Respiration drives phase synchronization between blood pressure and RR interval following loss of cardiovagal baroreflex during vasovagal syncope

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Ocon AJ, Medow MS, Taneja I, Stewart JM. Respiration drives phase synchronization between blood pressure and RR interval following loss of cardiovagal baroreflex during vasovagal syncope. Am J Physiol Heart Circ Physiol 300: H527–H540, 2011. First published November 12, 2010; doi:10.1152/ajpheart.00257.2010.—Loss of the cardiovagal baroreflex (CVB), thoracic hypovolemia, and hyperpnea contribute to the nonlinear time-dependent hemodynamic instability of vasovagal syncope. We used a nonlinear phase synchronization index (PhSI) to describe the extent of coupling between cardiorespiratory parameters, systolic blood pressure (SBP) or arterial pressure (AP), RR interval (RR), and ventilation, and a directional index (DI) measuring the direction of coupling. We also examined phase differences directly. We hypothesized that AP-RR interval PhSI would be normal during early upright tilt, indicating intact CVB, but would progressively decrease as faint approached and CVB failed. Continuous measurements of AP, RR interval, respiratory plethysmography, and end-tidal CO2 were recorded supine and during 70-degree head-up tilt in 15 control subjects and 15 fainters. Data were evaluated during five distinct times: baseline, early tilt, late tilt, faint, and recovery. During late tilt to faint, fainters exhibited a biphasic change in SBP-RR interval PhSI. Initially in fainters during late tilt, SBP-RR interval PhSI decreased (fainters, from 0.65 ± 0.04 to 0.24 ± 0.03 vs. control subjects, from 0.51 ± 0.03 to 0.48 ± 0.03; P < 0.01) but then increased at the time of faint (fainters = 0.80 ± 0.03 vs. control subjects = 0.42 ± 0.04; P < 0.01) coinciding with a change in phase difference from positive to negative. Starting in late tilt and continuing through faint, fainters exhibited increasing phase coupling between respiration and AP PhSI (fainters = 0.54 ± 0.06 vs. control subjects = 0.27 ± 0.03; P < 0.001) and between respiration and RR interval (fainters = 0.54 ± 0.05 vs. control subjects = 0.37 ± 0.04; P < 0.01). DI indicated respiratory driven AP (fainters = 0.84 ± 0.04 vs. control subjects = 0.39 ± 0.09; P < 0.01) and RR interval (fainters = 0.73 ± 0.10 vs. control subjects = 0.23 ± 0.11; P < 0.001) in fainters. The initial drop in the SBP-RR interval PhSI and directional change of phase difference at late tilt indicates loss of cardiovagal baroreflex. The subsequent increase in SBP-RR interval PhSI is due to a respiratory synchronization and drive on both AP and RR interval. Cardiovagal baroreflex is lost before syncope and supplanted by respiratory reflexes, producing hypotension and bradycardia.

orthostasis; nonlinear; fainting

The 2009 Guidelines for the diagnosis and management of syncope define syncope as a transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery (22). Vasovagal syncope, also known as simple faint, often occurs in young people following prolonged orthostasis. As illustrated in Fig. 1, loss of consciousness coincides with fairly abrupt hypotension, attributed to sympathoinhibitory vasodilation, and vagally mediated bradycardia (4, 14). The pathophysiology of vasovagal syncope is thought to be due to an inappropriate regulation of cardiovascular reflexes that results in a drop in arterial blood pressure (AP), causing cerebral hypoperfusion (22). The precise pathophysiology describing this occurrence remains elusive (21).

Previously, using multiresolution wavelet analysis during fainting, we showed a decrease in α-index of heart rate (HR) variability, suggesting impairment of cardiovagal baroreflex function (24). Initially during orthostatic stress, the cardiovagal baroreflex appears intact since changes in AP elicit appropriate changes in RR interval (RR). Yet at the time of faint, the fall in AP coincides with an increase in RR interval. The reasons for this are unknown but may relate to the loss of the baroreflex. We have shown in fainters that there is excessive gravitational pooling of blood within the dependent vasculature with resultant thoracic hypovolemia and impaired compensatory splanchnic vasocostriction and venoconstriction (24, 39, 41). Splanchnic pooling does not necessarily provoke fainting and can occur in forms of chronic orthostatic intolerance, in which fainting typically does not occur (40). As faint approaches, total peripheral resistance (TPR) decreases coincident with a gradual decrease in mean arterial blood pressure (MAP) in some young vasovagal fainters (Fig. 1) (24, 41). This leads inexorably to a stage of overt hypotension, bradycardia, and circulatory collapse, coinciding with increased respiratory tidal volume, hyperpnea, and hypocapnia (31, 41). Hyperpnea may relate to excessive thoracic hypovolemia and reduced cardiac output, which can directly affect peripheral chemoreflex function (stagnant hypoxia) or can indirectly affect the chemoreflex by unloading arterial baroreflexes (5, 41). Together, these findings suggest that changes in thoracic volume, AP, HR, and respiration may produce cardiovascular instability and failure during fainting.

Although contributions of baroreflex deficiency to circulatory collapse during vasovagal syncope have been proposed (11, 16, 17, 19, 20, 29, 37, 41, 43, 46), they remain controversial because prior investigations have predominantly used linear, time-invariant methods to relate AP, HR, and respiratory signals to one another (11, 17, 19, 43) via cross-correlation analyses (2) or transfer function analyses (9, 47). However, the time courses of AP, HR, and respiration during orthostasis in fainters are highly nonlinear and time dependent and therefore poorly amenable to such analyses (12). There is a need, therefore, for the application of nonlinear, time-dependent, nonstationary methods to evaluate these hemodynamic signals.

One simple nonlinear time-dependent analysis uses phase synchronization methods (33). Phase synchrony is independent of signal amplitudes and is a necessary and sufficient condition
for coupling between oscillatory systems. Recently, we developed and used nonlinear phase synchronization methods to quantify time-dependent changes in cerebral autoregulation at the time of faint (25). This analysis showed that initially efficient cerebral autoregulation deteriorated at the time of faint and remained ineffective for a time thereafter.

In the current experiments, we applied phase synchronization methods to study changes in the relationships between the systolic AP and RR interval, which yields a time-dependent measure of the integrity of the cardiovascular baroreflex throughout upright tilt table testing. A strong phase relationship is prerequisite for an intact baroreflex. Conversely, if there were no defined phase relation between AP and RR interval, there would be no functional relationship and the baroreflex would fail. We also applied phase synchronization methods to study the nonlinear coupling between respiration and AP and between respiration and RR interval during tilt. Furthermore, we employed directionality analyses to determine which parameter drives the other in terms of phase interaction.

We hypothesize that a high degree of AP-RR interval phase synchronization, initially present and consistent with an intact cardiovagal baroreflex, degrades during tilt resulting in progressive loss of cardiovagal integrity. Baroreflex loss coincides with increasing synchronization of both AP and RR interval to progressively hyperpneic respiration and effectively links AP and HR to pulmonary stretch reflexes with resultant sympathoinhibition and vagal bradycardia as faint approaches. Respiration and respiratory reflexes may therefore be a principal driving force in the progression to vasovagal syncope.

**METHODS**

**Subjects**

We recruited 15 subjects with a history of vasovagal syncope (10 female) and 15 healthy control subjects (9 female). The age range for all subjects was 15–25 years. The Institutional Review Board of New York Medical College approved this study and signed informed consent was obtained from all participants.

Recruitment of syncopal subjects was achieved through referral to our center following a history of at least three episodes of fainting during the last 6 mo. Previous medical assessment of syncopal subjects, including history, physical examination, electrocardiography, and echocardiography, ruled out cardiac causes of fainting. Recruitment of control subjects was based on responses to advertisements or from a database of previous volunteers. All control subjects were free of any form of orthostatic intolerance.

Systemic illnesses, including cardiac disease or other forms of orthostatic intolerance, competitive athletic training, pregnancy within the past 3 mo, nicotine use, or recent prolonged bed rest, were exclusionary criteria for participation. No subjects used medications. All subjects refrained from the ingestion of caffeine or other xanthine-containing products for at least 72 h before testing.

**Protocol**

Following a 12-h overnight fast, testing began at 9:30 AM in a climate controlled room at 70°F. Following familiarization with procedures, subjects were instrumented for ECG, finometer for beat-to-beat continuous blood pressure recording, respiratory plethysmography, and capnography. Subjects remained supine for a 30-min acclimation period. Continuous supine baseline recordings of at least 5 min followed acclimation. Subjects then underwent head-up tilt (HUT) table testing to 70° with continuous recording of measurements. For the fainting group, subjects were kept upright until faint occurred.

Upon fainting, subjects were returned to the supine position and continuous recording of measurements occurred for 5 min during the recovery period. All subjects in the syncope group exhibited a vasovagal faint (hypotension-bradycardia) without pharmaceutical provocation. For the control group, subjects were upright for 10 min, followed by a return to the supine position for 5 min. No subject in the control group exhibited a faint or presyncopal symptoms.

**Description of Methods**

**Time intervals.** Young fainting subjects exhibit varying temporal patterns during HUT. We have previously used intervals to describe physiologically related events that vary in time (25, 26, 41). For both groups, we defined our baseline interval as the 5-min supine period before HUT. We excluded the first 1 min after HUT because transient initial orthostatic hypotension often occurs in young subjects, both in fainting and healthy groups, and is unrelated to syncope (42, 45). For the fainting group, we defined early, late, faint, and recovery intervals. The early interval was defined as the initial portion of the tilt after first 1 min where blood pressure was maintained. The late interval was defined as the latter portion of tilt where blood pressure slowly declined. The faint interval was defined as a ~15-s or longer period during which blood pressure and then HR rapidly declined and the subjects fainted. The recovery interval was defined as 5-min supine post-faint.

For control subjects, we defined early, late, pseudo-faint, and recovery intervals. The early interval was minutes 1–6 of tilt. The late interval was the last 6–9.5 min of tilt. The pseudo-faint interval was the last 15 s of tilt; note that control subjects did not faint. The recovery interval was defined as 5-min supine post-HUT. Because prolonged upright tilt may be associated with fainting in healthy individuals, we limited the tilt to 10 min. The intervals selected corresponded on the average to the intervals measured in fainting subjects. Previously, we showed that this time period was sufficient for comparison with fainters and does not invoke a false-positive fainting response (24, 25, 41). Additionally, most of our fainters faint during a 10-min tilt, and the duration of the time intervals is similar between groups (see RESULTS).

**Instrumentation and measurements.** A single lead ECG continuously measured HR and RR interval. A Finometer (Finometer; FMS, Amsterdam, The Netherlands) device continuously measured beat-to-beat blood pressure via photoplethysmography of the right middle finger calibrated to brachial artery pressure. A height sensor corrected for finger-to-heart distance. MAP was calculated from systolic blood pressure (SBP) and diastolic blood pressure (DBP) using the equation: MAP = (1/3 * SBP) + (2/3 * DBP). Continuous respirations were measured via respiratory inductance plethysmography (Respiracite; NIMS Scientific, Miami Beach, FL) allowing for calculation of respiratory frequency and relative ventilation. Relative ventilation, an estimate of changes in tidal volume, was derived from the integral of the absolute value of the respiration waveform. Following integration, relative ventilation was calculated as the ratio of the slope during each time interval to the slope during baseline (41). End-tidal CO₂ (ETCO₂) was measured using a nasal cannula and capnography (Smith Medical PM, Waukesha, WI). All data were sampled at 200 Hz.

**Phase synchronization index methods.** Phase synchronization may be defined as a relationship between two weakly coupled oscillating signals such that their phases and frequencies become locked and entrained, whereas their amplitudes remain independent (33). In the present study, the phase synchronization relationship between SBP and RR interval was used to describe the integrity and activity of the cardiovagal baroreflex. Additionally, the phase synchronization relationships between respiration and AP and between respiration and RR interval were used to determine the independence of respiration with each signal. The direction of phase difference provided additional information as will be shown. Thus, it is known that under usual
operating conditions of the cardiovagal reflex, an increase in AP produces an increase in RR interval (or decrease in HR) and vice versa, and so the phase of AP and RR interval relation is positive.

Phase synchronizations between the parameters of SBP and RR interval (SBP-RR interval), respiration and AP (Resp-AP), and respiration and RR interval (Resp-RR interval) were calculated based on previously described methods (25). Briefly, real-valued, scalar, time-dependent signals of AP, RR interval, and respiration have no intrinsic phase. The real signals were introduced into the complex plane via the Hilbert transformation (1). A Butterworth forward and backward zero-phase shift preprocessing filter was used to band pass filter the signals from 0.01 to 0.5 Hz so that phase trajectories are around the origin. This also excluded oscillations from the cardiac cycle. Thus the signals contained a narrow range of low frequency oscillations, while excluding periodic cardiac cycle changes and also excluding direct current (DC) signals (0 Hz). Signals were resampled at 2 Hz. The phases Φ(t)AP, Φ(t)RR, and Φ(t)Resp were therefore defined for AP, RR interval, and respiration, respectively. Phase differences were constructed for each category measured: ΔΦ(t)SBP-RR = Φ(t)SBP−Φ(t)RR, ΔΦ(t)Resp-AP = Φ(t)Resp−Φ(t)AP, and ΔΦ(t)Resp-RR = Φ(t)Resp−Φ(t)RR. A phase synchronization index (PhSI) for each was defined as: PhSI = √((cos[ΔΦ(t)])^2 + (sin[ΔΦ(t)])^2) where |> > signify time averages using a 50-s moving average window, and this index was used for each respective category. Thus a PhSI value of 0 indicates complete lack of synchronization and a PhSI of 1 indicates perfect synchronization. The index depends on absolute value of ΔΦ(t) and not its sign, which also contains information as noted below.

Directionality index methods. A directionality analysis allows a type of causal determination of which parameter more strongly influences the coupling relationship (32, 34). It determines to what extent the interaction between two interdependent signals is symmetrical and bidirectionally driven or asymmetrical and unidirectionally driven by one of the signals (34). In regard to our current experiment, directionality analysis allows us to determine which, if either, signal more strongly drives the phase synchronization between the coupled systems of SBP-RR interval, Resp-AP, or Resp-RR interval. Thus it allows us to determine whether the cardiovagal baroreflex is influenced and driven by any of the three parameters measured.

A directionality index (DI) was calculated using the methods of Rosenblum and Pikovsky (34). A detailed description appears in the Appendix. In brief, we constructed time differences for each signal (ΔΦ(t)1, ΔΦ(t)2), which were fit to a finite Fourier series periodic in 2π for the independent variables Φ(t)1, Φ(t)2. When the value of DI = 1, oscillator 2 depended on Φ(t)1, but oscillator 1 did not depend on Φ(t)2 and, therefore, we said that oscillator 1 was driving oscillator 2. When the value of DI = −1, oscillator 1 depended on Φ(t)2, but oscillator 2 did not depend on Φ(t)1; and, therefore, we said that oscillator 2 was driving oscillator 1. In both cases, there would be asymmetrical unidirectional coupling. When DI = 0, perfect bidirectional symmetrical coupling occurred. For present purposes, we defined bidirectional drive as −0.25 ≤ DI ≤ 0.25. We defined mild unidirectional drive as 0.25 < DI ≤ 0.50 or −0.50 ≤ DI < −0.25. We defined strong unidirectional drive as 0.50 < DI ≤ 0.75 or −0.75 ≤ DI < −0.50. We defined strong unidirectional drive as 0.75 < DI ≤ 1.00 or −1.00 ≤ DI < −0.75.

Data Analysis and Statistics

Data were digitized and stored offline in a computer. NCSS 2007 statistical software (NCSS; LCC, Kaysville, Utah) was used for analysis. Data are presented in representative graphs and as averages over each time interval. Data were analyzed for normality using D’Agostino test for skewness, kurtosis, and omnibus and found to be normally distributed. Subject demographic and time interval data were compared between groups using an independent, two-tailed Student’s t-test. ANOVA for repeated measures with a post hoc Bonferroni multiple comparisons test was used to compare changes between and within each group. Values were presented as means ± SE. Significance was set at P < 0.05.

RESULTS

Demographics

Comparison between the fainters (F) and the control (C) subjects showed that age (F, 18 ± 1 vs. C, 19 ± 1), height (F, 163 ± 3 vs. C, 168 ± 2), and weight (F, 59 ± 3 vs. C, 62 ± 2) were not significantly different between groups.

Duration of Time Intervals

For the fainters, the mean time of tilt until faint was 10.21 ± 0.52 min and the range until faint was from 3 to 27 min. The time duration for the baseline (F, 5.1 ± 0.21 vs. C, 5.2 ± 0.41 min), early (F, 5.1 ± 0.69 vs. C, 5.0 ± 0.01 min), late (F, 4.8 ± 0.67 vs. C, 3.3 ± 0.01 min), faint (F, 0.3 ± 0.11 vs. C, 0.3 ± 0.01 min), and recovery (F, 5.1 ± 0.32 vs. C, 5.0 ± 0.23 min) time intervals were not different between groups [P = not significant (NS) for all intervals].

Hemodynamic Changes in Syncope and Control Subjects

Table 1 shows changes in SBP, DBP, MAP, HR, and RR interval from baseline to tilt conditions for the control subjects and fainters. At the time of faint, all fainters developed hypertension and a decrease in HR (increase in RR interval). None of the control subjects fainted, complained of dizziness, or developed hypotension or bradycardia. Figures 1, A and B, show MAP and HR, respectively, change during tilt for a representative fainter. A typical vasovagal response was observed at faint with MAP falling and HR decreasing. No

Table 1. Hemodynamic and respiratory values

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Early</th>
<th>Late</th>
<th>Faint</th>
<th>Recovery</th>
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<tr>
<td></td>
<td>Control</td>
<td>Fainter</td>
<td>Control</td>
<td>Fainter</td>
<td>Control</td>
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<tr>
<td>SBP, mmHg</td>
<td>121 ± 3</td>
<td>116 ± 2</td>
<td>121 ± 3</td>
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<td>117 ± 3</td>
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<td>DBP, mmHg</td>
<td>64 ± 2</td>
<td>62 ± 2</td>
<td>66 ± 2</td>
<td>64 ± 4</td>
<td>66 ± 3</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>83 ± 2</td>
<td>80 ± 2</td>
<td>85 ± 2</td>
<td>81 ± 3</td>
<td>83 ± 2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>66 ± 3</td>
<td>69 ± 5</td>
<td>81 ± 3</td>
<td>93 ± 4</td>
<td>87 ± 4</td>
</tr>
<tr>
<td>RR interval, ms</td>
<td>922 ± 37</td>
<td>881 ± 33</td>
<td>756 ± 33</td>
<td>661 ± 26</td>
<td>706 ± 32</td>
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<tr>
<td>Resp frequency, min−1</td>
<td>17 ± 1</td>
<td>18 ± 1</td>
<td>14 ± 1</td>
<td>19 ± 1*</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>Relative ventilation, AU</td>
<td>1 ± 0</td>
<td>1 ± 0</td>
<td>2 ± 0.3</td>
<td>3 ± 1</td>
<td>2 ± 0.4</td>
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<tr>
<td>ETCO2, mmHg</td>
<td>40 ± 1</td>
<td>44 ± 1</td>
<td>40 ± 1</td>
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</table>

Values are means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; Resp, respiratory; ETCO2, end-tidal CO2; AU, arbitrary units. When compared with control subjects: *P < 0.05; †P < 0.01; ‡P < 0.001.

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similar drop in MAP or decrease in HR was seen in control subjects during tilt.

Respiratory Changes in Syncope and Control Subjects

Table 1 shows respiratory changes during baseline and tilt conditions between the control subjects and fainters. The respiratory frequency of fainters significantly increased during the early and late intervals and remained elevated thereafter compared with control subjects. During the faint interval, relative ventilation increased significantly in the fainters compared with control subjects and was associated with a decrease in ETCO₂, similar to previous reports (25, 41). Figure 1D depicts these respiratory changes for a representative fainter during tilt. Control subjects maintained a relatively constant respiration throughout tilt.

PhSI Changes in Syncope and Control Subjects

Mean PhSI values for both groups are presented in Table 2. There were no differences in synchronization indexes between SBP-RR interval, Resp-RR interval, and Resp-AP between fainters and control subjects at baseline, early, or recovery time intervals. PhSI for SBP-RR interval, Resp-AP, and Resp-RR interval for a representative fainter is shown in Fig. 2, A–C, and for a representative control subject in Fig. 2, D–F.

Group comparisons are illustrated in Fig. 3. The SBP-RR interval PhSI during late tilt was lower in fainters compared with controls as seen in Table 2, and fainters exhibited a time-dependent decrease that is seen in Fig. 3A. During the late time interval, fainters exhibited a time-dependent decrease in SBP-RR interval synchronization from a value of 0.65 ± 0.04 to a value of 0.24 ± 0.03, whereas controls maintained a relatively stable PhSI from 0.51 ± 0.03 to 0.48 ± 0.03 (P < 0.01 compared with control). This decrease in PhSI is also shown in Fig. 2A for a representative fainter. As shown in Fig. 2D for a representative control subject, no similar time-dependent decrease was noted for SBP-RR interval PhSI. Following this time-dependent nadir

Table 2. PhSI and DI

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Early</th>
<th>Late</th>
<th>Faint</th>
<th>Recovery</th>
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<td>Control</td>
<td>Fainter</td>
<td>Control</td>
<td>Fainter</td>
<td>Control</td>
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<tr>
<td>PhSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP-RR</td>
<td>0.40 ± 0.03 †</td>
<td>0.44 ± 0.03</td>
<td>0.53 ± 0.03 †</td>
<td>0.48 ± 0.04 †</td>
<td>0.24 ± 0.03 †</td>
</tr>
<tr>
<td>Resp-RR</td>
<td>0.30 ± 0.02 †</td>
<td>0.37 ± 0.05</td>
<td>0.27 ± 0.01 †</td>
<td>0.36 ± 0.04 †</td>
<td>0.26 ± 0.04 †</td>
</tr>
<tr>
<td>Resp-AP</td>
<td>0.27 ± 0.03 †</td>
<td>0.36 ± 0.05</td>
<td>0.24 ± 0.01 †</td>
<td>0.30 ± 0.04 †</td>
<td>0.25 ± 0.01 †</td>
</tr>
<tr>
<td>DI</td>
<td>0.48 ± 0.04</td>
<td>0.21 ± 0.06</td>
<td>0.21 ± 0.06</td>
<td>0.05 ± 0.05</td>
<td>0.24 ± 0.08</td>
</tr>
<tr>
<td>SBP-AP</td>
<td>0.11 ± 0.06</td>
<td>0.05 ± 0.09</td>
<td>0.19 ± 0.06</td>
<td>0.36 ± 0.07</td>
<td>0.31 ± 0.05</td>
</tr>
<tr>
<td>Resp-AP</td>
<td>0.38 ± 0.08</td>
<td>0.23 ± 0.12</td>
<td>0.27 ± 0.07</td>
<td>0.18 ± 0.09</td>
<td>0.37 ± 0.04</td>
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</table>

Values are means ± SE. Note that the SBP-RR interval phase synchronization index (PhSI) during late tilt was steadily decreased in fainters, and we list the lower value. In fainters, SBP-RR interval PhSI decreased from 0.65 ± 0.04 to 0.24 ± 0.03, whereas controls had relatively no change in SBP-RR interval PhSI (0.51 ± 0.03 to 0.48 ± 0.03). See RESULTS section for details. DI, directional index. †P < 0.01 compared with control; ‡P < 0.001 compared with control.
in synchronization, fainters exhibited progressively increased phase synchronization in SBP and RR interval up to the time of faint compared with controls. The increase in SBP and RR interval synchronization in fainters coincided with increased synchronization between respiration and RR interval (Fig. 3B) and with increased synchronization between respiration and AP (Fig. 4C) during late tilt and at the time of faint compared with control subjects. This is also apparent by comparison of Fig. 2, B and C, of a representative fainter with Fig. 2, E and F, of a representative control subject.

Fig. 2. The phase synchronization index (PhSI) for a representative fainter and control subject during tilt. A: in the fainter, systolic blood pressure (SBP)-RR interval (RR) PhSI decreases throughout late tilt and then maximizes at the time of faint. B: in the fainter, respiration (Resp)-arterial pressure (AP) PhSI maximizes at the time of faint. C: in the fainter, Resp-RR PhSI maximizes at the time of faint. D: in the control, SBP-RR PhSI is relatively unchanged with tilt. E: in the control, Resp-AP PhSI is relatively unchanged with tilt. F: in the control, Resp-RR PhSI is relatively unchanged with tilt.

Fig. 3. Changes in the PhSI during head-up tilt in fainters (black) and control (gray) subjects. A: PhSI between SBP and RR in fainters significantly decreased during late tilt and, thereafter, significantly increased at the time of faint compared with control subjects. B: PhSI between Resp and RR interval was significantly greater in fainters at late tilt and at the time of faint compared with control subjects. C: PhSI between respiration and AP was significantly greater in fainters at late tilt and at the time of faint compared with control subjects. Means are ± SE. †P < 0.01 comparing syncope to control group control; ‡P < 0.001 comparing syncope to control group.
Phase Differences Between SBP-RR Interval

The phase difference between SBP-RR interval describes the lead or lag between the two signals such that a positive difference occurs with intact cardiovagal baroreflex integrity and a negative difference occurs with loss of the cardiovagal baroreflex. Thus, for example, as blood pressure increases RR interval increases (HR decreases) with an intact cardiovagal baroreflex. There were no variations in SBP-RR interval phase difference between the groups during baseline (F: 0.52 ± 0.08 vs. C: 0.52 ± 0.09 radians; P = NS) and early tilt (F: 0.69 ± 0.07 vs. C: 0.75 ± 0.05 radians; P = NS). During late tilt, the sign of the phase difference was negative for fainters, whereas controls maintained a positive phase difference (F: −0.50 ± 0.08 vs. 0.74 ± 0.07 radians; P < 0.001), and this continued through faint (F: −0.25 ± 0.23 vs. C: 0.67 ± 0.12 radians; P < 0.01). The phase difference was similar between groups at recovery (F: 0.39 ± 0.12 vs. C: 0.58 ± 0.10 radians; P = NS). These changes are shown in Fig. 4 for a representative fainter and control subject.

DI. Mean DI values for both groups are also presented in Table 2. There were no differences between groups at baseline, early, late, and recovery time intervals, whereas between-group differences are seen during the faint interval. Figure 5, A–C, depicts results for a representative fainter during tilt for the DI between SBP-RR interval, Resp-AP, and Resp-RR interval, respectively. Figure 5, D–F, depicts results for a representative control subject during tilt between SBP-RR interval, Resp-AP, and Resp-RR interval, respectively.

Between-group comparisons are shown in Fig. 6. The directional interaction between SBP and RR interval is shown in Fig. 6A. At baseline, there was bidirectional drive between SBP and RR interval in both groups, which was maintained relatively unchanged for both groups throughout tilt even as synchronization decayed. The directional interaction between respiration and RR interval and respiration and AP are shown in Fig. 6, B and C, respectively. At baseline, there was bidirectional drive between respiration and RR interval and AP in both groups. At the time of faint, fainters exhibited respiration, strongly driving both RR interval and AP, whereas control subjects showed no such unidirectional respiratory drive but rather maintained bidirectionality. This can also be seen by comparison of the representative fainter in Fig. 5, B and C, to the representative control in Fig. 5, E and F. For all directional analyses, the values for both groups at recovery were no different from baseline.

DISCUSSION

Main and Novel Findings

Our results are the first to describe time-dependent changes in the PhSI and DI between AP, RR interval, and respiration elicited by orthostatic stress. The time-dependent SBP-RR interval relationship defines the integrity but not the sensitivity of the time-dependent cardiovagal baroreflex, in which changes in SBP reflexively evoke changes in the RR interval (44). Entrainment between SBP and RR interval is present when the reflex is intact and absent when the reflex is not intact. Phase synchronization is thus a necessary condition for intact cardiovagal baroreflex function, and its decrease denotes loss of baroreflex integrity.

The data indicate significant differences between fainters compared with control subjects, which may account for the
cardiovascular changes exhibited at the time of faint. As faint approaches, there is a decrease in SBP-RR interval PhSI, which is then followed by an increase in SBP-RR interval PhSI. This late increase at faint in the SBP-RR interval PhSI seems paradoxical but can be explained by changes in respiration and by noticing the direction of phase difference between SBP-RR interval during early and late tilt. The late increase in SBP-RR interval PhSI coincides with increased PhSI between Resp-AP and Resp-RR interval. During the earlier stages of tilt synchronization between respiration and AP or RR interval is relatively weak until syncope is imminent when hyperpneic respiration strongly synchronizes with AP and RR interval. The apparent

Fig. 5. The directionality index (DI) for a representative fainter and control subject during tilt. A: in the fainter, the DI between SBP and RR shows bidirectional driving throughout tilt. B: in the fainter, the DI between Resp and AP shows unidirectional driving of Resp on AP at the time of faint. C: in the fainter, DI between Resp and RR shows unidirectional driving of Resp on RR at the time of faint. D: in the control, DI between SBP and RR shows bidirectional driving throughout tilt. E: in the control, DI between Resp and AP shows bidirectional driving during tilt. F: in the control, DI between Resp and RR shows bidirectional driving during tilt.

Fig. 6. DI during head-up tilt in fainters (black) and control (gray) subjects. A: SBP and RR interval DI. There were no differences between groups. Because directionality was close to zero at all times, bidirectional symmetric driving occurred between SBP and RR, such that neither dominated. B: Resp and RR DI. At the time of faint, there was a significant difference between groups. For the fainters, at faint, respiration drove RR. For the control group, at all time intervals, the DI was close to zero indicating bidirectional symmetric driving. C: respiration and AP DI. At the time of faint, fainters exhibited respiration strongly driving AP compared with control subjects. For control subjects, mild drive of respiration on AP occurred during all time intervals. Means are ± SE. †P < 0.01 compared with control subjects; ‡P < 0.001 compared with control subjects.
paradox is resolved when the direction of SBP-RR interval phase difference is considered: during intact cardiovagal function a change in blood pressure is reflected by a directionally similar change in RR interval. Thus, as SBP decreases, RR interval also decreases (and HR increases) and vice versa. From the point of minimum phase synchronization (when the cardiovagal baroreflex fails), phase direction reverses (see Fig. 4). This means that a decrease in SBP is associated with an increase in RR interval, or equivalently, that a fall in SBP is now linked to a fall in HR, which is exactly what happens during fainting. When respiration is compared with AP and to RR interval, ventilation now becomes negatively phase-locked with both AP and HR such that increased ventilation drives a decrease in both AP and HR.

Thus, although superficially it might seem that the cardiovagal baroreflex decreases and then increases activity as fainting approaches, in reality SBP falls and RR interval increases, which is directionally opposite (phase inversion) to expected changes with an intact cardiovagal baroreflex. This is also reflected in the SBP-RR interval DI, which shows an average value of $-0.08 \pm 0.14$. Neither signal drives the other. The data support our explanation that the cardiovagal baroreflex is no longer intact before and at faint and that respiration drives the SBP-RR interval PhSI to high values. Further support for this interpretation of the data is offered by increased respiration and AP PhSI and increased respiration and RR interval PhSI as fainting approaches. Oscillations in AP and RR interval are each linked with oscillations via respiration in a synchronized manner (see Fig. 2), providing the semblance of mutual interaction. The DI shows that respiration is driving both AP and RR interval. This is completely consistent with the nonlinear phase synchronization theory, which states that a strong oscillator (such as respiration) can influence a weakly phase synchronization theory, which states that a strong external oscillator (such as respiration) can influence a weakly coupled oscillatory system (SBP-RR interval) producing strong phase synchronization in the original system through the respiration driver. Thus, near faint, respiratory based reflexes supervene and cardiovagal reflexes fail.

Increased respiration can further destabilize cerebral hemodynamics by decreasing CO$_2$, causing cerebral vasocostriction and hypoperfusion. Interestingly, the temporal loss of the cardiovagal baroreflex in fainters coincides with the loss of cerebral autoregulation that we previously reported (25) and also coincides with maximum thoracic hypovolemia and the onset of hyperpnea (39, 41). Our previous data suggest that excessive thoracic hypovolemia during orthostasis results in progressive deterioration of the cardiovagal baroreflex, hyperpnea, and progressive enhancement of respiratory control of HR and blood pressure, which via pulmonary stretch sympatholytic and vagotonic reflexes contribute to the characteristic hypotension and bradycardia of vasovagal syncope.

Others have shown that neural signals from arterial or visceral mechanoreceptors, for example those in the cardiac left ventricle, may travel to the brain before fainting and play a role in the pathogenesis of faint (10). Central nervous system integration of arterial, baroreflex, cerebral, respiratory, mechanoreceptor, and volume signals responds to the physiological changes through peripheral parasympathetic outflow and sympathetic withdrawal, resulting in bradycardia and hypotension (10). Thus, AP, cerebral blood flow, and RR interval, which all seem controlled by respiration, become closely temporally entrained, both peripherally and centrally, culminating in loss of consciousness.

Comparison with the Literature

Since AP and RR interval are both highly coupled to respiration near the time of faint, it is not surprising that, as shown in the present report, they are also coupled to each other at the time of faint. Both are driven and entrained by the same strong oscillator. We have previously shown that high frequency (HF) HR variability power, characteristic of respiratory arrhythmia (variations in HR that occurs during breathing cycles), is increased for both AP and RR interval at the time of faint (24). Additionally, we (24) and Bernardi’s group (31) have previously demonstrated that respiratory power increases at the time of faint. Tzeng et al. (44) have reported respiratory

Fig. 7. The Resp-RR interval synchronization in 3 representative subjects. Overall synchronization calculated as in the text is shown in the top panels. A wavelet multiresolution analysis was performed for each patient, and the synchronization was recalculated at the scales corresponding to Mayer waves (wavelet Mayer) and to the respiratory frequency pressure (wavelet Resp). Other wavelet scales contributed to a lesser extent. In patient 1, synchronization at wavelet-Resp scale dominated overall synchronization; in patient 3, wavelet-Mayer scale dominated, whereas in patient 2, each scale was represented to a similar extent. All patients had discernible synchronization contributions at both scales that coincided with overall phase synchronization and with onset of syncope.
interaction on the cardiovagal baroreflex may affect its sensitivity. Thus changes in AP may be linked to changes in RR interval through their mutual coupling with respirations as faint approaches, whereas cardiovagal baroreflex and direct AP-RR interval coupling remain dysfunctional. Impairment of the cardiovagal reflex at the time of faint is consistent with previous reports (7, 8, 19, 43) using linear systems analysis applied during relatively stationary time periods preceding orthostasis or during the relatively stable earlier parts of upright tilts. However, our work is the first to use nonlinear phase synchronization combined with directionality index analyses to clearly demonstrate that the cardiovagal baroreflex becomes ineffective before fainting and is superseded by respiration driven AP and RR interval influence at or near the time of faint.

Others have demonstrated a respiratory link to SBP and RR interval. Pitzalis et al. (30) found that as breathing rate increases, the time lag between SBP and RR interval decreases. This may be similar to the increased synchronization between SBP and RR interval that we found when respiration increased. Gulli et al. (6) found that subjects with orthostatic intolerance have increased latency between baroreflexive changes in RR interval and SBP. This may be similar to the loss of cardiovagal baroreflex that we describe in fainters. Using lower body negative pressure (LBNP) as an orthostatic stimulus, Thomson et al. (43) found that cardiopulmonary baroreceptor sensitivity was decreased in patients with vasovagal syncope. Our current work furthers their findings since the latency and decreased sensitivity may be due to decreased direct phase synchronization between AP and RR interval and the increase in indirect LBNP driven synchronization caused by respiratory entrainment, which is in turn driven by thoracic hypovolemia.

Our findings differ from the early work of Lipstiz et al. (17), who concluded that the cardiovagal baroreflex is not altered during vasovagal syncope. These differences are most likely due to their initial use of time-independent, frequency-based linear transfer function methodology compared with our time-dependent nonlinear phase synchronization method. Indeed, during early upright tilt, there are no observable differences between our syncope patients and control subjects, which only become evident as changes in cardiorespiratory parameters ensue later during tilt and with impending faint. These investigators also used healthy subjects who happened to develop tilt-induced vasovagal syncope (so-called false-positives), whereas we used subjects with an established history of fainting. However, later work by Lipstiz’s group (16) using nonlinear complex demodulation methods generally supports our findings.

![Fig. 8. The changes in synchronization between Resp and SBP, respirations and RR interval, and systolic arterial pressure and RR interval. The right group is a time expansion of the left group. In each grouping, graph A shows Resp measured by a respiratory inductance plethysmograph (arbitrary scale), graph B shows SBP measured by Finometer, graph C shows RR interval measured by electrocardiogram, graph D shows Resp-SBP phase synchronization, graph E shows Resp-RR interval phase synchronization, and graph F shows SBP-RR interval phase synchronization.](http://ajpheart.physiology.org/)

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Although time-dependent suitable measurements of amplitude and frequency changes were used, complex demodulation methods did not offer easy ways to compare nonlinear coupling between signals without resorting to linear methods such as coherence or correlation methods. Nevertheless, they did show increased respiratory amplitudes due to increased tidal volume and breathing frequency as fainting approached that began as blood pressure fell (16). A functional relationship between respirations and blood pressure was therefore supported and is consistent with our finding of increased synchronization between AP and respiration as the time of faint approaches. Additionally, Lipstiz’s group found that as RR interval increased in fainters, there was an increase in respiratory amplitude, but were unable to determine whether this represented a functional relationship between respiration and cardiovagal activity (16). Phase synchronization methods succeed in demonstrating this link. Thus there is support for the proposal that cardiovagal activity is lost before fainting and superseded by hyperpnea and hyperventilation induced through thoracic hypovolemia, which in turn drives changes in HR and arterial pressure (16, 39, 41).

Limitations

Fainting is a variable event. The exact time until faint differs between subjects. We have used defined time intervals to model physiologically similar events before fainting that may have different time spans. Similarly, we used time intervals in control subjects that were close to the mean time for each event in our syncope group. This allows for equivalent forms of data to be analyzed for each group.

The algorithm used requires averaging and thus windowing of the original data. Moving average computations can affect the exact value of the synchronization indexes. However, we have used several different windows from 15 to 100 s, and all yielded similar results. The validity and significance of the data also are supported by the consistency of patterns of synchronization, which are similar for all fainters and are different from the patterns of synchronization determined in healthy control subjects.

Fainting is a nonlinear, nonstationary, time-dependent event. We have used nonlinear time-dependent methods of PhSI and DI to measure changes in the cardiovagal baroreflex. These methods do not allow for a measurement of baroreflex sensitivity; nor do we imply a measure of baroreflex performance. These methods allow one to conclude whether the baroreflex is intact or absent. Comparison of these results with linear methods (13) requires caution with interpretation.

We did not directly measure absolute tidal volume in our subjects although the Respirtrac provides accurate relative tidal volume and minute ventilation and resting respirations have been shown to be the same in fainters and healthy controls (41). Our previous work shows that tidal volume reaches a maximal value at the time of faint (41). Thus, hyperpnea-hyperventilation may play a role for the coupling of AP and RR interval to respiration.

We did not consider phase synchronization in relation to ETCO₂. Prior work has demonstrated a predictable inverse relationship between ventilation and ETCO₂ in our patients (38). Thus ventilation determines CO₂, and the measurement of CO₂ contributes little additional information.

APPENDIX

Physiological systems have been modeled as either linear or nonlinear. A linear system $f(x)$ obeys the superposition property $(f(x + y) = f(x) + f(y))$.
$f(y)$ and has first degree homogeneity $[f(ax) = af(x)]$, where $a$ is a constant, and $x$ and $y$ are inputs to a system having $f()$ as the system output. Superposition is fundamental to the use of Fourier analysis and discrete wavelet transforms. Linear properties are not always satisfied, and thus a time series of physiological phenomena may need to be modeled as a nonlinear phenomena. This is particularly true as applied to interacting intrinsic oscillatory systems. Previous studies have used nonlinear dynamics to describe cardiorespiratory changes in newborns.

Fig. 10. A simulation of the effects of increasing sinusoidal amplitudes on the synchronization index. The sinusoids of amplitude 0, 1, 2, 4, 8, 16, and 32 are added. There is no substantial influence on the synchronization index independent of phase difference of the sinusoids, until amplitude exceeds the variance of the AP and RR interval.
(23), as well as changes in EEG neural networks (15). In the current work, the cardiovagal baroreflex system is nonstationary and is nonlinear. We model AP, RR interval, and respiration as weakly coupled time-dependent, nonstationary, nonlinear chaotic oscillators. For weakly coupled oscillators, phases may become entrained, whereas amplitudes remain unaffected and independent from the coupling (28). In our previous work, we have used a nonlinear method of phase synchronization to describe the relationship between AP and cerebral blood flow velocity during syncope in young subjects (25).

Phase synchronization describes the strength of interaction between the phases of two weakly coupled self-sustaining oscillators (35). Yet this method fails to provide information concerning whether one oscillator drives the other or whether their interaction is symmetrical. A DI was developed by Rosenblum and Pikovsky to describe whether the coupling interaction between two oscillators is unidirectional and asymmetrical, as driven by one of the oscillators, or bidirectional and symmetrical, such that both oscillators mutually affect each other (34). We use their method and index (23, 32, 34) and describe and present that it bolsters our work.

The scalar time-dependent signals for AP, RR interval, and respiration have no intrinsic phase, which requires complex numbers. The phase \( \Phi \) for each was defined using the Hilbert Transformation as described in the METHODS section. For two coupled oscillators: \( \Phi_1 = \omega_1 + \varepsilon_1 f_1(\Phi_1, \Phi_2) + \xi_1(t) \) and \( \Phi_2 = \omega_2 + \varepsilon_2 f_2(\Phi_2, \Phi_1) + \xi_2(t) \), where \( \Phi_{1,2} \) are continuous unwrapped phase variables, the functions \( f_{1,2} \) are \( 2\pi \) periodic, \( \varepsilon_{1,2} \) are the strength of interaction for each oscillator that assumes \( \varepsilon_{1,2} < \omega_{1,2}, \omega_{1,2} \) are the natural frequencies of each oscillator, and \( \xi_{1,2} \) account for noise in the system (23). It should be noted that with perfect synchronization, a functional relationship appears between \( \varepsilon_{1,2}, \omega_{1,2}, \) and \( f_{1,2} \) that limits the ability to understand the meaning of directionality, thus nonperfect synchronization is necessary (23, 34). Because perfect synchronization (PhSI = 1) is not apparent in our results, directionality can be used.

For directionality to be estimated, a ratio of the coupling terms from the time series of phases \( \Phi_{1,2}(tk) \) is necessary, where \( n = \delta tk, \delta t \) is the sampling interval, and \( k = 1, \ldots, n \) (34). The incremental change of phase for each oscillator was observed for a temporal window length of \( \tau \) as (23):

\[
\Delta_{1,2}(k) = \Phi_{1,2}(tk + \tau) - \Phi_{1,2}(tk).
\]

The increments may be considered as generated by a unknown two-dimensional noisy map as (23):

\[
\Delta_{1,2}(k) = \omega_{1,2} x + F_{1,2}(\Phi_{1,2}(tk), \Phi_{1,2}(tk)) + \xi_{1,2}(tk).
\]

To estimate the coupling term \( F_{1,2} \) of the unknown map from time series \( \Phi_{1,2} \), we approximate \( F_{1,2} \) using a finite Fourier series by 10.220.33. The cross-dependency of phase dynamics of the two system is the least mean square coefficient \( A \) to fit the dependency of series \( F_{1,2} \), we approximate \( F_{1,2} \) using a finite Fourier series:

\[
A = \frac{\sum_{m,n} c_{1,2}^{m,n} \Phi_{1,2}^{m,n} \Phi_{1,2}^{* m,n}}{\sum_{m,n} c_{1,2}^{m,n} \Phi_{1,2}^{m,n} \Phi_{1,2}^{* m,n}},
\]

where \( m \) and \( n \) are less than 4 (23). The cross-dependency of phase dynamics of the two system is calculated by means of coefficients \( c_{1,2} \) as below (34):

\[
c_{1,2} = \int \int (\delta \Phi_{1,2}^m)^* \delta \Phi_{1,2}^n d\Phi_1 d\Phi_2.
\]

The coefficient \( c_{1,2} \) describes the strength of one oscillator to drive the other. If \( c_{1,2} \) is very small, the oscillators do not interact. Such is the case for the cardiovagal AP-RR interval interaction at its nadir. From \( c_1 \) and \( c_2 \), a DI can be obtained as (34):

\[
D_{1,2} = \frac{(c_2 - c_1)}{(c_2 + c_1)}.
\]

When the value of DI = 1, oscillator 1 is driving oscillator 2. When the value of DI = -1, oscillator 2 drives oscillator 1. In both cases, there is unidirectional asymmetrical coupling. When DI = 0, such that \( c_2 = c_1 \), then bidirectional symmetrical coupling occurs.

Testing the methodology: Whereas nonlinear phase synchronization methods are not new, their use in interpreting physiological phenomena is fairly recent (12, 33). We therefore offer several proofs of their utility in this regard based on ancillary experiments and analyses:

**The response of the cardiorespiratory system is nonlinear.** Linear signal processing supports the decomposition of signals into the sum of orthogonal bases, which may comprise sines and cosines in Fourier or time-scaled mother wavelets. In common, using Fourier and wavelet approaches assume superposition, although wavelets are more convenient and useful for slowly changing nonstationary systems. If linear decomposition and superposition are used to analyze our proposed nonlinear system, system inputs at one frequency or scale yield system outputs at multiple frequencies or scales, and we see cross-talk between the different orthogonal modes. The clean separation of higher frequency (smaller scale) respiratory and lower frequency (larger scale) baroreflex frequencies does not suffice, not only because respiratory sinus arrhythmia produces direct mechanical effects on blood pressure (decreases with inspiration, etc.), which are then transduced into a change in HR by the baroreflex, but also because of nonlinear mixing of respiratory frequencies with baroreflex frequencies, which is particularly evident in RR interval spectra.

The wavelet approach does not yield clear separations into scales corresponding to the respiratory and Mayer wave frequencies, but rather there is cross-talk between the bands.

As an example, we have performed discrete wavelet analyses using Daubechies 4 as the mother wavelet forming an orthonormal set (3). Other wavelet selections give similar results. We used discrete wavelets because our data were sampled and were therefore discrete and nonstationary. The Daubechies wavelets form complete orthonormal sets. We employed an extended version of the dyadic discrete wavelet transform (DWT) as described by Percival and Walden to produce a maximal overlap discrete wavelet transform (MODWT) (27). The MODWT fills all time points at each scale, allows precise alignment of the signal and its wavelets, has zero phase shift, and permits easy calculation of details (representing each scale’s contributions to the original signal as a function of time; a detail is the inverse DWT of the Wavelet coefficients at given scale) (24). In Fig. 7, phase synchronizations have been calculated from separate wavelet details of respirations and RR interval at scales corresponding to Mayer wave and respiratory frequencies. Similar figures can show calculations derived from respirations and blood pressure. Three syncopal patients are shown in Fig. 7. Synchronization was computed for each wavelet scale using the Hilbert transform to obtain the imaginary part. Discrete wavelet transform is real valued and thus requires the introduction of an imaginary part to compute phase and thus synchronization. Although overall phase synchronization increases near the time of faint for all patients, it is sometimes increased in the respiratory scale, sometimes in both the Mayer wave scale and the respiratory scale reflecting the kind of nonlinear cross-talk between orthonormal scales.

**Deep regular breathing illustrates nonlinear entrainment and phase synchronization.** Deep breathing includes effects on HR produced by cross-talk between the respiratory, sympathetic, and vagal regulators and mechanical pressure fluctuations. These fluctuations are produced by the increased and decreased filling of the heart by respiration, thereby causing oscillations in blood pressure at the respiratory frequency, which are transduced via the baroreflex and pulmonary reflexes. Both HR (respiratory sinus arrhythmia) and blood pressure, therefore, entrain to respirations (18); they are driven by the respiratory oscillator and produce excellent phase synchronization. Figure 8 illustrates the RR interval-AP, Resp-AP, and Resp-RR interval synchronizations derived from the Hilbert transform during timed deep breathing at 12 breaths per minute. All three signals have high

<table>
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<th>PhSI After Addition</th>
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<td>0.669</td>
</tr>
<tr>
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<tr>
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<tr>
<td>16</td>
<td>0.639</td>
<td>0.752</td>
</tr>
<tr>
<td>32</td>
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synchronization that is driven by deep breathing. Therefore, as shown below, it is appropriate to use these analyses of synchronization for the study of physiologically complex phenomenon such as fainting.

Simulation of adding sinusoidal components of multiple amplitudes to both AP and HR. We create a numerical simulation by adding a periodic (sinusoidal) component to both AP and HR signals of a healthy volunteer. The purpose is to examine the behavior of the synchronization index in the cross-over region obtained by bisecting AP and HR recordings into equal parts and adding the sinusoidal component to both second halves. The most natural choice of the driving frequency is the frequency of spontaneous respiration determined by spectral analysis. For the subject chosen, this is 0.271 Hz. The addition of a sinusoid of amplitude 32 is shown in Fig. 9. The HR tracing is then converted to an equivalent RR interval graphic. The addition of a sinusoid of amplitude 32 increases the synchronization index to a mean of 0.80 at faint. These consistent findings in all subjects.

A change in synchronization in the simulation occurs at amplitude 8 comprising a reduction in overall synchronization from 0.647 to 0.500, a 23% decrease. The decrease occurs throughout the portion of the signal containing the added sinusoidal component and does not immediately precede the addition of signal as observed in fainters. There is also no subsequent increase in synchronization index noted for amplitude 8. An increase in synchronization occurs for amplitudes 16 and 32, but is not preceded by a large decrease in the synchronization index. This is quite different from patient results. The mean change in synchronization in patients is from 0.65 to 0.24, a 63% decrease. This change of synchronization is confined to the period of late tilt immediately preceding the faint and is followed by a large increase in the synchronization index to a mean of 0.80 at faint. These are consistent findings in all subjects.

The amplitude 8 sinusoid exceeds the blood pressure variance but not RR interval variance. Overall synchronization suffers because simulated BP (true BP + sinusoid) and simulated RR interval are no longer as well synchronized. At higher amplitudes the overall synchronization increases because the sinusoidal components in BP and RR interval prevail. At lower amplitudes the overall synchronization is higher because the native synchronization of blood pressure-RR interval prevail. At lower amplitudes the overall synchronization decreases during development of tilt-induced syncope preceding sympathetic withdrawal and bradycardia. Am J Physiol Heart Circ Physiol 289: H1758–H1769, 2005.


