Effects of hypercapnia and hypocapnia on ventilatory variability and the chaotic dynamics of ventilatory flow in humans

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Fiamma M-N, Straus C, Thibault S, Wysocki M, Baconnier P, Similowski T. Effects of hypercapnia and hypocapnia on ventilatory variability and the chaotic dynamics of ventilatory flow in humans. Am J Physiol Regul Integr Comp Physiol 292: R1985–R1993, 2007. First published January 11, 2007; doi:10.1152/ajpregu.00792.2006.—In humans, lung ventilation exhibits breath-to-breath variability and dynamics that are nonlinear, complex, sensitive to initial conditions, unpredictable in the long-term, and chaotic. Hypercapnia, as produced by the inhalation of a CO2-enriched gas mixture, stimulates ventilation. Hypocapnia, as produced by mechanical hyperventilation, depresses ventilation in animals and in humans during sleep, but it does not induce apnea in awake humans. This emphasizes the suprapontine influences on ventilatory control. How cortical and subcortical commands interfere thus depend on the prevailing CO2 levels. However, CO2 also influences the variability and complexity of ventilation. This study was designed to describe how this occurs and to test the hypothesis that CO2 chemoreceptors are important determinants of ventilatory dynamics. Spontaneous ventilatory flow was recorded in eight healthy subjects. Breath-by-breath variability was studied through the coefficient of variation of several ventilatory variables. Chaos was assessed with the noise titration method (noise limit) and characterized with numerical indexes [largest Lyapunov exponent (LLE), sensitivity to initial conditions; Kolmogorov-Sinai entropy (KSE), unpredictability; and correlation dimension (CD), irregularity]. In all subjects, under all conditions, a positive noise limit confirmed chaos. Hypercapnia reduced breathing variability, increased LLE (P = 0.0338 vs. normocapnia; P = 0.0018 vs. hypocapnia), increased KSE, and slightly reduced CD. Hypocapnia increased variability, decreased LLE and KSE, and reduced CD. These results suggest that chemoreceptors exert a strong influence on ventilatory variability and complexity. However, complexity persists in the quasi-absence of automatic drive. Ventilatory variability and complexity could be determined by the interaction between the respiratory central pattern generator and suprapontine structures.

IN MAMMALS, GAS EXCHANGE THROUGH the lungs depends on their ventilation, which is produced by the translation of phasic neuronal activities governing upper airway and rib cage muscles into rib cage movements. The corresponding ventilatory flow signal, which can easily be measured at the airway opening by use of a pneumotachograph, therefore contains information about the activity of the neuronal oscillators that produce ventilation. These oscillators are located in the brain stem. In addition to generating the respiratory rhythm, they continuously adapt ventilation to metabolic bodily needs through the integration of afferent information. Suprapontine structures can modify ventilation independently from metabolic requirements. In humans, this possibility seems particularly well developed. It is underpinned by motor (12, 22, 23, 59) and premotor cortex representations (32, 48, 57) and has a major importance during phonation. Ventilation is thus determined by the reciprocal modulation of several types of commands (34, 64). Unsurprisingly therefore, the corresponding ventilatory flow is not periodic (38) but exhibits complexity, with this term implying irregularity, sensitivity to initial conditions, and unpredictability. In animals and in humans, ventilatory complexity has been characterized by various mathematical approaches popular in this field [correlation dimension (CD), approximate entropy (ApEn), Lyapunov exponents, etc.], used alone or in combination (Table 1). Beyond the notion of complexity, nonlinear determinism in ventilatory signals has been inferred through statistical comparison with randomly generated “surrogate” data (Table 1). Finally, use of the noise titration technique has demonstrated the chaotic nature of ventilatory flow in awake humans (20, 72). This technique is a robust way to detect and quantify chaos in short and noisy time series (45) through the computation of the quantity of white noise that must be added to a time series for it to be better fitted by a linear than by a nonlinear model [chaos is present if this “noise limit” (NL) has a positive value]. The determinants of ventilatory complexity are not precisely known. Keeping in mind the possible influence of the anisotropic mechanical behavior of the lung (3), these determinants are probably central in nature. Isolated in vitro, the pre-Bötzinger complex can produce chaos-like activity (15). More importantly, the production of ventilation is presently assigned to coupled oscillators [the pre-Bötzinger complex and the parafacial group (18)], which constitute a potential source of chaos (33). Ventilatory complexity can also stem from the modulation of oscillator activity by external influences. Indeed, in animals, vagotomy eliminates ventilatory complexity (55). In humans, slow-wave sleep is associated with lower respiratory complexity (7–9, 53, 61). Conversely, some indexes of ventilatory complexity are increased in patients with panic-anxiety disorders (74). For the present analysis, we will consider that the ventilatory complexity is of a chaotic nature when the noise titration technique yields a positive NL (see METHODS), and we will assess complexity quantita-
In the cardiovascular domain, baroreceptor denervation in dogs increases the variability of blood pressure but decreases its complexity and lessens its sensitivity to initial conditions (70). From the above, we designed the present study to test, in humans, the hypothesis that stimulating CO₂ chemoreceptors would reduce ventilatory variability but increase ventilatory complexity and, conversely, that deafferenting these receptors through hypocapnia would produce opposite effects.

**METHODS**

**Subjects**

Eight healthy subjects (7 men, 1 woman, age 24–26 yr) participated in the study after legal and ethical clearance (Comité de Protection des Personnes Pitie-Salpêtrière, Paris, France). The subjects were informed of the study procedures, its objectives, and the methods used and gave written consent to participate. None of the subjects had previously participated in respiratory physiology experiments. None of them presented known cardiac, respiratory, or neuromuscular disorders. They had been instructed to refrain from using any psychotropic substances of any nature during the week preceding the study and to avoid sleep deprivation.

**Measurements**

Ventilatory flows at rest and during hypocapnia were recorded with a heated low dead-space pneumotachograph linear from 0 to 160 l/min (3700A series; Hans Rudolf, Kansas City, MO; dead space 14 ml, flow resistance 0.02–0.04 cmH₂O l⁻¹ s⁻¹), connected to a ±2 cmH₂O linear differential pressure transducer (DP-45-18; Validyne, Northridge, CA). During hypercapnia, a low-resistance pneumotachograph linear from 0 to 1,000 l/min (MLT 1000L; AD Instruments, Castle Hill, Australia; dead space 350 ml, flow resistance 0.002 cmH₂O l⁻¹ s⁻¹) was used. End-tidal PCO₂ (PETCO₂) results were measured at the mouthpiece with an infrared CO₂ gas analyzer (ML 205; AD Instruments).

The PETCO₂ signals were digitized at a 40-Hz sampling rate (MacLab/16; AD Instruments) and recorded on the hard disk of a Power Macintosh G4 computer (Apple, Cupertino, CA) in the form of data files for subsequent analysis (Chart version 4; AD Instruments). The digitized files were then downsampled at 5 Hz (Dataplore software package; Datam, Telford, Germany) by retaining every one in eight points of the flow signal sampled at 40 Hz. This frequency has previously been shown to yield the best results for the detection of chaos using noise titration of ventilatory flow (72). Of note, in the present study as in our previous one on ventilatory chaos (72), the frequency content of the signal and hence was not likely to induce aliasing (see Frequency Content of the Signal in RESULTS).

**Procedures**

During the study, the subjects were comfortably seated. They wore a nose clip and breathed through a mouthpiece that permitted connection to a pneumotachograph or a mechanical ventilator depending on the study stage. They were asked to keep their eyes open to avoid falling asleep and to not stare at a fixed point. If they so desired, the subjects could listen through earphones to music of their choice, falling asleep and to not stare at a fixed point. If they so desired, the subjects could listen through earphones to music of their choice.

**Resting ventilation**. Normocapnic resting ventilation was recorded during both sessions, but only the first recording was retained for

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**Table 1. Methods used for nonlinear analysis and evaluation of complexity in studies of ventilation**

<table>
<thead>
<tr>
<th>Study</th>
<th>Nonlinear Analysis Tool</th>
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<tbody>
<tr>
<td>Sammon and Bruce (55)</td>
<td>CD</td>
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<tr>
<td>Donaldson (16)</td>
<td>LLE</td>
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<tr>
<td>Pilgram et al. (41)</td>
<td>CD</td>
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<tr>
<td>Patzak et al. (39)</td>
<td>CD</td>
</tr>
<tr>
<td>Small et al. (61)</td>
<td>CD Surrogate data</td>
</tr>
<tr>
<td>Burio et al. (7)</td>
<td>CD Surrogate data</td>
</tr>
<tr>
<td>Sako et al. (53)</td>
<td>CD Surrogate data</td>
</tr>
<tr>
<td>El Khatib et al. (17)</td>
<td>CD Kolmogorov-Sinai Entropy</td>
</tr>
<tr>
<td>Burio et al. (9)</td>
<td>ApEn CD Surrogate data</td>
</tr>
<tr>
<td>BuSha and Stella (10)</td>
<td>ApEn Surrogate data</td>
</tr>
<tr>
<td>Yeragani et al. (74)</td>
<td>ApEn LLE</td>
</tr>
<tr>
<td>Suyama et al. (65)</td>
<td>CD Surrogate data</td>
</tr>
<tr>
<td>Burio et al. (8)</td>
<td>ApEn Surrogate data</td>
</tr>
<tr>
<td>Thibault et al. (68)</td>
<td>LLE</td>
</tr>
<tr>
<td>Miyata et al. (36)</td>
<td>CD Surrogate data</td>
</tr>
<tr>
<td>Wysocki et al. (72)</td>
<td>Noise titration LLE CD</td>
</tr>
</tbody>
</table>

Numbers in parentheses is the reference number. CD, correlation dimension; LLE, largest Lyapunov exponent; ApEn, approximate entropy.
statistical analysis (with the exception of one subject who reported “having thought about breathing” during this session). To ensure steady state, the subjects were allowed 15 min to adapt to test conditions before the ventilatory flow signal was actually recorded.

**Hypocapnic ventilation.** Hypocapnia was induced with semi-passive hyperventilation using a mechanical ventilator (Siemens, Servo 900 C) in pressure-controlled mode, until a PETCO₂ of 15 Torr was reached. The subjects were requested to report any untoward sensation (e.g., dizziness, paresthesia) that resulted in the immediate stoppage of hyperventilation. When PETCO₂ had reached 15 Torr, the subjects were disconnected from the ventilator and their spontaneous ventilation was recorded until PETCO₂ was back to 25 Torr.

**Hypercapnic ventilation.** The subjects breathed a hypercapnic (7% CO₂)-hyperoxic (93% O₂) gas mixture through a one-way valve (2700 large type, Hans Rudolph), permitting separation of inspiratory and expiratory routes. Recordings were started after a 15-min equilibration period.

**Analysis**

**Frequency content.** For each recording, the frequency content of the signal was described with a 1,024 points fast-Fourier transform function (Hamming window, no overlap, zero values removed).

**Breath-by-breath analysis of ventilation.** A set of macro commands developed with AD Instrument’s Chart4.2 and Microsoft’s Excel permitted the calculation, for each ventilatory cycle, of VT, total cycle time (TTOT), TI, TE, mean inspiratory flow (VT/TI), duty cycle (TI/TTOT), and instantaneous ventilation (V̇I). The breath-by-breath variability of ventilation was expressed in terms of the coefficient of variation of these indexes (SD to mean ratio).

**Assessment of chaos with noise titration.** This was performed as previously described (72) and according to the principles set out by Poon and Barahona (45). A schematic description of the process is shown in Fig. 1. In brief, noise titration begins with an identification process capable of a robust and highly sensitive detection of deterministic dynamics within short and noisy time series. Several Volterra-Wiener-Korenberg series are generated, with different degrees of nonlinearity (d) and embedding dimension kappa (K), to produce a family of linear and nonlinear polynomial autoregressive models. The best linear model is obtained by adjusting the K value with d = 1 to minimize the Akaike information theoretic criterion, a measure of the goodness of fit of an estimated statistical model that relies on the concept of entropy (2). The best nonlinear model is obtained by sequentially increasing K values with d > 1. Both models are then compared, and the null hypothesis (linearity) is tested against the alternate hypothesis (nonlinearity) using parametric (F test) and nonparametric (Mann-Whitney U-test) statistics (4). If the null hypothesis is rejected, the titration process itself can be started. White noise of incrementally increasing SD is added to the time series until the null hypothesis can no longer be rejected. This defines an NL, which when above 0, indicates chaos and provides an estimate of its intensity. After downsampling the ventilatory flow data at 5 Hz, we performed the noise titration using a specific routine developed with Matlab version 6.5 R13 (MathWorks, Natick, MA), according to a trial-and-error process, including the testing of K values of 4–6 and of d of 3–5 [these ranges have been identified in a previous study (72) as having the best aptitude at detecting positive NLs]. The nine combinations of K values and d values were tested on each of the ventilatory flow recordings performed during normocapnia, hypocapnia, and hypercapnia (216 tests).

**Determination of nonlinear descriptors of predictability, complexity, and sensitivity to initial conditions.** A detailed description of the methods used appears in the Appendix of Ref. 72.

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**Fig. 1.** Schematic representation of the noise titration method. The noise titration process can be compared to a chemical titration in which the concentration of an acid (chaos) in a solution (the time series) is determined from the quantity of added base (noise) that is necessary to neutralize the solution. [Reprinted Wysocki et al. (73); copyright 2005 IEEE.]
Table 2. Ventilatory variables during hypo-, normo-, and hypercapnia

<table>
<thead>
<tr>
<th></th>
<th>Hypocapnia</th>
<th>Normocapnia</th>
<th>Hypercapnia</th>
<th>ANOVA</th>
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<tbody>
<tr>
<td>Instantaneous ventilation, l/min</td>
<td>8.940±0.2040†</td>
<td>7.080±0.2040†</td>
<td>46.40±0.9.06††</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Tidal volume, liter</td>
<td>0.562±0.272†</td>
<td>0.617±0.171††</td>
<td>2.091±0.483††</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Mean inspiratory flow, l/s</td>
<td>0.327±0.089†</td>
<td>0.260±0.047†</td>
<td>1.590±0.349††</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Total ventilatory cycle time, s</td>
<td>3.878±1.596*</td>
<td>5.757±2.494††</td>
<td>2.725±0.296††</td>
<td>P=0.0023</td>
</tr>
<tr>
<td>Inspiratory time, s</td>
<td>1.742±0.655*</td>
<td>2.466±0.743††</td>
<td>1.334±0.170†</td>
<td>P=0.0017</td>
</tr>
<tr>
<td>Expiratory time, s</td>
<td>2.132±0.958*</td>
<td>3.291±1.878††</td>
<td>1.392±0.183††</td>
<td>P=0.0055</td>
</tr>
<tr>
<td>Duty cycle</td>
<td>0.463±0.046</td>
<td>0.458±0.083</td>
<td>0.490±0.034</td>
<td>P=0.2992</td>
</tr>
</tbody>
</table>

Values are means ± SD. Significant differences (P < 0.005) between 2 conditions are as indicated: *difference between hypocapnia and normocapnia; †difference between hypocapnia and hypercapnia; ‡difference between normocapnia and hypercapnia.

Statistical Analysis

The distribution of the data sets was first tested for normality using the Kolmogorov-Smirnov test (Prism 4.01; GraphPad Software, San Diego, CA). Statistical analysis was then performed with StatView 5.0 software (Abacus Concepts, San Francisco, CA). The results obtained for each test condition were expressed as means ± SD and then compared with an ANOVA for repeated measures. In the presence of a significant difference (P < 0.05), paired comparisons were performed with Fisher’s protected least significant difference test.

RESULTS

Recordings

On average, normocapnic resting ventilatory flow was recorded for 8–14 min, permitting the acquisition of 120–160 cycles. During hypocapnia, recordings lasted from 2 to 12 min, depending on the time required for PETCO2 to return to 25 Torr. Inhalation of the hypercapnic gas mixture increased PETCO2 from 39.79 ± 1.12 to 53.40 ± 2.36 Torr (P < 0.0001). After stabilization of PETCO2, recordings lasted 7–8 min and permitted the acquisition of 120–160 cycles. None of the subjects reported adverse effects related to hypocapnia or hypercapnia.

Frequency Content of the Signal

The mean power frequency of the ventilatory signal obtained with a 40-Hz sampling rate was 0.365 ± 0.107 Hz in hypocapnia, 0.265 ± 0.093 Hz in normocapnia, and 0.450 ± 0.064 Hz in hypercapnia. The frequency at maximum was 0.299 ± 0.098 Hz in hypocapnia, 0.229 ± 0.092 Hz in normocapnia, and 0.378 ± 0.068 Hz in hypercapnia. The maximal frequency was 1.069 ± 0.202 Hz in hypocapnia, 0.937 ± 0.214 Hz in normocapnia, and 1.244 ± 0.096 Hz in hypercapnia.

Breath-by-Breath Analysis of Ventilation

Mean values according to test conditions. Vt1, VT, and VT/TI increased during hypercapnia (see Table 2 for details). TTOT significantly decreased according to test conditions, H11006 P=0.0007 and H11006 P=0.0174, respectively, but there was no significant difference in TTR between hypocapnia and hypercapnia (H11006 P=0.1200). The reduction of TTR was accompanied by a significant reduction of T1 and T2 in hypercapnia (H11006 P=0.0005 and H11006 P=0.0016, respectively) and in hypercapnia (H11006 P=0.0123 and H11006 P=0.0323, respectively) compared with normocapnia. Ti and T2 did not differ in hypocapnia and hypercapnia (H11006 P=0.1327 and H11006 P=0.1515, respectively).
Breath-by-breath variability. The coefficients of variation for the values $V_t$, $V_t/T_i$, $T_{TOT}$, $T_i$, and $T_e$ generally decreased with increasing $\text{PETCO}_2$ (see Fig. 2 for details).

Nonlinear Analysis of Ventilatory Flow

Noise titration. In all subjects and in all test conditions, NL was above zero. During hypocapnia, the mean value of NL was $26.62 \pm 19.40\%$ vs. $23.62 \pm 11.83\%$ during normocapnia and $33.12 \pm 15.13\%$ during hypercapnia (no significant difference, $P = 0.5520$).

Lyapunov exponents. In the three test conditions and for the eight subjects, at least one of the Lyapunov exponents was positive, at least one was negative, and their sum was always negative. Significant changes in LLE were detected by ANOVA ($P = 0.0031$). The value of the LLE (Fig. 3) was significantly greater in hypercapnia than in normocapnia ($P = 0.03438$) or in hypocapnia ($P = 0.0018$). There was no significant difference between normocapnic and hypocapnic conditions ($P = 0.2071$).

KSE. In all subjects and in all test conditions, KSE had a finite and positive value (Fig. 4). Its variation with CO$_2$ was similar to that of LLE, with significant differences between conditions (ANOVA, $P = 0.0024$). KSE was superior in hypercapnia to the values it reached in normocapnia ($P = 0.0097$) or in hypocapnia ($P = 0.0008$). KSE was not different in normocapnic and hypocapnic conditions ($P = 0.2239$).

CD. In all subjects and in all three test conditions, CD had noninteger values (Fig. 5). Significant changes were detected by ANOVA ($P < 0.0001$). CD values were smaller in hypocapnia than in normocapnia ($P < 0.0001$) and in hypercapnia ($P < 0.0001$). The mean value of CD in hypercapnia was also lower than the value of CD in normocapnia, but this difference was not significant ($P = 0.1112$).

Phase portraits. The phase portraits were characterized by divergent and nonreproducible trajectories. Although divergent and unpredictable, the trajectories were nevertheless confined to a precise zone of the phase space. Phase portrait shapes changed with increasing $\text{PETCO}_2$; from an “L” or “right-angled” shape in hypocapnia and normocapnia, the phase portraits took on an oblique figure-eight shape in hypercapnia (Fig. 6).

DISCUSSION

In this study, the noise titration approach confirmed our previous observations concerning the chaotic nature of resting ventilatory flow dynamics in awake humans (72) and showed that ventilatory flow remains chaotic during hypocapnia and hypercapnia.

Hypercapnia decreased the breath-to-breath variability of ventilation, whereas hypocapnia increased it (Fig. 2). In contrast, hypercapnia tended to increase the complexity of ventilation, whereas hypocapnia tended to decrease it. This is clearly visible on the phase portraits depicted in Fig. 6, where...
the trajectories are more numerous and have a more convoluted shape in hypercapnia than in normocapnia and hypocapnia (where they tend to occupy less of the phase space and to adopt a more rounded form). This pattern closely resembles the pattern described in rats by Sammon et al. (54) in response to negative airway pressure. In this study, the progressive activation of vagal feedback mechanisms responsive to lung deflation was associated with phase portraits of increasingly rich and elaborated aspect (see for example, Fig. 10 in Ref. 54), in line with an increased irregularity and an increased sensitivity to initial conditions. Likewise, in our subjects, hypercapnia increased both the visual tortuosity of the flow phase portraits, the sensitivity of the system to initial conditions (LLE, Fig. 3), and its unpredictability (KSE, Fig. 4). In contrast, hypocapnia “simplified” the phase portraits and decreased the irregularity of ventilatory flow (CD, Fig. 5).

Methodological Issue: Choice of the Flow Signal

Several studies of human ventilatory complexity looked at time series of discrete variables such as VT or ventilatory cycle time components (16, 17, 74). This approach may provide a partial vision of the overall ventilatory dynamics. Other studies have focused on signals describing thoracic or abdominal movements (7–9, 37, 39, 41, 53, 61, 65). As done by others (11, 68), we chose to study ventilatory flow because this signal is physiologically relevant, contains all the pertinent information regarding ventilatory dynamics (11), and can be studied with a minimal amount of distortion-inducing treatments of the signal. Ventilatory flow is, however, a highly “integrative” variable. Although it contains information about the activity of the respiratory central pattern generator, it depends on the chain of downstream events. These include the transmission of information along efferent nerves and through neuromuscular junctions, the contractile properties of ventilatory muscle, and the mechanical features of the thoracic cage and lungs. As a result, caution is needed before interpreting changes in ventilatory flow complexity as representing changes in the status of the ventilatory neuronal oscillators. This is, however, also the case of all the indexes that are accessible to measurement in humans.

Regarding the effects of hypercapnia on the complexity of breathing, our results are in line with data obtained by others in rats and in humans. In rats, hypercapnia increased the complexity of ventilatory dynamics as evaluated with ApEn (10). We observed a similar trend for KSE, which provided information roughly similar to ApEn (42, 43). In humans, hyperoxic hypercapnia has been found to decrease CD (65), but in our subjects this decrease was not statistically significant (Fig. 5). In terms of breath-by-breath variability, we observed a significant decrease in the coefficient of variation of all the ventilatory parameters so studied. This fits with the literature, which suggests that hypercapnia tends to make ventilation less variable in both humans and animals (10, 28) [however, in the human study by Jubran et al. (28), this was true only for part of the ventilatory variables considered].

Similar to the result of others (13), we found that hypocapnia tended to increase the breath-by-breath variability of discrete respiratory variables (Fig. 2). The effects of hypocapnia on ventilatory complexity have apparently not been described previously. In our subjects, hypocapnia seemed to influence LLE and KSE in a manner opposite to that of hypercapnia, but the differences with normocapnic breathing were not statistically significant. Hypocapnia significantly reduced the CD (Fig. 5), thus acting on this parameter in the same direction as hypercapnia. This can appear contradictory, but CD and LLE do not describe the same thing: such divergent patterns have been described before, for example, in developmental EEG studies (35), in fetal heart rate studies (29), and in patients with narcolepsia (19) or during various sleep stages (1, 40). These observations illustrate the importance of not limiting the description of a complex signal to a single index.

Of importance, hypercapnia influenced respiratory variability and respiratory complexity in opposite directions, as did hypocapnia. Such contrasts between variability and complexity have been described before in other domains. For example, Storella et al. (63) found weak correlations between the standard deviation of the R-R intervals and measures of the nonlinear dynamics of cardiac frequency. In neonates, Garde et al. (24) found that, during active vs. quiet sleep, the linear component of heart rate variability increased, whereas the

![Fig. 4. Kolmogorov-Sinai entropy (mean ± SD) during hypocapnia, normocapnia, and hypercapnia. *Significant difference (P < 0.05) during hypercapnia compared with other conditions.](image)

![Fig. 5. Correlation dimension (mean ± SD) during hypocapnia, normocapnia, and hypercapnia. *Significant difference (P < 0.05) during hypocapnia compared with other conditions.](image)
linear component decreased. Wagner et al. (70) assessed the variability of blood pressure (SD and power spectrum) and its complexity (CD and LLE) in intact animals and in a group of dogs subjected to total baroreceptor denervation. Baroreceptor denervation increased blood pressure variability (e.g., doubling in the coefficient of variation) and decreased its complexity (reduction of LLE by \( \sim 60\% \), reduction of the CD by \( >30\% \)).

**Physiological Considerations: Sources of Ventilatory Chaos**

The occurrence of ventilatory complexity can have several explanations that are not mutually exclusive. One possibility could be that complexity is an intrinsic property of the brain stem neuronal oscillators. Indeed, in vitro observations show that the neural output derived from a brain stem section only comprising the pre-Bötzinger complex can exhibit chaos-like dynamics when adequately stimulated (15). In our subjects, the greater complexity during hypercapnia, where the automatic ventilatory command prevails, could indicate that the brain stem ventilatory oscillators are major determinants of ventilatory complexity. Nevertheless, complexity and chaos persisted during hypocapnia, at \( \text{P}_{\text{ETCO}_2} \) levels (15–25 Torr zone) that were likely to inhibit automatic ventilation profoundly [in addition, the use of semipassive hyperventilation to produce hypocapnia made an after-discharge phenomenon unlikely (66)]. This suggests that ventilatory complexity is not only an intrinsic property of the brain stem oscillators. It could arise from cortical-subcortical interactions. In this frame, Yeragani et al. (74) reported an increase in ventilatory LLE and ApEn in patients with panic disorder, which lends support to this hypothesis. Ventilatory complexity could also be produced by afferent inputs to the neural oscillator, as predicted by mathematical models (33). There is experimental evidence to support this idea. In the respiratory domain, as mentioned above, an increasingly intense vagal stimulation increases ventilatory complexity in the rat (54), whereas vagotomy decreases complexity (54, 55). In the cardiovascular domain, Wagner et al.

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![Fig. 6. Examples of 3-dimensional phase portraits of the ventilatory flow attractor in one representative subject during hypocapnia (A), normocapnia (B), and hypercapnia (C). In each condition, the trajectories are reconstructed with the same number of points.](image-url)
(70) emphasized the role of the baroreflex as an important contributor to the dynamical properties of blood pressure regulation in dogs (see above). Savino et al. (56) showed, in the amphibian heart, that increasing the frequency of an external stimulation produced hierarchies of periodic behaviors leading to chaos, with Poincaré maps (which provide an alternative graphical approach to phase portraits) concurrently becoming more complicated visually. In this frame, our observations suggest that the CO2-related afferents (from central chemoreceptors or carried by the glossopharyngeal nerve from the peripheral chemoreceptors) could play a similar role. Indeed, hypocapnia, which can be thought of as an at least partial functional denervation of the CO2 chemoreceptors, reduced complexity, whereas CO2 stimulation increased it. Of note, we used a hyperoxic gas mixture to induce hypercapnia, meaning that the oxygen-sensitive chemoreceptors were functionally denervated. How hypoxia influences ventilatory complexity remains to be studied. The above “afferent” hypothesis predicts that normocapnic hypoxia should increase it and that hyperoxia should decrease it.

Practical Perspectives

Descriptors of ventilatory complexity have already been used with a diagnostic purpose [sleep apnea syndrome (36)] or with a prognostic intent [weaning from mechanical ventilation (17)]. In this frame, and whatever their underlying mechanisms, our results could have implications for the clinical assessment of the sensitivity to CO2 in humans. This response is routinely described in terms of the CO2-related increase in minute ventilation (49). This can be interpreted in terms of breathing control only if the translation of a CO2-related increase in respiratory neuronal activity into ventilation is not impeded by respiratory muscle weakness (31) or respiratory mechanics abnormalities (47). The hypothesis that CO2-related changes in numerical indexes of ventilatory complexity can track the corresponding neural changes irrespective of respiratory mechanics or respiratory muscles abnormalities therefore warrants testing.

Acknowledgments

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