Modes of Baroreceptor-Sympathetic Coordination

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Received 22 February 2000; accepted in final form 15 May 2000

Lewis, Craig D., Gerard L. Gebber, Sheng Zhong, Peter D. Larsen, and Susan M. Barman. Modes of baroreceptor-sympathetic coordination. J Neurophysiol 84: 1157–1167, 2000. We tested the hypothesis that the cardiac-related rhythm in sympathetic nerve discharge (SND) results from the forcing of a central oscillator to the frequency of the heart beat by pulse-synchronous baroreceptor afferent nerve activity. For this purpose, time series analysis was used to examine the phase relations between the brachial arterial pulse (AP) and cardiac-related activity recorded from the postganglionic inferior cardiac sympathetic nerve (CN) in urethan-anesthetized cats. Specifically, we made cycle-by-cycle measurements of peak systolic blood pressure, heart period, CN burst amplitude, and the phase angle (and corresponding interval) between peak systole and the next peak of CN activity. As the steady-state level of systolic blood pressure was raised by increasing the rate of a constant intravenous infusion of phenylephrine, we observed transitions from no phase-locking of CN activity to either phase-locking of variable strength or phase walk through part of the cardiac-cycle on the time scale of respiration. Phase walk is defined as a progressive and systematic change in the phase lag of cardiac-related CN activity relative to peak systole. Raising blood pressure strengthened phase-locking and either increased or decreased the mean interval between peak systole and the next peak of CN activity even when the change in heart period was small. CN burst amplitude and the interval between peak systole and the next peak of CN activity were inversely related, but the strength of the relationship varied considerably with experimental conditions. The relationship was strongest during phase walk. Step-wise increases in blood pressure induced by abdominal aortic obstruction led to an abrupt increase in the phase lag of CN activity relative to peak systole even when heart rate was not changed. We refer to such changes as sharp phase transitions that are a general property of dynamical nonlinear systems. The results support the view that the cardiac-related rhythm in SND is a forced nonlinear oscillation rather than the consequence of periodic inhibition of randomly generated activity.

INTRODUCTION

There are two conflicting hypotheses on the origin of the cardiac-related rhythm in the discharges of pre- and postganglionic sympathetic nerves. The classic hypothesis is that activity randomly generated in the CNS is periodically inhibited by pulse-synchronous baroreceptor afferent nerve discharge (Adrian et al. 1932; Green and Heffron 1968; Heymans and Neil 1958). The alternative view is that pulse-synchronous baroreceptor nerve activity entrains centrally generated oscillations in a 1:1 relation to the cardiac cycle (Gebber 1976; Taylor and Gebber 1975). This view is based on two lines of evidence. First, oscillations with a frequency (2- to 6-Hz range) close to that of the heart beat but not phase-locked to the cardiac cycle appear in sympathetic nerve discharge (SND) after baroreceptor denervation in the cat (Taylor and Gebber 1975). Second, Gebber (1976) reported that the interval between the R wave of the electrocardiogram (ECG) and the peak of the cardiac-related burst of SND is dependent on heart rate as demonstrated by pacing the heart. Although this interval is considered by some (e.g., Wallin et al. 1994) as a measure of baroreceptor reflex latency, dependency of the interval on heart rate would be expected for a nonlinear oscillator that receives forcing input at different times during its natural activity cycle (Glass and Mackey 1988; Pavlidis 1973; Winfree 1987).

The hypothesis that the cardiac-related rhythm in SND reflects the entrainment of a central oscillator has been criticized on several accounts. First, Camerer et al. (1977) have argued that the irregular 2- to 6-Hz oscillations in SND after baroreceptor denervation arise from central circuits distinct from those responsible for the cardiac-related rhythm. Second, Bachoo and Polosa (1987) have argued that the relatively broadband of 2- to 6-Hz SND observed after baroreceptor denervation is uncharacteristic of the output of a stable biological oscillator. The implication is that 2- to 6-Hz SND is filtered noise that cannot be entrained by pulse-synchronous baroreceptor nerve activity. Third, in direct contrast to the report by Gebber (1976), Hedman et al. (1994) reported that the interval between the R wave and the peak of the cardiac-related burst of SND remained constant in cats when heart rate was changed. This observation implies that the latency of baroreceptor reflex-induced inhibition of SND is invariant, a condition consistent with the classic hypothesis.

The criticisms and conflicting data cited in the preceding text have prompted us to reinvestigate the mechanisms responsible for the cardiac-related rhythm in SND using new experimental approaches and methods of analysis. In baroreceptor- innervated cats, we made cycle-by-cycle measurements of the phase angle between peak systolic pressure (representing pulse-synchronous baroreceptor nerve activity) and the next peak of cardiac-related activity recorded from the postganglionic inferior cardiac sympathetic nerve (CN). Phase angle was measured at different steady-state levels of blood pressure and during abrupt changes in blood pressure under conditions when changes in heart rate were small.

Forcing of a nonlinear oscillator to the frequency of the heart beat by pulse-synchronous baroreceptor nerve activity should lead to the following phenomena. First, as the strength of pulse-synchronous baroreceptor nerve activity is increased by raising blood pressure, transitions from no phase-locking to
weak and then strong phase-locking of SND to the arterial pulse (AP) should be observed. In addition, periods of phase walk may be introduced into this sequence. Phase walk, a property of weakly forced nonlinear oscillators, is characterized by a progressive and systematic change in the phase angle between the oscillator and its forcing input (Ermentrout and Rinzel 1984; Hanson 1978; Kelso 1995). In contrast to phase-locking, which is characterized by “fixed relationships,” phase walk is believed to reflect a state in which there is an attraction without true locking to preferred phase angles (Kelso 1995; von Holst 1973). Second, the average AP-SND phase angle should change by increasing the strength of pulse-synchronous baroreceptor nerve activity even in the absence of a change in heart rate. This follows from the fact that the magnitude of phase resetting of a nonlinear oscillator by a forcing input is dependent on the strength of the input. Moreover, depending on the timing of the input relative to the phase of the natural cycle, the next cycle can be either advanced or delayed (Glass and Mackey 1988; Pavlidis 1973; Winfree 1987). Third, abrupt increases in blood pressure should produce large stepwise changes in the AP-SND phase angle due to the increase in the intensity of the forcing input. Such sharp phase transitions (i.e., bifurcations) are believed to reflect qualitative changes in coupling dynamics (Strogatz 1994). Our results support the view that the cardiac-related rhythm in SND is an entrained nonlinear oscillation. In the accompanying paper, we have used partial spectral analysis to examine the relative importance of phase walk and phase-locking in generating the cardiac-related band of SND (Larsen et al. 2000).

Methods

Experimental subjects and general procedures

The protocols used in the experiments on 20 adult cats (2–4 kg) of either sex were approved by the All-University Committee on Animal Use and Care of Michigan State University. The cats were initially anesthetized with 2.5% isoflurane mixed with 100% oxygen. Urethan (1.2–1.8 g/kg iv) was then administered, and isoflurane inhalation terminated. This dose of urethan maintains a surgical level of anesthesia for a period (8–10 h) that exceeded the duration of our experiments (Flecknell 1987). As demonstrated by Gebber et al. (1999), the frontal-parietal ECG in urethan-anesthetized cats contains a mixture of 7- to 13-Hz spindles and delta-slow waves, indicative of unconsciousness and blockade of information transfer through the thalamus (Steriade and Llinas 1988).

Blood pressure was measured from a catheter inserted into the brachial artery, and drugs were infused into a femoral vein. Spontaneous respiration under urethan anesthesia was eupneic with end-tidal CO₂ ( Traverse Medical Monitors Capnometer, model 2200) in the normocapnic range. Subsequently, the animal was paralyzed with gallamine triethiodide (4 mg/kg iv initial dose), artificially ventilated with room air, and bilateral pneumothoracotomy was performed. End-tidal CO₂ was kept between 4.0 and 4.5% by adjusting the parameters of artificial ventilation; rectal temperature was maintained near 38°C with a heat lamp.

Nerve recordings

As described by Gebber et al. (1994), potentials were recorded monophasically with bipolar platinum electrodes from the central end of the cut left postganglionic inferior cardiac sympathetic nerve (CN) at its exit from the stellate ganglion. The band-pass of the Grass model 7P3 preamplifier was set at 1–1,000 Hz. The output of the preamplifier was passed to an analog filter (Avens, model AP-260-5) with a low-pass setting of 100 Hz. The attenuation slope of the filter was 24 dB/octave. Under these conditions, bursts of multiunit spikes appear as slow waves (Cohen and Gootman 1970; Gebber et al. 1994). The slow waves were eliminated by ganglionic blockade with hexamethonium bromide (5 mg/kg iv). In three cats, recordings were also made from the central end of the cut left phrenic nerve (PN) with the preamplifier band-pass set at 1–1,000 Hz. These recordings were passed through a moving average (CWE, Ardmore, PA; model MA-821 RSP) with a time constant of 100 ms.

Blood-pressure perturbations

Two methods were used to change blood pressure. In 10 cats, blood pressure was raised from one steady-state level to another by changing the rate of a constant intravenous infusion of phenylephrine hydrochloride (range, 2–20 μg/min). In seven other cats, abrupt increases in blood pressure (measured from the brachial artery) lasting <1 min were induced by rapid inflation of the balloon-tipped end of a Fogarty embolectomy catheter (Model 4F) inserted into the abdominal aorta (i.e., aortic obstruction).

Time series analysis

The cardiac-related band in the original recordings of CN activity (low-pass filtered at 100 Hz) was extracted by digital band-pass filtering. The software for the digital filter (symmetric, nonrecursive type with a Lanczos smoothing function) was obtained from RC Electronics (Santa Barbara, CA). The width of the band-pass was 4 Hz with the center frequency matched to that of the sharp peak at the frequency of the heart beat in the autospectrum of SND (see Gebber et al. 1999). The digital filter had a roll-off slope of 39%/Hz outside of the band-pass. As shown in Fig. 1, the digitally filtered records of CN activity are smoother and more sinusoidal in shape than the originals, thus aiding in the accurate detection of peaks and troughs during time series analysis (see following text). Note that the CN slow waves were correlated in a 1:1 relation to the AP and that the peaks and troughs in the original and digitally filtered records of CN activity coincide closely. The latter observation indicates that digital filtering produced a minimal amount of phase distortion. The AP was not subjected to digital filtering.

Software written by one of us (Lewis) (see Gebber et al. 1999) was used to construct time series showing cycle-by-cycle measurements of
peak systolic blood pressure (mmHg), heart period (interval in ms between successive readings of peak systolic pressure), trough-to-peak amplitude of the CN slow wave (after digital filtering), and the interval (ms) between the peak of the AP and the next peak of CN activity (AP-CN interval). Trough-to-peak slow-wave amplitude was measured using the trough that preceded each peak and then normalized on a scale of 0 to 1.0 with 1.0 representing the largest slow wave in the time series. The AP-CN interval was converted to a phase angle ($\varphi$, in degrees) by using the formula

$$\varphi = \frac{t}{T} \cdot 360^\circ$$

where $t$ is the AP-CN interval (ms) and $T$ is the interval (ms) between the peaks of the APs that immediately preceded and followed the CN slow wave. The resolution of measurement of the phase angle was $5.4^\circ$/bin (sampling period was 5 ms) when the period of the cardiac cycle was 333 ms (heart rate, 3 Hz).

Statistical analysis

The Pearson product-moment correlation coefficient ($r$ value) was used to test for a relationship between CN slow-wave amplitude and the AP-CN interval. The Student’s $t$-test for unpaired data were used to compare the mean intervals between the peak of the AP and the next peak of CN activity at different blood pressure levels. $P < 0.05$ was used as the criterion for statistical significance. Values in the text are means ± SE unless otherwise stated.

RESULTS

Modes of AP-CN coordination

We observed two modes of coordination (phase-locking and phase walk) of the AP and CN slow waves. The time series in Fig. 2 are from 1 of 10 experiments in which the AP-CN relationship was characterized at different steady-state levels of blood pressure. From top to bottom, the time series in Fig. 2, A–C, show cycle-by-cycle measurements of peak systolic blood pressure, heart period (HP), normalized trough-to-peak CN slow-wave amplitude, and the phase lag of the peak of the CN slow wave relative to the peak of the AP. Note that all but two of the values of phase angle were distributed in a wideband between 0 and 240° when peak systolic pressure was near 150 mmHg (Fig. 2A). Because the values of phase angles were restricted to a band $<360^\circ$, some phase-locking existed between the CN slow wave and AP. We define weak phase-locking as a condition in which the values of phase angle are randomly distributed in a band $180^\circ$ but $<360^\circ$ (i.e., greater than one-half of a cardiac cycle). Strong phase-locking is defined by an apparently random distribution of phase angles in a band $<180^\circ$. Weak phase-locking was transformed into phase walk through approximately one-half of the cardiac cycle when systolic pressure was increased to near 200 mmHg (Fig. 2B). Phase walk, which is characterized by a progressive and systematic cycle-by-cycle change in phase angle, repre-
Cortical pressure was further raised to near 250 mmHg (Fig. 2A) and 250 ms when blood pressure was elevated (Fig. 2B). The absence of pronounced reflex bradycardia in response to elevations in blood pressure was typical in our experiments and likely is attributable to the vagolytic action of the neuromuscular blocking agent, gallamine (Taylor 1980), and the fact that the left CN was cut. The phase walk in Fig. 2B recurred cyclically with a period of 210°. Note the progressive shortening of the AP-CN phase angle from near 210° to near 0° which was followed by a sharp snap-back to 210°. In some of the cycles of phase walk, its downward slope was increased sharply near 120°. Thus the rate of change in phase angle from 210° to 0° was not linear. Phase walk appeared at one or more steady-state levels of blood pressure in 7 of the 10 experiments. The amplitude of the CN slow wave also changed cyclically as will be described subsequently.

The oscilloscopic traces of the AP (top) and digitally filtered CN activity (bottom) in Fig. 3 illustrate one cycle of the phase walk taken from the time series in Fig. 2B. Using the dotted lines through peak systole as guides, one can follow the progressive shortening of the interval between peak systole and the peak of the next CN slow wave from about one-half of a cardiac cycle to a lag close to 0 ms. Note that progressive shortening of the interval occurred with little change in peak systolic pressure or the slope of the systolic phase of the AP. This suggests that the timing and strength of pulse-synchronous baroreceptor nerve discharge was virtually constant during the phase walk. The traces in Fig. 3 also show that CN slow-wave amplitude and the AP-CN interval were inversely related.

The pattern of phase walk was changed to one of strong phase-locking with some residual phase walk when peak systolic pressure was further raised to near 250 mmHg (Fig. 2C). At this time, the values of phase angle were restricted to a relatively narrowband between 60° and 150°. CN slow-wave amplitude was generally reduced but continued to change cyclically even when the residual phase walk was minimal (see segment of time series between 15 and 18 s). Heart period increased modestly from 250 to 263 ms. Strong phase-locking appeared at one or more steady-state levels of blood pressure in each of the 10 experiments.

In Fig. 4, A–C, normalized CN slow-wave amplitude is plotted against the AP-CN interval (ms) for the time series shown in Fig. 2, A–C, respectively. No significant relationship \( (r = 0.07; \ P = 0.56) \) existed at the lowest level of systolic blood pressure when phase-locking of the CN slow wave to the AP was weak (Fig. 4A). In contrast, a strong inverse relationship between CN slow-wave amplitude and the AP-CN interval existed during phase walk (Fig. 4B; \( r = -0.79; \ P < 0.0001 \)) and during strong phase-locking (Fig. 4C; \( r = -0.66; \ P < 0.0001 \)).

In three of the seven cats showing phase walk, the order in which phase walk and strong phase-locking occurred was the reverse of that shown in Fig. 2. Time series from one of these experiments are shown in Fig. 5. The values of AP-CN phase angle were distributed over 360° (no phase-locking) when systolic blood pressure was near 114 mmHg (Fig. 5A). On raising systolic blood pressure to near 200 mmHg, phase-locking became strong with all but one of the values of AP-CN phase angle restricted to a band between 0 and 90° (Fig. 5B). When peak systolic pressure was further raised to near 270 mmHg, a phase walk appeared in cycles lasting 3.8 s (Fig. 5C). Note the slow oscillations of systolic blood pressure with the same period. The phase walk back and forth between 0 and 210° was more symmetric than in the case shown in Fig. 2B.

**FIG. 3.** One cycle of phase walk of digitally filtered CN activity relative to peak systole. Records are from the time series in Fig. 2B. Vertical calibration is 100 μV; horizontal calibration is 250 ms.
Also, the phase angles tended to cluster for a time near 210° during each cycle of the walk. During the phase walk in Fig. 5, slow-wave amplitude was reduced and heart rate (3.5 beats/s) was essentially unchanged as compared with that during strong phase-locking. At this time, the inverse relationship between CN slow-wave amplitude and AP-CN interval was stronger ($r = 0.56; P < 0.0001$) than during phase-locking in Fig. 5B ($r = 0.34; P = 0.004$).

In the seven cats in which both modes of coordination were observed, mean blood pressure averaged 162 ± 11 mmHg when phase walk occurred over its widest range (152 ± 17°). Episodes of the strongest phase-locking (bandwidth, 91 ± 5°) in the same experiments occurred at a mean blood pressure of 173 ± 15 mmHg, a value not significantly different from that during phase walk.

In three additional cats, recordings of left phrenic nerve (PN) and CN activities were made simultaneously under the condition of AP-CN phase walk. In each of these experiments, the phase walk of the CN slow wave relative to peak systole occurred on the time scale of the respiratory cycle. The results from one of these experiments are shown in Fig. 6. The AP-CN phase angle gradually decreased from near 180° during the expiratory phase of PN activity to near 0° in the inspiratory phase. Phase angle then sharply returned to near 180°. The inverse relationship between CN slow-wave amplitude and the AP-CN interval was relatively weak in this case ($r = -0.14; P = 0.02$). Slow blood pressure oscillations with the period of the AP-CN phase walk were virtually absent in this experiment.

**Dynamics of phase-locking**

As reflected by a decrease in the width of the band of phase angles, phase-locking of the CN slow wave to the AP was strengthened as the steady-state level of blood pressure was raised. In 6 of 10 experiments, enhanced phase-locking was accompanied by a significant increase in the mean interval between peak systole and the peak of the next CN slow wave. The results from one of these experiments are illustrated in Figs. 7 and 8. Figure 7 shows three 80-s time series (A–C), each at a different level of systolic pressure. The histograms in Fig. 8, A–C, show the distribution of intervals corresponding to the AP-CN phase angles for the time series illustrated in Fig. 7, A–C, respectively. The wide dis-
bution of intervals in Fig. 8A supports the contention that phase-locking of the CN slow wave to the AP was virtually absent at the lowest level of systolic pressure. When systolic blood pressure was raised to 180 mmHg, the distribution was Gaussian-like in shape with a mean AP-CN interval of 77 ± 24 (SD) ms (Fig. 8B). At this time, CN slow-wave amplitude was inversely related to the AP-CN interval ($r = -0.26; P < 0.0001$). The average AP-CN interval was significantly increased to 169 ± 10 (SD) ms when systolic blood pressure was further raised to near 270 mmHg (Fig. 8C). At this time, CN slow-wave amplitude remained inversely related to AP-CN interval ($r = -0.23; P < 0.0001$).

In the remaining four experiments, the mean interval between peak systole and the peak of the next CN slow wave was significantly reduced when phase-locking was strengthened by raising blood pressure. The results from one of these experiments are shown in Fig. 9. The values of AP-CN phase angle were distributed over a range of 360° at peak systolic blood pressures between 70 and 110 mmHg (Fig. 9A). Raising systolic blood pressure to near 235 mmHg induced phase-locking with 90% of the data points falling in a band that was 118° in width (Fig. 9B). The mean AP-CN interval was 68 ± 29 (SD) ms for this time series. At this time, CN slow-wave amplitude was inversely related to the AP-CN interval ($r = -0.40; P < 0.0001$). With a further increase in systolic pressure to near 280 mmHg, 90% of the values of AP-CN phase angle were restricted to a band 85° in width and the corresponding mean interval was significantly reduced to 32 ± 40 (SD) ms (Fig. 9C). At this time, a direct relationship ($r = 0.22; P < 0.0001$) existed between CN slow-wave amplitude and the AP-CN interval. This was the only case in which these parameters were directly related.

**AP-CN relationships during short-term blood-pressure perturbations**

The changes in AP-CN phase angle and CN slow-wave amplitude shown in Fig. 10 are representative of those observed during abrupt increases in brachial arterial pressure induced by abdominal aortic obstruction in seven cats. In the first episode, systolic blood pressure was abruptly increased from near 150 to 200 mmHg. This change was accompanied by a step-wise increase in AP-CN phase angle of ~120° and reduced CN slow-wave amplitude. Heart period was little changed at this time. Narrowing of the band of AP-CN phase angles is also noticeable during the pressor response. CN slow-wave amplitude and phase angle began to recover during this 25-s period of aortic obstruction as the pressor response began to wane. Maximal aortic obstruction further raised systolic blood pressure to 240 mmHg. This abrupt change in blood pressure was accompanied by changes in AP-CN phase angle and slow-wave amplitude similar to those observed during the initial episode of aortic obstruction. In the second episode, heart period was increased from near 256 to near 312 ms. The release of aortic obstruction led to an undershoot of systolic blood pressure to 100 mmHg during which time the values of

![FIG. 6. Time series showing respiratory-related changes in the phase lag of the peak of CN slow wave relative to peak systole and CN slow-wave amplitude. Traces (top to bottom) are BP, HP, integrated phrenic nerve (PN) discharges, and cycle-by-cycle measurements of AP-CN phase angle and CN Amp. (normalized). Horizontal calibration is 2 s. Abbreviations as in Fig. 2.](http://jn.physiology.org/)

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AP-CN phase angle were quite variable as would be expected in a state of weakened or no phase-locking.

**Discussion**

The results of the current study are consistent with the hypothesis that the cardiac-related rhythm in SND reflects the forcing (i.e., entrainment) of a nonlinear oscillator to the frequency of the heart beat by pulse-synchronous baroreceptor afferent nerve activity. We observed several phenomena characteristic of the interactions of a nonlinear oscillator and a periodic forcing input: two distinct modes of coordination (phase walk and phase-locking of variable strength), sharp phase transitions in response to abrupt changes in the strength of forcing, and the dependency of the average interval between peak systole and CN activity on the strength of the forcing input.

Coordination of a nonlinear oscillator to a forcing input need not be limited to phase-locking. A second mode of coordination is characterized by phase walk in which an attraction exists between the forcing stimulus and the nonlinear oscillator but with a continuously changing phase relationship that is progressive and systematic in character (Ermentrout and Rinzel 1984; Hanson 1978; Kelso 1995). In the current study, phase walk of the CN activity relative to peak systole was commonly observed (see Figs. 2B, 3, 5C, and 6). Phase walk occurred over a portion of the cardiac cycle rather than over the whole cycle. Moreover the rate of change of the phase angle usually was not constant as evidenced by sharp snap-backs (see Figs. 2B and 6), abrupt changes in slope (see Fig. 2B), and/or clustering of data points around a preferred value during part of the walk (see Fig. 5C). Although the phase walks in our experiments did not extend over a whole cycle, they generally fit the mode of attraction of a nonlinear oscillator to its forcing input referred to as relative coordination by von Holst (1973) and Kelso (1995).

Relative coordination occurs when the attraction to certain phase relations between an oscillator and its forcing input is offset to some extent by differences between the coordinated components themselves. In our system, phase walk of CN activity relative to peak systole may reflect a condition when the difference between heart rate and the preferred frequency of a central oscillator generating the 2- to 6-Hz component of SND is of sufficient magnitude that true phase-locking of SND to pulse-synchronous baroreceptor nerve activity is no longer possible. In some of our experiments, phase walk occurred on the time scale of slow blood pressure oscillations (see Fig. 5C). In such cases, the strength of pulse-synchronous baroreceptor nerve activity would have waxed and waned on the same time scale. This could have led to the phase walk in the following way. The range of frequencies over which an oscillator can be entrained to a forcing input is directly related to the strength of the input (Ermentrout and Rinzel 1984). During the phase of the slow blood pressure oscillation when pulse-synchronous
baroreceptor nerve activity is relatively weak, the range would be narrowed. As a consequence, the preferred natural frequency of the central generator of 2- to 6-Hz SND might no longer be in the range of entrainment, and phase walk would ensue. However, the fact remains that phase walk of CN activity relative to the AP was observed even in the absence of slow blood pressure oscillations (see Figs. 2B and 6).

In each of the three experiments with PN recordings, phase walk of CN activity relative to the AP occurred on the time scale of the respiratory cycle. Assuming that PN activity was locked 1:1 to the artificial ventilation cycle, this observation suggests that the frequency range over which SND could be entrained by pulse-synchronous baroreceptor nerve activity is influenced by central respiratory neuronal activity and/or lung inflation afferent nerve activity. Phase walk of CN activity relative to peak systole on the time scale of the respiratory cycle could be explained in at least two ways. First, central inhibition induced by pulse-synchronous baroreceptor nerve discharge might be gated to varying degrees during different phases of the respiratory cycle. This would lead to the same consequences attendant to reduced pulse-synchronous baroreceptor nerve activity during the falling phase of the slow blood pressure oscillations seen in some experiments. That is, the forcing input would be weakened, and this would reduce the range over which SND can be entrained. The second possibility is that the excitability of the central generator of 2- to 6-Hz activity in the CN is modulated by inputs from central respiratory neurons and/or lung inflation afferent nerves. Such influences might move the preferred natural frequency of the generator outside the limits of entrainment by pulse-synchronous baroreceptor nerve activity. In the case of lung inflation afferents that exert an inhibitory effect on SND (Cohen et al. 1980), a move to just below the lower limit would be expected. A move to just above the upper limit would occur if central inspiratory neurons were involved in initiating phase walk via their excitatory influences on SND (Cohen and Gootman 1970). These possibilities are open to future investigation.

One would expect that transitions should occur in a sequence from no phase-locking to phase walk and then to phase-locking as the level of pulse-synchronous baroreceptor nerve activity is increased progressively by raising blood pressure. Yet in some of our experiments, phase walk of CN activity relative to peak systole succeeded rather than preceded strong phase-locking. We suspect that the sequence in which phase walk and phase-locking occurs in a particular experiment is due to complex interactions of the circuits responsible for sympathetic and respiratory rhythmogenesis. For example, the increase in baroreceptor nerve activity attendant to a rise in blood pressure would be expected to induce stronger baroreceptor forcing of the generator of 2- to 6-Hz SND. However, the degree to which the relationship between the forcing input and the generator is modulated by respiratory-related events might also be changed. Regarding this point, baroreceptor reflex activation has been reported to change respiratory rate and tidal volume (Brunner et al. 1982; Heistad et al. 1975). The nature of such complex interactions should be investigated.

Abrupt increases in blood pressure produced step-wise increases in the phase lag of CN activity relative to systole of large magnitude (see Fig. 10). Such sharp phase transitions (i.e., bifurcations) are believed to reflect qualitative changes in
the coupling dynamics in forced nonlinear systems (Haken 1996; Kelso 1995; Strogatz 1994). Thus the sharp phase transitions seen in our experiments provide additional evidence in support of the hypothesis that the cardiac-related rhythm in SND results from the entrainment of a nonlinear oscillator by pulse-synchronous baroreceptor nerve activity.

The strength of phase-locking of a nonlinear oscillator to a periodic forcing input is dependent on the intensity of the forcing input (Glass and Mackey 1988; Kelso 1995). Consistent with this property of nonlinear oscillators, we found that raising blood pressure to a new steady-state level restricted the values of AP-CN phase angle to a narrower band (see Figs. 7 and 9). Phase-locking implies a fixed relationship between the forcing input and the entrained oscillator. However, in no instance was the band of AP-CN phase angles narrower than 35° (see Fig. 7C), and on occasion, the band was 240° in width (see Fig. 2A). The commonly observed widebands of AP-CN phase angles might arise from randomly occurring perturbations of the generator of 2- to 6-Hz SND. Such perturbations would preclude strict phase-locking of SND to the cardiac cycle. The phase angle between the forcing input and the entrained oscillation can be either shortened or lengthened by increasing the strength of the input (Glass and Mackey 1988; Pavlidis 1973; Winfree 1987). The timing of the input relative to the phase of the natural cycle determines whether the oscillation is advanced or delayed. In our experiments, the periodic nature of the forcing input (pulse-synchronous baroreceptor nerve activity) and the small changes in heart rate induced by raising the steady-state level of blood pressure precluded the construction of phase-response curves. Nevertheless, we found that raising blood pressure led to either an increase (see Figs. 7 and 8) or a decrease (see Fig. 9) in the lag of the peak of the CN slow wave relative to peak systole. Large changes in either direction suggest to us that phase angle is a measure of the relationship between a nonlinear oscillator and its forcing input rather than of baroreceptor reflex latency as has been proposed by others (Wallin et al. 1994; Xie et al. 1999).

Wallin et al. (1994) reported that the interval between the R wave and the peak of the cardiac-related burst in human peroneal muscle nerve activity was inversely related to burst amplitude. The variation of the interval (0.12–0.2 s) during prolonged expiratory apnea amounted to 9–15% of the average control interval for the peroneal nerve. Under the assumption that the interval between the R wave and the peak of cardiac-related SND was a measure of baroreceptor reflex latency, Wallin et al. (1994) suggested that the variation might be explained by changes in the pathways used to carry vasoconstrictr activity to skeletal muscle. Using the “size principle” of Henneman and Mendell (1981), they proposed that as the level of central excitability is increased, there is an orderly recruitment of postganglionic sympathetic neurons with progressively faster conducting axons leading to larger burst amplitudes and shorter R wave to peak burst intervals. They
The shortest and longest AP-CN intervals (145 ms in Fig. 2) between these values is considerably less than those between responding conduction times is 9–100 ms. The difference in Fig. 5 represents the difference in Fig. 5 calculated from a phase walk of 0 to 210°.

The conclusion that the cardiac-related rhythm in SND reflects the entrainment of a central oscillator to the cardiac cycle that is characterized by progressive and systematic phase walk of CN activity relative to peak systole. Phase walk is consistent with the phenomenon of relative coordination, a hallmark of nonlinear dynamical systems. Switches between phase walk and phase-locking of variable strength occurred when the steady-state level of blood pressure was changed. Furthermore increases in the steady-state level of blood pressure led to either an increase or decrease in the mean AP-CN interval when phase-locking became tighter. Finally sharp phase transitions were observed in response to abrupt increases in blood pressure. These observations have led us to conclude that the cardiac-related rhythm in SND reflects the entrainment of a central oscillator by pulse-synchronous baroreceptor nerve activity rather than periodic inhibition of randomly generated activity.

In summary, we have identified for the first time a new mode of coordination of SND to the cardiac cycle that is characterized by progressive and systematic phase walk of CN activity relative to systole. Phase walk is consistent with the phenomenon of relative coordination, a hallmark of nonlinear dynamical systems. Switches between phase walk and phase-locking of variable strength occurred when the steady-state level of blood pressure was changed. Furthermore increases in the steady-state level of blood pressure led to either an increase or decrease in the mean AP-CN interval when phase-locking became tighter. Finally sharp phase transitions were observed in response to abrupt increases in blood pressure. These observations have led us to conclude that the cardiac-related rhythm in SND reflects the entrainment of a central oscillator by pulse-synchronous baroreceptor nerve activity rather than periodic inhibition of randomly generated activity.

In this study, we have shown that the cardiac-related rhythm in SND reflects the entrainment of a central oscillator to the cardiac cycle that is characterized by progressive and systematic phase walk of CN activity relative to peak systole. Phase walk is consistent with the phenomenon of relative coordination, a hallmark of nonlinear dynamical systems. Switches between phase walk and phase-locking of variable strength occurred when the steady-state level of blood pressure was changed. Furthermore increases in the steady-state level of blood pressure led to either an increase or decrease in the mean AP-CN interval when phase-locking became tighter. Finally sharp phase transitions were observed in response to abrupt increases in blood pressure. These observations have led us to conclude that the cardiac-related rhythm in SND reflects the entrainment of a central oscillator by pulse-synchronous baroreceptor nerve activity rather than periodic inhibition of randomly generated activity.

In the current study, we have identified for the first time a new mode of coordination of SND to the cardiac cycle that is characterized by progressive and systematic phase walk of CN activity relative to peak systole. Phase walk is consistent with the phenomenon of relative coordination, a hallmark of nonlinear dynamical systems. Switches between phase walk and phase-locking of variable strength occurred when the steady-state level of blood pressure was changed. Furthermore increases in the steady-state level of blood pressure led to either an increase or decrease in the mean AP-CN interval when phase-locking became tighter. Finally sharp phase transitions were observed in response to abrupt increases in blood pressure. These observations have led us to conclude that the cardiac-related rhythm in SND reflects the entrainment of a central oscillator by pulse-synchronous baroreceptor nerve activity rather than periodic inhibition of randomly generated activity.
ministic signal (i.e., a forced oscillation) sheds new light on the control of SND by baroreceptor input. As discussed by Bassingthwaighte et al. (1994), a deterministic signal, in principle, can be described mathematically, and this may be of use in predicting the future behavior of the system from which the signal arises. In contrast, random stochastic signals are unpredictable except in a statistical sense. Moreover, deterministic signals can be controlled as illustrated by the entrainment of irregular 2- to 6-Hz oscillations in a 1:1 relation to the cardiac cycle by pulse-synchronous baroreceptor nerve activity. The forcing of a nonlinear oscillator not only provides a mechanism for setting the predominant frequency of SND but also may be accompanied by resonance and thus frequency-dependent changes in amplitude of the signal not achievable for a random stochastic signal.

The authors thank S. Sykes for typing the manuscript. This study was supported by National Heart, Lung, and Blood Institute Grant HL-11387.

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