Disruption of phase synchronization between blood pressure and muscle sympathetic nerve activity in postural vasovagal syncope

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Schwartz CE, Lambert E, Medow MS, Stewart JM. Disruption of phase synchronization between blood pressure and muscle sympathetic nerve activity in postural vasovagal syncope. Am J Physiol Heart Circ Physiol 305: H1238–H1245, 2013. First published August 9, 2013; doi:10.1152/ajpheart.00415.2013.—Withdrawal of muscle sympathetic nerve activity (MSNA) may not be necessary for the precipitous fall of peripheral arterial resistance and arterial pressure (AP) during vasovagal syncope (VVS). We tested the hypothesis that the MSNA-AP baroreflex entrainment is disrupted before VVS regardless of MSNA withdrawal using the phase synchronization between blood pressure and MSNA during head-up tilt (HUT) to measure reflex coupling. We studied eight VVS subjects and eight healthy control subjects. Heart rate, AP, and MSNA were measured during supine baseline and at early, mid, late, and syncope stages of HUT. Phase synchronization indexes, measuring time-dependent differences between MSNA and AP phases, were computed. Directionality indexes, indicating the influence of AP on MSNA (neural arc) and MSNA on AP (peripheral arc), were computed. Heart rate was greater in VVS compared with control subjects during early, mid, and late stages of HUT and significantly declined at syncope (P = 0.04). AP significantly decreased during mid, late, and syncope stages of HUT. In VVS subjects only (P = 0.001), MSNA was not significantly different between groups during HUT (P = 0.700). However, the phase synchronization index significantly decreased during mid and late stages in VVS subjects but not in control subjects (P < 0.001). In addition, the neural arc was significantly affected more than the peripheral arc before syncope. In conclusion, VVS is accompanied by a loss of the synchronous AP-MSNA relationship with or without a loss in MSNA at faint. This provides insight into the mechanisms behind the loss of vasosconstriction and drop in AP independent of MSNA at the time of vasovagal faint.

vasovagal syncope; phase synchronization; blood pressure; muscle sympathetic nerve activity

MANY INDIVIDUALS will have at least one vasovagal syncope (VVS; fainting) episode in their lifetime, which often appears without warning. Others experience multiple episodes, sometimes several within a span of months. This can compromise quality of life and, when occurring in certain situations, can be life threatening. Although this is a common event, and we do not fully understand all the mechanisms involved in VVS, a disruption in the arterial baroreflex has been suggested to contribute to fainting (17, 28).

The arterial baroreflex is one of the main cardiovascular autoregulatory mechanisms in the body. Orthostatic stress results in a redistribution of blood to the lower body due to the pull of gravity. After a short delay, blood pressure is restored by sympathetic noradrenergic vasocostriction and venocostriction and by an increase in heart rate (HR) (39). During a VVS episode, there is evidence that ineffective reflex mechanisms may lead to excessive venous pooling in the periphery and/or splanchnic regions (1, 7, 12, 41). While this triggers increased vasoconstriction, ultimately vasodilation occurs, leading to a progressive drop in blood pressure and cerebral blood flow and ultimately results in a loss of consciousness (42). Vasodilation is associated with markedly enhanced vasotonia leading to a concomitant fall in HR (hence, the term “vasovagal syncope”) (24). The mechanisms governing the abrupt onset of vasodilation have been previously investigated but remain elusive (15, 26, 27, 41, 45).

One proposed mechanism for vasodilation has been a loss in sympathetic nerve traffic resulting in a decreased vasoconstriction and drop in blood pressure. Indeed, many investigations involving muscle sympathetic nerve activity (MSNA) have observed a reduction of MSNA in the moments leading up to faint (21, 27, 48), whereas others have reported an abrupt stop all together (26). In contrast, recent studies (15, 45) have shown MSNA persistence during VVS. Based on these findings, it remains unclear how persistent MSNA may be involved in the loss of vasoconstriction during syncope. We (32) have recently shown that the functional phase relationship between blood pressure and HR becomes deficient before the rapid decrease of blood pressure in VVS during upright tilt, and this may account for the accompanying bradycardia. We hypothesized that a similar loss in the functional relationship between MSNA and blood pressure occurs during VVS and accounts for the lack of blood pressure regulation despite persistence of MSNA.

METHODS

Subjects. We retrospectively analyzed 16 subjects [8 VVS subjects (1 man and 7 women) and 8 control subject (3 men and 5 women)]. All subjects had undergone similar protocols and were tested during supine baseline and up to 10 min of 70° head-up tilt (HUT). Subjects were taken from a pool of subjects from a larger study and included a few subjects with postural orthostatic tachycardia syndrome (POTS). However, neither control nor POTS individuals suffered or complained of recurrent syncope. Classification of VVS was determined when a subject experienced a vasovagal faint during the HUT, and this occurred in all eight of our VVS subjects, including three control subjects and five POTS subjects. The protocols were approved by the Institutional Review Board of New York Medical College and the Alfred Hospital Ethics Committee. All participants signed an informed consent and were not taking any medications or had ceased taking medications no less than 2 wk before the study. Subjects fasted for 12 h and abstained from caffeine and xanthine products and exercise for 24 h before being tested.

Protocol. All subjects were instrumented for testing. HR, blood pressure, and MSNA were recorded. After instrumentation, 10 min of supine baseline were recorded, after which subjects were tilted to 70°
HUT for 10 min (i.e., control group) or until presyncope symptoms occurred (mean: 365 ± 60 s, range: 251–697 s). This group was labeled as the VVS group. Presyncope was defined as a decrease in systolic blood pressure to <80 mmHg combined with symptoms of lightheadedness, dizziness, nausea, sweating, etc., upon which subjects were tilted back to the supine position (29). A 10-min recovery period followed. None of our subjects lost consciousness during the testing protocol.

Measurements. HR was measured using a single lead ECG. Beat-to-beat blood pressure was recorded using finger photoplethysmography (Finometer, FMS, Amsterdam, The Netherlands) and calibrated to an automated arm sphygmomanometer throughout the experiment. Cardiac output (CO) and total peripheral resistance (TPR) estimates were derived from the model flow measurement taken with the Finometer. MSNA was recorded using a tungsten microelectrode inserted subcutaneously into the common peroneal nerve located near the fibular head of the leg. A subcutaneous reference electrode was inserted 2–3 cm away from the recording electrode. Electrodes were connected to a preamplifier, which was further connected to an amplifier where the signal was amplified with a gain of 100,000. The noise was bandpass filtered (0.7–200 kHz), rectified, and integrated to obtain a sympathetic burst of activity. Efferent sympathetic bursts were isolated and confirmed using end-expiratory apnea to increase MSNA and did not elicit a response to auditory stimulus or stroking of the skin. All measurements (HR, blood pressure, and MSNA bursts) were sampled at 200 Hz and recorded and analyzed using custom data-acquisition software.

Data analysis. Baseline data were analyzed as the 10-min supine rest period before HUT. The first minute of tilt was recorded, but the data were not used for analysis due to initial orthostatic hypotension (IOH) immediately after HUT (44). Upright measurements were divided into four stages; early, mid, late, and syncope. Representative data of HR and arterial pressure (AP) responses to a syncope episode as well as our designated stages are shown in Fig. 1. The stages in our VVS group were designated based on the time from the initial upright position to the time of presyncope. Briefly, the early stage was defined as the period of relatively stable blood pressure immediately after IOH. The mid stage was defined as the period of a visibly gradual decrease in blood pressure with an accompanying increase in HR. The late stage was a period of nonuniform oscillatory changes in both blood pressure and HR. The syncope stage was defined as the period where blood pressure and HR rapidly fell and subjects reported symptoms of lightheadedness, dizziness, nausea, and sweating. None of the subjects in the control group reached presyncope, and after IOH, the stages were thus designated as equal time periods up to 10 min into the tilt.

Beat-to-beat changes in systolic AP (SAP), diastolic AP (DAP), and mean AP (MAP) were analyzed using the Finometer, and HR was derived from the ECG recording. The Finometer is an indirect method of blood pressure measurement but has been demonstrated to be well correlated with the more direct intra-arterial method (11, 34). For synchronization purposes, MSNA was compared with DAP after correction for a 1.3-s time lag from the triggering R wave of the ECG signal (13, 46). Bursts of activity were designated as having a >3:1 burst-to-noise ratio, and all MSNA signals were analyzed and reviewed by a single investigator for accuracy. Burst frequency (in bursts/minute) and total MSNA (the product of bursts/minute and the area underneath the burst) were reported. Total activity was normalized to the largest single burst area occurring during the baseline period and assigned a value of 1,000. We were able to successfully record MSNA in all reported subjects during baseline, early, mid, and late stages. During the syncope stage, nerve signals were lost in four VVS subjects due to leg movements or excessive artifacts.

Phase synchronization. The phase synchronization index (PhSI) was analyzed using previously described methods (32). Briefly, nonlinear coupling of two autonomously oscillating signals, such as MSNA and DAP, results in phase synchronization during a period of time in which there is a nearly fixed phase difference between the signals and they are therefore oscillating at the same frequency. This could also be designated as a period of frequency entrainment. Typically, phase synchronization occurs within a narrow band of frequencies. Therefore, preprocessing was performed with a Butterworth forward and backward zero-phase shift filter to bandpass between 0.01 and 0.5 Hz. This excluded oscillations from beat-to-beat cardiac cycles and also direct current signals (0 Hz). Thereafter, real-valued, scalar, time-dependent signals of AP and MSNA were introduced to the complex plane via a Hilbert transformation (2), and signals were resampled at 2 Hz. MSNA and DAP phases were defined as $\Phi(t)_{\text{MSNA}}$ and $\Phi(t)_{\text{DAP}}$, respectively. Phases of MSNA and DAP oscillators were calculated as continuous unwrapped phase variables. Phase differences were calculated as follows:

$$\Delta \Phi(t)_{\text{MSNA-AP}} = \Phi(t)_{\text{MSNA}} - \Phi(t)_{\text{DAP}}.$$  

PhSI was calculated and defined as follows:

$$\text{PhSI} = \sqrt{\langle \cos(\Delta \Phi(t)) \rangle^2 + \langle \sin(\Delta \Phi(t)) \rangle^2},$$

where $< >$ indicate time averages using a 50-s moving average window.

Thus, a PhSI = 0 indicates complete lack of synchronization and a PhSI = 1 indicates perfect synchronization. PhSI depends on the absolute value of $\Delta \Phi(t)$ and not its sign.

Directionality index of phase synchronization. To determine if a causal relationship exists between the signals (i.e., which oscillating signal drives the other), we adapted the directionality index (DI) approach of Rosenblum and Pikovsky (37). Briefly, the DI determines
the dependence of $\Phi(t)_{MSNA}$ on $\Phi(t)_{AP}$ and the dependence of $\Phi(t)_{AP}$ on $\Phi(t)_{MSNA}$. To accomplish this, we calculated the change in phase for each sampling interval as generated by an unknown two-di-

$$
\Delta \Phi(t)_{1,2} = \omega_{1,2} + e_{1,2} F_{1,2}(\Phi_{1,2}, \Phi_{1,2}) + \xi_{1,2}(t)
$$

where subscript $l$ refers MSNA, subscript 2 refers to AP, and $\Delta \Phi(t)_{1,2}$ refers to $\Phi(t + \tau_{MSNA}) - \Phi(t)_{MSNA}$ and $\Phi(t + \tau_{AP}) - \Phi(t)_{AP}$. The functions $F_{1,2}$ are $2\pi$ periodic, $e_{1,2}$ are the strength of interaction for each oscillator that assumes $e_{1,2} \ll \omega_{1,2}$, $\omega_{1,2}$ are the natural frequencies of each oscillator, and $\xi_{1,2}(t)$ account for noise in the system (30). To estimate the coupling term $F_{1,2}$ of the unknown map from time series $\Phi_{1,2}$, we approximated $F_{1,2}$ using a finite Fourier series $F$ with the least square coefficient $A$ to fit the dependency of $\Delta$ on $\Phi_1$ and $\Phi_2$, as follows:

$$
F_{1,2} = \sum_{m,n} A_{m,n} \times e^{i(m\Phi_1+n\Phi_2)}
$$

where $m$ and $n$ are <4 (30). The cross-dependency of phase dynamics of the two system was then calculated by means of coefficients ($c_{1,2}$), as follows (37):

$$
\xi_{1,2}^2 = \int_0^\pi \int_0^{2\pi} (\partial F_{1,2}/\partial \Phi_1)^2 d\Phi_1 d\Phi_2
$$

DI was calculated as the ratio of the relative differences between the coupling coefficients, $e_{AP,MSNA}$ and $\epsilon_{MSNA,AP}$, and their sum. The coupling coefficient $e_{AP,MSNA}$ represents the effect of blood pressure on MSNA in the neural arc, and the coupling coefficient $\epsilon_{MSNA,AP}$ represents the effect of MSNA on blood pressure in the peripheral arc. DI was calculated as $DI = (e_{AP,MSNA} - \epsilon_{MSNA,AP})/(e_{AP,MSNA} + \epsilon_{MSNA,AP})$. DI $= 1$ indicates that oscillator 2 depends on oscillator 1, but not vice versa, and therefore oscillator 1 drives oscillator 2. DI $= -1$ signifies that oscillator 1 depends on oscillator 2, and not vice versa, and therefore oscillator 2 drives oscillator 1. If DI = 0, the oscillators were bidirectional and symmetrically coupled. Strong unidirectionality was defined as 0.75 $< DI \leq 1.00$ or $-1.00 \leq DI < -0.75$, moderate unidirectional drive was defined as 0.50 $< DI \leq 0.75$ or $-0.75 \leq DI < -0.50$, and mild unidirectional drive was defined as 0.25 $< DI \leq 0.50$ or $-0.50 \leq DI < -0.25$. Bidirectional coupling was defined as $-0.25 \leq DI \leq 0.25$.

The DI determines if the two interdependent signals, AP and MSNA, once synchronized, are symmetrical and bidirectional or asymmetrical and unidirectional compared with the other signal. In other words, we can determine how much the MSNA signal depends on DAP and how much the DAP depends on MSNA. Thus, directional analysis of phase synchronous signals can be used to infer a causal relationship of whether one signal is driving the other signal. These have previously been described as the “neural” and “peripheral arc” of the open-loop baroreflex (19). The neural arc is the arm of the baroreflex from the baroreceptor stimulation to the efferent sympathetic nerve (i.e., MSNA), whereas the peripheral arc is the arm of the baroreflex from the sympathetic nerve to the effector (i.e., blood vessels).

**Statistics.** Statistical analyses were done using SPSS 13.0 (SPSS, Chicago, IL). Baseline measurements were analyzed using independent $t$-tests between VVS ($n = 8$) and control ($n = 8$) subjects. Hemodynamic measurements were compared with baseline using two-way ANOVA with repeated measures for early, mid, late, and syncope stages of HUT. MSNA and PhSI measurements were compared with baseline using two-way ANOVA with repeated measures for early, mid, and late stages of HUT. MSNA and PhSI during the tilt back after syncope are reported but were not included in the statistical analyses due to lack of statistical power (VVS, $n = 4$ subjects; control, $n = 8$ subjects). Coupling coefficients, as a measure of the DI, were compared baseline, early, mid, and late stages using two-way ANOVA with repeated measures. Syncope stage was not included in

the coupling coefficient analyses because of lack of statistical power in the VVS group.

Statistically significant time $\times$ group interactions were further analyzed using independent $t$-tests for between-group comparisons and paired $t$-tests for within group comparisons across the baseline, early, mid, late, and syncope stages. Significance was determined as $P \leq 0.05$. Data are presented as means $\pm$ SE.

**RESULTS.**

**Hemodynamics and MSNA.** Baseline measurements are shown in Table 1. Supine resting blood pressure, HR, and MSNA count were not significantly different between control and VVS groups. During HUT (Fig. 2), HR was significantly greater in the VVS group compared with the control group during early (105 $\pm$ 9 vs. 84 $\pm$ 4 beats/min, $P < 0.05$), mid (113 $\pm$ 10 vs. 84 $\pm$ 3 beats/min, $P < 0.05$), and late (110 $\pm$ 10 vs. 84 $\pm$ 3 beats/min, $P < 0.05$) stages, respectively. During the syncope stage, HR significantly dropped in the VVS group (110 $\pm$ 10 to 56 $\pm$ 10 beats/min, $P < 0.05$) but not in the control group (84 $\pm$ 3 to 86 $\pm$ 4 beats/min). MAP was not significantly different between groups during the early stage of HUT (VVS group: 85 $\pm$ 3 mmHg and control group: 90 $\pm$ 4 mmHg). However, during the mid (VVS group: 76 $\pm$ 3 mmHg and control group: 90 $\pm$ 4 mmHg, $P < 0.05$), late (VVS group: 65 $\pm$ 3 mmHg and control group: 89 $\pm$ 4 mmHg, $P < 0.05$), and syncope (VVS group: 39 $\pm$ 5 mmHg and control group: 89 $\pm$ 4 mmHg, $P < 0.05$) stages of HUT, MAP was significantly lower in the VVS group compared with the control group. MSNA area and count responses to HUT were not significantly lower in the VVS group compared with the control group (84 $\pm$ 62 vs. 84 $\pm$ 65 bursts/min, $P = 0.700$) stages of HUT, MAP was significantly lower in the VVS group compared with the control group. MSNA area and count responses to HUT were not significantly different when the VVS group was compared with the control group (time $\times$ group, $P > 0.700$). MSNA appeared to decrease, but did not completely disappear, at the point of syncope. However, due to lack of statistical power, as described above, analyses could not be performed on this data.

CO and TPR measurements are shown in Table 2. CO did not change during the early, mid, and late stages of HUT in both the control and VVS groups. At the point of syncope, CO significantly decreased in the VVS group but not in the control group. TPR initially increased during HUT in both VVS and control groups. However, TPR fell during the late and syncope stages in the VVS group but not in the control group.

**PhSI analysis.** A representation of the relationship between blood pressure, MSNA, and the phase synchronization of these two signals is shown in Fig. 3. PhSIs calculated during baseline and early, mid, late, and syncope stages for both MSNA area and count are shown in Fig. 4. There was a significant time $\times

| Table 1. Subject anthropometrics and supine resting baseline measurements in control and VVS groups |
|-----------------------------|-----------------------------|
|                             | Control Group               | VVS Group                |
| Age, yr                     | 24 $\pm$ 0.6                | 21 $\pm$ 2               |
| Height, m                   | 1.7 $\pm$ 0.02              | 1.65 $\pm$ 0.01          |
| Weight, kg                  | 67 $\pm$ 4                  | 64 $\pm$ 2               |
| Body mass index, kg/m\(^2\) | 23 $\pm$ 1                  | 23 $\pm$ 0.5             |
| Heart rate, beats/min       | 61 $\pm$ 3                  | 69 $\pm$ 4               |
| Systolic arterial pressure, mmHg | 119 $\pm$ 4           | 121 $\pm$ 6              |
| Diastolic arterial pressure, mmHg | 55 $\pm$ 4               | 52 $\pm$ 3               |
| Mean arterial pressure, mmHg | 76 $\pm$ 4                  | 75 $\pm$ 4               |
| MSNA count, bursts/min      | 15 $\pm$ 2                  | 21 $\pm$ 3               |

Values are means $\pm$ SE. VVS, vasovagal syncope; MSNA, muscle sympathetic nerve activity.
group interaction of PhSI between the VVS and control groups ($P < 0.001$). Phases between MSNA area and DAP were synchronized in the VVS [$0.51 \pm 0.03$ arbitrary units (au)] and control ($0.46 \pm 0.02$ au) groups and were not significantly different between groups during baseline ($P = 0.211$). During HUT, PhSIs increased in both groups during the early stage, suggesting greater synchronization (VVS group: $0.61 \pm 0.04$ au, $P < 0.001$; control group: $0.62 \pm 0.02$ au, $P < 0.001$). PhSIs began to decrease during the mid stage in the VVS group ($0.46 \pm 0.05$ au, $P = 0.004$) and further decreased during the late stage ($0.29 \pm 0.03$ au, $P = 0.001$). PhSIs in the control group did not significantly change during mid ($0.59 \pm 0.02$ au, $P = 0.174$) and late ($0.65 \pm 0.02$ au, $P = 0.179$) stages of HUT.

Similarly, phases of MSNA count and DAP were synchronized at baseline in the VVS ($0.47 \pm 0.03$ au) and control ($0.42 \pm 0.02$ au) groups and were not significantly different between groups. During HUT, in both groups, PhSIs significantly increased during the early stage (VVS group: $0.62 \pm 0.03$ au, $P = 0.03$; control group: $0.61 \pm 0.04$ au, $P = 0.001$). PhSIs began to significantly decrease during the mid stage in the VVS group ($0.46 \pm 0.05$ au, $P = 0.04$) and further decreased during the late stage ($0.31 \pm 0.03$ au, $P < 0.001$), but PhSIs in the control group remained similar to the early stage (mid stage: $0.59 \pm 0.02$ au, $P = 0.294$; late stage: $0.60 \pm 0.03$ au, $P = 0.644$).

DI analysis. The directionality component of the PhSI was calculated during both supine and HUT. This relationship is shown in Fig. 5. During baseline, DI was significantly different in the VVS group ($0.23 \pm 0.10$ au, $P < 0.001$) compared with the control group ($-0.23 \pm 0.10$ au, $P < 0.001$) for MSNA area. However, both groups still remained in the bidirectional range of the phase synchronization (Fig. 5). During HUT, the MSNA area and DAP relationship became unidirectional in the positive direction during the early stage (VVS group: $0.44 \pm 0.06$ au and control group: $0.43 \pm 0.10$ au) and mid stage (VVS group: $0.48 \pm 0.11$ au and control group: $0.64 \pm 0.08$ au) of HUT. At the late stage of HUT, and right before syncope, DI remained consistent in the control group ($0.39 \pm 0.12$ au), whereas DI lost its unidirectionality in the VVS group ($-0.08 \pm 0.10$ au, $P < 0.05$). The positive DI indicates that the primary driving signal was in the neural arc. This demonstrates that, while upright, there is a stronger control of the baroreceptors on MSNA compared with the sympathetic nerves controlling vasomotor constrictions (i.e., peripheral arc), that is, blood pressure predominantly drives MSNA.

It is worth noting that when MSNA was expressed as a count, there were no significant differences between VVS and control groups. Directionality became unidirectional in the positive direction during the early (VVS group: $0.38 \pm 0.1$ au and control group: $0.48 \pm 0.10$ au), mid (VVS group: $0.48 \pm 0.11$ au and control group: $0.64 \pm 0.08$ au), and late (VVS group: $0.25 \pm 0.1$ au and control group: $0.51 \pm 0.1$ au) stages of HUT, and there was a trend toward a return to bidirectionality at late stage, but this was not significant ($P < 0.5$).

**DISCUSSION**

In the present investigation, we demonstrate that phase-locked signals of blood pressure and MSNA are disrupted before vasovagal faint. However, regardless of whether MSNA...
diminishes or not, the AP-MSNA relationship becomes desynchronized. This may represent an ineffectual maintenance of peripheral vasoconstriction. Furthermore, the directionality analysis of the phase synchronization indicated that the loss of entrainment may take place within the neural arc (AP influence on MSNA) relationship rather than the peripheral arc (MSNA influence on AP).

The loss of phase synchronization of the AP-MSNA relationship in the moments leading up to faint are in keeping with previous findings of decreased cerebral autoregulation (3, 31) and loss of the cardiovagal baroreflex (32) before faint. It has been suggested that VVS is a result of loss of sympathetic activity, as demonstrated by a gradual or abrupt loss in MSNA at the point of faint (15, 21, 26, 48). However, others (15, 45) have demonstrated persistent MSNA during VVS. Our findings, combined with those of the previous investigations, suggest that persistent MSNA is not necessary for the loss in peripheral vasoconstriction during a fainting episode. We show a possible decrease in MSNA with a combined decrease in TPR. Additionally, although MSNA does not completely disappear, as has been previously suggested (26, 48), the disruption of the MSNA-AP relationship may represent a loss of sympathetic baroreflex control of cardiovascular regulation (15, 21). This determination would be consistent with our previous findings of a loss in the cardiovagal baroreflex during faint (32).

The link between blood pressure and MSNA is well documented (5, 10, 17, 43, 47). As blood pressure falls, the baroreceptors located in the aortic arch, carotid sinus, and cardiopulmonary arteries transmit afferent nerve stimuli to the brain. The regulatory centers located in the medulla trigger efferent sympathetic nerve traffic to increase vasoconstriction and blood pressure (8, 25). Under resting conditions and with sympathetic activation, muscle sympathetic nerve recordings have shown a strong inverse relationship with DAP, where a decrease in blood pressure was accompanied by an increase in MSNA (16, 17, 23, 43), and vice versa. This phasic relationship between MSNA and AP represents the sympathetic baroreflex and is, in general, time dependent. Current methods used to measure this relationship are done in the frequency domain, such as power spectral analysis and coherence analysis (6, 18). However, these methods may be unsuited for nonlinear relationships that change with time. Our methods introduce time dependency while examining the baroreflex defining phasic relationships between MSNA and AP.

To effectively analyze a binary bidirectional time-dependent system, we used phase synchronization analysis, which is a well-accepted method of nonlinear system analysis (30, 32, 36, 38, 40). This type of dynamic analysis is suitable to measure two signals (i.e., blood pressure and MSNA), where each are influenced by the other. This relationship can then be applied to an analysis of coupling (frequency entrainment) and an estimate of directional coupling (i.e., whether one signal is driving the other). The phasic relationship of one signal (AP) on the other signal (MSNA) may, in part, give a representation of the sympathetic baroreflex but cannot measure direct causality of one system on the other system in a biological system. The baroreflex regulates blood pressure, and it is believed that a
rapid decrease in cerebral perfusion, which is a primary cause of syncope (9, 22, 31), depends on maintaining blood pressure. An intact functional baroreflex relationship between blood pressure, HR, and sympathetic activity (i.e., vasoconstriction) would maintain pressure and cerebral perfusion. These intact phase relationships (blood pressure goes down, HR and MSNA go up) are the minimum requirement for regulating and maintaining blood pressure and cerebral perfusion to prevent syncope.

However, for there to be a sympathetic baroreflex relationship at all depends on phase synchronization between the signals and thus varying degrees of coupling. Thus, blood pressure decreases, MSNA increases, and vice versa. Currently, the effects of blood pressure on MSNA are often investigated by open-loop analyses that control pressure. Therefore, AP is the controlling, or independent, variable, whereas MSNA becomes the controlled, or dependent, variable. The dependence of AP on MSNA is not investigated, although one might expect that an increase in MSNA increases blood pressure via increased vasoconstriction.

However, in intact humans, the relationship between AP and MSNA is a closed-loop system. Thus, the closed-loop sympathetic baroreflex, comprising both neural and peripheral arcs, is not easily teased apart, and methods that essentially “open the loop,” such as the modified Oxford method control AP, are not able to effectively measure both sides of the reflex. Neither changes in AP nor MSNA can occur without influencing the other; thus, the phase link is usually bidirectional. It is this dynamic relationship that becomes difficult to measure in pure static ways (i.e., measuring mean changes and/or spectral analysis over a given timeframe). These stationary methods are currently the primary techniques used to measure this dynamic baroreflex relationship. Using slope analysis, it has only been shown that sensitivity decreases at the point of syncope (18).
The discrepancies between previous studies and ours could be due to methodology. While these slope analysis methods of baroreflex sensitivity are informative, the phase synchronization method we used helps us to understand more of the dynamic relationship. This offers a broader perspective on the AP-MSNA interaction. Indeed, we have shown that even before syncopal symptoms occur during late and syncope stages, there is a disconnect between the regulation of AP and MSNA.

Using a bidirectional approach, we demonstrated that, while supine, there is a bidirectional coupling between blood pressure and MSNA, although the VVS group favored the neural side and the control group favored the peripheral arc. However, while upright, both groups become unidirectional in favoring the neural arc, and blood pressure and MSNA were “phase locked.” While similar increased phase synchronization also occurs during early orthostasis in VVS patients, it progressively decreases and is entirely lost even before syncope occurs. Consistent with our expectations, supine directionality analysis demonstrated a bidirectional control of blood pressure. In this fashion, both the baroreceptor influence on MSNA and the sympathetic nerve influence on vasoconstriction are equally activated. However, during orthostatic stress, the neural arc dominates. While upright, sympathetic nerve traffic still influences AP, but the stronger relationship resides in the direction of AP drive on the MSNA response. This relationship appears to be lost during faint.

During VVS, the entire AP-MSNA link becomes disrupted. During HUT, the directionality shifts toward blood pressure driving MSNA in both fainters and nonfainters alike. However, this relationship appears to switch back toward bidirectionality in the moments leading up to VVS. The sympathetic baroreflex is dysfunctional during VVS, related to failure of the neural arc. Dysfunction can occur with or without a loss in MSNA (15, 26, 27, 45). This is in keeping with evidence demonstrating that the cardiovagal arm of the baroreflex (32, 33), cerebral autoregulation (31), and aspects of sympathetic baroreflex sensitivity (20, 27) are reduced during syncope and suggests a disruption in the sympathetic baroreflex. However, the mechanism remains still unknown.

Our methods demonstrated a maladaptive change in the relationship between blood pressure and MSNA and may help in our understanding of VVS in the presence of persistent MSNA. Multiple factors can be involved in fainting, but syncope ultimately results from critically reduced cerebral blood flow. As cerebral autoregulation fails before syncope, cerebral blood flow becomes increasingly driven by a declining AP. Why cerebral autoregulation and both cardiovagal and sympathetic baroreflex fail before syncope is not known, although excessive pooling in the lower body and the splanchnic region seem to be prerequisites for postural faint (1, 7, 12, 41).

Limitations. There are several limitations of our present study that deserve attention. Due to the difficulty of successfully triggering a fainting episode without the use of pharmacological or other external interventions, in addition to difficulties performing the microneurography, we were only able to capture data from eight VVS subjects. Although we found statistical significance in some of our measures, we did not see significance differences in our MSNA measurements. This may be due to the low sample size; however, because similar sample sizes have been consistently been reported in other investigations (15, 32, 45), we feel that our data demonstrate an accurate representation of these populations.

A potential limitation of the phase synchronization analysis is that it measures the relationship between only two signals. This may not account for potential outside influences (i.e. local vasodilators, respiration, adrenergic responses, etc.) on changes in blood pressure during VVS. Nevertheless, our conclusions only claim to measure the singular relationship of MSNA on AP, and vice versa, and demonstrate them to be dysfunctional. Another limitation of the present study is that we recorded isolated sympathetic activity from the peroneal muscle nerve in the leg. This may not reflect sympathetic activation in other vascular beds, such as the splanchnic area.

Sex may also be a potential limitation. We only had one male subject experience a vasovagal faint during the tilt test. Orthostatic intolerance is known to occur more in young women than men (35). Future investigations should be conducted using phase synchronization methods to elucidate the differences between men and women. Likewise, we did not control for menstrual cycle in our female subjects. It has previously been demonstrated that hormone fluctuations in women may play a role in orthostatic intolerance (4, 14). Nevertheless, in the present investigation, we focused on the mechanisms involved in a vasovagal faint rather than the prevalence of syncope.

Conclusions. We have demonstrated that the phasic relationship between blood pressure and MSNA decreases during a VVS, and this can occur with or without the presence of persistent MSNA. Our analyses using DI further showed that during HUT, the direction of the relationship occurs in the neural arc (blood pressure effecting MSNA) rather than the peripheral arc (MSNA effecting blood pressure), but that as syncope supervenes, this functional relationship is lost. A contributing mechanism to simple faint is demonstrably centrally mediated, although further research needs to be conducted to determine more specific mechanisms.

Perspectives. Our demonstration of a loss of phase synchronization in vasovagal faint has important implications for future research. Previous reports have demonstrated a change in the AP-MSNA relationship at the moment of syncope. However, we suggest that this disruption occurs much sooner in the time course of VVS. This is may be important in developing treatment modalities for chronic orthostatic intolerance and furthering our understanding of the mechanisms contributing to VVS. More research is necessary to elucidate the mechanisms behind this early disruption, which might be driven by a change in the sympathetic baroreflex.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: C.E.S., E.A.L., M.S.M., and J.M.S. conception and design of research; C.E.S., E.A.L., and J.M.S. performed experiments; C.E.S. and J.M.S. interpreted results of experiments; C.E.S. prepared figures; C.E.S. drafted manuscript; C.E.S., E.A.L., M.S.M., and J.M.S. edited and revised manuscript; C.E.S., E.A.L., M.S.M., and J.M.S. approved final version of manuscript.

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