Chemical Instability, State Instability and Arousals in the Pathogenesis of Periodic Breathing in Heart Failure Patients

GD Pinna[1], R Maestri[1], E Robbi[2], MT La Rovere[2]

[1]Department of Biomedical Engineering, S Maugeri Foundation, IRCCS, Montescano, Italy
[2]Department of Cardiology, S Maugeri Foundation, IRCCS, Montescano, Italy

Abstract

Periodic Breathing (PB, cyclic waxing and waning of tidal volume) is very common in heart failure patients. It is commonly thought that PB is causedby an instability in the closed-loop chemical control of ventilation. Some investigators, however, have suggested that it may also result from fluctuations in sleep/wake state, namely state instability. The aim of this study was i) to set up a methodology for semi-automated state fluctuation analysis and ii) to assess whether state instability is a necessary condition for the development of PB. We carried out daytime and nighttime standard polysomnographic recordings in 9 patients. During daytime, 86%. of state transitions were synchronous with an apneic event. Synchronous state and ventilatory changes were also observed during nighttime, but during the deeper stages of sleep PB occurred without concurrent state transitions. We conclude that state instability is not necessary for the development of PB.

1.   Introduction

Nocturnal breathing disorders are very common in heart failure patients (prevalence: 50% - 70%) and typically manifest as a waxing and waning of tidal volume in which hyperventilation phases are separated by periods of apnea or hypopnea [1]. This breathing pattern has been commonly referred to as periodic breathing (PB). PB has also been frequently observed during daytime, supine resting recordings (prevalence around 50%) [2]. Several studies have recently shown that PB is a significant and independent predictor of poor prognosis in heart failure patients [2,3].

There are two major forms of PB: obstructive and central. Obstructive apneas/hypopneas are observed in about one-third of heart failure patients with breathing disorders and are caused by complete/partial collapse of upper airways during sleep. Central apneas/hypopneas, on the contrary, are caused by cyclic cessations/reductions of central neural drive to respiratory muscles, but the mechanisms responsible for this modulation of the respiratory drive have not been completely elucidated. Theoretical considerations and experimental data support the hypothesis that central PB is caused by an instability in the closed-loop chemical control of ventilation [4] due to the concurrent presence of a slow circulation time between lungs and chemoreceptors and enhanced loop gain.

Some investigators have suggested that fluctuations between wakefulness and non-REM (NREM) light sleep may importantly contribute to the development of ventilatory oscillations that are often observed in healthy individuals at sleep onset [5]. These fluctuations are characterized by repeated transitions between alpha and theta EEG activity and are referred to as state instability [6]. Therefore, in patients with heart failure and PB, state instability is likely to coexist and interact with chemical instability. Experimental evidence of state instability during PB in these patients, however, is lacking.

The aim of this study was twofold: 1) to set up a methodology for semi-automated state fluctuation analysis, and 2) to assess if and to what extent state instability is involved in the development of PB in heart failure patients.

2.   Methods

2.1.   Subjects and protocol

We studied 9 stable, optimally treated, male heart failure patients (age: 58±3 yrs, NYHA class: II-III, LVEF: 25±6%, ischemic etiology) with central PB as determined by a screening test.

Subjects were randomly allocated to two different recording protocols: i) a 20-min supine resting recording in controlled laboratory conditions between 9:00 a.m. and 11:30 a.m., and ii) an in-hospital nighttime recording between 11:00 p.m. and 6:00 a.m.. Before starting the daytime recording, patients were requested to relax but not fall asleep. Since heart failure patients, and particularly those with breathing disorders, have a poor

quality of sleep [3], we expected some wake-sleep transitions to occur during the recording.

Standard polysomnographic signals were acquired during both daytime and nighttime recordings: ECG, oronasal airflow (pressure detector), thoraco-abdominal movements (inductive plethysmography), O_2 saturation (finger pulse oximeter), electroencephalogram (EEG; derivations: O1-M2, O2-M1, C3-M2, C4-M1), electrooculogram (EOG; derivations: E1-M2, E2-M1) and chin electromyogram (EMG).

2.2. Detection of ventilatory events

We computed an uncalibrated lung volume signal by summing chest and abdominal movements. From this sum, we derived an instantaneous tidal volume signal by first fitting the end-expiratory and end-inspiratory points with two cubic splines and then sampling the difference between the two curves [2]. Apneic events were first detected as the regions where the tidal volume signal

dropped below 90% of the peak of the previous hyperventilation phase (smoothing was applied before peak detection). To refine the estimation of the onset and end of the event, the analysis software inspected the oronasal airflow signal and identified, respectively, the nadir preceding the first breath that was clearly reduced (90% criterion) and the beginning of the first breath that exceeded the 90% threshold (fig. 1). The final result was the construction of a ventilatory event diagram.

2.3. State fluctuation analysis

State fluctuation analysis was carried out using a hybrid approach that included visual scoring of the EEG according to standard rules [7] and automated software procedures. The overall process comprised 5 steps.

Step 1. Using a dedicated interactive software, an expert scorer, blind to respiratory signals, performed a manual scoring of EEG microstructure by identifying all
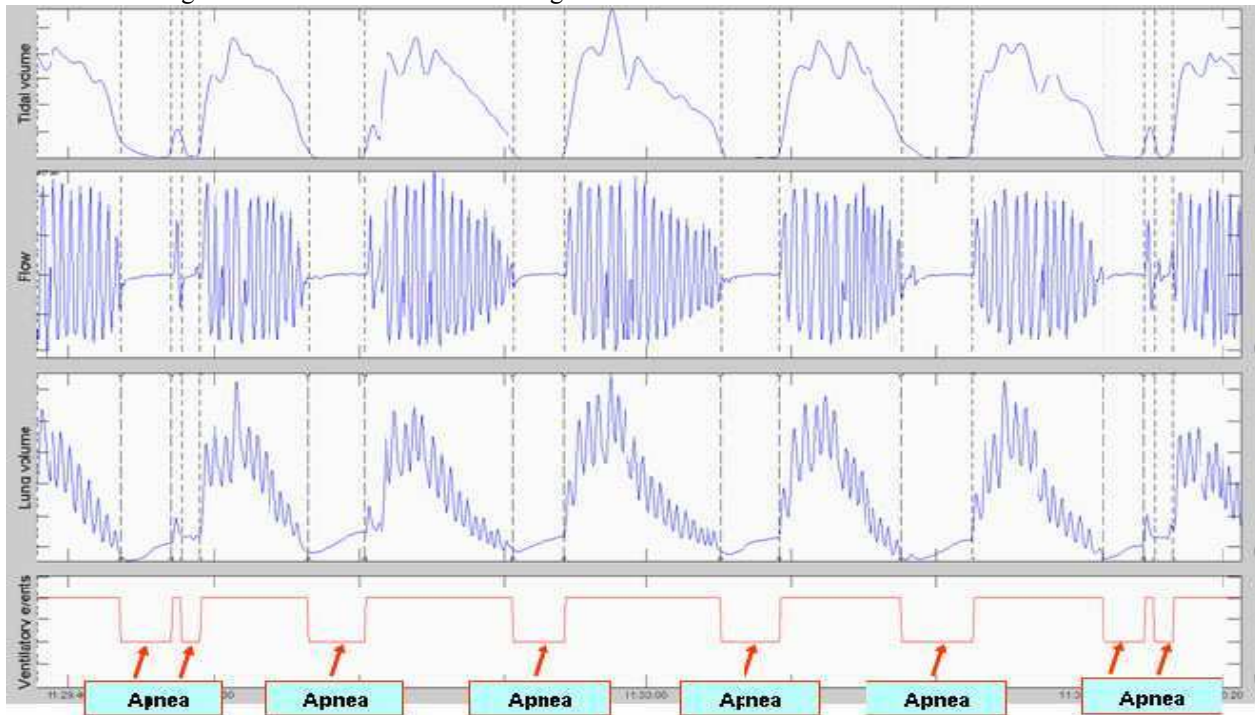

Fig. 1. Representative example of respiratory signals during an episode of periodic breathing. From top to bottom: 1) instantaneous tidal volume, 2) oronasal airflow, 3) lung volume, and 4) diagram of ventilatory events.

segments containing: i) artifacts, ii) unambiguous alpha activity, iii) unambiguous theta activity, iv) vertex sharp waves, K complexes, sleep spindles, and v) arousals. Moreover, the scorer accurately identified in the EOG tracings the eyes-open and eyes-closed periods, and all segments containing: i) awake eye movements, or ii)

slow eye movements (SEMs). Segments containing artifacts were discarded.

Step 2. An automated program identified the periods of dominant alpha and dominant theta activity during the eyes-closed condition, excluding segments i, iv and v, as defined above. The following is a detailed description of

the identification procedure. A band-pass bi-directional digital filter was applied to the occipital derivation with the highest signal-to-noise ratio to retain alpha activity. This signal was then squared to obtain the instantaneous alpha energy. Similarly, theta energy was derived from a central derivation and the instantaneous alpha/theta energy ratio was computed.

Step 3. The empirical probability density histogram of the alpha/theta ratio was separately estimated in the segments with unambiguous alpha activity and in the segments with unambiguous theta activity identified in step 1. A 5th order polynomial was fitted to both histograms to estimate the underlying probability density functions. The corresponding likelihood ratio was computed as:

$$L(\alpha/\theta) = \frac{\hat{p}(\alpha/\theta | \alpha_{\text{unambiguous}})}{\hat{p}(\alpha/\theta | \theta_{\text{unambiguous}})}$$

The optimal discriminating threshold (Thopt) of the detector was then determined as the value of the alpha/theta ratio where the likelihood ratio was=1.

Step 4. The EEG epochs where the instantaneous alpha/theta ratio was ≥Thopt were classified as "dominant alpha activity", while those were the ratio was < Thopt were classified as "dominant theta activity".

Step 5. Three different EEG states were automatically identified according to the following rules:

- W(wakefulness): includes all epochs with open eyes and those classified as dominant alpha activity or arousal.

- Theta1: includes all epochs classified as dominant theta activity that are preceded by a W state. This state continues until the occurrence of an arousal or the appearance of a K complex or sleep spindle. Theta1 corresponds to traditional stage NREM-1 [7].

- Theta2: includes all epochs classified as dominant theta activity that begin with a K complex or sleep spindle. This state ends when an arousal or a stable transition to state W occurs. Theta2 corresponds to traditional stage NREM-2 [7].

According to these definitions, the following state transitions were considered: i) W - Theta1, ii) Theta1 - W, iii) Theta1 - Theta2, iv) Theta2 - W.

The output of state transition analysis was a state-transition diagram having the form of a 3-level staircase waveform (W, Theta1 and Theta2). By relating this diagram to the diagram of ventilatory events, we were in a position to assess the time relationship between state changes and apneas. An apnea was considered to be synchronous with a state change if the onset and end of the apnea was within ±5 s the beginning and end of the

state transition.

3. Results

During daytime recordings, 3 out of the 5 studied patients showed a sustained PB during the overall 20 min recording, while in the remaining a normal or irregular breathing pattern was observed in 20% and 42% of the recording duraion. A representative segment of the lung volume signal together with the state transition and ventilatory event diagrams is shown in fig. 2. It can be seen that the patient's EEG state is highly unstable, with repetitive transitions between W and Theta1 states. The most striking result is the remarkable synchrony between all apneic events and the changes in state: apneas begin at the transition between W and Theta1, continue during Theta1 and end at the transition between Theta1 and W. It can also be appreciated that two state transitions were not associated with any ventilatory change. During PB, the time spent in the W, Theta1 and Theta2 state was, respectively, (mean±SD) 55±17%, 25±15 and 17±17. The proportion of apneic events occurring in synchrony with state transitions ranged between 57% and 100%, with a mean value of 86±17%. In two patients, most apneas included a Theta2 state.

During nighttime recordings, one subject developed PB while fully awake. At sleep onset, repetitive state transitions occurred in all subjects but they were synchronous with the cyclic pattern of PB only intermittently. During stage NREM-2, 30% to 70% of hyperventilation phases were associated with an arousal. Sustained ventilatory oscillations without concurrent fluctuations in state or spontaneous arousals were observed in 3/4 patients during stage NREM-3. PB never occurred during REM sleep.

4. Discussion and conclusions

This preliminary study shows that in heart failure patients EEG state changes between wakefulness and NREM light sleep are common during daytime supine PB and are very often associated with synchronous ventilatory changes. Cyclic apneas begin in synchrony with transitions from wakefulness to theta activity, and end in synchrony with transitions from theta activity to wakefulness. This result is consistent with previous observations in normal subjects at sleep onset [6] and with computer modelling studies on sleep-induced PB [8].

State changes synchronous with ventilatory were also observed during nighttime, particularly at sleep onset. If we had used a standard scoring of polysomnographic tracings [7], state changes would mostly have gone unnoticed because sleep staging is carried out on consecutive 30-s epochs and does not consider state changes that last < 15 s.
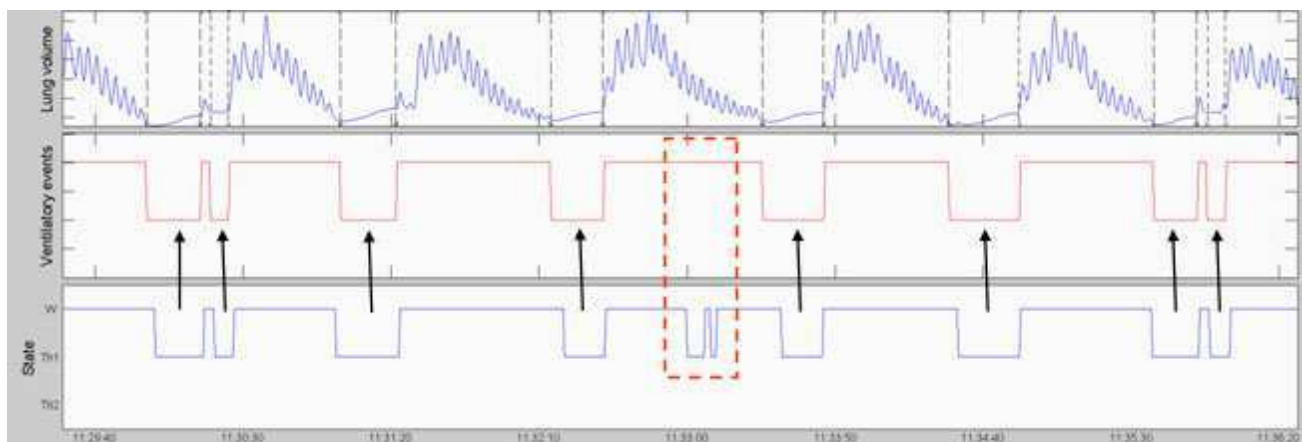
Fig. 2. From top to bottom: 1) lung volume during an episode of periodic breathing, 2) diagram of ventilatory events and 3) state transition diagram. The arrows indicate synchronous relationships between state changes and ventilatory events (apneas). The dashed box highlights two consecutive state transitions without simultaneous ventilatory events.

During nighttime, however, sustained episodes of PB without concurrent changes in state were consistently observed in the deeper stages of sleep (NREM-3). These findings clearly indicate that state instability is not necessary for the development of ventilatory oscillations.

Taken together, the results of this study support the widely accepted notion that chemical instability represents the underlying basic mechanism of PB in HF patients [9]. Under certain circumstances and to a different extent from patient to patient, however, state instability coexists and is temporally linked to chemical instability. It is therefore conceivable, as suggested by previous modelling studies [8], that the two mechanisms are mutually reinforcing. Our study does not lend support to this speculation, but provides the first observational evidence that such interaction might exist

References

[1] Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007; 9 (3): 251-257.

[2] La Rovere MT, Pinna GD, Maestri R, Robbi E, Mortara A, Fanfulla F, Febo O, Sleight P. Clinical relevance of short-term day-time breathing disorders in chronic heart failure patients. Eur J Heart Fail 2007; 9 (9): 949-954.

[3] Javaheri S, ShuklaR, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol 2007; 49 (20): 2028-2034.

[4] Khoo MC, Kronauer RE, Strohl KP, Slutsky AS. Factors inducing periodic breathing in humans: a general model. J Appl Physiol, Respirat Environ Excercise Physiol 1982; 53 (3): 644-659.

[5] Phillipson EA, Bowes G. Control of breathing during sleep. In: Handbook of Physiology, The Respiratory System. Control of breathing.. Cherniack NS and Widdicombe JG Editors, Bethesda, MD: American Physiological Society 1986; 2: 649-690.

[6] Trinder J, Whitworth F, Kay A, Wilkin P. Respiratory instability during sleep onset. J Appl Physiol 1992; 73 (6): 2462-2469.

[7] Iber C, Ancoli-Israel S, Chesson A, Quan SF for the American Academy of Sleep Medicine. The AASM Manual for the scoring of sleep and associated events: rules, terminology and technical specifications, first edition. Westchester, Illinois: American Academy of Sleep Medicine. 2007

[8] Khoo MC, Gottschalk A, Pack AI. Sleep-induced periodic breathing and apnea: a theoretical study. J Appl Physiol 1991; 70 (5): 2014-2024.

[9] Pinna GD, Maestri R, Mortara A, La Rovere MT, Fanfulla F, Sleight P. Periodic breathing in heart failure patients: testing the hypothesis of instability of the chemoreflex loop. J Appl Physiol 2000; 89(6): 2147-2157.

Address for correspondence

Ing. Gian Domenico Pinna,
Servizio di Bioingegneria
Fondazione S. Maugeri - IRCCS
Istituto Scientifico di Montescano,
I-27040, Montescano (PV), ITALY
giandomenico.pinna@fsm.it