to what might happen clinically during spontaneous syncope in the pediatric age group. Less than 10% of NMCS episodes result from a primary cardioinhibitory event (17).

Previous studies have suggested that the observed autonomic and hemodynamic changes studied vary depending on the type of NMCS response elicited and whether or not a provocative agent was used to cause syncope. Furthermore, age and gender also influence the results (18,19).

Hemodynamic changes. In NMCS, fainting is the direct result of sustained hypotension, which occurs secondary to vasodilation, bradycardia or a combination of the two. The vasodepressor component appears clinically to be the more important of the two because cardiac pacing with rate drop response (increased pacing rate to an initial decrease in spontaneous rate) fails to prevent syncope or at best delays its onset in adult subjects (20).

The initial effect of upright tilting is the displacement of blood into the venous system of the lower extremities, which is manifested as a decrease in measured central venous pressure and a decrease in left ventricular end diastolic volume (21). Yamanouchi et al. (22) failed to detect any difference in the absolute extent of left ventricular end diastolic volume reduction between tilt-positive adult patients and controls.

Cardiac contractility has been conjectured to increase in response to the elicited hypovolemia and decreased end diastolic volume during upright tilting. Petersen et al. (23) continuously monitored right ventricle pressure and max dP/dT during upright tilt table testing. Whereas RV pres-
Figure 3. Serial radial artery pulse contour changes in response to a positive upright tilt test. Electrocardiographic lead II and blood pressure are displayed. (A) Supine position. (B) Early-tilt. (C) Early to mid-tilt.
Figure 3. Continued. (D) Mid to late-tilt. (E) Faint. See text for description. Time scale = 50 mm/s, Blood pressure scale = 0 to 200 mm Hg.
sure decreased slightly during tilt, max dP/dT increased by 15% in the early tilt period and then progressively fell by 30% from its maximum value several minutes before syncope. In contrast to these results, Liu et al. (24) demonstrated throughout the upright phase of tilting a decrease in end systolic wall stress (a load-independent measure of cardiac contractility) in tilt-positive patients.

We noted, at the time of syncope in our pediatric population, profound hypotension without clinically significant bradycardia. Hypotension may have resulted from either inadequate cardiac output (decreased contractility or low stroke volume secondary to hypovolemia) or a decrease in systemic vascular resistance (SVR). The changes we observed in the arterial pulse contour data are compatible with progressive vasodilation. Kroeker and Wood (25) and O’Rourke (26) described similar changes in pulse contour (loss of pulse wave reflectance) in response to drug-induced vasodilation (decreased SVR).

In response to tilting, we observed a progressive decrease in systolic BP max dP/dT. This decrease may be a function of a decrease in cardiac contractility, a decrease in stroke volume or a decrease in SVR. Max systolic BP dP/dT has been demonstrated to concordantly mirror changes in LV max dP/dT (27,28), changes in systolic time intervals (29) and LV ejection fraction (30). Additionally, in our study we documented a progressive prolongation of the electrical-mechanical activation time. Given the methodology we used for its derivation, this interval reflected the pre-ejection period (12). The progressive increase in the pre-ejection period we observed in the tilt-positive subjects was either a result of a decrease in preload (hypovolemia) or a decrease in cardiac contractility (sympathetic withdrawal). The pre-ejection period has been found to increase in the setting of either a decrease in preload or a decrease in cardiac contractility (12). Both of these changes could be occurring simultaneously in the tilt-positive subjects. In contrast, the pre-ejection period shortened slightly in the tilt-negative group and remained unchanged throughout the rest of the upright phase. If hypovolemia and a decrease in preload primarily accounted for the change in the pre-ejection period, we would have expected a response similar to the tilt-positive subjects. As discussed earlier, most studies have been unable to detect any differences in the decrease in left ventricular end-diastolic volume or central venous pressure between tilt-positive and -negative subjects. Hence, the prolongation of the electrical-mechanical activation time observed in our study most likely reflected a decrease in cardiac contractility. Our observations, in conjunction with the evidence reviewed by Mosqueda-Garcia et al (31), fail to support the “ventricular theory” (ventricular mechanoreceptor activation) as the causal mechanism that results in NMCS.

Autonomic changes. The hemodynamic changes just reviewed result from and probably result in further changes in autonomic tone via feedback loops. A high coherence between changes in heart rate and BPV has previously been noted in normal subjects subject to tilt stress. In contrast, changes in heart rate and BP have been demonstrated to be out of phase in patients with NMCS (32). Controversial is whether BP or HRV is the dominant leading force. The hemodynamic response to tilting alone cannot explain the level of hypotension that develops in tilt-positive individuals and requires supplemental factors to come to bear to elicit the severe level of hypotension that we observed.
The techniques we used to study autonomic changes are well founded. LF HPV and LF BPV have been amply demonstrated to measure changes in sympathetic activity (16). Sloan et al. (33) have demonstrated the independence of LF BPV in measuring sympathetic tone to the peripheral vasculature. These investigators used cardiac pacing to fix the heart rate constant and observed its effect on HPV and BPV. Cardiac pacing eliminated HPV and HF BPV but not LF BPV. Chronic sympathectomy, as well as alpha-adrenergic blockade, has been shown to decrease LF BPV, thereby validating its utility as a measure of sympathetic tone to the peripheral vasculature. Furthermore, changes in LF HPV and LF BPV have shown excellent correlation with alterations in muscle sympathetic nerve activity (34).

Analysis of our data revealed a biphasic response of the sympathetic nervous system to upright tilting in the tilt-positive group. Both HP and BP LF power increased during the early tilt period. This was shortly followed by a gradual decline in LF power. In the case of HP LF power, the decline in LF power was only statistically significant at the time of the faint, with LF power returning to near-supine values. In contrast, the changes in BP LF power were more impressive. BP LF power statistically declined earlier in the tilt than did HP LF power and decreased to a greater extent, below supine values, at the time of syncope. The tilt-negative group exhibited similar changes to the tilt-positive group during the early phase of the tilt. However, LF power (HP and BP) continued to be maintained throughout the duration of the tilt study.

The decrease in BP max dP/dT and the increase in the pre-ejection period can similarly be explained by sympathetic withdrawal. Therefore, sympathetic withdrawal appeared important in decreasing SVR, producing peripheral vasodilation and decreasing cardiac contractility, both of which result in dramatic hypotension.

Study limitations. Our tilt-negative group was comprised of subjects with clinical symptoms of syncope and pre-syncope and therefore could not strictly be considered a control group of normal patients. However, this group did provide some advantages given that the patients in this group would have been predicted as demonstrating a positive tilt but failed to do so. From a pathophysiologic perspective, this group enhanced our insight into the mechanism(s) underlying a positive tilt in that what distinguished these subjects from the tilt-positive group was a negative tilt study and not some underlying genetic/autonomic background.

Conclusions. In our study, we were able to demonstrate a paradoxical decline in LF BP power and LF HP variability in children with a positive HUT, with the changes in BPV occurring earlier and being of greater magnitude. We also observed a decrease in systolic BP max dP/dT and pre-ejection period in tilt-positive subjects. Analysis of the arterial waveform changes during HUT was compatible with loss of wave reflection secondary to vasodilation. All of these changes considered in total provide evidence support-

ing the hypothesis of sympathetic withdrawal/failure, resulting in a decrease in SVR and cardiac contractility, which results in profound hypotension in children with NCMS.

REFERENCES

17. Moak et al.