Respiratory phase locking during mechanical ventilation in anesthetized human subjects

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GRAVES, CARL, LEON GLASS, DONALD LAPORTA, ROGER MELOCHE, AND ALEX GRASSINO. *Respiratory phase locking during mechanical ventilation in anesthetized human subjects.* Am. J. Physiol. 250 (Regulatory Integrative Comp. Physiol. 19): R902–R909, 1986.—The coupling patterns between the rhythm of a mechanical ventilator and the rhythm of spontaneous breathing were studied in enflurane-anesthetized adult human subjects. The spontaneous breathing pattern was altered in response to different frequencies and amplitudes of forced lung inflations. A 1:1 phase locking (the frequency of the mechanical ventilator is matched by the frequency of spontaneous breathing with a fixed phase between the 2 rhythms) was observed in a range of up to ±40% of some of the subject's spontaneous breathing frequencies. During 1:1 phase locking, there were marked changes in the expiratory duration as measured from the electromyogram of the diaphragm. The phase relationship between onset of inflation and onset of inspiration depended on the frequency and amplitude of mechanical inflation. At ventilator settings that did not give 1:1 phase locking, other simple phase-locked patterns, such as 1:2 and 2:1, or irregular non-phase-locked patterns were observed. Reflexes arising from lung inflation, which may underlie the entrainment, are discussed in the context of these results.

entrainment; respiratory reflexes; control of breathing

PERIODIC INPUTS HAVE POWERFUL effects on biological oscillators. At some stimulation parameters one observes stable entrainment or phase locking in which the stimulation frequency and the frequency of the autonomous oscillator assume fixed ratios of small whole numbers. For stimulation parameters that do not lead to phase locking, irregular dynamics are observed (14, 20, 26, 29). Phase-locking phenomena have been observed in a large number of different theoretical and experimental studies and are of particular importance in the generation and control of the circadian rhythm (6, 12, 20, 29), locomotory rhythms in vertebrates (25), and normal and pathological cardiac rhythms (16, 17).

Entrainment of the respiratory rhythm generated in the brain stem to periodic lung inflations delivered by a mechanical ventilator in experimental animals was demonstrated at the end of the last century (3) and has been often examined subsequently (2, 7, 9, 21, 22, 27). The entrainment in these studies was mediated by the Hering-Breuer reflexes (3, 4, 18) in which lung inflation during the inspiratory (expiratory) phase shortens (prolongs) the duration of inspiration (expiration).

Mechanical ventilation is a common clinical procedure, and entrainment or lack of it between patients and a mechanical ventilator can be readily observed. However, there are surprisingly few studies of phase locking of respiratory rhythm by mechanical ventilators in humans (1, 5). This study was undertaken to determine if the main properties expected during periodic stimulation of an autonomous oscillator, including phase locking in simple patterns and irregular dynamics, could also be observed during mechanical ventilation in humans. Specifically, we investigated the relationship of frequency and phase between the spontaneous respiratory rhythm of anesthetized normal subjects and that of a mechanical ventilator with forced inflation.

MATERIALS AND METHODS

General. Data were collected for analysis from eight anesthetized subjects, who were young adults of both sexes without history of cardiorespiratory or neurological diseases, undergoing minor surgery requiring general anesthesia. Written informed consent was obtained from patients. The protocol was approved by the Ethics Committee of the Notre Dame Hospital, Montreal.

Patients were given an intravenous injection of Pentothal Sodium (Pentothal, 5 mg/kg) for induction of anesthesia and succinylcholine chloride (Anectine, 100 mg) for short-lasting paralysis to facilitate intubation (Portex, tube size 8–9 mm). Patients were then ventilated with inhaled enflurane anesthetic (Ethrane, 1 minimum alveolar concentration) in 100% O_2. The electrocardiogram (ECG) was monitored during the course of the experiments, and no arrhythmias were observed.

Recordings. In four experiments an esophageal electrode, a modified Swan-Ganz with two silver plate rings 2 mm wide placed 2 cm apart near its distal end, was positioned in the esophagus and secured to the gastroesophageal junction by inflation of the small balloon at its end. In the other four experiments the surface electrodes were placed in the sixth and seventh intercostal spaces, close to the anterior costal border (where there is absence of inspiration of intercostal muscles). In both cases the electrodes monitored the electromyogram (EMG) of the diaphragm.

Figure 1 schematically presents the experimental setup used for the acquisition of data. A typical trace of the parameters measured is shown in Fig. 2 that depicts a segment of mechanical ventilation followed by spontaneous breathing. The inflation and deflation phases of the ventilator are shown in the first line. Other variables
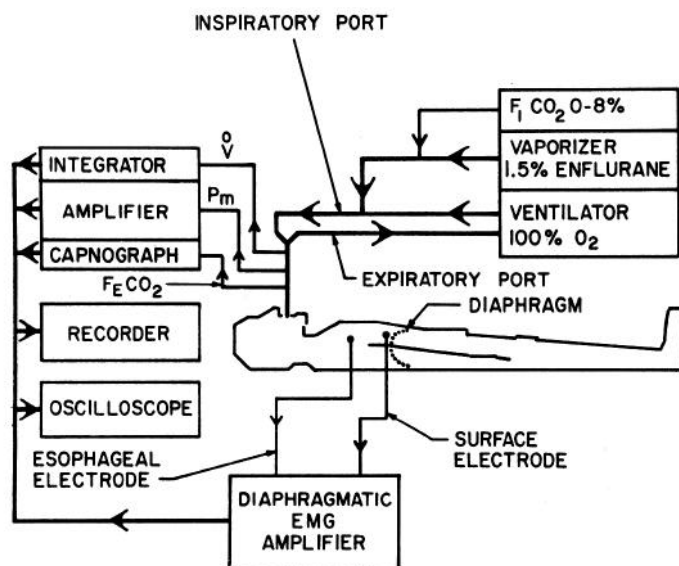

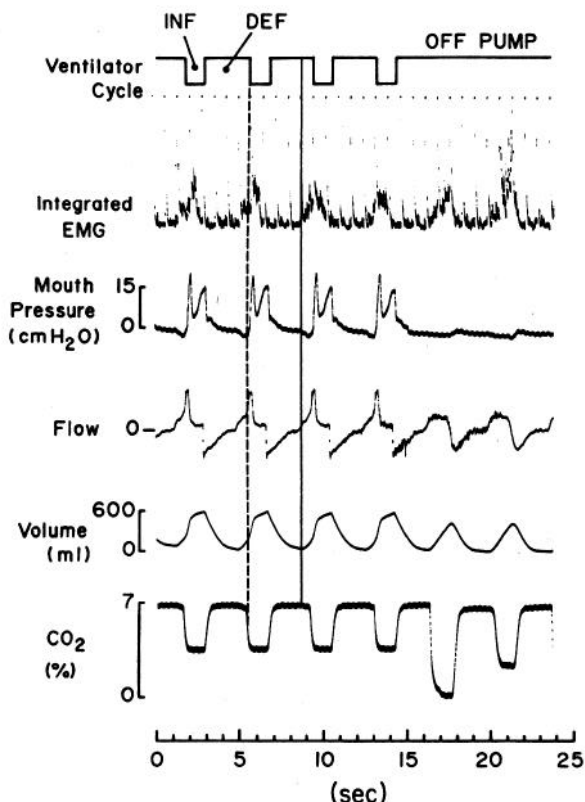FIG. 1. Experimental setup for acquisition of data.

FIG. 2. Example of 25-s recording of experiment. *Tracing* depicts a segment of mechanical ventilation followed by spontaneous breathing ("off pump"). From *top*, traces are ventilator phases [inflation (INF) and deflation (DEF)], "integrated" electromyogram (EMG), mouth pressure, flow, ventilation volume, and end-tidal CO_2 percentage. *Dashed line*, start of ventilator inflation; *solid line*, start of spontaneous inspiration.

recorded were as follows. *1*) Diaphragmatic EMG activity was amplified and low-pass filtered (Teca TE4 EMG). The EMG was rectified, band-passed filtered (150–350 Hz), and then integrated with a leaky integrator using a time constant of 0.03 s. This signal was used to assess timing of the output of the central inspiratory activity. The processed signal is defined as the "integrated" EMG activity. The superimposed spikes are ECG artifacts. *2*) Airway pressure was measured at the endothracheal tube with a pressure transducer (Validyne, ±50 cmH$_2$O). The airway pressure is deflected up for the large positive pressures generated by the ventilator inflations and deflected slightly below zero during inspiratory efforts of a subject in the absence of ventilator inflations at the end of the trace. The superimposed negative pressure of inspiration accounts for the double peak in the positive deflection of the presence tracing during a ventilator inflation. *3*) Flow at the mouth was measured with a Fleisch pneumotachograph no. 2. The flow signal was integrated (respiratory integrator, Hewlett-Packard 8815) to determine the volume. The flow at the mouth is deflected up for movement of air into the lungs. The sharp upward deflections indicate the beginning of a ventilator inflation, and the sudden downward deflections indicate the end of an inflation, i.e., the end of an occlusion to expiratory flow during the inflation phase. *4*) The ventilator volume is the integrated flow signal. *5*) The fractional percentage of CO_2, sampled at the endotracheal tube, was continuously monitored using a Beckman rapid gas analyzer (LB2). The trace has been shifted by 0.3 s to account for the time lag of its measurement.

Ventilator system. Patients were ventilated with an Engstrom-Respiratory constant volume ventilator (system ER300) that adjusts the pressure so as to deliver the desired volume (Fig. 1). The ventilator operates over a frequency range of 12–30 breaths/min and is capable of delivering inflation volumes up to 1.50 liters. The periodicity and volume of lung inflations were not altered by the subject's respiratory efforts.

The ventilator applied a forced inflation for one-third of the ventilator cycle at which time no expiratory flow of air was possible. The ventilatory inflation is characterized by an initial high flow, followed by a more prolonged slower flow of air (Fig. 2, line 4). During the remaining two-thirds of the ventilator cycle there was a passive deflation at which time expiratory flow was possible. At any time in the cycle it was possible for the patient to make an inspiratory effort.

The ventilator system was slightly modified for these experiments. To keep end-expired CO_2 constant, CO_2 (100%) was mixed with other inspired gases using a gas flowmeter (Gilmont 12) at variable flow rates achieving volumes of CO_2 <25 ml. The gas was administered on the outport tubing of a vaporizer unit (Ohio Medical Products) that delivered the inhaled anesthetic (Fig. 1). This setup permitted the manipulation of the inspired CO_2 from 0 to 8.0% (Fig. 1). A microswitch was also fitted onto the ventilator to measure the exact frequency of the ventilator.

Definition of terms. The ventilator tracing consists of an inflation phase and deflation phase. The ventilator

period (T_v) is the sum of the inflation duration (INF) and deflation duration (DEF), and the ventilator frequency (f_v) equals $1/T_v$. The subject's spontaneous respiratory activity consists of an inspiratory duration (T_I) and an expiratory duration (T_E). In this study T_I is the time from the start of rise to half of the decaying "integrated" diaphragmatic EMG activity from its maximal amplitude. This choice for the end of inspiration facilitated data analysis of the noisy signal. T_E is the time from the end of inspiration to the beginning of the next breath. The respiratory period (T_T) is the sum of T_I and T_E. The situation without mechanical ventilation, defined as "off pump," provides the control respiratory timing. The control respiratory period ($T\mathring{T}$) is the sum of the control inspiratory and expiratory durations ($T\mathring{I}$, $T\mathring{E}$, respectively). The instantaneous respiratory frequency (f) equals $1/T_T$ and $f° = 1/T\mathring{T}$.

The volume of the mechanical inflations is V_v, and the tidal volume during spontaneous off-pump breathing is $V\mathring{T}$. The term inflation refers to the action of lung inflation by the ventilator, and the term tidal volume refers to lung inflation by a spontaneous inspiration.

The phase relationship of inspiration with respect to the inflation by the ventilator is measured as a delay. The delay is the time from the beginning of a mechanical inflation to the onset of a spontaneous inspiration. The phase angle is derived by dividing the delay by the period of the ventilator and multiplying by 360°. In instances where the phase angle is >180°, we have subtracted 360°. Thus the phase angle lies between −180 and 180°. For values of the phase angle equal to 0°, a spontaneous inspiration will commence in synchrony with a ventilator inflation.

In this study we define respiratory phase locking as the situation that arises when the inspiratory efforts of the patient occur at a specific phase, or specific phases, of the ventilator cycle, and the inspirations are periodic in time. This situation can also be called respiratory entrainment or synchronization. A phase-locking pattern can be associated with a ratio of ventilator frequency to breathing frequency. For example, in 1:2 phase locking there is one ventilator cycle for two respiratory periods.

Experimental protocol. Mechanical ventilation trials were performed to examine the respiratory pattern in response to different frequencies and volumes of lung inflation. After the initial paralysis the patient was allowed a period of recovery to regain the ability to breathe spontaneously. This was ascertained by the appearance of EMG activity and chest wall movements. Once spontaneous breathing recommenced under inhaled anesthesia and mechanical ventilation, a further stabilization period of 5–10 min was allowed before recording. The patient was then disconnected from the ventilator, and the control spontaneous breathing rhythm, V_T, and end-expired CO_2 concentration were recorded.

A series of mechanical ventilation trials were performed at various levels of minute ventilation. Initial experiments demonstrated that a decrease of end-expired CO_2 from the control values by >0.5% led to loss of the EMG signal and the spontaneous breathing. This finding is in accord with previous investigations, where sponta-

neous breathing disappears for smaller decreases in P_{CO_2} during sleep or anesthesia than for the awake state (11). To maintain an adequate EMG signal, the end-expired CO_2 concentration was usually kept slightly above or near the control value. If either the end-expired CO_2 or the amplitude of the integrated EMG signal began to decrease, one of two procedures was initiated. The simpler method was to decrease the minute ventilation by decreasing the inflation volume or frequency of ventilation. If this would conflict with the protocol, a second method was to increase the inspired CO_2. After two or three of the above trials, lasting between 30 s and 4 min, a brief recording of spontaneous breathing was obtained.

An experiment lasted ~20–40 min allowing 5–10 trials to be performed. The range of frequencies of ventilation was between 12 and 30 breaths/min, and the range of inflation volumes was between 100 and 700 ml. A sequence of three or four trials was generally performed at constant inflation volumes while increasing or decreasing ventilator frequency.

For each trial 5–20 measurements were made of T_I, T_E, and phase angle during mechanical ventilation. At the beginning and the end of the intermittent off pumps the initial three or four respiratory cycles were measured that were then averaged over a whole experiment. These measurements provided mean respiratory variables that could be compared with the respiratory variables during mechanical ventilation. It should be mentioned that though the variation from the mean of f° was <10% for any one experiment, the variation from the mean of $V\mathring{T}$ could be as high as 40% in an experiment where end-expired CO_2 was not well controlled.

The measurements were performed by digitizing events from recorded data played back on paper at speeds of 5 and 10 mm/s. The measurements were stored on magnetic disks for statistical analysis.

RESULTS

Frequency coupling patterns. The experiments demonstrate that characteristic coupling patterns between the frequency of respiration and frequency of mechanical ventilation can be described for different f_v and V_v. The 1:1 phase locking is the most commonly observed pattern. Figure 3 illustrates three examples of 1:1 phase-locking patterns in one patient. Each example consists of three continuous tracings of the ventilator phases of inflation and deflation, the integrated EMG activity, and the ventilation volume. The 1:1 phase locking occurs at a large range of frequencies of mechanical ventilation below and above the spontaneous respiratory frequency. Furthermore, the phase relationship between onset of inflation and onset of inspiration, indicated by the dashed and solid lines, respectively, vary for the different f_v and V_v.

For ranges of ventilator inflation volume and frequency at which 1:1 phase locking was not observed, both irregular non-phase-locked and simple phase-locked patterns were observed. An illustrative tracing of a non-phase-locked pattern using an inflation volume of 350 ml is shown in Fig. 4A. In this example, with a high f_v
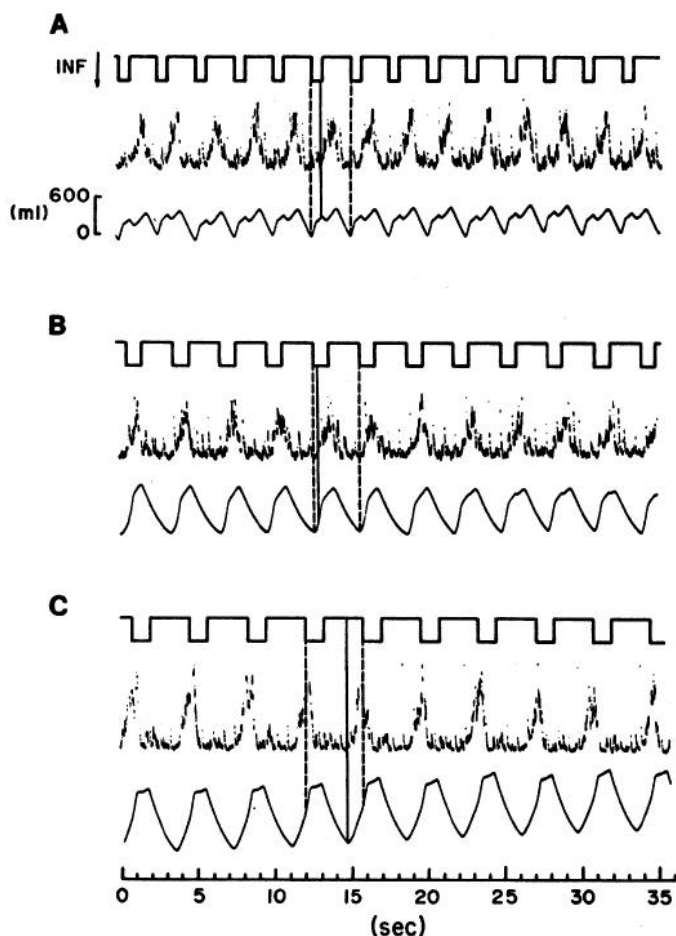
FIG. 3. 1:1 phase-locked patterns of ventilator-respiratory coupling. From the top, *traces* are ventilator phases [inflation (INF) and deflation (DEF)], "integrated" electromyogram, and ventilation volume. Patterns are at following ventilator settings. *A*: ventilator frequency (f_v) = 24/min, volume of mechanical inflations (V_v) = 400 ml; *B*: f_v = 19.4/min, V_v = 500 ml; *C*: f_v = 15.6/min, V_v = 600 ml. *Dashed* and *solid lines*, onset of inflation and inspiration, respectively.
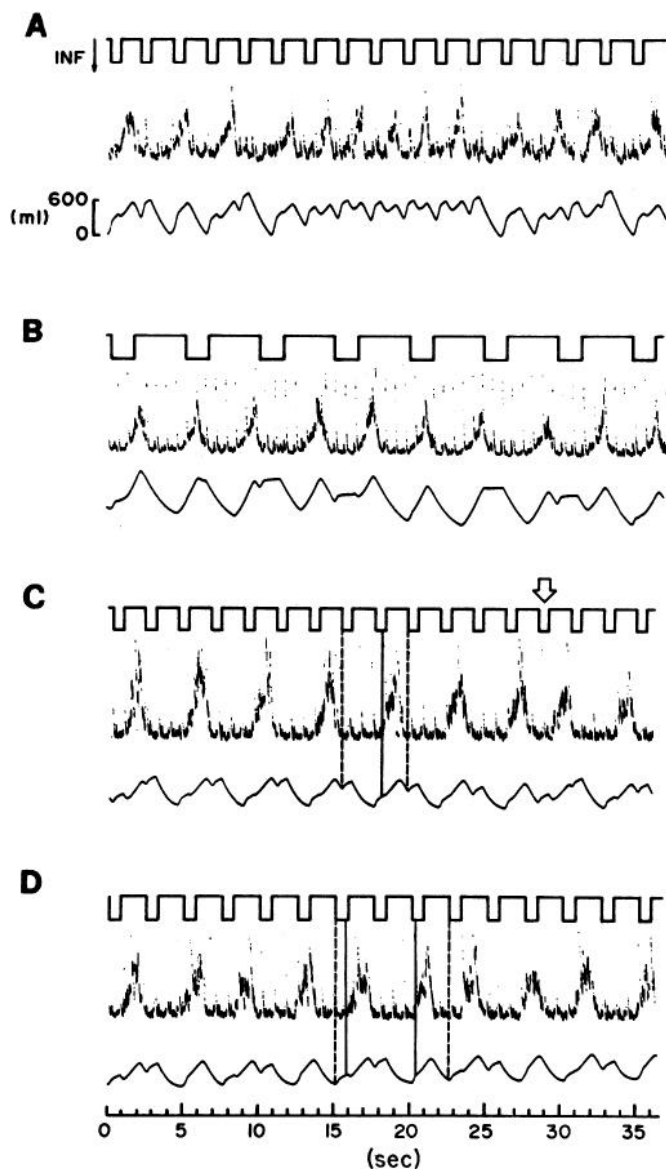

FIG. 4. Four coupling patterns with traces of ventilator phases, "integrated" electromyogram and ventilation volume. Two sample tracings are shown of irregular non-phase-locked patterns found at following ventilator settings. *A*: ventilatory frequency (f_v) = 27.2/min, volume of mechanical inflations (V_v) = 350 ml; *B*: f_v = 12.0/min, V_v = 150 ml. Two sample tracings are also shown of simple phase-locked patterns found at following ventilator settings. *C*: 2:1, f_v = 27.3/min, V_v = 175 ml; *D*: 3:2, f_v = 25.6/min, V_v = 175 ml. In *C* and *D*, *dashed line*, indicating onset of inflation, and *solid line*, indicating onset of inspiration, help distinguish phase-locked pattern. *Arrow* at *top* of traces in *C*, 2:1 pattern was briefly interrupted.

outside the 1:1 phase-locking range, the integrated EMG is characterized by a random sequence of short and long respiratory periods; no spontaneous inspirations occur during some ventilator cycles. The phase relationship is changing irregularly. In Fig. 4*B* another irregular coupling pattern is shown during mechanical ventilation at a low inflation volume of <150 ml and at f_v equal to 12/min.

The three simple phase-locked patterns of 2:1, 3:2, and 1:2 were observed in some of the subjects. The patterns were short lived; they were interrupted by irregular patterns every 7–15 respiratory cycles. With f_v approximately twice the control respiratory frequency, 2:1 phase locking was observed in one patient (Fig. 4*C*). The arrow at the top of Fig. 4 indicates when the pattern is briefly interrupted by an alternate pattern. With f_v ~50% higher than the average off-pump respiratory frequency, 3:2 phase locking was observed (Fig. 4*D*).

The respiratory frequency of seven subjects could be phase locked 1:1 to the ventilator frequency. A synopsis of each experiment is shown by Fig. 6 in which the mean EMG burst frequency for each run is plotted as a function of ventilator frequency for each patient. Filled circles represent the average respiratory frequencies during mechanical ventilation trials, and the open circles are the average off-pump respiratory frequencies of an entire experiment. Filled circles that lie on the line labeled 1:1 correspond to 1:1 locking. The frequency range of 1:1 phase locking is much greater than the range of $f°$. Outside the range of 1:1 locking other regular and irregular dynamic patterns were observed. In the eighth subject not displaying 1:1 locking (Fig. 5*B*), the ventilator frequencies used were <35% of the control respiratory
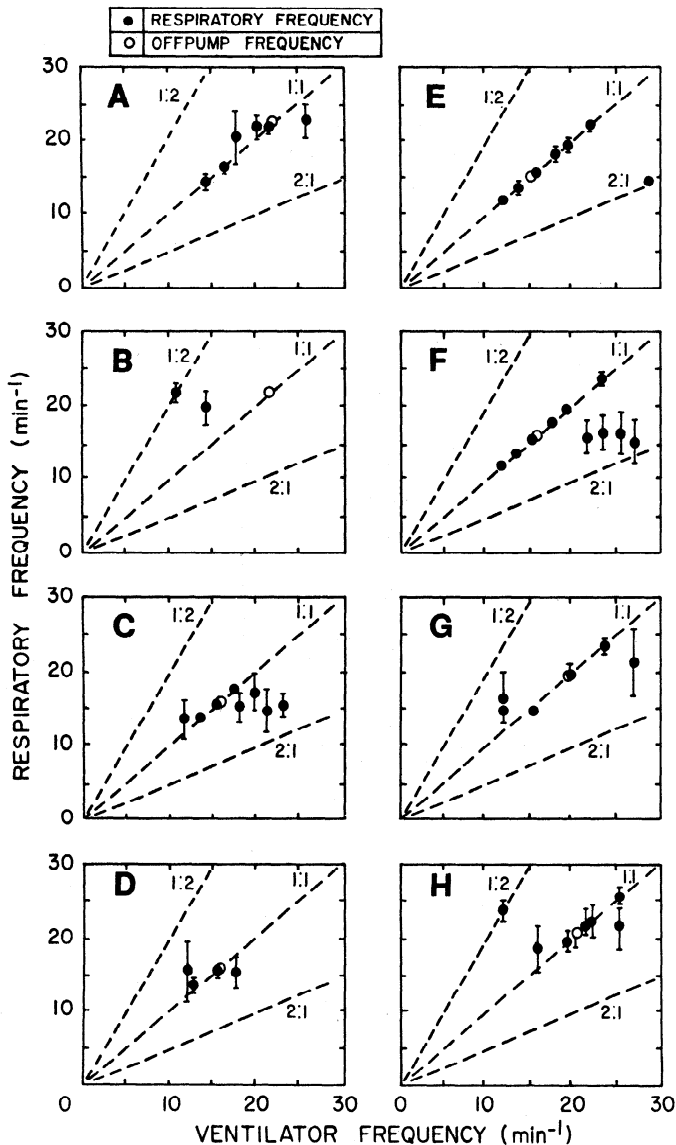
FIG. 5. Summary of changes in respiratory frequency for each trial of 8 experiments. *Filled circles*, mean respiratory frequency plotted against ventilator frequency. Some points represent more than 1 trial because a ventilatory frequency at different volumes of mechanical inflations gave rise to an identical respiratory frequency, especially for 1:1 phase locking. *Open circles*, mean "off-pump" respiratory frequencies of subject; *dashed lines*, simple phase-locking patterns; *error bars*, ±SD.
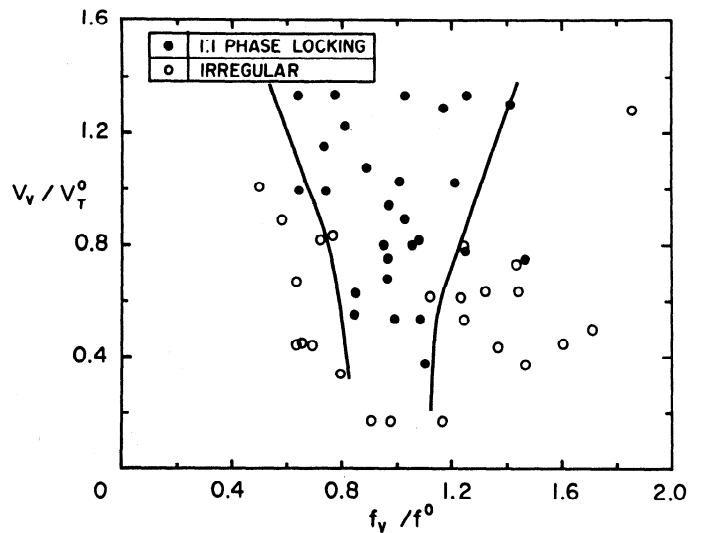

FIG. 6. Composite plot of 1:1 phase-locking behavior in volume and frequency parameter space obtained from 7 subjects. Frequency axis has been normalized to mean off-pump respiratory frequency ($f_v/f°$), and volume axis has been normalized to off-pump tidal volume ($V_v/$V†) of separate experiments. *Filled circles*, 1:1 phase locking; *open circles*, patterns found outside range of 1:1 phase locking, which include irregular dynamics and simple phase-locked patterns. A boundary of 1:1 phase-locking zone has been arbitrarily drawn to facilitate separation between regions.

frequency.

The different coupling patterns observed are plotted as a function of V_v and f_v for seven of the experiments in Fig. 6. Technical difficulties prevented the successful recording of volume in one experiment (Fig. 5D). The ventilator frequency axis is normalized to the off-pump respiratory frequency, and the volume axis is normalized to the off-pump V†. The filled circles represent the 1:1 phase-locking patterns, and the open circles represent other patterns. Approximate boundaries for the zone of 1:1 phase locking in the frequency-volume parameter space are shown. The maximum range of f_v for 1:1 phase locking was between 24 and 12/min, and the maximum range of V_v for 1:1 phase locking was between 40 and

140% of V$_T$. For V_v (less than ~150 ml) 1:1 phase locking was not found.

To show interrun respiratory frequency stability and phase angle stability between the ventilator and the patient, a breath-by-breath representation of five different trials of mechanical ventilation in one patient is shown in Fig. 7. The instantaneous respiratory frequencies for 24 consecutive breaths are shown in the left panels. The solid horizontal line indicates the ventilator frequency, and the dashed horizontal line indicates the average off-pump respiratory frequency. In the right panel of Fig. 7 the phase angles for each of the 24 breaths of the left panel are plotted.

Figure 7, B–D, corresponds to the 1:1 phase-locking examples shown in Fig. 3. Figures 3 and 7 (B–D) demonstrate an essential feature of stable 1:1 phase locking: the respiratory frequency matches the f_v, and the phase angle remains relatively constant. However, the phase angle depends on f_v. During 1:1 phase locking at $f_v > f°$, the phase angle is constant in the range of 0–180° (Fig. 7B), which corresponds to ventilator inflations occurring before the onset of inspiration (Fig. 3A). For entrainment at f_v near the intrinsic respiratory frequency (Fig. 7C) the phase angle is near 0°, indicating that the ventilator inflation and subjects' inspirations are occurring in synchrony (Fig. 3B). For $f_v < f°$, the phase angle remains relatively constant somewhere in the range of −180–0° (Fig. 7D) so that the ventilator inflations occur after the onset of inspiration (Fig. 3C).

Figure 7A is a breath-by-breath representation of the irregular pattern in Fig. 4A. The instantaneous respiratory frequencies vary over a large range from below the off-pump respiratory frequency up to the f_v. The phase angles are between −90 and 160°.

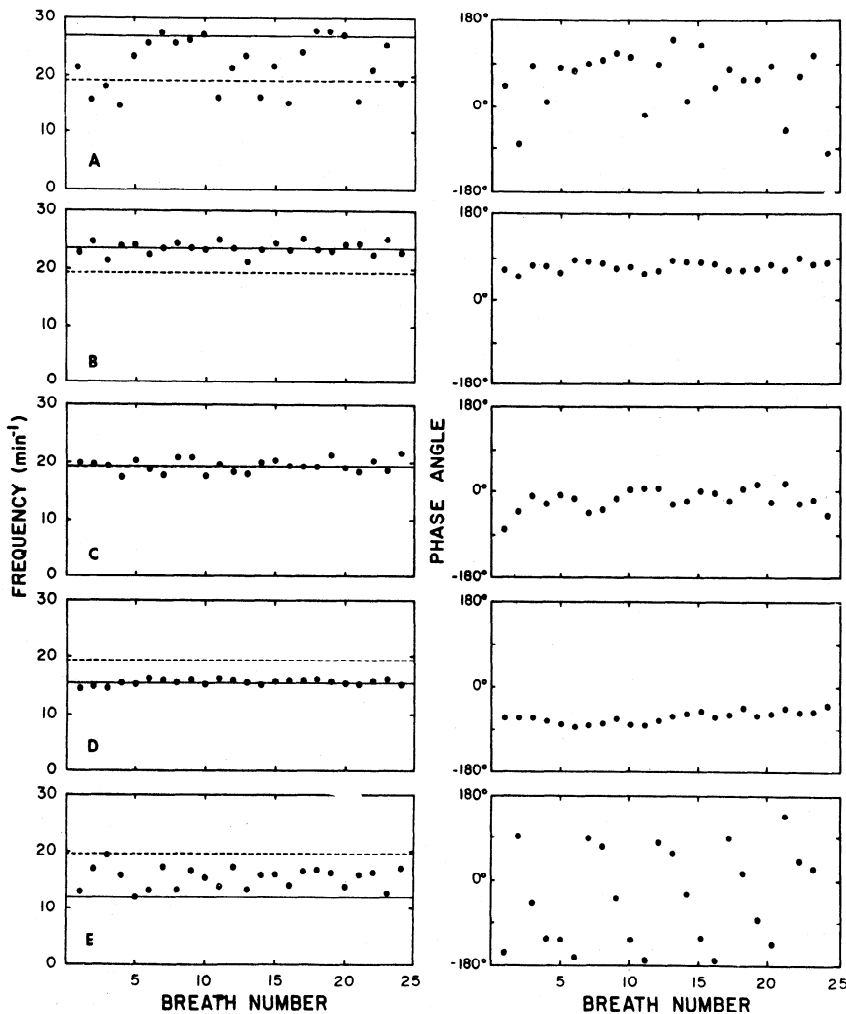Figure 7E is a breath-by-breath representation of the

FIG. 7. Breath-by-breath analysis of respiratory variables during mechanical ventilation. *Left panels* plot instantaneous frequency of breathing of 24 breaths. *Dashed line*, off-pump respiratory frequency; *solid line*, ventilator frequency. *Right panels* plot successive phase angles of each breath for *left panels*. Five coupling patterns are at following ventilator settings. *A*: ventilatory frequency (f_v) = 27.2/min, volume of mechanical inflations (V_v) = 350 ml; *B*: f_v = 24.0/min, V_v = 400 ml; *C*: f_v = 19.4/min, V_v = 500 ml; *D*: f_v = 15.6/min, V_v = 600 ml; *E*: f_v = 12/min, V_v = 150 ml.

irregular pattern shown in Fig. 4*B*. There is a much smaller variation in the instantaneous respiratory frequencies compared with Fig. 7*A*, and the corresponding phase angles change in a regular fashion over a range from −180 to +180°. Such patterns are often called quasiperiodic (15) and arise at small ventilator volumes.

Timing of the subject's breathing cycle. In four experiments an analysis of the timing of TI and TE during 1:1 phase locking was performed. Figure 8 shows changes in TI, TE, and TT as a function of T_v during 1:1 phase locking in four experiments. The changes in TI and TE as a function of T_v can be expressed by linear relationships

$$\text{TI} = A\text{T.} + B \tag{1a}$$

$$\text{TE} = C\text{T}_v + D \tag{1b}$$

The linear regressions were calculated for each patient and are given in Fig. 8 legend. The *slopes A* and *C* provide a measure of the relative contribution of TI and TE to the overall change in TT. The range of the slopes of *A* are from 0.01 to 0.21 and of *C* are from 0.77 to 0.96. The maximal value of *A* = 0.21 and the minimal value of *B* = 0.77 were calculated for the experiment that demonstrated a small range of T_v for 1:1 phase locking (Fig. 8*D*). Figure 8 shows that in 1:1 phase locking in humans

there is much larger variation in TE than TI. Thus modulation of TE by the periodic stimulation of mechanical inflations appears to be the main mechanism underlying the entrainment.

DISCUSSION

Phase-locked and irregular non-phase-locked patterns are observed as a function of the frequency and volume of mechanical ventilation (Figs. 3, 4, and 7). The changes in the frequency of bursts of diaphragmatic EMG suggest that the regulation of the respiratory pattern is subjected to afferent information initiated by the periodic lung inflation. One way to think about the regulation of the respiratory rhythm is from a general perspective of the theory of nonlinear oscillations (20, 29). Thus the present results will be initially discussed in the context of previous theoretical results on phase locking of biological oscillations. Then possible respiratory reflexes underlying the mechanisms of phase locking will be discussed.

Theory of phase locking. Many simple mathematical models have been proposed to describe the periodic stimulation of an autonomous oscillator (6, 12, 14, 17, 22, 26). Despite many differences between the formulation of these models and the fine details of the properties of the models, the models also share many common fea-
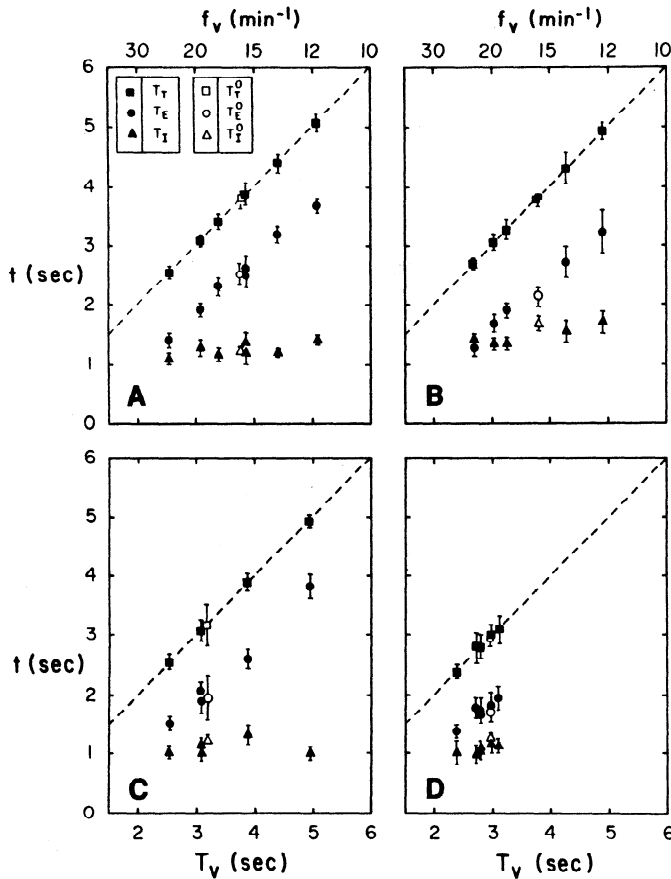
FIG. 8. Respiratory period (TT), expiratory duration (TE), and inspiratory duration (TI), are plotted as a figure of ventilator period (T_v) within 1:1 phase-locking zone for 4 different experiments. There are a variety of inflation volumes used, ranging from 150 to 600 ml. Average off-pump values of TT, TE, and TI are shown for comparison and are indicated by *unshaded symbols*. Linear regressions are as follows. *A*: TI = 0.09 T_v + 0.91, TE = 0.89 T_v − 0.83; *B*: TI = 0.16 T_v + 0.90, TE = 0.86 T_v − 0.95; *C*: TI = 0.01 T_v + 1.07, TE = 0.96 T_v − 0.98; *D*: TI = 0.21 T_v + 0.49, TE = 0.77 T_v − 0.42. *Error bars*, ±SD.

tures. These main features are as follows. *1*) Phase locking is observed. The properties of the phase locking depend on the frequency and amplitude of the periodic input. *2*) The zones displaying simple patterns, e.g., 2:1, 1:1, and 1:2, occupy the largest area in the frequency-amplitude parameter space. *3*) Complex coupling patterns are found in narrow regions of frequency-amplitude parameter space. *4*) In the presence of small amounts of stochastic noise, complex phase-locking patterns are selectively destroyed. In their place are found irregular non-phase-locked patterns (15). *5*) In some models there are irregular coupling patterns even without the presence of noise. Such irregular dynamics in deterministic models are often referred to as "chaotic" dynamics (17).

In these experiments we observe phase locking in simple ratios 1:2, 2:1, 1:1, 3:2 and also irregular dynamics. For the 1:1 phase locking, it is possible to delineate a zone of frequencies and amplitudes over which this pattern is observed. As well, irregular dynamics are observed. The observation of phase locking does not in itself give information about the detailed mathematical structure of a model for ventilator-respiratory coupling in humans. A much more careful dissection of the bound-

aries of the different locking regions and the dynamics observed between these regions are required to allow a detailed mathematical analysis of these experiments. Mathematical analysis has been possible in studies of phase locking in mechanically ventilated cats (2, 22, 27) but is not feasible in the current human study. Despite the difficulties involved in formulation of a mathematical model for this system, an analysis of the 1:1 phase locking does give further information about physiological mechanisms underlying the entrainment.

Reflex mechanisms of 1:1 phase locking. Previous experiments in animals showed that vagal reflexes were important in the entrainment of respiration by a mechanical ventilator (2, 21, 27). It is possible that contributions to the observed dynamics also arise from periodic stimulation of intercostal afferents (24) and the carotid body (8) via the positive-pressure effects of mechanical ventilation on chest wall movements and blood pressure. However, bilateral vagotomy in the animal experiments abolished the entrainment (9, 21), indicating the vagal afferent input was necessary for effective synchronization of the respiratory rhythm. At present it is not possible to assess the contribution of intercostal afferent or carotid body in the control of respiration during mechanical ventilation of humans.

As described in the RESULTS (Fig. 8), the major determinant of reflex changes in respiratory timing arise from changes in TE. The Hering-Breuer expiratory promoting reflex appears to be active in human subjects during 1:1 phase locking at T_v > TT̂. The ventilator inflations occur during the inspiratory-expiratory transition (Fig. 3*C*, top), causing an increased lung volume during expiration over that of control which prolongs TE. This is consistent with work on the Hering-Breuer reflexes in adult humans (13, 28) and with reflexes observed in phase-locking studies of anesthetized animals (2, 9, 21, 27).

For 1:1 phase locking at T_v < TT̂ the mechanical inflations commence late in expiration and supplement lung inflation during inspiration (Fig. 3*A*). There is observed a shortening of TE from control with small inconsistent changes in TI (Fig. 8). This is in contrast to previous animal phase-locking studies (2, 9, 21, 27) where the shortening of TT, via decreases in both TI and TE, occurred with ventilator inflations commencing during inspiration. In the previous studies the decrease in TI was attributed to the Hering-Breuer inspiratory inhibitory reflex acting in response to lung inflation during inspiration with a subsequent proportional decrease in TE mediated by the respiratory centers (4, 10).

The role of the Hering-Breuer inhibitory inspiratory reflex in human adults is controversial. Clark and von Euler (4) found that only large lung inflations well above normal VT were able to shorten TI (*range 2*) in eupneic awake adults. However, Polacheck et al. (23) found that occlusion during inspiration led to a lengthening of TI and augmented inflations led to a shortening of TI in enflurane-anesthetized patients. It is difficult to evaluate the Hering-Breuer inhibitory inspiratory reflex in our experiments. Changes of TI did not show strong and consistent dependence on ventilator period (Fig. 8). There are at least two possible reasons for our failure to

observe a strong inspiratory inhibitory reflex. *1*) Ventilator volumes were not sufficiently large, with a maximum volume of 40% above V_T (Fig. 6). *2*) At high ventilator frequencies there is a more powerful reflex controlling the shortening of expiration (Fig. 8) that is elicited when ventilator inflations occur in the latter part of expiration (Fig. 3*A*).

The Hering-Breuer reflexes have previously been attributed to afferent information from the slowly adapting receptors (4, 10, 18). In contrast, the shortening of T_E in human subjects in this experiment may be due to a rapidly adapting receptor reflex in anesthetized humans initiated by the rapid onset of mechanical lung inflation. Such a rapidly adapting reflex may be responsible for shortening of T_E and augmentation of inspiration in experiments in cats (10, 18), dogs (19), and rabbits (7). This paper provides the first evidence, albeit of a preliminary nature, in favor of an analogous reflex in humans.

The current study is the first systematic study of the effects of periodic perturbation of the respiratory rhythm of humans. In view of the widespread use of mechanical ventilation, an understanding of physiological mechanisms underlying entrainment is of practical importance. Furthermore, the observation of entrainment at some stimulation parameters and irregular dynamics at other stimulation parameters confirms similar findings in many other experimental and theoretical studies on periodic forcing of nonlinear oscillators.

REFERENCES

1. AYERS, S. M., R. L. KOZAM, AND D. S. LUKUS. The effect of intermittent positive pressure breathing on intrathoracic pressure, pulmonary mechanics, and the work of breathing. *Am. Rev. Respir. Dis.* 87: 370–379, 1963.

2. BACONNIER, P., G. BENCHETRIT, J. DEMONGEOT, AND T. PHAM DINH. Simulation of the entrainment of the respiratory rhythm by two conceptually different models. *Lect. Notes Biomath.* 49: 2–16, 1983.

3. BREUER, J. Die Selbststeuerung der Athmung durch den Nervus Vagus. *Sber. Akad. Wiss. Wien:* 58: 909–937, 1968. English translation by E. Ullman. In: *Breathing: Hering-Breuer Centenary Symposium,* edited by R. Porter. London: Churchill, 1970, p. 365–394.

4. CLARK, F. J., AND C. VON EULER. On the regulation of depth and control of breathing. *J. Physiol. Lond.* 222: 267–295, 1972.

5. CURZI-DASCALOVA, L., M. F. RADVANYI, G. MORIETTE, F. MOREL-KAHN, AND G. KORM. Respiratory variability according to sleep states during mechanical ventilation: a polygraphic study in a baby with bilateral diaphragmatic paralysis. *Neuropaediatrie* 10: 361–369, 1979.

6. DAAN, S., D. G. M. BEERSMA, AND A. A. BORBÉLY. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am. J. Physiol.* 246 (*Regulatory Integrative Comp. Physiol.* 15): R161–R178, 1984.

7. DAVIES, A., F. SANT'AMBROGIO, AND G. E. SANT'AMBROGIO. Onset of inspiration in rabbits during artificial ventilation. *J. Physiol. Lond.* 318: 17–23, 1981.

8. ELDRIDGE, F. The importance of timing on the respiratory effects of intermittent carotid sinus nerve stimulation. *J. Physiol. Lond.* 222: 297–318, 1972.

9. FALLERT, M., AND R. MUHLEMANN. Der Hering-Breuer-Reflex bei künstlicher Beatmung des Kaninchens. I. Die Auslosung der reflektorischen Inspirationen durch den Respirator. *Pfluegers Arch.* 330: 162–174, 1971.

10. FELDMAN, J. L., AND H. GAUTIER. Interaction of pulmonary afferents and pneumotaxic center in control of respiratory patterns in cats. *J. Neurophysiol.* 39: 31–44, 1976.

11. FINK, B. R., E. C. HANKS, S. H. NGAI, AND E. M. PAPPER. Central regulation of respiration during anesthesia and wakefulness. *Ann. NY Acad. Sci.* 109: 892–900, 1963.

12. GANDER, P. H., R. E. KRONAUER, C. A. CZEISLER, AND M. C. MOORE-EDE. Simulating the action of zeitgebers on a coupled two-oscillator model of the human circadian system. *Am. J. Physiol.* 247 (*Regulatory Integrative Comp. Physiol.* 16): R418–R426, 1984.

13. GAUTIER, H., M. BONORA, AND J. H. GAUDY. Breuer-Hering inflation reflex and breathing pattern in anesthetized humans and cats. *J. Appl. Physiol.* 51: 1162–1168, 1981.

14. GLASS, L., AND M. C. MACKEY. A simple model for phase locking of biological oscillators. *J. Math. Biol.* 7: 339–352, 1979.

15. GLASS, L., C. GRAVES, G. A. PETRILLO, AND M. C. MACKEY. Unstable dynamics of a periodically driven oscillator in the presence of noise. *J. Theor. Biol.* 86: 455–475, 1980.

16. GLASS, L., M. R. GUEVARA, J. BELAIR, AND A. SHRIER. Global bifurcations of a periodically forced biological oscillator. *Physiol. Rev.* 29: 1348–1357, 1984.

17. GUEVARA, M. R., AND L. GLASS. Phase locking, period doubling bifurcations and chaos in a mathematical model of a periodically driven oscillator. A theory for the entrainment of biological oscillators and the generation of cardiac dysrhythmias. *J. Math. Biol.* 14: 1–23, 1982.

18. KNOX, C. K. Characteristics of inflation and deflation reflexes during expiration in the cat. *J. Neurophysiol.* 36: 284–295, 1973.

19. NOSHIRO, M., AND S. SUZUKI. Synchronization of respiratory rhythm with electrical stimulation of the phrenic nerve. *IEEE Trans. Biomed. Eng.* 25: 550–554, 1978.

20. PAVLIDIS, T. *Biological Oscillators: Their Mathematical Analysis.* New York: Academic, 1973.

21. PETRILLO, G. A., L. GLASS, AND T. TRIPPENBACH. Phase locking of the respiratory rhythm in cats to a mechanical ventilator. *Can. J. Physiol. Pharmacol.* 61: 599–607, 1983.

22. PETRILLO, G. A., AND L. GLASS. A theory for phase locking respiration in cats to a mechanical ventilator. *Am. J. Physiol.* 246 (*Regulatory Integrative Comp. Physiol.* 15): R311–R320, 1984.

23. POLACHECK, J., R. STRONG, J. ARENS, C. DAVIES, I. METCALF, AND M. YOUNES. Phasic vagal influence on inspiratory motor output in anesthetized human subjects. *J. Appl. Physiol.* 49: 609–619, 1980.

24. REMMERS, J. E., AND J. MARTILLA. Action of intercostal muscle afferents on the respiratory rhythm of anesthetized cats. *Respir. Physiol.* 24: 31–41, 1975.

25. STEIN, P. S. G. Application of the mathematics of coupled oscillator systems to the analysis of the neural control of locomotion. *Federation Proc.* 36: 2056–2059, 1977.

26. VAN DER POL, B. On relaxation oscillations. *Phil. Mag.* 2: 978–992, 1926.

27. VIBERT, J.-F., D. CAILLE, AND J. P. SEGUNDO. Respiratory oscillator entrainment by periodic vagal afferents. *Biol. Cybern.* 41: 119–130, 1981.

28. WIDDICOMBE, J. G. Respiratory reflexes in man and other mammalian species. *Clin. Sci. Lond.* 21: 163–170, 1961.

29. WINFREE, A. T. *The Geometry of Biological Time. Biomathematics.* New York: Springer-Verlag, 1980, vol. 8.