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Relationship Between Ventilatory Oscillations and Fractal Dimension of the EEG During Daytime Periodic Breathing in Heart Failure Patients

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Abstract—**In this study we investigated the existence and the nature of rhythmic changes in EEG associated with ventilatory oscillations in heart failure (HF) patients with periodic breathing (PB). Since nonlinear mechanisms are thought to be involved in the generation of EEG, we hypothesized that a mathematical approach based on nonlinear methods would provide relevant information on the association between EEG and ventilatory oscillations. We studied five patients who developed a sustained non-obstructive PB pattern during a 20 min laboratory recording. The time course of the fractal dimension of the EEG signal (HFD) was estimated dividing this signal into 2 s segments, with a 1.5 s overlap and computing for each EEG segment the fractal dimension using the Higuchi's algorithm. From the lung volume signal, an instantaneous minute ventilation (IMV) signal was also computed. The relationship between IMV and HFD was assessed by bivariate spectral analysis, computing the magnitude square coherence function (MSC). In four patients the value of the MSC was very high, ranging from 0.75 to 0.91, while in one patient the value was only 0.29.**

Our results suggest that in patients with PB, rhythmic changes in the EEG signal are very common and, when present, they are associated with ventilatory oscillations. We have also demonstrated that such oscillations can be detected very effectively by a technique based on nonlinear methods.

I. Introduction

Periodic breathing (PB), a cyclic rise and fall in ventilation in which hyperventilation phases are separated by periods of apnea or hypopnea [1, 2], is a breathing disorder very common in heart failure (HF) patients both during daytime and nighttime (prevalence: 50-85%). We have recently shown that in these patients, the measure of the duration of PB during the night provides strong independent prognostic information [3]. Mathematical models of respiratory control system support the hypothesis that PB represents a self-sustaining oscillation due to the loss of stability in the closed-loop chemical control of ventilation [4]. In HF patients, this loss of stability is very likely to occur, due to an impaired hemodynamics which determines slow circulation time between lungs and chemoreceptors and an enhanced loop gain [5, 6, 7].

There are, however, other factors which might play a role in the genesis of PB. Indeed, changes in ventilation may also occur due to fluctuations in sleep state during sleep onset. Therefore, if state instability contributes to PB, a certain degree of correlation would be expected between EEG activity and ventilation [8].

Pack and colleagues showed, using classical spectral techniques, the existence of a correlation between oscillations in the frequency content of the EEG and oscillations in ventilation in patients with nocturnal PB [9]. It has been suggested that nonlinear mechanisms are involved in the generation of EEG fluctuations [10]. We therefore hypothesized that a mathematical approach based on nonlinear methods would provide relevant information on the association between EEG and ventilatory oscillations.

Hence, we devised this study to assess the existence and the nature of rhythmic changes in EEG associated with ventilatory oscillations in HF patients with PB using a novel technique based on the estimation of the time course of the fractal dimension. Fractal dimension measures the self-similarity of a signal directly from the time series, can be used to analyze short time intervals (well below the conventional Rechtschaffen and Kales 30s scoring epochs) and has already been shown to be able to discriminate different EEG states [11].

II. Methods

A. Study protocol

Recordings for the study were carried out in our laboratory for the assessment of the autonomic nervous system. Since HF patients with breathing disorders have a poor quality of sleep and daytime somnolence, we expected that while lying supine in the quiet environment of the laboratory, at least some of them would show occasional fluctuations between wake and sleep.

After a preliminary screening in 11 patients, we studied five patients who developed a sustained non-obstructive PB pattern during the laboratory recording. Recordings were carried out between 9:00 a.m. and 11:30 a.m. and lasted 20 minutes. Subjects were requested to relax but not to fall asleep during the overall recording. We recorded lung volume (LV, Respitrace Plus, Non-Invasive Monitoring Systems), oronasal airflow (pressure detector), O2 saturation (SpO2, finger pulse oximeter), electro-encephalogram (EEG; derivations: O1-M2, O2-M1, C3-M2, C4-M1, 200 Hz sampling frequency, low-pass filtered at 50 Hz), electrooculogram (EOG; derivations: E1-M2, E2-M1) and chin electromyogram (EMG). Calibration of lung volume

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measurements was carried out by taking a simultaneous 30 s recording of the respiratory flow using a Fleisch pneumotachograph (47304A, Hewlett Packard). Flow was digitally integrated and regressed on the lung volume signal to obtain the calibration factor.

B. Signal processing

From the LV signal we derived a tidal volume signal by first fitting with two cubic splines respectively the end expiratory and end inspiratory points and then sampling at 2 Hz the difference between the two curves. A cubic spline was also used to interpolate the time series of breath duration, giving an instantaneous breath duration signal. Dividing the tidal volume signal by this spline, an instantaneous minute ventilation (IMV) signal was obtained [12].

The EEG signal from the central derivation with the highest signal-to-noise ratio was divided into 2 s segments (400 samples), with a 1.5 s overlap. This choice was a good compromise between stability of the computations and capability to track fast changes.

For each EEG segment, we computed the fractal dimension using the Higuchi's algorithm [11, 13]. From a given time series X(1), X(2), ... X(N), k new time series are constructed; each of them, Xmk, is defined as:

Xmk: X(m),X(m+k),X(m+2*k),..., X(m+int((N-m)/k)*k) m=1,2,...,k

where m and k are integers indicating the initial time and the interval time, respectively.

Then, for each series Xmk, the length Lm(k) is calculated by the normalised sum of the absolute value of the difference in the ordinates of pairs of points distant k samples, starting from the m-th sample. Finally, L(k) is obtained taking the mean value of Lm(k). If the curve is fractal-like with dimension D, then the L(k) value must be proportional to k^{-D}. Hence, if L(k) is plotted against k, for k ranging from 1 to kmax, on a double logarithmic scale, the data should fall on a straight line with a slope equal to -D. The estimate of the fractal dimension D is calculated as the angular coefficient of the linear regression of the graph ln(L(k)) vs. ln(1/k).

For each segment, we also computed the mean frequency in the alpha band [9]. Briefly, we estimated the power spectral density (PSD) by the Blackman-Tukey method, and from each PSD we extracted the mean frequency summing all the frequencies in the band 8-13 Hz weighted by the corresponding PSD value, and dividing by the sum of weights.

According to this procedure, both the fractal dimension and the mean frequency were computed every 0.5 s obtaining, after smoothing by a low-pass zero-phase bi-directional digital Butterworth filter, two new signals (HFD and Mfreq) giving the time course of these parameters.

The curves of LV, IMV, Mfreq and HFD were plotted together on the PC screen and a sub-record 10 min long with all signals free from artifacts and large transients was interactively selected [14]. Univariate spectral analysis was performed on the IMV signal to determine the frequency of PB. The relationship between different couples of signals was assessed either by graphical time domain analysis and by means of bivariate spectral analysis, estimating the magnitude square coherence function (MSC). The coherence function is a measure of the strength of linear association between two time series at each frequency, and is the analogue of the square of the correlation coefficient in linear regression analysis.

III. Results

Clinical and demographic characteristics of studied patients are given in Table I.

TABLE I
CHARACTERISTICS OF STUDIED PATIENTS

N=5	
Age, years	64 ± 5
Male, N	5
BMI, Kg/m2	27.3 ± 0.7
LVEF, %	26 ± 8
β-blockers, N	5
ACE inhibitors, N	5
Diuretics, N	5

Data are mean ± standard deviation. BMI: body mass index, LVEF: left ventricular ejection fraction

As shown in the first column of Table II, PB frequency ranged from 0.016 Hz to 0.020 Hz, values in line with those previously observed in similar patients and experimental conditions [15].

An example of recorded and computed signals is shown in Figure 1. It can be seen that in this patient (Patient #2) the HFD shows an oscillatory behaviour very similar to that of the IMV signal, with a remarkable synchrony between drops in fractal dimension and apneic/hypopneic events. The Mfreq signal is more erratic, and the oscillation at the PB frequency can be hardly detected by eye. Four out of the 5 studied patients showed patterns very similar to this one.

The signals from the patient with a different pattern (Patient #5) are shown in Figure 2. A well defined oscillation can be seen in IMV, but neither HFD nor Mfreq show any clear oscillatory behaviour.

The power spectral density of IMV and HFD and the MSC between these signals is shown in Figure 3 for Patient #2. The values of the MSC between IMV and HFD and between IMV and Mfreq at the PB frequency are reported in

Table II. It can be noticed that in four patients the values of the MSC between IMV and HFD are very high, ranging from 0.75 to 0.91, while this value is only 0.29 for Patient #5.

In all patients, the MSC values between IMV and Mfreq are much lower.

TABLE II.
FREQUENCY OF PERIODIC BREATHING (PB) AND MAGNITUDE SQUARE COHERENCE (MSC) BETWEEN MINUTE VENTILATION (IMV) AND HFD AND MFREQ RESPECTIVELY IN STUDIED PATIENTS

	PB freq (Hz)	MSC IMV vs HFD	MSC IMV vs Mfreq
Pt #1	0.017	0.91	0.69
Pt #2	0.017	0.89	0.77
Pt #3	0.016	0.89	0.64
Pt #4	0.020	0.75	0.49
Pt #5	0.017	0.29	0.09

PB: periodic breathing, MSC: magnitude square coherence, IMV: instantaneous minute ventilation, HFD: Higuchi fractal dimension, Mfreq: mean frequency in the alpha band

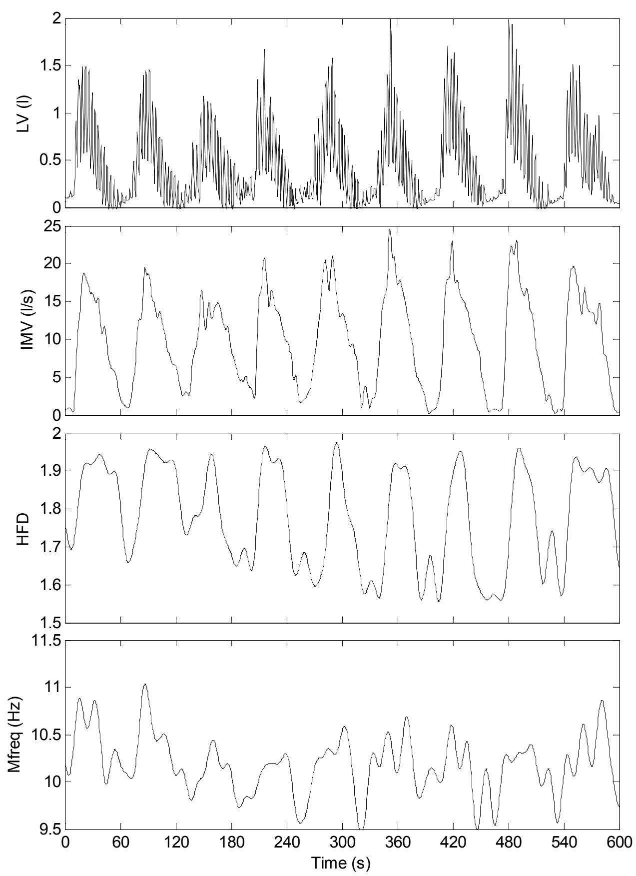

Figure 1 - Signals from Patient # 2.
From top to bottom: lung volume (LV), instantaneous minute ventilation (IMV), Higuchi fractal dimension (HFD) and alpha mean frequency (Mfreq).

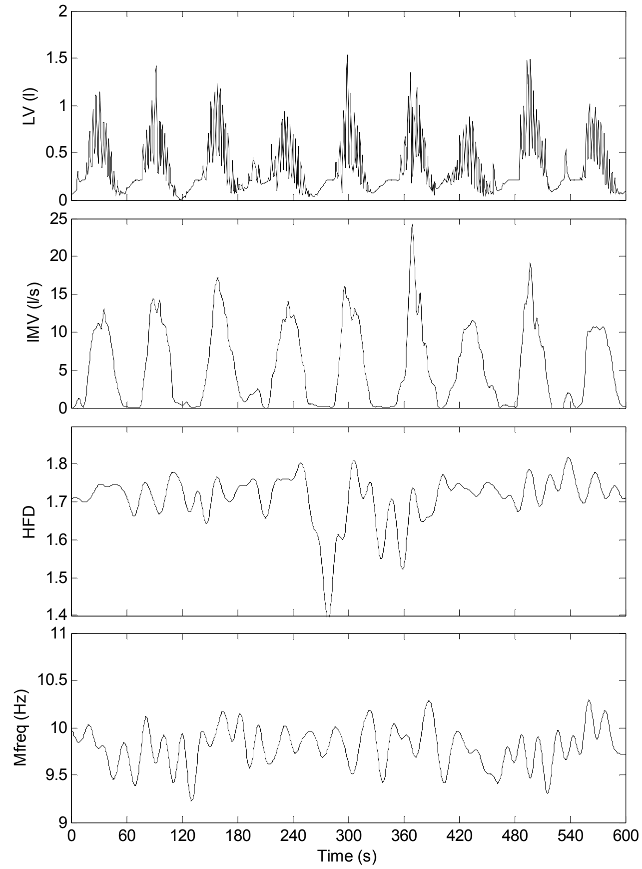

Figure 2 - Signals from Patient # 5.
From top to bottom: lung volume (LV), instantaneous minute ventilation (IMV), Higuchi fractal dimension (HFD) and alpha mean frequency (Mfreq).

IV. DISCUSSION

The novel findings of this study provide useful information for a better understanding of the physiopathological mechanisms involved in the development of PB in HF patients. We have found that in our sample of five patients with daytime supine PB, rhythmic changes in the EEG signal are common and, when present, they are associated with ventilatory oscillations. The high values of coherence between oscillations in fractal dimension and ventilation observed in most of our patients indicates a strong linear association. We have also demonstrated that such oscillations are better detected by a technique based on nonlinear methods rather than by classical spectral analysis techniques.

The existence of a correlation between oscillations in ventilation and the frequency content of the EEG was shown by Pack et al in elderly subjects during sleep, but no consistent relationship was observed in wakefulness [9]. In a recent study [16] we found that apneic/hypopneic events during daytime supine PB in HF patients are often associated with transitions from wakefulness to non-REM stage I-II sleep. These state transitions might provide a key to interpret the findings of the present study, since the drops in fractal dimension occurred during periods of apneas/hypopneas. Therefore, drops in fractal dimension appear to reflect the recurrent transitions from wakefulness to light sleep during PB. This finding is consistent with previous studies showing that the values of fractal dimension falls gradually during sleep [17].

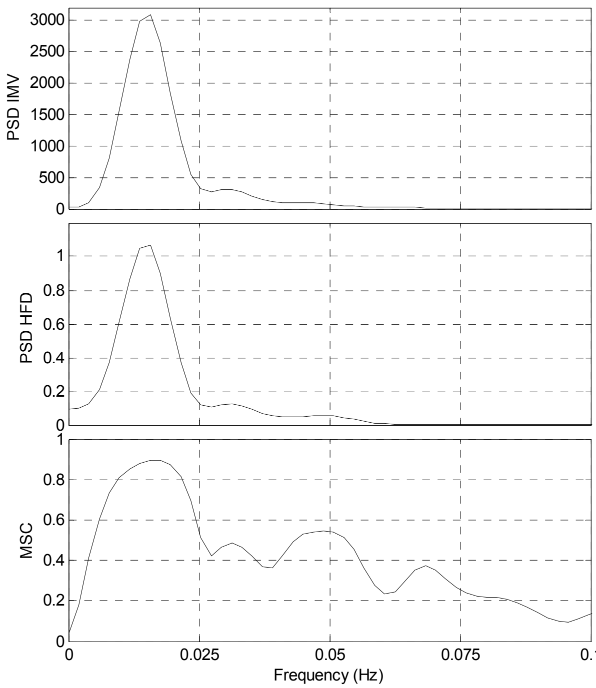

Figure 3 - Spectral measurements from Patient # 2.
From top to bottom: power spectral density (PSD) of instantaneous minute ventilation (IMV), power spectral density (PSD) of Higuchi fractal dimension (HFD), magnitude square coherence (MSC) between IMV and HFD.

It is widely accepted that chemical instability plays a major role in the development of PB in heart failure patients [4], but the contribution from state instability has not been fully elucidated. The results of this study confirm that EEG state instability do often occur during PB in HF patients, thus suggesting that it may coexist and interact with chemical instability.

Assessing wake-sleep transitions by EEG microstructure analysis using conventional interactive scoring, is a highly time consuming and demanding task. The new method proposed in this study for automatic analysis of the EEG seems to be a much more efficient tool to obtain a similar information. Besides the investigation of EEG-ventilatory oscillations during PB, such methodology might therefore be used in other fields in which the tracking of the wakefulness state is of concern (e.g. car driving). Obviously, due to the limited number of patients studied, our results need further confirmations from larger populations.

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