CHAOTIC DYNAMICS OF CARDIOVENTILATORY COUPLING IN HUMANS: EFFECTS OF VENTILATORY MODES

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Running title: Chaotic dynamics of cardioventilatory coupling

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Abstract
Cardioventilatory coupling (CVC), a transient temporal alignment between the heartbeat and inspiratory activity, has been studied in animals and humans mainly during anesthesia. The origin of the coupling remains uncertain, whether or not ventilation is a main determinant in the CVC process and whether the coupling exhibits chaotic behavior. In this frame, we studied sedative free, mechanically ventilated patients experiencing rapid sequential changes in breathing control during ventilator weaning (during a switch from a machine-controlled assistance mode (assist-controlled ventilation ACV) to a patient driven mode (inspiratory pressure support (IPS) and unsupported spontaneous breathing (USB)). Time series were computed as R to start inspiration (RI) and R to the start of expiration (RE). Chaos was characterized with the noise titration method (noise limit), largest Lyapunov exponent (LLE) and correlation dimension (CD). All the RI and RE time series exhibit chaotic behavior. Specific coupling patterns were displayed in each ventilatory mode and these patterns exhibited different linear and chaotic dynamics. When switching from ACV to IPS, partial inspiratory loading decreases the noise limit value, the LLE and the correlation dimension of the RI and RE time series in parallel whereas decreasing intra-thoracic pressure from IPS to USB has the opposite effect. Coupling with expiration exhibits higher complexity than coupling with inspiration during mechanical ventilation either during ACV or IPS probably due to active expiration. Only 33% of the cardiac time series (RR interval) exhibit complexity either during ACV, IPS or USB making the contribution of the cardiac signal to the chaotic feature of the coupling minimal. We conclude: (i) Cardioventilatory coupling in unsedated human exhibits a complex dynamic that can be chaotic. (ii) Ventilatory mode has major effects on the linear and chaotic features of the coupling. Taken together these findings reinforce the role of ventilation in the CVC process.

Keywords: cardioventilatory coupling, chaos, respiration, mechanical ventilation
Introduction

Heartbeats and ventilation are both rhythmic processes. Automaticity of the heart is generated by the pacemaker cells within the sino-atrial node and the resulting regular heartbeat is modulated by vagal and sympathetic autonomous system. Ventilation depends on phasic neuronal activities taking place within central respiratory pattern generators located in the brainstem and on their transformation into rib cage movements by the respiratory muscles. Both systems interact with each other at the central and peripheral level (35). Heart rate increases during inspiration and decreases during expiration. This respiratory-related change in heart rate is known as respiratory sinus arrhythmia (RSA) (13). RSA reflects the modulation of the central autonomic outflow (7) caused by respiration-related factors, such as oscillations of respiratory centers, pulmonary stretch receptor afferents, and hemodynamic factors through the baroreflex (26, 35), and is known to be chaotic (32). Another type of interactions between heartbeat and ventilation, i.e phase-locking, has been evidenced in recordings of 30 min in resting human (32). For some subjects, plotting instantaneous respiratory phases at each occurrence of heartbeat against the beat number lead to horizontally striped plots indicating that synchronization exists during short period for sufficiently long recording. A central coupling between cardiovascular and respiratory neuronal activities has been hypothesized as a possible mechanism underlying such synchronization (32). Indeed, reciprocal interactions exist at the central level: respiratory-modulated activity of neurons controlling the cardiovascular system is established and the cardiac cycle is represented functionally in the activity of medullary respiratory neurons (4, 5). Cardioventilatory coupling (CVC) has also been characterized through the coefficient of variation of bivariate data, i.e. the interval between the start of inspiration of the ventilatory flow and the preceding R wave of the electrocardiogram (the RI interval). CVC, a transient temporal alignment between the heartbeat and inspiratory activity has been recognized in short human recordings mainly
during anesthesia (11, 17). Characteristic patterns of the coupling have been described according to the coefficient of variation of the RI interval with a variety of different heart rate to respiratory rate ratio (11, 18, 38, 39). Furthermore, nonrandom coupling of heart rate to expiratory and inspiratory onsets have been evidenced during spontaneous breathing in humans (23). These findings suggest that the CVC exhibits complexity.

The origin of the coupling remains uncertain. Several hypotheses have been proposed that are not mutually exclusive: (i) reciprocal interaction of brain stem oscillators (32, 33) involving the respiratory central pattern generator (RCPG) and the cardiovascular center, (ii) a vagal reflex with afferent input from pulmonary stretch receptors and efferent input to the sinus node (40). This hypothesis points out the role of respiration in determining the CVC process and the heart rate to respiratory rate ratio. (iii) The “cardiac trigger hypothesis” which involves a sympathetic input from the baroreceptors to the brainstem (RCPG) (11, 38, 39). This latest assumption implies that the heart beat triggers inspiration via the baroreflex pathway to determine the coupling (39). In this frame, using data-analysis technique derived from dynamic system theory, we studied sedative free, mechanically ventilated patients experiencing rapid sequential changes in breathing control to address the following questions: (i) Does the coupling between heart beat and ventilation exhibit chaotic dynamics? (ii) If ventilation is a main determinant in the CVC process, specific coupling pattern depending on the ventilatory mode should be evidenced when ventilation is artificially paced. (iii) Are there any different effects of the expiratory vs inspiratory activity and trans-thoracic pressure (positive vs negative) on the coupling?
Materiel and Methods

The database analyzed for this study was an existing set of simultaneously recorded ventilatory flow signals and electrocardiograms (Unité de réanimation, service de pneumologie Groupe Hospitalier Pitié-Salpêtrière). The methods used to acquire this data set have been previously described (22). The study did not involve any intervention or interference with the care of the patients. In this context, the appropriate external authority confirmed that the observational nature of the study made informed consent unnecessary.

Protocol

Twelve consecutive mechanically ventilated patients (Servo 900C or 900D ventilators, Siemens-Elema, Solna, Sweden) in sinus rhythm were studied during the ventilator weaning process, under three sequential modes of ventilatory assistance (assist-control ventilation (ACV), inspiratory pressure support (IPS) and unsupported spontaneous breathing (USB)). The characteristics of the patients are given in Table 1. For each patient, the inclusion began when the clinician decided to initiate the weaning process. Patients were included if they experienced rapid changes in breathing control. In the ACV mode, the patient has minimal neurorespiratory activity, if any; inspiratory flow is invariant and the duration of inspiration is fixed set by the machine. The respiratory frequency cannot be inferior to the value set by the clinician but it can be higher if the patient triggers the ventilator, hence a variability in the expiratory time TE. In the IPS mode the frequency of breathing and the duration of inspiration depend on the activity of the respiratory central pattern generator. Inspiration is subordinated to the activity of the inspiratory muscles, but is aided by airway pressurization that partially unloads the system. As a result, tidal volume VT depends on the level of positive pressure, the mechanical characteristics of the respiratory system and the duration of inspiration, which is highly variable. During USB, both inspiratory timing and tidal volume depend on the unaided
activity of the central and peripheral neurorespiratory system. Of note, switching from IPS to USB implies a change from a positive to a negative thoracic pressure regimen.

Data acquisition

Recordings of the ventilatory flow and electrocardiogram were made while the patient had been free of sedative drugs and neuromuscular blocking agents for at least 24 hours. Each recording lasted 15 min and was performed at the same moment of the day, while the patient was awake. A first recording was carried out under assist-control ventilation, immediately before the switch to inspiratory pressure support. A second recording (same duration) was performed fifteen to thirty minutes after the switch. A third recording was performed after the switch to unsupported spontaneous breathing. The second and third recordings were not separated by more than 24 hours (FiO2 and blood pressure were unchanged during the three recordings as positive end expiratory pressure PEEP). Endotracheal suctioning was done before the recordings.

Ventilatory flow ($V'$) was measured with a heated low dead space pneumotachograph linear from 0 to 160 L.min$^{-1}$ (3700A series, Hans Rudolf, Kansas City, MO, USA, dead space 14ml, flow resistance 0.02 to 0.04 cmH$_2$O L.s$^{-1}$), fitted on the endotracheal tube and connected to a ± 2 cm H$_2$O linear differential pressure transducer (DP-45-18, Validyne, Northridge, CA, USA).

Flow signal and ECG (3 leads producing a prominent R wave) sampled at 500Hz (PowerLab/4SPP®, AD instruments, Castle Hill, Australia) were simultaneously acquired on a personal computer for subsequent analysis (Chart software, ADInstruments). $V_T$ was calculated on a breath-to-breath basis after digital integration of the flow signal. The following time series were then computed on a breath-by-breath basis (Matlab® 7.0,
Mathworks, USA): R to start inspiration (RI), R to the start of expiration (RE). Both time series (RI and RE intervals) represent cardioventilatory coupling (18, 23, 38, 39). Figure 1 illustrates the computation of the RI and RE interval couplings.

**Time domain analysis**

RI and RE plots were classified according to different patterns visually identified. The mean and coefficient of variation (ratio of the standard deviation to the mean) of the time series were computed. In addition the instantaneous heart rate to respiratory rate ratio was also computed.

**Nonlinear analysis**

*Detection and quantification of chaos.* The noise titration technique (25) was used on the experimental time series described above. First the method involved the simulations of time series with linear and nonlinear polynomial autoregressive model (Volterra-Wiener series) (1). The best linear and nonlinear models are chosen according to the minimal information theoretic criterion, and subsequently the null hypothesis (best linear model) is tested against the alternate hypothesis (best nonlinear model) using parametric (F-test) and nonparametric (Mann Whitney) statistics.

If the null hypothesis is rejected, namely if a nonlinear model best describes the data, the titration process is applied. White noise of increasing standard deviation is added to the time series until its nonlinearity goes undetected by the above process. The corresponding amount of noise is called “noise limit” (NL). A NL above zero indicates the presence of chaos within the experimental time series. Conversely if NL = 0 nonlinearity is not detected. This can mean that the time series is not chaotic or that the chaotic component of the signal is already
neutralized by the background noise in the data. The noise titration approach is a highly sensitive, specific and robust detection of chaos in short noisy data and gives a relative measure of chaos intensity (25). It has already been used on experimental time series to evidence the chaotic nature of human ventilation during mechanical ventilation (22), during hypo-or hypercapnia (9).

Characterization of chaos.

Sensitivity to initial conditions. Complex dynamical systems are sensitive to initial conditions, and exhibit an exponential divergence in the phase space. This can be quantify through the study of the Lyapunov exponents spectrum and the calculation of the largest Lyapunov exponent ($\lambda_L$). Consider two points on two nearby trajectories in the phase space, and assume the distance between them to be $d(0)$. After time $t$, if the distance between the two trajectories becomes $d(t)$, then the average divergence (separation after time $t$) can be written as:

$$d(t) = d(0) e^{\lambda_L \Delta t}$$

where $\lambda_L$ is the largest Lyapunov exponent of the system. In the present study, we used the algorithm proposed by Rosenstein et al that has been shown to be particularly useful for small data series (29).

Irregularity. The correlation dimension ($D_{corr}$) is a fractal dimension reflecting the irregularity of the attractor of the system. $D_{corr}$ characterizes the “aperiodicity” of the system in the phase space. It is estimating by examining the scaling properties of the correlation sum (12, 29). From a time series ($x_1, x_2, \ldots, x_N$), where $N$ is the total number of points, the $m$ dimensional vector in the phase space can be constructed by delay embedding:

$$\hat{X}_i = [x_i, x_{i+1}, \ldots, x_{i+(m-1)\tau}]$$
where, $\tau$ is the fixed time lag and $m$ is the embedding dimension. Then the reconstructed trajectory of the actual dynamics can be written as $X = (X_1; X_2; X_3; \ldots X_M)$, where $M = N - (m-1) \tau$.

The correlation dimension can be calculated from the correlation integral of the time series. The correlation integral can be computed as follows (12, 29):

$$C(r, m) = \frac{2}{N(N-1)} \sum_{i=1}^{N} \sum_{j=i+1}^{N} \Theta(r - |X_i - X_j|)$$

where, $r$ is scale length, and $\Theta$ is the Heavyside step function. Scaling of the function $C(r, m)$ can be written as:

$$C(r, m) = r^D$$

The correlation dimension ($D_{corr}$) can be defined by

$$D_{corr} = \lim_{r \to \infty} \lim_{N \to \infty} \frac{\partial C(r, m)}{\partial \ln r}$$

and for practical purpose, $D_{corr}$ can be obtained from the slope of $\ln C(r)$ vs $\ln r$ plot.

The optimal dimension is obtained after calculating the percentage of false nearest neighbors between points in state space. A minimal number of false nearest neighbors is required (19). The embedding dimension that adequately represents the system is the dimension that eliminates most of the false nearest neighbors allowing an adequate phase-space reconstruction of the underlying dynamics (19). The embedding dimension 3 was therefore chosen for subsequent statistical comparison.

In order to test the nonlinearity that governs the dynamics, we have applied surrogate test (36). The surrogate data has been generated by Phase Shuffled surrogate method, in which phase are randomized by shuffling the Fourier phase, and hence power spectrum is preserved.
and nonlinear structures are destroyed. Correlation dimension have been estimated for both the original data and five surrogates that match each original signal, for an embedding dimension of 3. A global test was carried out by a Wilcoxon signed rank test comparing the correlation dimension values computed on the original data paired with the corresponding average correlation dimension values from the matching surrogate. Significant Wilcoxon rank test between the original and surrogates implies the nonlinear dynamics of the original data.

**Statistical analysis**

The Matlab 7.0 software (Mathwoks, USA) was used for statistical analyses. The distribution of the data sets was first tested for normality using the Kolmogorov-Smirnov test. One-way analysis of variance was performed to characterize the coupling patterns according to linear measures of the time series and the heart rate to respiratory rate ratio. $\chi^2$ test allowed the comparison of the patterns according to the ventilatory mode. $t$ test, one-way and two-way analyses of variance were performed to study the effects of the ventilatory mode (ACV, IPS, USB) and respiratory timing (RI, RE) on the time and nonlinear descriptors of the time series.

Finally analyses of variance characterized the different coupling patterns according to the nonlinear descriptors, i.e. the noise limit value, the correlation dimension and the largest Lyapunov exponent. In the presence of a significant difference ($p<0.05$), multiple comparisons were performed using the “Tukey-Kramer” test.
**Results**

Blood gases and blood pressure were similar during the three ventilatory conditions (Table 2).

**Time domain**

Ventilatory mode and respiratory timing had no significant effect on the mean of the time series (RI, RE) and their coefficients of variation. Sixty time series were qualitatively classified according to various types of dynamics behavior of the coupling interval (Figure 2). These patterns evidence the different dynamics of the coupling for the RI and RE intervals during the 3 ventilatory conditions. Pattern A coupling is illustrated by a varying interval from one breath to another but with a certain periodicity: from a nonlinear dynamics point of view, it can be interpreted as a cycle where the period is alternatively varying from period 8, 6, 2. This pattern also contained short epochs of aperiodic oscillatory behavior. The corresponding heart rate to respiratory rate ratio in this particular case displayed a stable ratio that oscillates from 5:1 to 6:1. In pattern B, short segments of horizontal organized banding alternate with increased or decreased interval. The corresponding ratio is much more variable than in pattern A. Pattern C coupling is illustrated by large and progressive increases or decreases of the intervals with no horizontal band. The corresponding ratio alternates between 7:1 to 2:1. Finally pattern D coupling shows oscillations but not in a periodic manner. This “uncoupled pattern” is associated with a ratio varying from 7:1 to 2:1. These four patterns differ according to their statistical properties as evidenced in Table 3. Pattern D has higher coefficient of variations of the RI and RE time series and higher coefficient of variation of the heart rate to respiratory rate ratio, as compared to pattern A. Patterns C and D exhibit higher coefficient of variations of the RI and RE time series than patterns A and B. In addition, specific patterns are displayed in each ventilatory mode. Sixty plots were analyzed: 28% were classified as being a type A, 10% type B, 32% a type C and 30% a type D. A significant effect
due to ventilatory mode ($p=0.02$, Chi$^2$ test) was evidenced with the pattern A occurring more frequently during ACV (88%), whereas the type B was exclusively observed during IPS and USB. The pattern D was more frequent during IPS (61%) and the type C was observed either during ACV, IPS and USB. No significant effect was shown according to respiratory timing ($p=0.4$, Chi$^2$ test).

**Nonlinear domain**

*Noise titration.* All the time series (RI and RE intervals) exhibited a positive noise limit during the three ventilatory conditions. There was a significant effect on the noise limit value due to ventilatory mode and respiratory timing ($p<0.001$, $p=0.03$, two-way ANOVA). Multiple comparisons are shown in Figure 3 (left panel). Switching from ACV to IPS decreased the noise limit values of the RI and RE intervals whereas decreasing intrathoracic pressure from IPS to USB had the opposite effect. Coupling with expiration exhibits higher noise limit value than coupling with inspiration either during ACV or IPS (Figure 4, left panel).

*Largest Lyapunov exponent.* There was a significant effect of the ventilatory mode and respiratory timing ($p=0.06$, $p=0.04$ two-way ANOVA) on the largest Lyapunov exponent (LLE) of the RI and RE time series. Multiple comparisons are shown in Figure 3 and 4 (right panel): the change in LLE paralleled those of the NL values either for the effect of ventilatory mode and respiratory timing ($R=0.4$, $p=0.009$, Pearson’s linear correlation coefficient).

*Correlation dimension.* In all the time series, the correlation dimension had a noninteger value. There was a significant effect of the ventilatory mode and respiratory timing on the correlation dimension value of the RI and RE time series with a decrease from ACV to IPS and an increase from IPS to USB (Table 4, $p=0.03$, two-way ANOVA). Coupling with expiration exhibited higher correlation dimension value than coupling with inspiration (Table
Comparisons between the correlation dimension of the original RI and RE time series with surrogates are given in Table 4. Furthermore, Figure 5 illustrates the correlation integral and correlation dimension of the coupling in one patient for dimension 3 to 6 and for the three different ventilatory modes. Different embedding dimensions give an entire description of the attractor of the system. Ventilatory mode differently alters the coupling: during ACV (black curves), the structure of the correlation curves evidence a single transition band for both the RI and RE coupling whereas during IPS (green curves), single transition band is only observed for the coupling with inspiration.

**Nonlinear descriptors according to specific coupling patterns.** Significant differences were evidenced between the four types of coupling according to the noise limit value, the correlation dimension and the largest Lyapunov exponent (Table 5). In addition, the combined effects of respiratory timing (expiratory vs inspiratory activity) and different coupling types were significant on the mean of the noise limit value (p=0.08, p=0.04, two-way ANOVA), the largest Lyapunov exponent (p=0.04, p=0.05, two-way ANOVA) and the correlation dimension (p=0.06, p=0.02, two-way ANOVA). Using three-way ANOVA, the effects of the different coupling types, the respiratory timing and the ventilatory mode were also significant on the mean of the nonlinear descriptors (data not shown).

**Noise titration of the RR interval time series.** In order to estimate the contribution of the cardiac signal to the chaotic feature of the CVC, we computed the noise limit value of all the RR interval time series. Few time series exhibit a positive noise limit. Only thirty three percent (10/30) exhibit a positive value (in 67% of cases, no nonlinearity was evidenced in the RR interval). Among the time series that exhibit complexity, thirty three percents (4/12) were during ACV, 25% (3/12) during IPS and 50% (3/6) during USB. The mean value of the noise limit was 32±18% during ACV, 16±7% during IPS and 14±8 during USB (p=0.2, one-way ANOVA).
Discussion

Our major findings are as follow: (i) Cardioventilatory coupling in humans exhibit a complex dynamics that can be chaotic. (ii) Ventilatory mode has major effects on the complexity of the CVC: during the switch from ACV to IPS, partial inspiratory loading decreases the noise limit value, the LLE and the correlation dimension in parallel whereas decreasing intra-thoracic pressure from IPS to USB has the opposite effect. (iii) Coupling with expiration exhibits higher complexity than coupling with inspiration during mechanical ventilation either during ACV or IPS. (iv) Specific coupling patterns are displayed in each ventilatory mode and these patterns exhibit different linear and chaotic dynamics. (v) Only 33% of the cardiac time series (RR interval) exhibit complexity either during ACV, IPS or USB making the contribution of the cardiac signal to the chaotic feature of the coupling minimal. Taken together these findings reinforce the role of ventilation in the CVC process.

Characterizing chaos

Previous strategies to characterize the chaotic features of time series were to infer the presence of nonlinear determinism through a statistical comparison with randomly generated surrogate data. Indeed the shapes of the correlation curves given in Figure 5 with a single transition band for the RI and RE time series underline the complexity of the coupling. Comparisons with surrogate data (Table 4) for the correlation dimension estimate reinforce the nonlinear nature, a prerequisite for chaos, of the coupling. However nonlinearity and determinism are only necessary conditions for chaos but do not themselves constitute a sufficient proof of chaotic dynamics (2). The method of chaos titration with added noise gives a relative measure of chaos intensity that correlates well with other descriptors, principally LLE (R=0.4, p=0.009, Pearson’s linear correlation coefficient) (25). The noise limit is the
minimum amount of added white noise that prevents the detection of nonlinearity. Using several nonlinear differential equations, it was shown that the noise limit follows Lyapunov exponents in all standard routes to chaos (25). It has been suggested that the noise limit characterizes chaotic dynamics even when the chaos is induced by dynamic noise instead of produced spontaneously (30, 42). Our results on short time series show that the noise limit value was positive for the RI and RE intervals for all ventilatory conditions.

The relationships between the nonlinear descriptors of the coupling (noise limit value, largest Lyapunov exponent and correlation dimension) show that their alterations were more concordant according to ventilatory modes (Figure 3 and 4) than according to their ordinal classification (Table 5). However, the noise limit value was low in pattern D and was associated with the lowest level of the largest Lyapunov exponent. Furthermore, the noise limit value and the correlation dimension were the highest in pattern A and the lowest in pattern B. It seems that the nonlinear descriptors are more sensitive to ventilatory mode alterations (Figure 3 and 4). Indeed each pattern of the ordinal classification shares different ventilatory modes that possibly explain the greater variability of their alterations. In addition, only 6 patterns B were evidenced above all of the identified patterns. Finally we point out that each nonlinear descriptor doesn’t represent the same chaotic property.

The chaotic dynamics of the cardioventilator coupling and the effects of ventilatory mode

This study is the first to characterize the complexity of the coupling between heartbeat and ventilation in experimental data. We used the analyses technique derived from dynamic system theory to show that cardioventilatory coupling (CVC) may be a complex deterministic process. In patients free of sedative drugs, CVC exhibits chaotic dynamics either for the coupling with inspiration and expiration and during the 3 modes of ventilation. Previous
studies characterized the temporal relations of cardioventilatory coupling mainly during anesthesia (18, 39), a condition known to reduce mechanoreceptor activity, central sensitivity to a variety of respiratory stimuli, and to decrease the mechanical output of the respiratory system (6, 28). In this particular condition, the temporal relationships between the Rwave preceding the onset of inspiration have been described as a coupling pattern with horizontal bands in the time series (11, 39). However, horizontal banding identifying constant coupling were not identified in 52% of RI plots in the anaesthetized rats (39). “Uncoupled pattern” was also shown in the study of Tze ng et al. (39) and justified the use of techniques derived from dynamic system theory. In unsedated subjects, we found different and specific coupling patterns depending on ventilatory mode. Their statistical properties described in table 5 point out their chaotic nature. Short segments of horizontal band were also evidenced in the pattern B coupling. Ten percent of the coupling interval were classified as being a type B and were exclusively displayed during pressure support and spontaneous ventilation. Pattern A coupling that exhibits a certain periodicity with a circle of a varying period was promoted by the assist-control and inspiratory pressure mode.

What makes the RI and RE patterns chaotic? Both heart rate and ventilation should contribute to the chaotic features of the coupling. Ventilatory chaos predominantly has a neural origin (intrinsic to the respiratory central pattern generators (5, 27), resulting from their perturbation by respiratory afferents (9, 22), or both). Sympathovagal interactions cause the heartbeat to exhibit complexity in response to various central and peripheral influences (baroreflexes, chemoreflexes). However, whereas all RI and RE time series exhibit complexity, only few cardiac time series display chaotic behavior which makes the cardiac contribution to the coupling minimal in these conditions. Furthermore the coupling depends on the ventilatory loading conditions and timing. Coupling with expiration exhibits higher complexity than coupling with inspiration during mechanical ventilation either during controlled ventilation or
pressure support. We previously evidenced in patients passively driven by a mechanical ventilator (22) that some patients exhibited signs of active expiratory control. Indeed the only degree of freedom for breath-by-breath variability during ACV is the expiratory time. Greater complexity of the coupling with expiration could then, speculatively, be due to an active expiratory central pattern generator (15, 22, 41). During pressure support, the complexity of the coupling is also higher during expiration than inspiration. It is possible that inspiratory drive alone is not yet optimal to sustain breathing, therefore a slight recruitment of expiratory activity is necessary (41). Switching from assist-control ventilation to pressure support decreases the complexity of the RI and RE coupling. Changes in mechanical ventilatory condition with partial inspiratory loading and a decrease in expiratory activity may explain these alterations. Inspiratory pressure inhibits the respiratory drive (8, 34). Its removal when switching from pressure support to spontaneous breathing enhances the respiratory drive partly due to the increased vagal afferent feedback (31). Consequently, reduction in transthoracic pressure causes the patterns of coupling to become more complex. In addition, the hemodynamic consequences of decreasing intra-thoracic pressure and subsequently the decline of baroreflex sensitivity could also partly contribute to explain these findings (10, 20).

The effects of mechanical ventilation on the cardioventilatory coupling have been studied in the dogs and humans mainly in the time domain (40): in dogs, the coupling defined as a whole number ratio of heart rate and breathing frequency was observed during mechanical ventilation. These authors showed that respiration modifies the heart rate to form the whole number ratio (WNR). Although the WNR is not synonymous of the intervals we studied, our findings are consistent with this view. Statistical properties of the coupling in Table 3 evidence that both the coefficient of variation of the time series and the HR to respiratory rate ratio display similar alterations. However, discrepancies have been evidenced in humans concerning the effect of mechanical ventilation on the coupling. Larsen et al. (18) found that
CVC is entirely disrupted during intermittent positive pressure ventilation with no horizontal bands on the RI time series plots. However, their protocol was different. They studied the coupling during deep anesthesia and two different groups were compared, one during spontaneous ventilation and the other undergoing positive pressure ventilation. The length of the time series for subsequent analysis was limited to fifty breaths and they quantified the strength of the coupling using one method, the Shannon entropy statistics. Finally the clinical characteristics of the studied subjects were not similar.

*The determinants of the cardioventilatory coupling*

In the conditions where ventilation drives the cardiac signal during mechanical ventilation, different type of coupling patterns are evidenced and the “horizontal bands” in pattern B during inspiratory pressure support show that a transient temporal alignment still persists when ventilation is artificially paced. It is highly likely that ventilation, in the context of the CVC process, adjusts the heartbeat possibly through several mechanisms included respiratory sinus arrhythmia (7, 13, 16, 17, 21). Moreover, the contribution of the cardiac time series to the chaotic feature of the coupling is minimal since in 67% of cases no nonlinearity is evidenced in the RR interval. This implies that the “cardiac trigger hypothesis” which attributes to the cardiac signal a major role in triggering inspiration and in determining the respiratory variability is unlikely in these conditions (11, 38). Tzeng *et al* hypothesized that the coupling mainly involves a cardiac input that triggers inspiration through a sympathetic baroreflex pathway (39). In anaesthetized rats, bilateral sinoaortic denervation was associated with marked reduction in the coupling with little contribution of the vagus nerve (39). However sympatho-vagal balance in rats is shift towards high sympathetic level that potentially mitigates a contribution from vagal afferents. It seems that the reflex pathway
involved in the coupling depends on the species (35): for instance cardiorespiratory synchrony exists in dogfish (14). Because they lack sympathetic innervation to the heart, cardioventilatory coupling is interpreted as variations in vagal tone. This coupling is abolished after injection of atropine. Ventilation is an important determinant of the coupling process. The involvement of the respiratory central pattern generator is evidenced since coupling with expiration exhibit higher complexity than inspiration during assist-control ventilation and inspiratory pressure support (15, 22, 41). Finally, direct mechanical consequences of ventilation on the heart, without reflex pathway to the brainstem could also be involved in the coupling process. Indeed coupling is established in heart transplant patients whereas these patients have no central nervous control (37), which means that coupling may occur in the absence of autonomous control of the heart.

**Perspectives and Significance**

Cardioventilatory coupling studied through the RI and RE intervals represents new integrated indexes of the cardiorespiratory interaction. Their chaotic features vary according to different breathing control. It seems that the determinants and the characteristics of the coupling also vary depending on the state of consciousness. Consequently studying the characteristics and complexity of the coupling could be useful in clinical situations to identify different stages of anesthesia or in situations where breathing control and/or cardiac failures are involved during the unsuccessfull weaning from a mechanical ventilator. Finally these indexes may have potential clinical relevance to help understand certain diagnoses of unexplained dyspnea by studying their dynamics characteristics during exercice (a model of active expiration and sympathetic stimulation).
**Study limitation**

It could be argued that the study did not follow a cross over design, because the patient were always switched from assist-control ventilation to inspiratory pressure support and finally unsupported spontaneous breathing and not the reverse. This was due to the inherent observational nature of the study. This study was performed in critically ill patients and not in healthy subjects. This could have influenced our results. However, the clinical status of the patients was stable, because otherwise the decision to change the ventilatory mode would not have been taken. In addition, we included patients experiencing rapid sequential changes in breathing control, i.e. no more than 24 hours separate the recordings from the assist-control ventilatory mode to the unsupported spontaneous breathing mode.

**Conclusion**

We conclude from our study that the coupling between heartbeat and ventilation can be chaotic. Rapid sequential changes in breathing control specifically alter the chaotic properties of the coupling patterns. In unsedated subjects, the contribution of the cardiac signal to the chaotic properties of the coupling is minimal. Taken together, these findings reinforce the role played by ventilation in determining the CVC process.
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Figure legends

Figure 1.

Computation of the RI and RE interval couplings is shown for 3 successive breaths. Schematic representation is given for the ventilator cycle and the ECG.

Figure 2.

RI and RE time series are classified according to 4 coupling patterns. These patterns exhibit different linear and chaotic dynamics. Time series for pattern A to D are given in the left panel and the corresponding heart rate to respiratory rate ratio on the right panel (See text for comments).

Figure 3.

Noise limit value (%) (left panel) and largest Lyapunov exponent (LLE) (right panel) for RI and RE coupling during ACV, IPS and USB. Inspiratory loading during switching from ACV to IPS decreases the noise limit value and the LLE in parallel whereas decreasing intrathoracic pressure has the opposite effects. The boxes encompass the interquartile range with indication of the median, the whiskers delimit the 95th percentile of the data distribution (ANOVA).

Figure 4.

Noise limit value (%) (left panel) and LLE (right panel) for both types of coupling during ACV, IPS and USB (from top to bottom). During ACV and IPS, coupling with expiration exhibits a higher complexity (noise limit value and LLE) than coupling with inspiration. The boxes encompass the interquartile range with indication of the median, the whiskers delimit the 95th percentile of the data distribution (ttest).
Figure 5.

Correlation sum (left panel) and correlation dimension (right panel) from dimension 2 to 6 for RI (top panel) and RE coupling (bottom panel) during assist-control ventilation (ACV: black curves), inspiratory pressure support (IPS: green curves) and unsupported spontaneous breathing USB (red curves) in one patient. Ventilatory mode and respiratory timing have different effects on the correlation dimension of the coupling interval. In this example, during both ACV and IPS, the curves of the RI coupling converge to a single value which gives the value of the correlation dimension. For statistical analysis an embedding dimension of 3 was chosen to estimate the correlation dimension of the experimental data. The RE coupling exhibits different correlation curves with curves converging to a single value only in the ACV mode. Black arrow shows the point of convergence during ACV and green arrow during IPS.
Table 1. Characteristics of the patients

<table>
<thead>
<tr>
<th>#</th>
<th>age (yr) /gender</th>
<th>diagnosis</th>
<th>Mechanical Ventilation (week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54 / F</td>
<td>Neuroleptic poisoning</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>52 / M</td>
<td>Epilepsy</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>54 / M</td>
<td>ARDS</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>63 / M</td>
<td>Epilepsy</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>47 / M</td>
<td>Epilepsy</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>26 / F</td>
<td>ARDS</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>73 / M</td>
<td>ARDS (sepsis)</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>33 / M</td>
<td>ARDS (sepsis)</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>79 / M</td>
<td>Septic shock</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>58 / F</td>
<td>ARDS (sepsis)</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>79 / M</td>
<td>Septic shock</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>36 / M</td>
<td>ARDS (sepsis)</td>
<td>1</td>
</tr>
</tbody>
</table>

M, male; F, female; ARDS, acute respiratory distress syndrome.
Table 2. Ventilator settings, blood gases and blood pressure in the assist-control (ACV), inspiratory pressure support (IPS) and unsupported spontaneous breathing (USB) modes.

<table>
<thead>
<tr>
<th></th>
<th>ACV</th>
<th>IPS</th>
<th>USB</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Ventilator settings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency (cycles per minutes)</td>
<td>20±5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pressure support (cm H2O)</td>
<td>—</td>
<td>15±4</td>
<td>—</td>
</tr>
<tr>
<td>Positive end expiratory pressure (cm H2O)</td>
<td>5±2</td>
<td>5±3</td>
<td>—</td>
</tr>
<tr>
<td>Blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FiO2</td>
<td>45±10</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>95±22</td>
<td>98±27</td>
<td>92±17</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>44±12</td>
<td>42±9</td>
<td>44±4</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>132±73/73±11</td>
<td>140±28/76±14</td>
<td>150±22/85±10</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation
Table 3. Differences among mean and coefficient of variation (CV) of the time series, the heart rate (HR)-to-respiratory rate (f) ratio according to the different coupling patterns.

<table>
<thead>
<tr>
<th>Coupling Pattern</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>6</td>
<td>19</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>ventilatory mode</td>
<td>ACV (15)</td>
<td>ACV (0)</td>
<td>ACV (6)</td>
<td>ACV (3)</td>
<td>p=0.02</td>
</tr>
<tr>
<td></td>
<td>IPS (2)</td>
<td>IPS (4)</td>
<td>IPS (7)</td>
<td>IPS (11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>USB (0)</td>
<td>USB (2)</td>
<td>USB (6)</td>
<td>USB (4)</td>
<td></td>
</tr>
<tr>
<td>mean RI/RE</td>
<td>0.31±0.05</td>
<td>0.29±0.09</td>
<td>0.38±0.04</td>
<td>0.29±0.05</td>
<td>p=0.005; A, D vs C</td>
</tr>
<tr>
<td>CV RI/RE</td>
<td>0.48±0.03</td>
<td>0.45±0.05</td>
<td>0.53±0.03</td>
<td>0.53±0.03</td>
<td>p=0.0006; C, D vs A and B</td>
</tr>
<tr>
<td>mean HR / f</td>
<td>4.6±1.1</td>
<td>8.1±1.9</td>
<td>4.3±1.05</td>
<td>4.5±1.1</td>
<td>p=0.001; A, C, D vs B</td>
</tr>
<tr>
<td>CV HR / f</td>
<td>0.13±0.09</td>
<td>0.24±0.16</td>
<td>0.24±0.08</td>
<td>0.27±0.08</td>
<td>p=0.02; A vs D</td>
</tr>
</tbody>
</table>

Data are mean±SD. p with Chi2 test for ventilatory mode, and one-way ANOVA for mean and coefficient of variation of the time series and heart rate to respiratory rate ratio. Mean and CV of RI/RE time series are in s.
Table 4. Correlation dimension (Dcorr) of the RI and RE time series during the three ventilatory modes and comparison with surrogate data.

<table>
<thead>
<tr>
<th></th>
<th>ACV</th>
<th>IPS</th>
<th>USB</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RI</td>
<td>RE</td>
<td>RI</td>
<td>RE</td>
<td>RI</td>
</tr>
<tr>
<td>Original</td>
<td>2.47±0.21</td>
<td>2.51±0.33</td>
<td>2.22±0.22</td>
<td>2.38±0.19</td>
<td>2.36±0.29</td>
</tr>
<tr>
<td>Surrogate</td>
<td>2.67±0.27</td>
<td>2.8±0.11</td>
<td>2.42±0.21</td>
<td>2.57±0.18</td>
<td>2.55±0.29</td>
</tr>
</tbody>
</table>

Data are mean±SD, ACV: Assist-control ventilation, IPS: Inspiratory pressure support, USB: Unsupported spontaneous breathing. Two-ways ANOVA was used to study the effects of ventilator mode (ACV, IPS, USB) and respiratory timing (RI vs RE) on the original time series. Comparison between surrogate data and original data was performed using Wilcoxon matched-pairs signed rank test.
Table 5. The noise limit values, the correlation dimension (Dcorr) and the largest Lyapunov exponents (LLE) of the time series according to the different coupling patterns.

<table>
<thead>
<tr>
<th>Coupling Pattern</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>6</td>
<td>19</td>
<td>18</td>
<td>p</td>
</tr>
<tr>
<td>Noise limit (%)</td>
<td>21±12</td>
<td>9.33±4.13</td>
<td>18±11</td>
<td>13±8.6</td>
<td>p=0.04, I vs II</td>
</tr>
<tr>
<td>Correlation dimension (Dcorr)</td>
<td>2.5 ±0.2</td>
<td>2.3±0.4</td>
<td>2.3±0.3</td>
<td>2.5±0.3</td>
<td>p=0.03, I vs III</td>
</tr>
<tr>
<td>LLE</td>
<td>0.18±0.06</td>
<td>0.21±0.05</td>
<td>0.2±0.05</td>
<td>0.16±0.04</td>
<td>p=0.04, III vs IV</td>
</tr>
</tbody>
</table>

Data are mean±SD. Statistical analysis: one-way ANOVA.
Figure 1.
Figure 2.
Figure 3.
Figure 4.
Figure 5.