Effect of Hyperoxic Hypercapnia on Variational Activity of Breathing

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Dysrhythmias of breathing occur in several clinical disorders, but their mechanistic basis is obscure. To understand their pathophysiology, factors responsible for the variability of breathing need to be defined. We studied the effect of hyperoxic hypercapnia (CO_2) on the variational activity of breathing in 14 volunteers before and after delivering CO_2 nonobstrusively via a plastic hood. Compared with air, CO_2 increased the gross variability of minute ventilation ($\dot{V}_I$) and tidal volume (V_T), and decreased that of inspiratory time (T_I) and expiratory time (T_E) (all $p < 0.03$). CO_2 increased the autocorrelation coefficient at a lag of one breath for $\dot{V}_I$ ($p < 0.05$), the number of consecutive breath lags having significant autocorrelation coefficients for $\dot{V}_I$ and V_T (both $p < 0.01$), and the cycle time of oscillations in $\dot{V}_I$ ($p = 0.03$) and V_T ($p = 0.04$). Uncorrelated random behavior constituted $\geq 80\%$ of the variance of each breath component, correlated behavior represented 9 to 20%, and oscillatory behavior represented $< 1\%$ during both air and CO_2. CO_2 increased the correlated behavior of volume components, which was accompanied by development of low-frequency oscillations with a cycle time consistent with central chemoreceptor activation. **Jubran A, Grant BJB, Tobin MJ. Effect of hyperoxic hypercapnia on variational activity of breathing.** AM J RESPIR CRIT CARE MED 1997;156:1129–1139.

We and others have shown that breath components display considerable breath-to-breath variability in healthy human subjects (1–7). This variability in breathing can be considered to be composed of a fixed part, namely, the mean of the entire breath series, and a variable part, which is the deviation of the magnitude of each breath from the mean. This variable deviation from the mean, in turn, can be considered to have a nonrandom (correlated) fraction and an uncorrelated random fraction. In a study of steady-state ventilation of eucapnic healthy subjects, we (8) performed autocorrelation analysis to determine the fraction of variational activity that was correlated on a breath-to-breath basis. The group mean autocorrelation coefficient at a lag of one breath for each of the primary breath components, tidal volume (V_T), inspiratory time (T_I), and expiratory time (T_E), were significantly different from zero, indicating that the magnitude of each component in a given breath was positively correlated with the magnitude of the same component in the immediately preceding breath. The autocorrelation coefficients for each component remained significant for approximately three consecutive breaths, suggesting the presence of short-term memory (9).

The factors that determine the variational activity in breathing are largely unknown. Breathing is controlled by multiple feedback loops, and factors such as central neural networks and chemical stimulation are likely to be important in determining the extent of breath-to-breath variability of breathing, which may be important in the development of dyspnea (10). Although an enormous literature pertains to the influence of hypercapnia on mean changes in respiratory motor output, research on the effect of carbon dioxide (CO_2) on the variability of breathing in humans is scant to non-existent. On the basis of studies in vagotomized animals, it has been suggested that hyperoxic hypercapnia may strengthen the interrelationship between breath components in neighboring breaths because of the dominant activation of the central chemoreceptors under these conditions (11). The central chemoreceptors have a prolonged time constant, and, thus, induced deviations from the mean level of ventilation should return more slowly to the mean level, leading to an increase in correlated behavior. Several investigators (2, 12) have postulated that CO_2 stabilizes the respiratory controller and decreases the occurrence of ventilatory oscillations. This reasoning is partly based on the linear ventilatory response to an increase in CO_2, indicating that the gain of the chemoreceptors is constant, and, therefore, a more stable breathing pattern is expected during hypercapnia (2). Indeed, irregularities of breathing have been reported to disappear with CO_2 inhalation (2). In addition, CO_2 may act as a stabilizing influence by raising the apneic threshold (13).

Ventilatory oscillations are thought to be mediated largely by the peripheral chemoreceptors (12). However, Waggener and colleagues (14) observed ventilatory oscillations in premature infants that had a cycle time considerably longer than that expected for oscillations originating in the peripheral chemoreceptors. They attributed these low-frequency ventilatory oscillations to central chemoreceptor activity, although the role of the latter was not systematically investigated. Ven-

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tilatory oscillations are particularly common in the setting of combined hypoxia and sleep (13). In a study of sleeping subjects exposed to hypoxia, Chapman and colleagues (15) found that CO_2 gain, quantitated as the ventilatory response to hypercapnia (16), was higher in subjects who developed ventilatory oscillations than in those who remained free of oscillations. The role of CO_2 gain as a determinant of this and other fractions of variational activity in breathing has not been systematically examined in awake subjects.

To investigate the role of central chemoreceptor stimulation on variational activity of breathing, we recorded ventilation in healthy volunteers before and after the induction of a steady-state increase in end-tidal CO_2 tension ($P_{ET}CO_2$). The study was conducted in the presence of hyperoxia since the latter diminishes peripheral chemoreceptor activity in humans, and, in this setting, step changes in $P_{ET}CO_2$ are considered to represent a relatively pure central chemoreceptor stimulus (17). The subjects inhaled CO_2 through an open-ended plastic hood, and ventilation was measured nonobtrusively with an inductive plethysmograph to avoid the confounding effects resulting from instrumentation attached to the face (18). We tested the following hypotheses: (*1*) hyperoxic hypercapnia increases the nonrandom fraction of variational activity in breathing; (*2*) the change in the nonrandom fraction with hyperoxic hypercapnia is a function of CO_2 gain.

METHODS

Subjects

Fourteen nonsmoking volunteers (12 men and two women) with a mean age of 35 yr (range, 26 to 44 yr) participated in this study. All had normal pulmonary function. Informed consent was obtained from all subjects, and the study was approved by the Human Studies Subcommittee of Edward Hines Jr. Veterans Administration Hospital.

Respiratory Inductive Plethysmograph

Ventilation was measured nonobtrusively with a respiratory inductive plethysmograph (Non-Invasive Monitoring Systems, Miami Beach, FL). The inductive plethysmograph was calibrated against spirometry by the least squares method (7, 18). Validation was checked during tidal breathing in the horizontal and semirecumbent positions. Inductive plethysmographic data were considered acceptable if they displayed a $\leq$ 10% difference from spirometry at both the beginning and the end of the study. Validation of the inductive plethysmograph against spirometry in the horizontal and semirecumbent positions revealed mean $\pm$ SD arithmetic differences of 3.5 $\pm$ 2.8% and 4.9 $\pm$ 3.1%, respectively, before the experiments and 4.2 $\pm$ 3.3 and 5.0 $\pm$ 3.9%, respectively, after the experiments. The signals from the inductive plethysmograph were recorded on a microprocessor system (Non-Invasive Monitoring Systems, Miami Beach, FL), which sampled the data at 20 Hz. On a breath-by-breath basis, the microprocessor continuously calculated the values of minute ventilation ($\dot{V}_I$), V_T, T_I, and T_E. The data were processed by taking the duration of the respiratory cycle (Ttot) as the unit of time.

End-tidal CO_2

$P_{ET}CO_2$ was recorded from nasal prongs using an infrared CO_2 analyzer (No. 4700; Ohmeda, Louisville, CO). The infrared analyzer was calibrated before each study. Continuous breath-by-breath recordings of $P_{ET}CO_2$ were obtained and stored on a computer disk.

Inspired Gas Administration

To avoid the significant changes in breathing pattern induced by instrumentation attached to the face (19), an open-ended hood was employed for the delivery of CO_2. The hood consisted of transparent material that was not in direct contact with the subject's head and did not produce uncomfortable feelings such as claustrophobia. The hood was loosely positioned over the subject's head and it was ventilated with the desired gas composition. Compressed gas cylinders of pure oxygen (O_2) and pure CO_2 were connected to a flowmeter (Fischer and Porter Co., Warminister, PA), and the outlet of the latter was connected to the hood.

Protocol

The study was conducted while the subject lay semirecumbent on a bed in a quiet room. After successful validation of the inductive plethysmograph, the plastic hood was positioned over the subject's head while he or she rested quietly for 15 min before the initiation of data recording. Subjects were instructed to remain motionless, keeping arms by the side, and to remain awake for the duration of the study; electroencephalography was not monitored. The subjects watched a single recording of a video tape player. Subjects first breathed room air through the hood for 60 min. Then, the mixture of O_2 and CO_2 flowing into the hood was adjusted to achieve an increase in $P_{ET}CO_2$ of $\sim$ 10 mm Hg from baseline; in reality, $P_{ET}CO_2$ increased from 33.7 $\pm$ 3.4 to 46.6 $\pm$ 4.0 mm Hg. This level of $P_{ET}CO_2$ was maintained for at least 60 min. Breathing pattern and $P_{ET}CO_2$ were continuously recorded on a computer and stored on disk for later analysis (Figure 1).

Ventilatory Response Progressive Hypercapnia

On a separate day, the CO_2 gain was assessed by measuring the ventilatory response to hypercapnia using a modification of the Read rebreathing technique (16). The subjects rebreathed a 7% CO_2-93% O_2 mixture from a 6-L anesthesia bag, and ventilation was measured by a pneumotachograph (Hans Rudolf; Kansas City, MO) attached to the inspiratory side of a mouthpiece. Expired gas was continuously sampled by an infrared CO_2 analyzer (Datex, Helsinki, Finland). Signals from the recording amplifiers were digitized continuously at 50 Hz using a 16-bit analog-to-digital converter (DATAQ Instruments, Inc., Akron, OH) connected to a computer and stored on disk. To reduce random variability, three CO_2 response curves (separated by a 15-min rest period) were obtained and averaged. In each subject, the ventila-

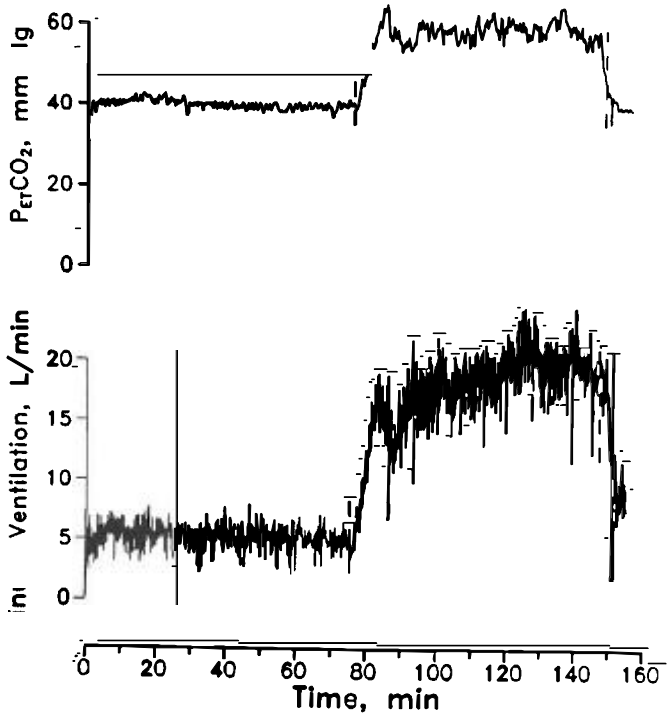

Figure 1. Time-series plot of end-tidal P_{CO_2} ($P_{ET}CO_2$) and minute ventilation in a subject breathing air and hyperoxic hypercapnia. Compared with air, hyperoxic hypercapnia (section between *dashed vertical lines*) produced an increase in $P_{ET}CO_2$ (40 to 60 mm Hg) and in minute ventilation (5.3 to 20.1 L/min). Two sets of 700 consecutive breaths were selected during air breathing (15 to 66 min) and hyperoxic hypercapnia (111 to 144 min) for analysis.

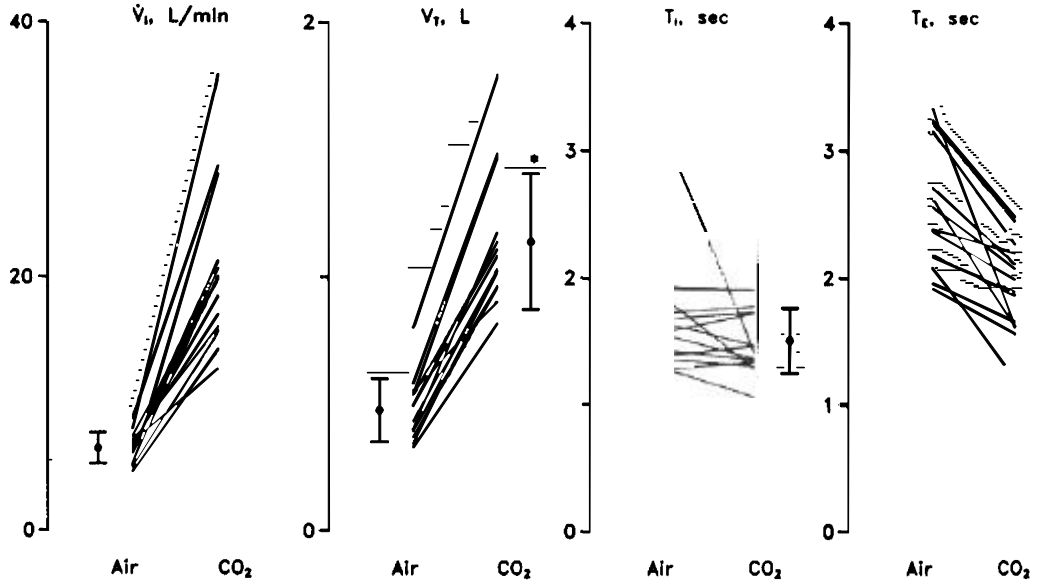

Figure 2. Minute ventilation ($\dot{V}_I$), tidal volume (V_T), inspiratory time (T_I), and expiratory time (T_E) during air and hyperoxic hypercapnia (CO_2) in 14 subjects (mean of 700 breaths for each condition in each subject). Hyperoxic hypercapnia increased $\dot{V}_I$ and V_T, and decreased T_E ($p < 0.001$ in all instances); T_I tended to decrease ($p = 0.14$). *Circles* and *bars* represent group mean ± SD.

tory response to CO_2 was linear with a high correlation coefficient (mean, 0.97 ± 0.01).

Data Analysis

Breath components in a breath series display breath-to-breath variability, which may consist of correlated, oscillatory, and random components. Autocorrelation and spectral analysis enable the determination of the relative magnitudes of these components.

Gross variability. The standard deviation, *viz.*, the square root of the variance, for each breath component was calculated in each subject during air and hyperoxic hypercapnia. To ensure that the standard deviations approximated a Gaussian distribution, they were logarithmically transformed. Then, the log-transformed data for each breath component during air were compared with those during hyperoxic hypercapnia using paired *t* tests.

Autocorrelation analysis. Autocorrelation analysis was employed to determine what fraction of variational activity is correlated on a breath-to-breath basis (*see* APPENDIX). By its ability to extract correlated activity from data obscured by random noise, autocorrelation analysis can determine if there is a strong relationship between one breath and another at some interval (or lag) away. It also determines the relative strength of "short-term memory" for each breath component, i.e., a given breath is followed by several breaths that persist in similar magnitude, as if by "memory" (19). Although memory is the term used to describe this statistical relationship, it does not necessarily signify that the consecutive serial autocorrelation coefficients have a neural origin (8, 9).

Spectral analysis. Power spectral analysis can also be used to quantitate breath-to-breath variability in a breath component (20). The power spectrum expresses the variance of a signal as a function of frequency. The presence of a significant peak (*see* APPENDIX) in the spectrum indicates that some of the variance in the data is due to a periodic oscillation with a period equal to the inverse of the frequency of the peak. The area inscribed by the peak (amount of power) reflects the degree of variability in the signal resulting from fluctuations at that frequency (19).

Although spectral analysis and autocorrelation analysis are mathematically related, periodic oscillations as detected by spectral analysis can represent physiologic mechanisms other than autoregressive behavior (4); in particular, spectral analysis can reveal low-frequency (slow) oscillations of breath components that might be missed by autocorrelation analysis; it has also been shown (4) that both types of analysis should be done in order to correctly partition the total variability of breathing without corrupting the autocorrelation coefficients.

Fractionation of variational activity. The variational activity of breathing was partitioned into autoregressive, periodic, and white noise fractions employing the approach described and validated by

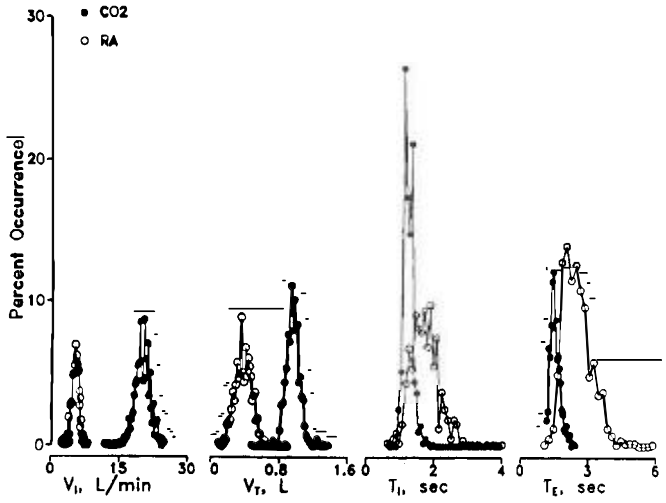

Figure 3. Frequency histogram of minute ventilation ($\dot{V}_I$), tidal volume (V_T), inspiratory time (T_I), and expiratory time (T_E) during air (*open symbols*) and hyperoxic hypercapnia (*closed symbols*) in the same subject as in Figure 1. Hyperoxic hypercapnia broadened the histogram of $\dot{V}_I$ and narrowed the histograms of T_I and T_E; it had no effect on the histogram of V_T. The standard deviation for $\dot{V}_I$ increased from 0.85 L/min during air breathing to 1.73 L/min during hyperoxic hypercapnia; respective values for V_T were 0.10 and 0.09 L; respective values for T_I were 0.43 and 0.17 s; respective values for T_E were 0.65 and 0.22 s.

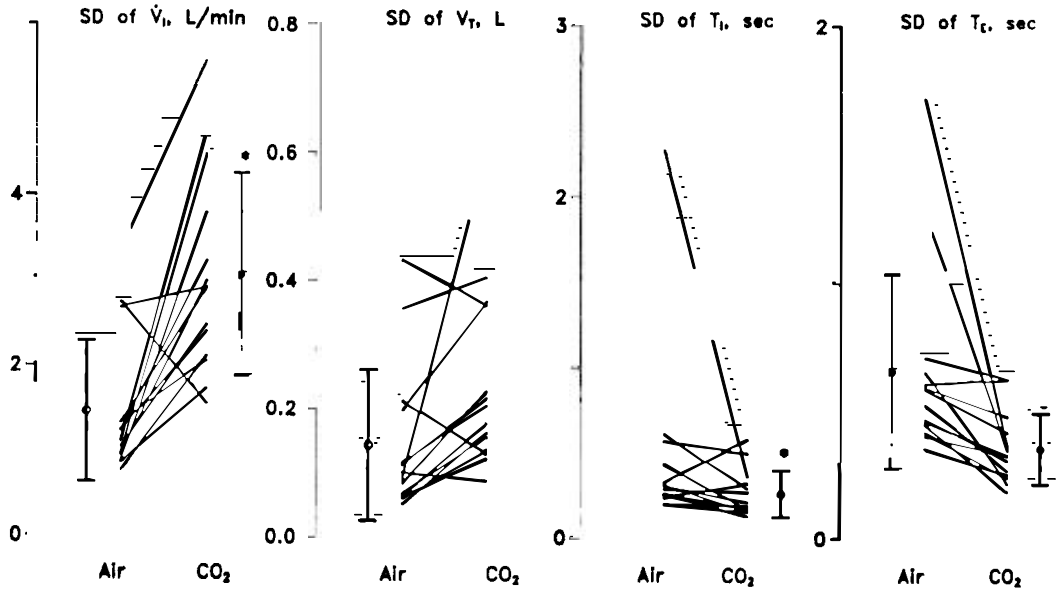

Figure 4. Standard deviations (SDs) of minute ventilation ($\dot{V}_I$), tidal volume (V_T), inspiratory time (T_I), and expiratory time (T_E) during air and hyperoxic hypercapnia (CO_2) in 14 subjects (mean of 700 breaths for each component in each subject). Hyperoxic hypercapnia increased the SDs of $\dot{V}_I$ ($p < 0.001$) and V_T ($p < 0.005$) and decreased SDs of T_I ($p < 0.025$) and T_E ($p < 0.001$). *Circles* and *bars* represent group mean ± SD.

Modarreszadeh and colleagues (4) (*see* APPENDIX). This model enables the quantification of each fraction and its contribution to the entire variational activity of breathing. Fractionation of variational activity allows the influence of hyperoxic hypercapnia on the composition of the total variational activity to be investigated.

RESULTS

Mean Change in Breathing Component

Mean values of the breath components in each subject during air and hyperoxic hypercapnia are shown in Figure 2. $\dot{V}_I$ increased from 6.47 ± 1.20 (SD) L/min during air breathing to 20.66 ± 6.33 L/min during hyperoxic hypercapnia ($p < 0.001$); the respective values for V_T were 0.47 ± 0.13 and 1.14 ± 0.27 L ($p < 0.001$); the respective values for T_I were 1.7 ± 0.4 and 1.5 ± 0.3 s ($p = 0.14$); the respective values for T_E were 2.6 ± 0.5 and 1.9 ± 0.4 ($p < 0.001$).

Gross Variability of Breath Components

Frequency histograms of $\dot{V}_I$, V_T, T_I, and T_E during air and hyperoxic hypercapnia in a representative subject are shown in Figure 3. Standard deviations of the breath components in each subject during air and hyperoxic hypercapnia are shown in Figure 4. The standard deviation of $\dot{V}_I$ for the group increased from 1.45 ± 0.83 L/min during air breathing to 3.07 ± 1.19 L/min during hyperoxic hypercapnia ($p < 0.001$); the respective values for V_T were 0.143 ± 0.118 and 0.241 ± 0.146 L ($p < 0.005$); the respective values for T_I were 0.46 ± 0.53 and 0.26 ± 0.14 ($p < 0.025$); the respective values for T_E were 0.66 ± 0.38 and 0.35 ± 0.14 ($p < 0.001$).

Nonrandom Variability Analysis

Autocorrelograms of $\dot{V}_I$ during air and hyperoxic hypercapnia in our representative subject are shown in Figure 5. Hyperoxic hypercapnia increased the autocorrelation coefficient at a lag of one breath and the number of breath lags with significant ($p < 0.01$) serial correlations. Power spectra of $\dot{V}_I$ during air and hyperoxic hypercapnia in our representative subject are shown in Figure 6. Although no oscillations were observed during air breathing, a low frequency oscillation was detected during hyperoxic hypercapnia.

Autocorrelation analysis. The autocorrelation coefficients at a lag of one breath for each breath component during air and hyperoxic hypercapnia in the 14 subjects are shown in Figure 7. The autocorrelation coefficient for $\dot{V}_I$ increased from 0.194 ± 0.163 during air breathing to 0.329 ± 0.212 during hyperoxic hypercapnia ($p < 0.05$); the respective values for V_T were 0.302 ± 0.171 and 0.342 ± 0.157 ($p = 0.41$); the respective values for T_I were 0.232 ± 0.167 and 0.278 ± 0.135 ($p =$

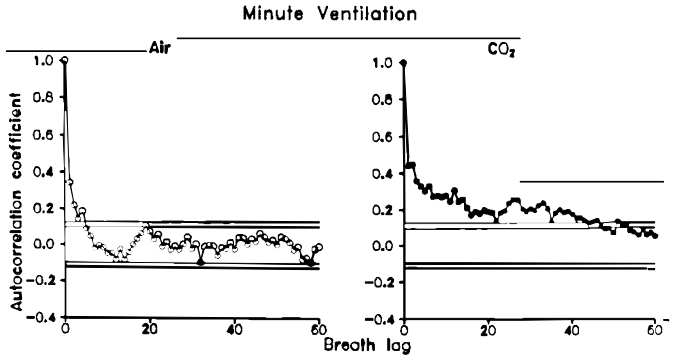

Figure 5. Autocorrelogram of minute ventilation in the same subject as in Figure 1 during air and hyperoxic hypercapnia (CO_2). The autocorrelation coefficient at a lag of one breath increased from 0.34 during air breathing to 0.44 during hyperoxic hypercapnia. The number of breath lags with significant serial correlations ($p < 0.01$) increased from four during air breathing to 49 during hyperoxic hypercapnia. On the autocorrelograms, points lying outside the inner pair of isopleths are statistically different than zero, at $p < 0.05$, and outside the outer pair of isopleths, at $p < 0.01$.

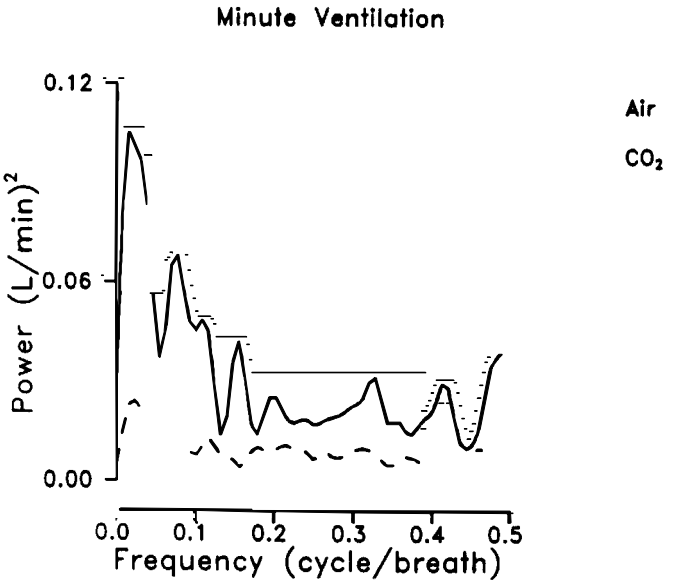

Figure 6. Power spectra of minute ventilation during air (*dashed tracing*) and hyperoxic hypercapnia (*solid tracing*) in the same subject as in Figure 1. A significant peak was not observed during air breathing, whereas one occurred at 0.02 cycle/breath during hyperoxic hypercapnia. The centroid frequency decreased from 0.11 cycle/breath for $\dot{V}_I$ during air breathing to 0.05 cycle/breath during hyperoxic hypercapnia.

0.29); the respective values for T_E were 0.286 ± 0.137 and 0.286 ± 0.144 ($p = 0.99$).

The number of consecutive breath lags having significant (non-zero, $p < 0.01$) autocorrelation coefficients for $\dot{V}_I$ increased from 2.7 ± 4.8 during air breathing to 22.5 ± 25.1 during hyperoxic hypercapnia ($p < 0.01$); the respective values for V_T were 3.2 ± 4.2 and 15.1 ± 16.3 lags ($p < 0.01$); the respective values for T_I were 3.7 ± 4.6 and 6.3 ± 6.3 lags ($p = 0.17$); the respective values for T_E were 4.1 ± 4.9 and 4.4 ± 2.7 lags ($p = 0.82$).

Spectral analysis. The centroid frequency, i.e., the mathematically weighted median frequency of the entire spectrum (0.0 to 0.5 cycle/breath), decreased from 0.16 ± 0.09 cycle/breath for $\dot{V}_I$ during air breathing to 0.11 ± 0.08 cycle/breath during hyperoxic hypercapnia ($p < 0.05$); the respective values for V_T were 0.14 ± 0.06 and 0.09 ± 0.07 cycle/breath ($p < 0.05$); the respective values for T_I were 0.17 ± 0.07 and 0.13 ± 0.05 cycle/breath ($p = 0.11$); the respective values for T_E were 0.14 ± 0.06 and 0.12 ± 0.05 cycle/breath ($p = 0.17$).

The number of subjects who displayed a significant peak, and the corresponding frequency and power of the significant oscillations for each breath component in the combined low- and high-frequency bands, are listed in Table 1. An increase in the number of subjects with significant peaks during hyperoxic hypercapnia was observed for V_T only. Hyperoxic hypercapnia caused a significant shift in the oscillations for $\dot{V}_I$ ($p = 0.03$) and V_T ($p = 0.04$) to lower frequencies, whereas it had no effect on those of T_I and T_E. Hyperoxic hypercapnia tended to decrease the power of the oscillations for T_I ($p = 0.11$) and T_E ($p = 0.09$), whereas it had no effect on the power of the oscillations for $\dot{V}_I$ and V_T.

Fractionation of variational activity of breathing. The fractions of variational activity of breathing secondary to oscillatory behavior, correlated behavior, and uncorrelated random [w(n)] behavior for each breath component during air and hyperoxic hypercapnia are listed in Table 2. During both air and hyperoxic hypercapnia, uncorrelated random [w(n)] behavior constituted > 80% of the variance of each breath component, correlated behavior represented 9 to 20%, and oscillatory behavior represented < 1%.

The effect of hyperoxic hypercapnia resulted in an increase in the total variational activity in $\dot{V}_I$ ($p < 0.01$) and a decrease in the total variational activity in T_E ($p < 0.04$). Hyperoxic hypercapnia decreased the uncorrelated random [w(n)] fraction of $\dot{V}_I$ ($p = 0.05$), and it tended to increase the correlated frac-

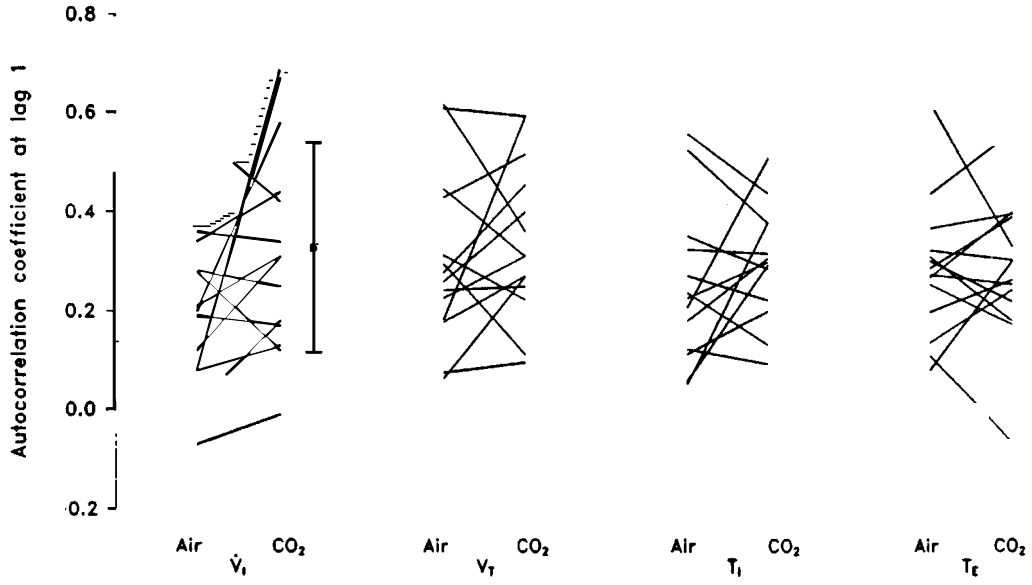

Figure 7. Autocorrelation coefficients at lag of one breath for minute ventilation ($\dot{V}_I$), tidal volume (V_T), inspiratory time (T_I), and expiratory time (T_E) during air and hyperoxic hypercapnia (CO_2) in 14 subjects. The autocorrelation coefficient for $\dot{V}_I$ increased during hyperoxic hypercapnia ($p < 0.05$), whereas those for V_T, T_I, and T_E did not change. *Circles* and *bars* represent group mean ± SD.

TABLE 1

SPECTRAL CHARACTERISTICS OF SIGNIFICANT OSCILLATIONS DURING AIR AND CO_2 BREATHING*

	Subjects Showing a Significant Peak (*n*)			Frequency (*cycles/breath*)			Power† (*absolute units*)		
				Air	CO_2	p Value	Air	CO_2	p Value
$\dot{V}_I$	8	11	0.25	0.12 ± 0.10	0.04 ± 0.06	0.03	0.22 ± 0.19	0.28 ± 0.15	0.60
V_T	5	10	0.04	0.10 ± 0.10	0.03 ± 0.02	0.04	1.04 ± 1.08	1.24 ± 1.39	0.79
T_I	7	7	1.0	0.02 ± 0.01	0.05 ± 0.07	0.30	0.003 ± 0.003	0.001 ± 0.001	0.11
T_E	7	8	0.71	0.06 ± 0.08	0.05 ± 0.07	0.78	0.011 ± 0.011	0.004 ± 0.002	0.09

* The numerical data are derived from subjects showing significant oscillations in either the low-frequency (0.0 to 0.2 cycle/breath) or high-frequency (0.2 to 0.5 cycle/breath) band. This division of the spectrum was performed because of possible nonuniform baseline power, which predisposes to overestimation and underestimation of the number of significant oscillations in the low-frequency and high-frequency bands, respectively (22).

† Units for the power of minute ventilation ($\dot{V}_I$) = L/min^2; tidal volume (V_T) = L^2; inspiratory time (T_I) = s^2; and expiratory time (T_E) = s^2.

tion of $\dot{V}_I$ ($p = 0.06$) (Table 2 and Figure 8). Hyperoxic hypercapnia produced a very small, although statistically significant increase in the oscillatory fraction for V_T ($p = 0.03$).

Ventilatory Response to Progressive Hypercapnia

CO_2 gain, quantitated as the slope of the ventilatory response to CO_2 rebreathing, was 4.29 ± 2.09 (range, 1.29 to 8.00) L/min/mm Hg in the 14 subjects. The autocorrelation coefficient at a lag of one breath for any breath component during air breathing or hyperoxic hypercapnia was not related to CO_2 gain (Table 3). The number of consecutive breath lags having significant (non-zero) autocorrelation coefficients for the breath components was not related to CO_2 gain, with the exception of a negative correlation with T_I ($r = -0.52$, $p = 0.05$) during hyperoxic hypercapnia—that is, the number of significant lags were increased in subjects with a low CO_2 gain. Likewise, the fractions of variational activity in each breath component during air and hyperoxic hypercapnia were not related to CO_2 gain (Table 4).

We were surprised by the lack of a relationship between measurements of the variational activity in breathing and CO_2 gain. We wondered if this occurrence might be due to the fact that the variational activity of breathing was assessed under steady-state conditions, whereas CO_2 rebreathing was not. Also, the CO_2 rebreathing maneuver and the steady-state measurements were not performed on the same day. Accordingly, we derived a quasi-steady-state measurement of CO_2 gain in each individual subject by taking the difference in mean $\dot{V}_I$ between air and hyperoxic hypercapnia and dividing it by the mean change in $P_{ET_{CO_2}}$ between air and hyperoxic hypercapnia. This quasi-steady-state measurement of CO_2 gain was negatively correlated with the autocorrelation coefficient at a lag of one breath for $\dot{V}_I$ during hyperoxic hypercapnia ($r = -0.52$, $p = 0.05$). None of the other measurements of variational activity of any breath component was related to this measurement of CO_2 gain.

DISCUSSION

Hyperoxic hypercapnia increased the gross variability of $\dot{V}_I$ and V_T, and decreased that of T_I and T_E. It increased the autocorrelation coefficient at a lag of one breath for $\dot{V}_I$ and the number of consecutive breath lags having sufficient autocorrelation coefficients for $\dot{V}_I$ and V_T. Hyperoxic hypercapnia increased the number of subjects displaying oscillations in V_T and it produced about a three-fold increase in the cycle time of oscillations in $\dot{V}_I$ and V_T. Fractionation revealed that at least 80% of the total variance of each breath component was due to uncorrelated random [w(n)] behavior, correlated behavior represented 9 to 20%, and oscillatory behavior constituted substantially less than 1% during both air and hyperoxic hypercapnia. Hyperoxic hypercapnia decreased the fraction of variational activity in $\dot{V}_I$ because of noise, largely by increasing its fraction of correlated behavior.

Significance of CO_2 Stimulus

In human studies, investigators have concluded that hypercapnic stimulation in the presence of hyperoxia causes central chemoreceptor stimulation with little or no contribution of the

TABLE 2

FRACTIONATION OF VARIATIONAL ACTIVITY OF BREATH COMPONENTS DURING AIR AND HYPEROXIC HYPERCAPNIA*

	Air			Hyperoxic Hypercapnia		
			Noise Fraction	Oscillatory Fraction	Correlated Fraction	Noise Fraction
$\dot{V}_I$	0.26 ± 0.41	8.59 ± 9.13	91.48 ± 8.96	0.31 ± 0.45	20.10 ± 19.14	79.65 ± 18.86†
V_T	0.03 ± 0.06	13.05 ± 12.31	87.19 ± 12.46	0.15 ± 0.20†	17.54 ± 13.23	82.51 ± 13.20
T_I	0.08 ± 0.11	9.56 ± 10.78	90.46 ± 10.98	0.13 ± 0.23	10.99 ± 7.85	88.96 ± 8.21
T_E	0.12 ± 0.19	11.13 ± 10.75	89.03 ± 10.77	0.17 ± 0.39	11.86 ± 8.51	88.15 ± 8.71

Definition of abbreviations: $\dot{V}_I$ = minute ventilation; V_T = tidal volume; T_I = inspiratory time; and T_E = expiratory time.

* Fractionation was performed on data in the low-frequency band (0.0 to 0.2 cycle/breath) since most of the power in the spectrum resided in this band.

† $p = 0.05$ for that value compared with the corresponding value during air breathing.

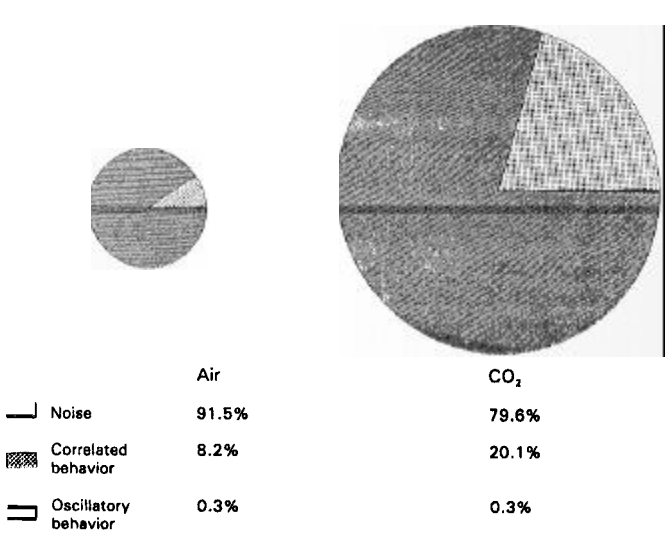

Figure 8. The fractions of variational activity in minute ventilation ($\dot{V}_I$) caused by uncorrelated random [w(n)], correlated, and oscillatory behavior during air and hyperoxic hypercapnia (CO_2) in 14 subjects. Hyperoxic hypercapnia caused a marked increase in the variance of $\dot{V}_I$, represented by an increase in the area of the pie, and it decreased the fraction of w(n) ($p = 0.05$) and tended to increase the correlated fraction ($p = 0.06$). (Note, we took minor license in altering the fractions listed in this figure so that their sum was 100%, whereas summation in Table 2 slightly exceeded 100% because of averaging.)

peripheral chemoreceptors (17, 21, 22); indeed, hyperoxic hypercapnia has been regarded as "an almost pure intracranial chemoreceptor stimulus" (17). Ledlie and colleagues (23) examined the effects of hyperoxic hypercapnia in an "open loop" system in dogs, in which respiratory motor output was prevented by paralysis from affecting ventilation and, thus, influencing the input chemical signals. They found that phrenic nerve activity and T_E responses to hypercapnia were the same whether or not the carotid sinus nerves were severed. This further supports the notion that the response to hyperoxic hypercapnia stimulation is mediated by the central chemoreceptors.

TABLE 3

RELATIONSHIP BETWEEN CO_2 GAIN AND AUTOCORRELATION COEFFICIENT AND NUMBER OF SIGNIFICANT LAGS OF BREATH COMPONENTS*

	Autocorrelation Coefficient at a Lag of One Breath		Significant Lags (*n*)	
	Air	CO_2	Air	CO_2
$\dot{V}_I$	0.04	0.08	0.33	0.22
V_T	−0.12	0.01	0.19	0.10
T_I	0.03	−0.19	−0.15	−0.52†
T_E	−0.12	−0.09	−0.35	−0.02

For definition of abbreviations, *see* Table 2.

* The numeric entries in the table represent the correlation coefficients (r) obtained from a linear regression analysis between CO_2 gain and autocorrelation coefficients and number of significant lags.

† $p < 0.05$.

TABLE 4

RELATIONSHIP BETWEEN CO_2 GAIN AND FRACTIONATION OF VARIATIONAL ACTIVITY OF BREATH COMPONENTS DURING AIR AND CO_2 BREATHING

	Air			CO_2		
	Oscillatory Fraction	Correlated Fraction	Noise Fraction	Oscillatory Fraction	Correlated Fraction	Noise Fraction
$\dot{V}_I$	0.06	0.10	−0.09	0.07	0.09	−0.10
V_T	−0.24	−0.04	0.05	−0.18	0.01	−0.01
T_I	−0.11	0.06	−0.05	0.15	−0.32	0.31
T_E	−0.21	−0.27	0.28	0.45	−0.17	0.13

For definition of abbreviations, *see* Table 2.

* The numeric entries in the table represent the correlation coefficients (r) obtained from a linear regression analysis between CO_2 gain and oscillatory, correlated, and noise fractions.

Effect of Hypercapnia on Mean Change and Gross Variability of Breathing

CO_2 produced increases in $\dot{V}_I$ and V_T, a decrease in T_E, and no change in T_I. Other investigators (24) have reported findings qualitatively similar to ours, although they used instrumentation requiring the use of a mouthpiece and noseclips—factors that produce marked alterations in the pattern of breathing (18).

In a study that focused primarily on the interrelationships between V_T, T_I, and T_E during air breathing, Newsom-Davis and Stagg (5) studied six healthy subjects who inhaled mixtures of 1.5 and 3% CO_2 in air. Unfortunately, these investigators provided few details on this aspect of their investigation, except to state that the coefficients of variation of V_T, T_I, and T_E tended to decrease in one subject, although numerical values were not given (*see* Figure 5 of their report). However, coefficients of variation are influenced by a change in the mean value (as occurs with CO_2) and thus imperfectly reflect the true variability of breath components. We quantitated gross variability in terms of standard deviations, which increased for the volume components and decreased for the time components during hyperoxic hypercapnia (Figure 4). The increase in gross variability of $\dot{V}_I$ with hyperoxic hypercapnia was also supported by inspection of the frequency histogram plots, which exhibited a broader dispersion of values with hyperoxic hypercapnia in 13 of the 14 study subjects. Moreover, the absolute variance of $\dot{V}_I$ because of correlated behavior increased from 0.20 L/min during air breathing to 1.57 L/min during hyperoxic hypercapnia ($p < 0.03$), and the absolute variance of $\dot{V}_I$ because of random behavior increased from 2.52 L/min during air breathing to 7.92 L/min during hyperoxic hypercapnia ($p < 0.009$). We are not aware of other systematic studies of gross variability of breath components in awake human subjects during steady-state hypercapnic stimulation with which to compare our results.

Interrelationships between Breath Components

The nonrandom fraction of breathing variability was first examined by Priban (6). Using the analysis of "run lengths" as a measure of randomness of data, Priban found that the average run length was 1.79 breaths compared with a value of 1.50 breaths per run that is expected for a random series. In four rebreathing experiments, he reported that CO_2-induced hyperpnea (level of P_{CO_2} or $\dot{V}_I$ not stated) did not alter the number of breaths per run. A similar experimental approach was employed by Bolton and Marsh (25) in three healthy men. They also reported that hyperoxic hypercapnia (magnitude

not stated) did not alter the run length. These results suggest that hypercapnia does not influence the overall variability of breathing; however, the investigators did not attempt to determine if correlated or oscillatory behavior was altered by CO_2.

Khatib and colleagues (11) fitted a first-order autoregressive model to consecutive values of V_T in anesthetized, vagotomized spontaneously breathing rats. While breathing air, five of seven rats had negative autoregressive coefficients, signifying that when V_T of a given breath had a value above the mean, the value of the next breath was likely to be below the mean. In contrast, none of our subjects—nor in our previous study of 33 subjects (8)—had negative autocorrelation coefficients for V_T while breathing air. When the rats breathed 4% CO_2 in O_2, however, three of three had positive autoregressive coefficients with an estimated average of $\sim$ 0.29 (extrapolated from Figure 3) (11). We also found a positive autocorrelation coefficient at a lag of one breath for V_T in all subjects during hyperoxic hypercapnia with an average autocorrelation coefficient of 0.34—comparable to that of Khatib and colleagues (11).

Hyperoxic hypercapnia increased the strength of the relationship of $\dot{V}_I$ in immediately adjoining breaths, and it also increased the number of breath lags having significant autocorrelation coefficients for $\dot{V}_I$ and V_T. Of interest, this conditioning influence was confined to the volume components, which is consistent with the predominant effect of hypercapnia on the mean values (Figure 2). The mechanism underlying the dependence of breath components on the characteristics of the preceding respiratory cycle is not known. We (8) and others (26) have speculated that it might be related to afterdischarge (facilitatory memory), that is, the augmentation of ventilatory output that persists after cessation of a primary stimulus (9). Indirect evidence suggests that the level of preceding hyperpnea contributes to the manifestation and magnitude of ventilatory afterdischarge (1, 27). Thus, the considerable hyperpnea in our subjects—a greater than threefold increase in $\dot{V}_I$—might have enhanced afterdischarge and so contributed to the increase in correlated variational activity. Afterdischarge is extremely sensitive to the prevailing level of P_{CO_2}, and even a slight decrease in P_{CO_2}, accompanying the increase in $\dot{V}_I$, greatly attenuates the magnitude and duration of afterdischarge (28). Conversely, Engwall and colleagues (29) showed in awake goats that quite mild hypercapnia ($\sim$ 2 mm Hg increase in arterial P_{CO_2}) substantially enhanced the magnitude of afterdischarge and prolonged its duration 2.4-fold. The investigators attributed the enhancement of afterdischarge to central CO_2 chemical drive rather than to the level of ventilation.

Another contributor to the stronger relationship between volume components of neighboring breaths during hyperoxic hypercapnia may be the blunting of the peripheral chemoreceptors (17). The fast response time of the peripheral chemoreceptors makes them especially important in achieving rapid adjustments around the mean level of ventilation from one breath to the next. Blunting their activity with hyperoxia could have reduced this fine-adjustment mechanism, causing deviations to return more slowly to the mean level, with consequent increase in correlated behavior.

Employing the same mathematical techniques, we recently examined the effect of increasing inspiratory elastic loads on variational activity of breathing in healthy subjects (30). Loading decreased the total variational activity of V_T and T_E without altering the correlated behavior. The differing responses suggest that the alteration in variational activity of breathing is specific to the nature of the stimulus, probably reflecting behavioral (cortical) influences on the respiratory controller during elastic loading, and automatic (subcortical) influences during hypercapnia.

Oscillatory Behavior

Hyperoxic hypercapnia increased the number of subjects displaying significant ventilatory oscillations and altered their cycle time (Table 1). The development of ventilatory oscillations is thought to result from unstable dynamics in chemical feedback of the respiratory control system (2). In a mathematical model, Khoo and colleagues (12) demonstrated that an increase in loop gain of the respiratory control system resulted in oscillatory behavior. Hypercapnia is considered to decrease loop gain and it eliminates the periodic breathing induced by hypoxia (12, 13). However, the action of CO_2 as a stabilizing influence has generally been demonstrated in a system rendered unstable through use of hypoxia, whereas we compared hyperoxic hypercapnia with a stable state, *viz.*, normal resting breathing. Another factor that can lead to ventilatory oscillations is increased circulation time; however, this is an unlikely source of the oscillations with hypercapnia since the latter increases cardiac output (12). Decreased dampening of the respiratory system secondary to a decrease in lung volume can also cause oscillations (9), but this is a less likely mechanism since hypercapnia does not consistently decrease functional residual capacity.

The most striking action of hyperoxic hypercapnia on the oscillatory behavior of breathing was the threefold reduction in the frequency of significant oscillations in $\dot{V}_I$ and V_T. For $\dot{V}_I$, the frequency of oscillations decreased from 0.12 cycle/breath during air breathing to 0.04 cycle/breath during hyperoxic hypercapnia; this signifies an increase in the number of breaths per cycle from eight during air breathing to 25 during hyperoxic hypercapnia—alternatively, this can be considered in terms of an increase in cycle time from $\sim$ 28 to 88 s (assuming an average breath duration of 3.5 s) (7). This prolongation of cycle time during hyperoxic hypercapnia is compatible with the slower response of the central chemoreceptors compared with the peripheral chemoreceptors (14). Swanson and Bellville (31) quantitated the response time to step changes in $P_{ET_{CO_2}}$ while keeping end-tidal O_2 concentration constant. The average time constant of the slow component, considered to reflect central chemoreceptor activity, was 75 s. This response time is compatible with the cycle length of the low-frequency oscillations during hyperoxic hypercapnia in our subjects, suggesting that activation of the central chemoreceptors plays an important role in their development. Employing a system to buffer breath-to-breath variations in $P_{ET_{CO_2}}$, Modarreszadeh and Bruce (32) achieved a marked reduction in spontaneous variability in $\dot{V}_I$ in healthy subjects. Although the experimental conditions in their study were necessarily constrained compared with the free breathing permitted in our subjects, the results of the two studies complement each other. Modarreszadeh and Bruce (32) found that a decrease in spontaneous fluctuations of P_{CO_2} had its greatest effect on the low-frequency band of the power spectrum for $\dot{V}_I$, and we found that an increase in mean P_{CO_2} also had its predominant influence on the low-frequency band of the spectra for $\dot{V}_I$ and V_T (Figures 6 and 8 and Table 1).

Activation of the peripheral chemoreceptors are considered to play an important role in the development of ventilatory oscillations (2, 12, 13). In awake ponies, however, Brown and colleagues (33) observed ventilatory oscillations when the carotid bodies were denervated, indicating that the peripheral chemoreceptors are not essential for the development of oscillatory behavior. In elderly subjects displaying ventilatory oscillations during sleep, Pack and colleagues (34) observed vir-

tual synchrony of electroencephalographic and $\dot{V}_I$ time series on cross-correlation analysis. This result led them to conclude that the ventilatory oscillations were due to changes occurring in the state-dependent input to the respiratory control system at sleep onset, rather than resulting from instability in the peripheral chemoreceptors. In addition to chemical feedback loops, nonchemical factors almost certainly contribute to the variational activity in breathing (32). Multiple central pattern generators are believed to exist in the neuronal networks of the brainstem (35), which generate a coordinated output to different groups of respiratory motor neurons resulting in multiple breathing patterns (33). It is conceivable that hyperoxic hypercapnia may have a direct effect, or an indirect effect via release of neurotransmitters, on the central pattern generators resulting in altered oscillatory behavior of the type observed in our subjects.

Ventilatory Response to Hypercapnia (CO_2 Gain)

Virtually none of the fractions of the variational activity in breathing was related to CO_2 gain (Tables 3 and 4). This may be partly due to limitations of the technique for measuring CO_2 gain since the ventilatory response to CO_2 has limited reproducibility. We sought to minimize this factor by selecting responses that showed a high correlation between $\dot{V}_I$ and P_{CO_2}, and taking the average of three measurements. Another reason for the lack of a relationship between the fractions of variational activity and CO_2 gain might be the relatively small range of measured CO_2 gains; however, the observed fourfold increase in CO_2 gain makes this a less likely possibility. In addition to this technical consideration, the lack of a significant relationship between the variability fractions and CO_2 gain suggest that primary neuronal processes rather than direct chemoreceptor activity might be responsible for the observed changes in variational activity of breathing.

The lack of a significant relationship between variational activity in breathing and CO_2 gain might also be related to the fact that the measurements were obtained on separate days. To overcome this problem, we examined the relationship between the various components of variational activity and a measure of quasi-steady-state CO_2 gain, based on the ratio of change in $\dot{V}_I$ between breathing air and hyperoxic hypercapnia to the change in $P_{ET_{CO_2}}$ between air and hyperoxic hypercapnia. A negative correlation was observed between the autocorrelation coefficient at a lag of one breath for $\dot{V}_I$ during hyperoxic hypercapnia and this measurement of CO_2 gain ($r = -0.52$, $p = 0.05$). That is, subjects with a high CO_2 gain exhibited a weak correlation between values of $\dot{V}_I$ in immediately adjoining breaths during hyperoxic hypercapnia. This negative correlation suggests that the higher the CO_2 gain, the more random or "noisy" the breath-to-breath variability in $\dot{V}_I$ during hyperoxic hypercapnia.

In summary, hyperoxic hypercapnia produced an increase in the gross variational activity of $\dot{V}_I$ and V_T and a reduction in that of T_I and T_E. Greater than 80% of the variational activity for each breath component consisted of uncorrelated random fluctuations (white noise), correlated behavior represented 9 to 20%, and oscillatory behavior represented much less than 1% of the variational activity during both air and hyperoxic hypercapnia. Hyperoxic hypercapnia increased the relationship of $\dot{V}_I$ in immediately adjoining breaths, and it increased the number of consecutive significant autocorrelation coefficients (i.e., short-term memory) of $\dot{V}_I$ and V_T. Hyperoxic hypercapnia induced low-frequency oscillations in $\dot{V}_I$ and V_T. Virtually none of the fractions of variational activity in breathing correlated with CO_2 gain, although the autocorrelation coefficient at a lag of one breath for $\dot{V}_I$ during hyperoxic hypercapnia was negatively correlated with a quasi-steady-state measure of CO_2 gain. In conclusion, although the increase in variability of volume components with hyperoxic hypercapnia was predominantly due to uncorrelated random fluctuations, a significant portion resulted from increased correlated behavior accompanied by the development of low-frequency oscillations with a cycle time consistent with central chemoreceptor activation.

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APPENDIX

Mathematical Methods

Stationary. Time-series analysis such as autocorrelation requires stationary data, i.e., the statistical properties of the breath series should be time-invariant. To ensure data stationarity, 700 consecutive breaths during air and hyperoxic hypercapnia in which the values of $\dot{V}_I$, V_T, T_I, and T_E did not display large deviations from the mean on visual inspection were chosen for data analysis. Because a small number of outliers can substantially affect a correlogram (19), we employed the clamping technique described by Pack and colleagues (20). Data points that were more than 2 SD above or below the mean value were identified and replaced by values that were equal to the mean plus 2 SD or the mean minus 2 SD, respectively. Next, polynomial equations of increasing order were employed to detrend the chosen data strings. The polynomial equation, with the breath number as the independent variable and the corresponding breath component as dependent variable, that best fitted the clamped data was found by multiple regression (8, 19). This entails calculation of the residual sum of squares as each successive term was added, then calculating the F-value as follows:

$$F = [(RSS_n - RSS_{n+1})/(P_{n+1} - P_n)]/[RSS_{n+1}/(N - P_{n+1})]$$

where RSS is the residual sum of squares, subscript n refers to the lower order polynomial, subscript n + 1 is the next higher order polynomial, P is the number of adjustable parameters (order of polynomial plus 1 for intercept), and N is the number of points in the data string. The F-value was calculated for successive orders of polynomials, and the highest order with a significant F-value signified the polynomial that yielded the best fit to the data string. The order of the polynomials were similar for air and hyperoxic hypercapnia for all breath components. The data were detrended by subtracting the polynomial fit from the breath series on a breath-by-breath basis. Autocorrelation analysis was then performed on the detrended data.

Autocorrelation analysis. Autocorrelation analysis was performed to calculate the fraction of variational activity that is correlated among serial breaths, as opposed to random, uncorrelated fluctuations (white noise) in breathing (8, 19). Autocorrelation coefficients at a lag of one breath for $\dot{V}_I$, V_T, T_I, and T_E were calculated for each data string. The relative strength of short-term memory of each breath component was computed as the number of consecutive lags, starting at a lag of one breath, that displayed autocorrelation coefficients that were statistically different from zero at $p < 0.01$. Thus, memory extended to the point at which the autocorrelation coefficient first lost statistical significance at the $p < 0.01$ level.

We rigorously investigated the adequacy of this detrending procedure in achieving stationarity. The data strings of 640 breaths during air and hyperoxic hypercapnia were each divided into two segments: an "early" segment consisting of breaths 0 to 320, and a "late" segment consisting of breaths 321 to 640. Then, polynomial equations of increasing order were fitted to each segment of the clamped data. The data were detrended by subtracting the polynomial fit from the breath series on a breath-by-breath basis. Next, the autocorrelation coefficients and the number of lags with significant serial correlations during air breathing for each breath component were calculated for the early and late segments; a similar analysis was performed on the data obtained during hyperoxic hypercapnia. the autocorrelation coefficients at a lag of one breath for $\dot{V}_I$, V_T, T_I, and T_E were equivalent in the early and late segments during both air breathing ($p > 0.49$ in all instances) and hyperoxic hypercapnia ($p > 0.22$ in all instances). Likewise, the number of breath lags displaying significant correlations for $\dot{V}_I$, V_T, T_I, and T_E were not different between the early and late segments during either air breathing ($p > 0.21$ in all instances) or hyperoxic hypercapnia ($p > 0.20$ in all instances).

The distribution of sample values of a correlation coefficient (r) is restricted to r values between −1.0 and +1.0, and is, in general, asymmetrical (i.e., not Gaussian); thus, a Fisher's z transformation was performed on each r value. After each r value was transformed to a function z, standard parametric statistics were performed. Specifically, the autocorrelation coefficients and number of lags with significant serial correlations for breath components during air breathing were compared with those during hyperoxic hypercapnia using Fisher's z transformation with paired *t* tests.

Spectral analysis. Power spectra of the data strings during air and hyperoxic hypercapnia were obtained using a fast Fourier transform (FFT) algorithm to detect significant oscillations and to quantify their magnitude. After removing any linear trend, the data were multiplied by a cosine-tapered rectangular (Hanning) window, and a FFT was applied to obtain the power spectrum. Spectral analysis was performed on 640 consecutive breaths, subdivided into 10 segments of 64 breaths each; final spectral estimates were calculated by averaging the

spectra of the 10 subsegments (4). Each power spectrum was first characterized by calculation of the centroid frequency, which is the mathematically weighted median frequency of the spectrum. To allow for the possibility of nonuniform baseline power, we divided the spectrum into a low-frequency (0.0 to 0.2 cycle/breath) and high-frequency band (0.2 to 0.5 cycle/breath); otherwise, the number of significant oscillations in the low-frequency band are likely to be overestimated, whereas the number of significant oscillations in the high-frequency band are likely to be underestimated (4). Significant peaks were detected in each of the frequency bands by comparing the power at each frequency with the mean power in that band. Peaks were considered significant when at least two consecutive data points lay above the 95% confidence interval of each spectral estimate (15). The presence of a significant peak in the power spectrum indicates that part of the variance in the data is due to an oscillation with a period equal to the inverse of the frequency of the peak. The area inscribed by the peak (amount of power) reflects the degree of variability in the signal resulting from oscillations at that frequency. Differences in centroid frequencies, number of significant peaks, frequencies of significant peaks, and the power of significant peaks were compared during air and hyperoxic hypercapnia by paired *t* tests.

Fractionation of variational activity. The total variational activity of the data was modeled as a mixture of autoregressive variations using a first-order autoregressive model (AR1), oscilatory variations, and uncorrelated white noise [w(n)] using the technique described by Modarreszadeh and colleagues (4):

$$x(n) = a_1 x(n-1) + \sum_{j}^{\rho} [b_{j1}\sin(2\pi f_j n) + b_{j2}\cos(2\pi f_j n)] + w(n)$$

where x = ventilatory variable, n = breath number, a_1 = autoregressive coefficient, ρ = the maximal number of significant peaks, f_j = frequency of significant peaks, and b_{j1} and b_{j2} = amplitudes of the sinusoids. The expression within the brackets is the contribution of each discrete oscillation, having a frequency of f_j, to the variance of the data. The coefficients a_1, b_{j1}, and b_{j2} were calculated by the least-squares method. The variance secondary to autoregressive components and w(n), i.e., σ^2_{AR}, was calculated using the standard error of the estimate (SEE): $(SEE)^2/1 - a_1^2$; the variance caused by w(n) was calculated as $(SEE)^2$, whereas the variance caused by the autoregressive fraction was calculated as $\sigma^2_{AR} - (SEE)^2$. If the a_1 coefficient of the data string for a breath component in a subject was statistically different from zero, a second-order autoregressive model (AR2) was then fitted to the data and the entire fractionating process was repeated (19). For the AR2 model, the variance secondary to the autoregressive fraction and w(n), i.e., σ^2_{AR2}, was calculated as:

$$\sigma^2_{AR2} = (SEE)^2(1-a_2)/(1+a_2)*(1+a_1-a_2)*(1-a_1-a_2)$$

The variance secondary to the oscillatory fraction (σ^2_{osc}) was calculated as: $0.5[b_{j1}^2 + b_{j2}^2]$. Some caution is needed in interpreting the separation of the nonrandom fractions into correlated and oscillatory behavior. The autoregressive coefficients are the characteristic features of the time domain transformed into the z domain. The Fourier coefficients are the characteristic features of the time domain transformed into the frequency domain. The z domain and frequency domain are closely related to each other. Although the partitioning between the two fractions has implications for inferring different mechanisms, it could result from the differences in statistical efficiency of the two fractions. Analysis of variance (ANOVA) was used to compare the fractions of the total variability caused by correlated, oscillatory, and uncorrelated random behavior in each subject during air and hyperoxic hypercapnia. If ANOVA was statistically significant, then a Newman-Keuls test, with appropriate correction for multiple comparisons, was performed to determine which of the fractions of the variational activity of breathing was different during air and hyperoxic hypercapnia.