Complex Demodulation of Cardiorespiratory Dynamics Preceding Vasovagal Syncope

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Background—The dynamic autonomic processes leading to vasovagal syncope are poorly understood.

Methods and Results—We used complex demodulation to continuously assess changes in respiration, R-R interval, and arterial pressure (blood pressure) variability during 60 degree head-up tilt in 25 healthy subjects with tilt-induced vasovagal syncope and 25 age-matched nonsyncopal control subjects. Coherence and transfer function analyses were used to examine the relation between respiration and R-R interval variability before syncope. Baseline blood pressure, R-R, and ventilation were similar between syncope subjects and control subjects. Syncope subjects experienced an increase in tidal volume and decrease in BP beginning 3 minutes before impending syncope (systolic blood pressure <80 mm Hg) necessitated termination of tilt. Approximately 90 seconds before syncope there was a sudden prolongation of R-R interval and increase in amplitude of high and low frequency R-R interval variability, indicating an abrupt enhancement of vagal tone. The increase in respiratory amplitude between 180 and 90 seconds before syncope was not accompanied by changes in R-R interval or R-R variability, suggesting a dissociation between respiration and the respiratory sinus arrhythmia. The coherence analysis showed fewer syncope subjects with coherence between respiratory and R-R interval variabilities and lower transfer magnitudes in syncope subjects compared with control subjects. Nonsyncopal subjects had no change in respiratory, R-R interval, or blood pressure dynamics during matched time periods before the time of syncope.

Conclusions—Vasovagal syncope is preceded by a period of hyperpnea and cardiorespiratory decoupling followed by an abrupt increase in cardiovagal tone. Respiratory pumping without inspiratory cardiac slowing may partially counteract preload reduction until sudden bradycardia precipitates syncope. (Circulation. 1998;98:977-983.)

Key Words: respiration • heart rate • Fourier analysis

Vasovagal syncope is a common and potentially dangerous clinical problem that can be provoked by passive head-up tilt. Although previous investigations have focussed primarily on cardiac and vascular responses preceding vasovagal syncope, changes in breathing patterns may also occur before fainting. Subjects have been observed to yawn, sigh, or hyperventilate before syncope, suggesting that alterations in respiration may accompany sudden changes in autonomic control of the heart and vasculature. In a previous study, we demonstrated vasomotor instability preceding syncope and showed that it is probably not related to respiration. However, to our knowledge, the relation between respiration and cardiovascualr activity in neurally mediated syncope has not been previously investigated.

Frequency domain (Fourier) analysis of cardiac interbeat interval (R-R) variability has been widely used to assess autonomic control of cardiovascular function. High-frequency variability in the range of 0.15 to 0.45 Hz represents respiration-related vagal modulation of heart rate, and its amplitude has been used as an index of vagal tone. Low frequency variability between 0.04 and 0.15 Hz probably reflects the effects of both respiration and baroreflex-mediated sympathetic outflow on the heart. Fourier analysis of R-R interval variability is appealing for the assessment of autonomic mechanisms underlying syncope; however, its interpretation is confounded by alterations in respiratory frequency and amplitude that may precede the development of symptoms. Furthermore, this technique cannot be used to assess sudden, time-dependent changes in the amplitude of a particular frequency. Recently, the technique of complex demodulation has been developed to provide a continuous assessment of the amplitude of cardiovascular variabilities and thereby identify changing autonomic responses to cardiovascular events. We used this method to investigate alterations in cardiac interbeat interval and respiratory dynamics preceding vasovagal syncope and their relation to each other. Since vasovagal syncope is thought to be due to a sudden increase in vagal outflow from the central nervous system, we hypothesized that there would be a marked increase in high frequency R-R interval variability...
preceeding the development of tilt-induced syncope and that this increase would be independent of respiration.

Methods

Subjects

The subjects included 50 healthy volunteers (age range 20 to 64, mean age±SD=45±20. 29 women and 21 men) who underwent passive head-up tilt tests as described below. Twenty-five of the subjects who developed syncope or presyncope during head-up tilt were matched to 25 who remained asymptomatic during the procedure. Subjects with and those without syncope were matched by age to control for age-related differences in respiratory sinus arrhythmia. Of the 50 subjects, 3 were excluded due to technical problems with the Respitrace PPG sensor. The study was approved by the Institutional Review Board of the Hebrew Rehabilitation Center for Aged, and all subjects provided informed consent.

Instrumentation

Subjects reported to the Cardiovascular Research Laboratory at the Hebrew Rehabilitation Center for Aged at 7:30 on the morning of the study in the fasting state, after an overnight rest. Premenopausal women were studied between days 7 and 14 of their menstrual cycle. While lying supine at rest on a tilt table, electrodes were attached to the chest for continuous recording of the ECG signal. The right arm was kept level with the right atrium at all times during the study, and a noninvasive tonometric arterial pressure (BP) transducer, connected to a Colin Electronics BP monitor was strapped over the right radial artery. The sphygomanometric cuff of an oscillometric BP recording device, used for internal calibration of the Colin monitor, was attached to the upper right arm.

A continuous respiration signal was recorded by an inductive plethysmograph (Respitrace, Ambulatory Monitoring) from two elastic respiratory transducer bands, one around the mid chest and the other around the abdomen. The Respitrace output was calibrated according to the procedure of Sackner et al. by having subjects exhale and inhale to fill and empty an 800 mL spirometer bag. Minute ventilation (respiratory rate times average tidal volume) was measured by having subjects follow a tape-recorded auditory signal and line on the spirometer bag. The subjects became symptomatic or hypotensive (systolic BP <80 mm Hg) during tilt, they were returned immediately to the supine position. The tilt was usually terminated before actual loss of consciousness occurred.

Data Processing

All data were digitized at 250 Hz and displayed in real time with the use of commercially available data acquisition software (Windaq, Dataq Instruments) on a personal computer. Continuous ECG and BP data before and during tilt were visually inspected and edited off-line for artifact and ectopy with the use of an automated arrhythmia detection program for the ECG and manual editing for BP. Five to 10 minute data segments during tilt were used for analysis. These included intervals during paced breathing and spontaneous breathing just before syncope or at the same time points coinciding with the presyncopal period in matched nonsyncopal control subjects. The presyncopal segments were at least 5 minutes long and did not overlap with paced breathing. For each matched control subject, the same length data segment was analyzed.

Beat-to-beat R-R intervals were determined from the R wave of the ECG, and beat-to-beat systolic and diastolic pressures were derived from the maximum and minimum of the arterial pressure waveform. The continuous respiration signal was sampled at each R wave and used to determine instantaneous lung volume. Each R-R interval, systolic and diastolic blood pressure, and respiratory time series was interpolated by cubic spline function and resampled at 1 Hz to obtain equidistant time intervals. The resampled series were analyzed with the use of complex demodulation as described previously and briefly below.

Complex Demodulation

Complex demodulation is a nonlinear time-domain method of time series analysis suited to investigation of nonstationary/unstable oscillations. In contrast to spectral analysis that provides average properties (power and frequency) of oscillatory components in stationary time series, complex demodulation provides instantaneous amplitude and frequency as a function of time for oscillations in a frequency band of interest.

The time dependent changes in the amplitude and frequency of the low frequency (0.04 to 0.15 Hz) and high frequency (0.15 to 0.45 Hz) components of respiration, R-R interval, and blood pressure were assessed on a personal computer with a subroutine CDM written in FORTRAN (the detailed code has been deposited with the National Auxiliary Publications Service). For the analyses of the low and high frequency components of these variables, reference frequencies were set at 0.095 Hz and 0.30 Hz. The low pass filtering was performed with a zero-phase-shift least-squares filter with convergence factors. The length of the filter was set at 61 terms, resulting in a transitional bandwidth of 0.033 Hz. The low-pass corner frequencies were set at 0.055 and 0.15 Hz for the low and high frequency components so that the frequency bands for demodulating these components were 0.04 to 0.15 Hz and 0.15 to 0.45 Hz, respectively.

It is important to note that the respiratory amplitudes obtained with the use of complex demodulation are relative measures of tidal volume rather than absolute lung volumes. This is due to several factors including the following: (1) the amplitude computed by complex demodulation is half the range of the respiratory signal excursion; (2) the signal is not exactly sinusoidal, especially when expiration is longer than inspiration or brief periods of apnea occur between breaths; and (3) average tidal volume within a given period of analysis represents the sum of high and low frequency breaths, whereas complex demodulation, by definition, separates out the amplitudes at each frequency.

Statistical Analysis

Within-group changes in raw values, frequencies, and amplitudes for each cardiovascular signal were evaluated over time with repeated-measures ANOVA. To determine the times at which changes occurred before syncope, we contrasted each point during the last 5 minutes of tilt to the mean of the preceding 5-minute period.
Between-group differences in each signal were assessed by Student’s t tests and a general linear model, repeated-measures ANOVA with interaction terms. To determine individual time points at which differences were significant, the Helmert transformation was used. All analyses were performed with SAS software on a personal computer. Data are expressed as mean values ± SE.

To determine whether there was a relation, and if so, the strength of that relation between respiratory (input signal) and R-R interval (output) fluctuations, in the low (0.04 to 0.15 Hz) and high (0.15 to 0.45 Hz) frequency ranges during upright tilt, we calculated the coherence, transfer magnitudes, and phase relations between the signals by using the technique of Saul et al. Coherence was calculated from the cross-spectra and autospectra of 256-second stationary data segments over 2 time intervals before the end of tilt: 90 to 346 seconds, and 344 to 600 seconds. The following formula was used: Coherence = (cross-spectra)²/(input signal autospectrum) × (output signal autospectrum). The signals were considered coherent over the frequencies at which coherence values exceeded 0.5. Transfer magnitudes and phases were calculated for each subject over the frequency range meeting this criterion. Transfer magnitudes were determined by dividing the cross-spectrum by the input autospectrum.

Results

Cardiovascular Responses Before Syncope

There were no significant group differences in subject ages, or their average systolic and diastolic BPs, interbeat intervals, tidal volumes, and corresponding spectral powers during paced or spontaneous breathing under pretilt and initial tilt (first 15 minutes) conditions. The 25 subjects with syncope developed pallor, diaphoresis, dizziness and/or transient loss of consciousness within 17 to 40 minutes of head-up tilt. Blood pressure began to fall at the time symptoms developed, and relative bradycardia followed. The tilt was terminated when systolic BP fell below 80 mm Hg. All subjects recovered spontaneously on return to the supine position.

The mean changes in R-R interval and systolic and diastolic BP for the 2 groups of subjects over 10 minutes before the time of syncope are shown in Figure 1. If the tilt was terminated before a full 10 minutes of spontaneous breathing data could be obtained, shorter segments (at least 5 minutes) were analyzed for both the syncope subject and their matched control subject and are included in Figure 1. There were no significant differences in R-R interval, or systolic and diastolic BP between the groups until approximately 3.5 minutes before the end of tilt. In the syncope group, systolic and diastolic BP began to fall at 210 seconds and R-R interval began to increase at 90 seconds before the end of tilt. There was a small change in R-R interval during the same time period in nonsyncopal subjects, but this was significantly smaller than the change in syncope subjects (P = 0.0001, time by group interaction). There were no significant changes in BP in the nonsyncope group.

Illustrative R-R interval, systolic BP, and respiratory time series over 2 minutes before the time of syncope for 1 syncope subject and 1 age-matched control subject are shown in Figure 2. Note the large respiratory amplitude in the syncope subject compared with the control subject as BP fell before syncope. This subject also had large fluctuations in systolic BP that appeared to coincide with respiratory oscillations. However, these systolic BP fluctuations were not significantly greater among the group of syncope patients than among the control subjects.

Complex Demodulation of Cardiovascular and Respiratory Dynamics Before Syncope

Complex demodulation of cardiovascular and respiratory dynamics before syncope assessed the changes in frequencies and amplitudes in the high and low frequency bands for respiration (Figure 3), R-R interval (Figure 4), and systolic BP (Figure 5) during the 10 minutes before the time of syncope for both groups of subjects. In syncope patients, the respiratory amplitude in both high and low frequency bands began to increase significantly at 180 seconds before the onset of syncope (Figure 3). This was due to greater volumes of rapid (high frequency) shallow breaths as well as slower (low frequency) cycles of deeper breaths. The amplitude of R-R interval variability in the low frequency band did not change significantly until immediately before syncope (Fig-
The amplitude of R-R interval variability in the high frequency band began to increase 90 seconds before terminating the tilt (Figure 4), the same time at which bradycardia began to develop (Figure 1). The amplitudes of respiration and R-R interval did not change in either frequency band during matched time periods in the nonsyncopal control subjects. There were no significant changes in the frequency within the low and high frequency bands of respiration or R-R interval before the time of syncope for either group.

Systolic (Figure 5) and diastolic BP (not shown) variabilities were similar in both groups before the time of syncope. Although there were small changes in the frequency of systolic and diastolic BP in the low frequency band among control subjects, these changes were not significantly different from those in the syncope group.

**Individual Changes in Respiratory Amplitude**

Because the mean changes in amplitude of fast and slow breaths could be influenced by a few outliers, we also analyzed the distributions of individual responses before the time of syncope. Using the 5 minute period of paced breathing during early tilt as a uniform reference for all subjects, we determined the number of subjects who doubled or tripled the amplitude of low frequency breaths, or halved the amplitude of high frequency breaths, during 5 minutes of spontaneous breathing before the termination of tilt for syncopal subjects, or during matched time periods for control subjects. As shown in Table 1, significantly more syncope than nonsyncope subjects at least doubled or tripled the amplitude of low frequency (slow) breaths. Only 1 syncope subject reduced high frequency amplitude by 50% or more compared with 10 of the control subjects ($P=0.002$).

**Coherence of Respiration and R-R Interval Variabilities**

Table 2 shows the number of subjects in each group with coherence between their respiratory and R-R interval time series, with corresponding coherence, transfer magnitude, and phase data over 2 time intervals: just before the time of syncope (90 to 346 seconds) and more distant (344 to 600 seconds).
Fewer syncope than nonsyncope subjects showed coherence during the 344- to 600-second period ($P < 0.05$). In the period just before the time of syncope, the transfer magnitudes tended to decrease in the syncope subjects and became significantly lower compared with nonsyncopal control subjects ($P < 0.003$). The phase relation between the two signals was consistently negative, indicating that respiration led R-R interval changes.

**Discussion**

**Principal Findings**

The principal results of this study are as follows: (1) Healthy subjects with tilt-induced vasovagal syncope experience increases in respiratory amplitude beginning 3 minutes before systolic BP reaches 80 mm Hg and syncope is imminent. The increase in respiratory amplitude begins at the time that blood pressure begins to fall. Because respiratory frequency remains unchanged during this time period, the subjects are probably hyperventilating. (2) At approximately 90 seconds before syncope there is a sudden prolongation of R-R interval and increase in high and low frequency R-R interval amplitude that indicates an abrupt enhancement of vagal tone. (3) The increase in respiratory amplitude between 180 and 90 seconds before syncope is not accompanied by changes in
sudden onset of a vagal reflex precipitated by preload due to an underlying state of hypervagotonia but to the just before the fainting. Thus vasovagal syncope may not be cardiovagal tone is not different between syncopal and that precipitate syncope. Our results indicate that baseline control of cardiovascular function during dynamic conditions permits the continuous assessment of changes in autonomic

**TABLE 2. Coherence, Transfer Magnitudes, and Phase Between Respiration (Instantaneous Lung Volume) and R-R Interval Variabilities**

<table>
<thead>
<tr>
<th></th>
<th>Syncope (n=18)</th>
<th>Nonsyncope (n=17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 to 344 seconds before time of syncope</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) coherent</td>
<td>8 (44%)</td>
<td>13 (76%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean (SE) coherence</td>
<td>0.64 (0.03)</td>
<td>0.69 (0.03)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SE) transfer magnitudes</td>
<td>0.14 (0.05)</td>
<td>0.16 (0.04)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SE) phase</td>
<td>-70 (36)</td>
<td>-75 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>346 to 90 seconds before time of syncope</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) coherent</td>
<td>9 (50%)</td>
<td>12 (71%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SE) coherence</td>
<td>0.61 (0.02)</td>
<td>0.65 (0.03)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SE) transfer magnitudes</td>
<td>0.07 (0.01)</td>
<td>0.14 (0.02)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean (SE) phase</td>
<td>-118 (13)</td>
<td>-53 (27)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

R-R interval or R-R interval variability, suggesting there is dissociation between respiration and the vagally-mediated “respiratory sinus arrhythmia.” This finding is reinforced by the coherence analysis, which showed fewer syncyne subjects with coherence between respiratory and R-R interval variabilities before the end of tilt and lower transfer magnitudes in syncyne subjects compared with control subjects during this time period.

Although BP fell during the last 3 minutes before syncope, there was no significant change in low or high frequency BP amplitude during this time period. This may be due to the counterbalancing effect of large respiratory amplitudes on BP, thus masking the decline in low frequency BP fluctuations (Mayer waves) that would otherwise be expected to occur as sympathetic activity is withdrawn from the vasculature.

Several previous studies have used time and frequency domain analyses of heart rate variability to determine whether subjects who are prone to vasovagal syncope have an increase in baseline vagal tone. The results of these studies are conflicting; some show increases in heart rate variability, whereas others show no difference or decreases in syncopal subjects compared with control subjects. The advantage of complex demodulation over previous methods is that it permits the continuous assessment of changes in autonomic control of cardiovascular function during dynamic conditions that precipitate syncope. Our results indicate that baseline cardiovagal tone is not different between syncopal and nonsyncopal subjects but that vagal tone suddenly increases just before the fainting. Thus vasovagal syncope may not be due to an underlying state of hypervagotonia but to the sudden onset of a vagal reflex precipitated by preload reduction and possibly hyperventilation.

**Potential Mechanisms and Effects of Hyperpnea Before Syncope**

Although hyperpnea has been observed in individual patients before syncope and is popularly known to produce syncope when used in combination with the Valsalva maneuver, it has not been widely recognized as a typical physiological response preceding a vasovagal faint. Hyperpnea may be a primary or secondary event. It may result from autonomic outflow to the lungs from brain centers that are stimulated at the onset of vasovagal syncope. Or, it may be a secondary response to the vasodilatation and hypotension that also precedes syncope. Hyperpnea can generate large negative intrathoracic pressures that may act as a “respiratory pump” to enhance venous return. This may account for the large respiratory and BP fluctuations seen in the syncope patient shown in Figure 2. The respiratory pump might prevent syncope unless such large pressures are generated that intrathoracic veins actually collapse. Although large intrathoracic pressures might explain the sudden cardiovascular collapse that occurred when respiratory amplitude reached its peak, it is unlikely that sufficiently large pressures were generated to produce syncope. Alternatively, a respiratory alkalosis associated with hyperventilation may cause cerebral vasoconstriction. The consequent reduction in cerebral blood flow could predispose to the development of syncope. Unfortunately, we were unable to measure pH, PCO₂, or cerebral blood flow during the study.

**Potential Mechanism of Dissociation Between Respiration and R-R Interval Variability**

Respiration is usually closely coupled to heart rate, producing the respiratory sinus arrhythmia (RSA). However, our data suggest that respiratory and cardiac interval oscillations can also occur independently. During conditions when vagal tone remains constant, increases in tidal volume have been shown to increase the amplitude of the RSA. Our results during the 5 minutes before the time of syncope show that respiratory amplitude increases for at least 1.5 minutes before there is any change in R-R interval variability. Furthermore, during this increase in respiratory amplitude the transfer magnitude between respiration and R-R interval is low. When vagal tone later increases, as is evident by an increase in R-R interval just before syncope, the amplitude of RSA also increases, along with further increases in respiratory amplitude. It is not clear whether respiration becomes coupled with cardiovascular activity at this point or whether these two systems continue to operate relatively independently.

There are several possible explanations for the dissociation between respiration and R-R interval variability. First, high sympathetic tone during tilt may suppress RSA until sympathetic withdrawal before syncope allows RSA to increase. This hypothesis is supported by the finding in rats that noradrenaline stimulation of aqueductal gray matter inhibits vagal-induced bradycardia. Furthermore, in humans, heightened β-adrenergic activity during exercise reduces RSA, whereas β-blockade may enhance it.

A second possible explanation for the dissociation between respiratory and R-R interval variability before syncope is that hyperventilation may suppress RSA. Hyperventilation abolishes the bradycardia induced by electrical stimulation of the carotid sinus nerve in dogs. By augmenting central inspiratory drive and increasing the activity of pulmonary stretch receptors, hyperventilation reduces the excitability of cardiac vagal motoneurons. The decoupling of respiration and RSA...
during hyperventilation may permit respiratory pumping without inspiratory cardiac slowing, thereby partially countering preload reduction during head-up tilt.

Third, it is possible that the increase in respiratory tidal volume did not produce a detectable change in RSA until it reached a critical threshold. Eckberg\(^5\) has shown that a 50% increase in tidal volume increases the average R-R interval amplitude by only 15%. Data from Hirsh and Bishop\(^18\) suggest that changes of < 1 L in tidal volume at respiratory frequencies >0.15 Hz have relatively little effect on RSA (<0.5 bpm). Therefore we may not be able to detect changes in RSA until tidal volume increases substantially.

Finally, it is possible that during baroreflex suppression of vagal outflow in response to head-up tilt, respiratory gating has a minimal effect on cardiac vagal motoneuron activity. Saul et al.\(^10\) showed that the transfer magnitude of respiration to heart rate is lower during upright posture compared with supine posture. Therefore respiratory and cardiac interval oscillations could be relatively independent of one another until vagal tone increases before syncope. This possibility requires further study.

**Limitations**

There are several limitations to this study. First, we were unable to measure sympathetic nervous system activity directly, and therefore do not know whether high sympathetic tone suppressed the respiratory sinus arrhythmia or whether a sudden reduction in sympathetic tone preceded syncope. Also, because we did not measure arterial PCO\(_2\) and pH, we cannot confirm the presence of hyperventilation or whether hyperventilation produced a respiratory alkalosis and associated hemodynamic collapse. Although the primary study variables (respiration, R-R interval, and BP) were the same for both groups until 3.5 minutes before the end of tilt, the absence of other hemodynamic measurements makes it difficult to know for sure whether the two study groups experienced the same orthostatic stress. Because the resolution of complex demodulation is approximately 30 seconds, we cannot ascertain the exact timing of autonomic changes before syncope. Nevertheless, complex demodulation enabled us to identify distinct changes in respiratory and cardiac interval dynamics before syncope that previous studies have been unable to address. Finally, we studied healthy subjects with no recent history of spontaneous syncope. Therefore our findings may not be generalizable to patients who are seen by physicians for the evaluation of spontaneous syncope.

In otherwise healthy subjects, tilt-induced vasovagal syncope appears to be preceded by a period of hyperpnea that is followed by an abrupt increase in cardiac vagal tone. Whether prevention of the hyperpneic response will prevent the development of syncope requires further investigation.

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