Human sinus arrhythmia as an index of vagal cardiac outflow

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ECKBERG, DWAIN L. *Human sinus arrhythmia as an index of vagal cardiac outflow.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 54(4): 961–966, 1983.—Since changes of heart period follow changes of cardiac vagal efferent activity quantitatively with nearly fixed latencies, measurements of respiratory sinus arrhythmia may provide insights into human central vagal mechanisms. Accordingly, I measured intervals between heartbeats during controlled breathing (at breathing intervals of 2.5–10 s and nominal tidal volumes of 1,000 and 1,500 ml) in six healthy young men and women. As breathing interval increased, the longest heart periods became longer, the shortest heart periods became shorter, and the peak-valley P-P intervals increased asymptotically. Peak-valley P-P intervals also increased in proportion to tidal volume. However, this influence was small: a 50% increase of tidal volume increased the average peak-valley P-P interval by only about 15%. The phase angles between heart period changes and respiration varied as linear functions of breathing interval. Heart period shortening (cardioacceleration) began in inspiration at short breathing intervals and in expiration at long breathing intervals. Heart period lengthening, however, began in early expiration at all breathing intervals studied. These results point toward a close relationship between variations of respiratory depth and interval and the quantity, periodicity, and timing of vagal cardiac outflow in conscious humans. They suggest that, at usual breathing rates, phasic respiration-related changes of vagal motoneuron activity begin in expiration, progress slowly, and are incompletely expressed at fast breathing rates.

parasympathetic; tidal volume; breathing

MOST CURRENT UNDERSTANDING of central vagal cardiac mechanisms derives from research conducted in anesthetized animals. This is unfortunate for several reasons. First, vagal cardiac motoneurons are notoriously susceptible to the influence of anesthetic agents (23); it is unclear to what extent use of general anesthesia has confounded understanding of vagal physiology. Second, certain important aspects of vagal cardiac control, such as its interaction with respiration, cannot be studied systematically in the presence of anesthesia; such studies may require conscious cooperative (and therefore, human) subjects. Finally, physiology learned from healthy anesthetized experimental animals may provide an inadequate foundation for understanding of pathophysiological processes, such as acute myocardial infarction (1) and sudden death (5) in conscious patients. Thus a case can be made for accurate delineation of mechanisms governing vagal cardiac efferent activity in conscious human subjects.

Efferent vagal outflow to the heart has not been measured directly in conscious humans or laboratory animals, but several indirect methods have been proposed as substitutes for direct measurements. Base-line heart rate is determined in part by vagal efferent activity, but it is also determined by other factors, including intrinsic sinus node function and neurohumoral sympathetic drive. Therefore, the correlation between base-line heart rate and the level of vagal cardiac efferent activity is weak (16). The amount of acceleration of heart rate after muscarinic blockade by large doses of intravenous atropine sulfate has been used to gauge the level of efferent vagal traffic present before the dose (15). This approach is not ideal because it provides only one measurement during an experiment, and cardioacceleration after atropine probably does not result merely from blockade of the effects of existing levels of cardiac vagal efferent traffic (21).

Measurements of respiratory sinus arrhythmia may provide the best available indirect estimates of the level of vagal cardiac efferent activity: in anesthetized animals, the magnitude of sinus arrhythmia (gauged by maximum-minimum R-R intervals) correlates well with total cardiac vagal efferent traffic (16); changes in the magnitude of sinus arrhythmia occur in parallel with changes of vagal traffic (16); and sinus arrhythmia can be measured continuously, without use of drugs. Therefore, in this study, I measured sinus arrhythmia to gain insight into how respiration modulates vagal cardiac efferent activity in healthy human volunteers.

METHODS

I measured intervals between heartbeats in healthy young subjects who voluntarily regulated their tidal volumes and respiratory rates.

Subjects. Six healthy men and women, ages 24–26 yr, were studied in recumbency, in a quiet darkened room. All volunteers gave their written consent to participate in this approved research.

Measurements. The electrocardiogram, beat-by-beat cardiac interval, integrated tidal volume (Fleisch pneumotachograph), and end-tidal carbon dioxide concentration (infrared analyzer) were transcribed by a direct ink-writing recorder. Arterial pressure was measured nonin-

vasively with an ultrasonic sensor (Arteriosonde 1225). Experiments were analyzed with a processing digital oscilloscope and a digital computer.

Control of respiration. Subjects voluntarily controlled their respiratory frequencies and tidal volumes. They wore an airtight anesthesia face mask that was connected to the pneumotachograph and a three-way respiratory valve (Ewald Koegel, San Antonio, TX). The dead space of this system was about 235 ml. Subjects breathed room air, supplemented as necessary by 10% carbon dioxide in room air.

Subjects breathed with an auditory signal, at rates between 6 and 24 breaths/min (at respiratory intervals of 10, 8, 6, 4, 3.5, 3, and 2.5 s). Tidal volume also was controlled (at nominal levels of 1,000 and 1,500 ml) by the volunteers, who observed their integrated pneumotachograph signals on a calibrated oscilloscope. All subjects breathed at all respiratory intervals at both tidal volumes. Carbon dioxide was delivered to the respiratory system to maintain end-tidal carbon dioxide concentration at the level established by each subject during the smallest ventilation level used.

Experimental protocol. Initial measurements were obtained at a respiratory interval of 10 s and at a nominal tidal volume of 1,000 ml. The end-tidal carbon dioxide concentration established at this minimum ventilation level was maintained throughout the remainder of the experiment. (Thus all measurements were made during mild hypercapnia.) Other respiratory intervals and one other nominal tidal volume (of 1,500 ml) were used thereafter in random sequence. Data for each respiratory rate and tidal volume were obtained during one continuous period of constant breathing that lasted from about 5 to 10 min. Responses were measured during a minimum of 15 breathing cycles. Respiratory rate and tidal volume were not controlled between data collection periods.

Data analyses. Data were analyzed in on-line and batch modes by a signal processing digital oscilloscope (Norland 3001, Norland, Fort Atkinson, WI) and a digital computer (Hewlett-Packard 1000 series). Since P-R intervals did not appear to change at different breathing rates in these subjects, P-P intervals equaled R-R intervals and are referred to as such. Statistical comparisons were made with least-squares linear regression and the paired t test (24). Differences were considered significant when P was less than 0.05. Data are presented as means ± SE unless indicated otherwise.

RESULTS

Continuous records of the electrocardiogram, R-R interval, and tidal volume from one volunteer breathing at a tidal volume of about 1,000 ml and at respiratory intervals of 10 and 2.5 s are shown in Fig. 1. These records provide some indication of the degree of control of respiration by volunteers, and they illustrate (Fig. 1, left) one common pattern of heart rate fluctuation with breathing (heart period lengthening beginning early in expiration). In this study, averaged measurements from all subjects indicated that airflow was continuous from the onset of expiration until the onset of the next inspiration; there was no sharply defined expiratory pause separating the end of active expiration and the beginning of inspiration.

Average breathing intervals were extremely close to targeted levels: the average standard deviation for all measurements was 0.017 s (range 0–0.06), or 0.3% (range 0–0.6). Volunteers did not control tidal volumes as well

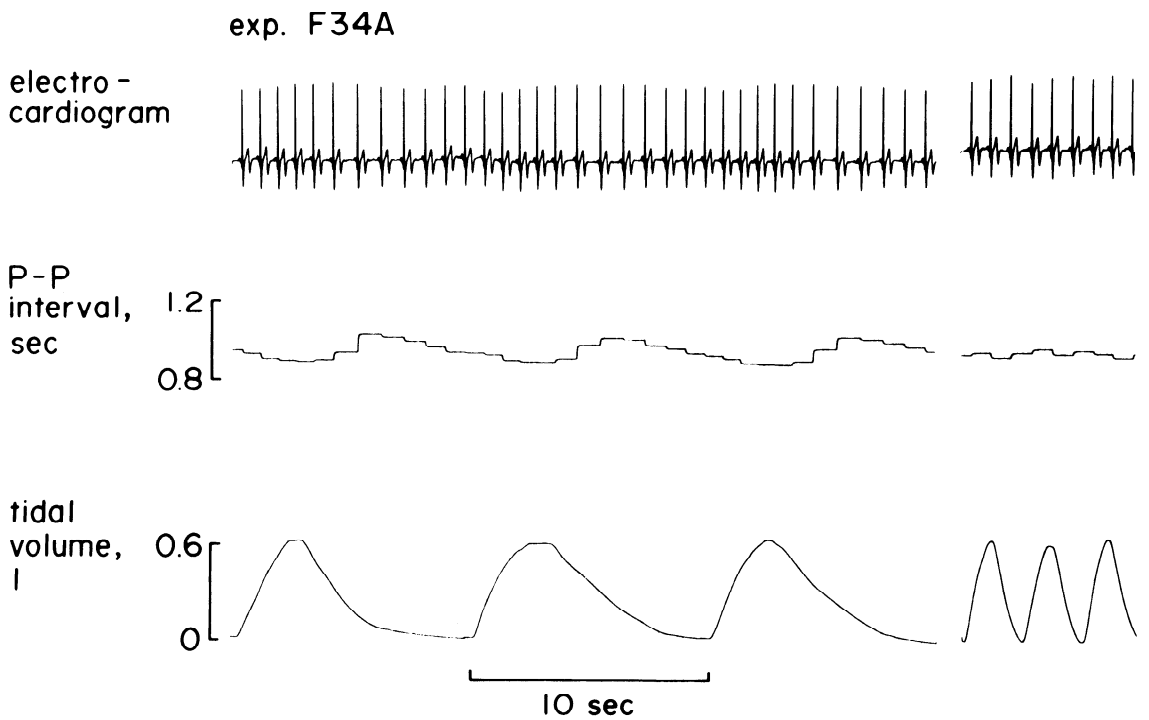

FIG. 1. Experimental record from 1 subject. Fluctuations of heart period were much more striking at slow (*left*) than at rapid breathing rate. This and Figs. 2–6 depict responses measured at lower tidal volume studied.

as breathing intervals: tidal volume averaged 903 ml (range 839–972) at the lower volume, and 1,361 ml (range 1,208–1,444) at the higher volume. Average end-tidal carbon dioxide concentrations were comparable ($P > 0.05$) at all breathing frequencies and at both tidal volumes, and ranged between 5.8 and 6.0%. Blood pressure was less than 140/90 mmHg in all subjects.

Fluctuations of P-P interval with breathing. The relation between P-P and breathing intervals at the lower tidal volume is depicted in Figs. 2 and 3. Figure 2 shows that the average peak-valley change of P-P interval increased in an asymptotic fashion with respiratory interval. Figure 3 indicates that both an increase of the average maximum and a decrease of the average minimum P-P interval contributed to the increase of sinus arrhythmia. Since maximum P-P intervals increased more than minimum P-P intervals decreased, average P-P intervals during breathing increased. Fluctuations of P-P interval were significantly ($P < 0.001$) greater (by an average of 0.025 ± 0.005 s) with larger than with smaller tidal volumes.

Average P-P interval changes for all subjects at all breathing intervals are depicted as Lissajous figures in Fig. 4. In these plots, instantaneous P-P interval is plotted as a function of volume above functional residual capacity during one complete breath. The extreme left of each figure marks the onset of each breath, and the arrows indicate the direction of changes occurring during each breath. P-P intervals fluctuated as deterministic functions of breathing interval; the correlation coefficient between average breathing and respiratory intervals was 1.00. Lissajous figures for the two longest breathing intervals were complex: the relation inscribed a figure-of-eight pattern in which there was an abrupt major P-P interval prolongation beginning shortly after the onset of expiratory airflow.

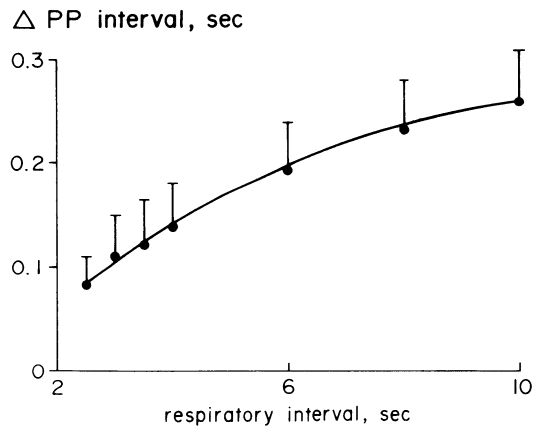

FIG. 2. Average difference between peak and valley P-P intervals at different respiratory intervals for all subjects. *Brackets* encompass 1 SE.

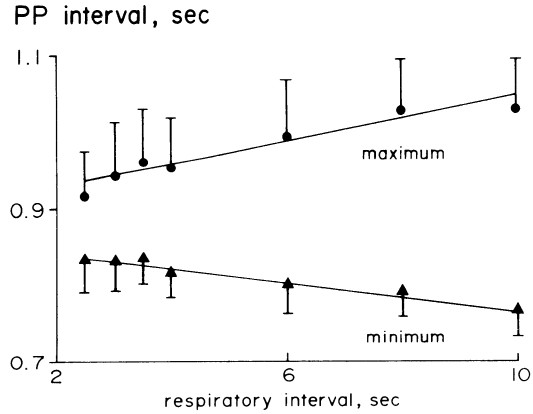

FIG. 3. Average peak and valley P-P intervals at all breathing intervals studied for all subjects.

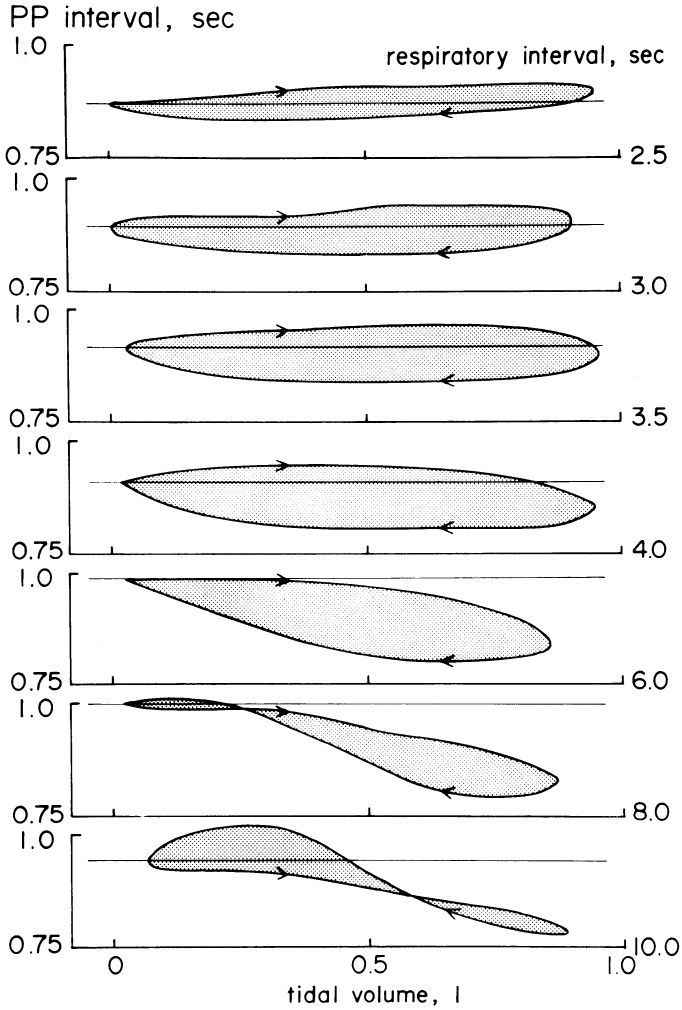

FIG. 4. Average data from all subjects plotted as Lissajous figures (see RESULTS). *Horizontal line* indicates control P-P interval. Each breath began at extreme left and proceeded in direction indicated by *arrows*.

Phase angle between P-P interval and respiration. Figure 5 depicts the average timing of P-P interval shortening and lengthening within the respiratory cycle. Data in the left panel were aligned according to the onset of expiratory airflow. Average P-P interval prolongation (**) began after the onset of expiration at all respiratory intervals studied. Average P-P interval shortening (*), however, began progressively earlier in the respiratory cycle as breathing interval increased; at breathing intervals of 8 and 10 s, P-P interval shortening began before the onset of inspiration. The right panel shows phase angles between P-P interval changes and breathing. Each phase angle was calculated as the time at which 5% of

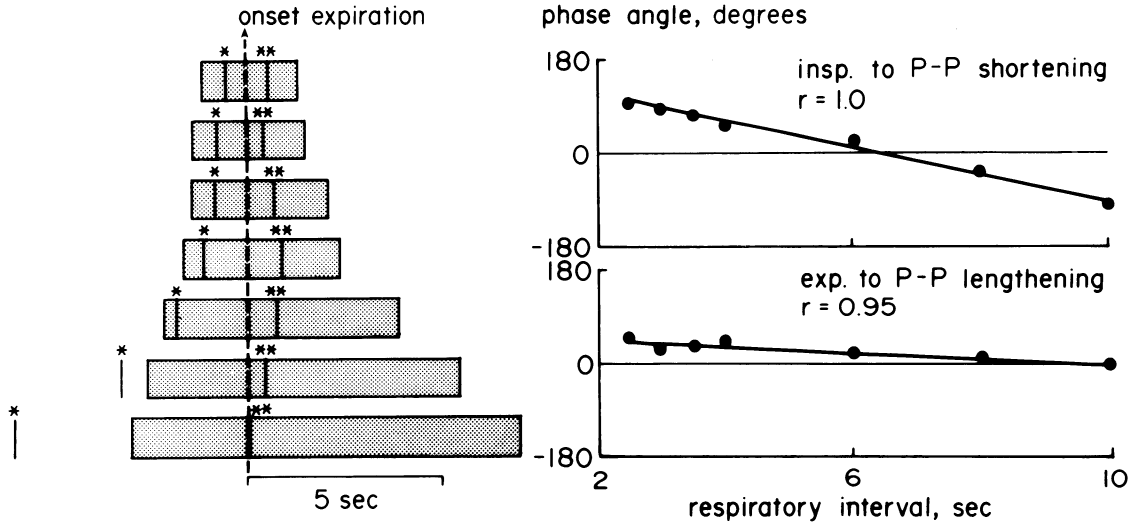

FIG. 5. *Left*: timing of onset of P-P interval shortening (*) and lengthening (**) during respiratory cycle. Respiratory cycles were aligned according to timing of onset of expiratory airflow. *Right*: phase angle shifts (see METHODS). P-P interval shortening coinciding with onset of inspiration was depicted as 0 phase angle (*upper portion*); P-P interval lengthening coinciding with the onset of expiration was depicted as 0 phase angle (*lower portion*).

inspiratory (or expiratory) air flow had occurred minus the time at which 5% of P-P interval shortening (or lengthening) had occurred, divided by respiratory interval, multiplied by 360°. Phase angles were linear functions of respiratory interval. Average phase angle changes (between the onset of inspiration and heart period shortening) at the smaller and larger tidal volumes were similar ($P = 0.52$).

Interval histograms. Distributions of P-P intervals for one subject breathing at a tidal volume of 1,014 ± 43 ml are shown in Fig. 6. In this subject, mean and variability of P-P intervals tended to increase as breathing interval increased. The distribution of P-P intervals became bimodal at the longest breathing interval (10 s). The Lissajous analysis (Fig. 4) shows that the longest P-P intervals occurred terminally, toward the end of the expiratory phases of the longest respiratory cycles. These trends also were apparent in average data for all subjects: mean and standard deviation of P-P intervals increased in proportion to breathing interval ($r = 0.69$ and $r = 0.96$, $P < 0.001$). Standard deviation also correlated closely with peak-valley P-P interval changes ($r = 0.97$, $P < 0.001$) and phase angles (between inspiration and heart period shortening, $r = 0.94$, $P < 0.001$).

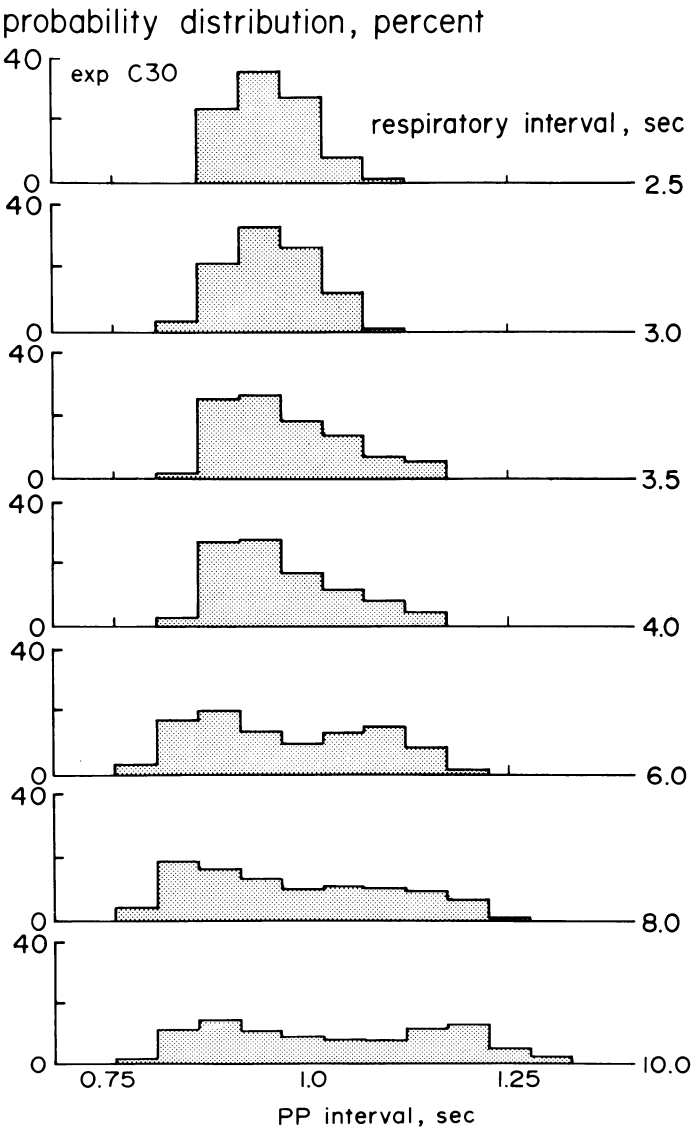

FIG. 6. Distributions of P-P intervals at different breathing intervals in 1 subject.

DISCUSSION

My results suggest that respiration exerts profound influences on the quantity, periodicity, and timing of vagal cardiac efferent activity in conscious humans.

There are numerous earlier reports of human heart rate changes during respiration (2, 6, 11, 12). The present study differs from earlier ones in several ways. First, volunteers controlled their breathing very closely; in many earlier studies (2, 6, 12), tidal volume was not controlled. Second, to reduce the number of factors influencing vagal cardiac outflow, end-tidal carbon dioxide concentrations were maintained at constant levels despite changes of ventilation. I am aware of no earlier study in which carbon dioxide levels were held constant.

Third, this report focuses on aspects of respiratory sinus arrhythmia (including the time course of heart period changes during breathing) which are different from those emphasized in earlier studies. Fourth, I tried to interpret my results in terms of their implications for central vagal cardiac mechanisms; many earlier workers have dealt with the implications of sinus arrhythmia for control theory (2, 11). Finally, I correlated a variety of indices of sinus arrhythmia with one another to identify those which might be useful for on-line estimations of fluxes of human vagal cardiac outflow.

Others (2, 6, 11, 12) have found that cardiac intervals increase as respiratory interval increases. My results are in essential agreement with those of Hirsch and Bishop (11), notwithstanding their use of different methods (Bode plots of heart rates and breathing frequencies) to plot their data. However, their data and data from this laboratory published earlier (10) are in disagreement with those of Angelone and Coulter (2), who found that heart rate fluctuations are maximal at about 5 breaths/min and are less at slower as well as faster breathing rates. Angelone and Coulter may have obtained different results in the single subject they studied because tidal volumes and carbon dioxide concentrations were not held constant. My results also confirm other observations of Hirsch and Bishop (11), that respiratory sinus arrhythmia increases as tidal volume increases, and extend these earlier observations by providing an indication of the quantitative importance of this effect in a group of subjects (a 50% increase in tidal volume led to only a 15% increase in the peak-valley P-P interval). The Lissajous analysis (Fig. 4) suggests that respiratory modulation of vagal activity is complex, and it belies the notion (6) that heart rate changes occur simply in the inspiratory phase of respiration. I am aware of no earlier study in which the influence of respiratory interval on minimum cardiac intervals (Fig. 3) or on the phase lag between the onset of expiration and P-P interval lengthening (Fig. 5, right lower panel) was measured.

Sinus arrhythmia as an index of human cardiac vagal efferent activity. My use of respiratory sinus arrhythmia to study vagal cardiac mechanisms is grounded on the critical assumption that this measurement quantitatively reflects changes of vagal cardiac efferent activity. This usage is expedient, since efferent cardiac vagal traffic has not been measured directly in any conscious experimental animal or human subject. Moreover, this usage is supported by data obtained from anesthetized animals. Changes of heart period are nearly linearly related to changes of vagal cardiac efferent activity during moderate prolonged fluctuations of arterial pressure (17). Brief changes of heart period associated with breathing are nearly linearly related to total average vagal cardiac efferent traffic (16), and they follow changes of vagal efferent activity in a predictable way: heart period lengthening follows spontaneous bursts of vagal activity (20).

A second assumption is that the timing of respiratory changes of heart period can be used to gauge the timing of central vagal discharge. This seems reasonable on two counts. First, latency between changes of vagal neural activity, triggered by electrical vagus nerve stimulation, and corresponding heart period changes are independent of the level of stimulation (7). Second, the rate of decay of vagal cardiac inhibition appears to be independent of the level of inhibition (9). Thus published data support the view that changes of heart period follow changes of central vagal cardiac motoneuron activity with nearly fixed delays.

Respiratory modulation of the quantity of vagal cardiac outflow. Both peak and valley cardiac intervals contributed to the increase of sinus arrhythmia with increasing breathing intervals; the longest P-P intervals became longer and the shortest P-P intervals became shorter (Fig. 3). These findings suggest that the time course of central respiration-related fluctuations of vagal activity (18, 19) may be long relative to usual breathing intervals. Since prolongation of maximum P-P intervals was greater than shortening of minimum P-P intervals, average P-P intervals increased as breathing interval increased. This suggests that respiratory interval determines in part the average quantity of vagal cardiac motoneuron activity.

Timing of phasic changes of vagal cardiac activity. My results point toward exquisite respiratory modulation of both the period and the timing of vagal cardiac outflow. The average period of changes of cardiac interval was a deterministic function of respiratory interval: the correlation coefficient between the periods of respiratory and cardiac intervals was 1.00. Although this result was expected, Bond et al. (4) found, in one awake subject, that the interval between heart period changes may be a multiple of the interval between breaths.

In addition, the occurrence of heart period prolongation seemed to be tied, in a nearly deterministic fashion, to the onset of expiratory airflow. The phase angle between the onset of expiration and the onset of heart period prolongation was positive (heart period prolongation followed the onset of expiration) at all breathing intervals studied and varied in only a minor fashion with changes of breathing interval (Fig. 5, right lower panel). These results are consistent with the findings of virtually all investigators who have correlated direct measurements of vagal cardiac efferent nerve activity with respiration (13, 14, 16, 20, 22), which show that vagal cardiac motoneuron discharge occurs during expiration.

Variations of the phase angle between the onset of inspiration and the onset of heart period shortening were much more striking than those between the onset of expiration and heart period lengthening (Fig. 5, right panel). Not only was the rate of change of this phase angle more steep, but the polarity changed from positive to negative as breathing interval increased. At rapid breathing rates (at respiratory intervals of less than about 6 s), the onset of heart period shortening lagged behind the onset of inspiration. This phase lag probably occurs primarily because of the latency between reductions of central vagal activity and reductions of heart period [the minimal latency is about 250 ms in man (8)]. However, this mechanism cannot explain the phase lead which occurs at slow breathing rates. I speculate that, in conscious humans, reductions of vagal cardiac efferent activity always begin during expiration but that they begin progressively earlier in expiration as breathing interval

increases.

Data from anesthetized cats published by Barman and Gebber (3), suggest that, during spontaneous changes of respiratory rate, sympathetic and respiratory neural activity become dissociated. I found no evidence for dissociation of vagal and respiratory periodicities in the present study. The deterministic relationship between these two variables I observed probably cannot be attributed to the experimental constraint that subjects regulate their breathing voluntarily; Hirsch and Bishop (11) found that heart rate changes are comparable during controlled and spontaneous breathing. However, as indicated above, under other circumstances, fluctuations of heart period may become dissociated from respiratory activity in the human (4). Thus the close coupling I observed between respiration and putative vagal cardiac efferent activity does not necessarily point toward fixed locking of these two oscillations under all experimental circumstances.

Indices of respiratory sinus arrhythmia. The present study points toward several quantitative measures of sinus arrhythmia that could be used to obtain running estimates of the level of cardiac vagal efferent activity. It may be unnecessary to measure tidal volume if the depth of breathing is relatively constant, since a 50% increase of tidal volume increased peak-valley P-P interval changes by only about 15%. Moreover, if the goal of measurements of sinus arrhythmia is to obtain an on-line estimate of the magnitude of human vagal cardiac outflow, it may not be important to know what factors, such as variations of tidal volume or breathing rate, caused vagal cardiac outflow to change. I found that standard deviations of P-P intervals correlated closely with other indices of sinus arrhythmia, such as phasic peak-valley P-P intervals, that require (in this experiment, obtrusive) measurement of tidal volume.

In conclusion, I have studied human heart period changes during controlled breathing to gain insight into central vagal cardiac mechanisms. This usage is supported by direct measurements of vagal activity made earlier in anesthetized animals by others. My results document close respiratory modulation of the quantity, periodicity, and phase of cardiac vagal efferent activity and support the conclusion of other workers that vagal firing occurs during expiration. Moreover, they extend this earlier work (in ways that would be difficult or impossible in experimental animals) by providing systematic information about changes of the time course of vagal activity at different breathing intervals and tidal volumes.

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