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Instability of spontaneous breathing patterns in patients with persistent vegetative state

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Abstract

We investigated the breathing patterns of 27 patients in a persistent vegetative state (PVS) and 15 normal control volunteers. During the baseline period breathing air, 15 patients (the PVS-IB) exhibited irregular breathing (IB), whereas the other 12 (the PVS-OB) displayed oscillatory breathing (OB). Both groups maintained an average value for tidal volume (V_T), total breath duration (T_{TOT}), minute ventilation ($\dot{V}_E$), oxygen saturation (SpO_2) similar to the control, but the PVS-OB displayed significantly lower end-tidal CO_2 tension ($P_{ET}CO_2$) than the control. The V_T, T_{TOT}, $\dot{V}_E$ and $P_{ET}CO_2$ of the PVS-OB showed cyclic changes. The coefficients of variation of V_T, T_{TOT} and $\dot{V}_I$ were: PVS-OB > PVS-IB > control. Inhalation of 100% O_2 significantly reduced the respiratory variability and prevented OB of the PVS-OB. We concluded that PVS patients display respiratory instability and that brain damage, hypocapnia, and/or increased loop gain of arterial chemoreceptors may contribute to the pathogenesis of OB, whereas brain damage presumably may be the cause of IB.
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Keywords: Control of breathing; Oscillatory breathing; Irregular breathing; Brain damage; Peripheral chemoreceptors; Respiratory plasticity

1. Introduction

Persistent vegetative state (PVS) resulting from traumatic or non-traumatic brain injuries is a state of eyes-open unconsciousness with sleep–wake cycles in which the patients are incapable of awareness of themselves or their environment for at least 1 month (The Multi-Society Task Force on PVS, 1994; Zeman, 1997). Due to damage to the cerebral hemispheres, PVS patients show no evidence of sustained, reproducible, purposeful, or voluntary behavior responses to visual, auditory, tactile, or noxious stimuli, and also

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show no language comprehension or expression (The Multi-Society Task Force on PVS, 1994). Because PVS patients have complete or partial preservation of the hypothalamic and brainstem autonomic functions, they have spontaneous respiration (The Multi-Society Task Force on PVS, 1994; Zeman, 1997). It is known that the rhythmic breathing patterns of human arise from a brainstem mechanism and are regulated by various factors such as higher center inputs as well as via feedback loops of the visceral and somatic afferents (Caruana-Montaldo et al., 2000). PVS patients apparently have defects in cortical influences on, and other higher center inputs to, respiratory control mechanisms. Additionally, clinical studies have reported that acute brain damage with lesions at various diverse sites may disturb breathing (North and Jennett, 1974). Furthermore, the long period of time after acute brain damage in PVS patients may make possible adjustments in their control of breathing following the initial central disturbance. While PVS patients appear to have a type of unique respiratory control, their spontaneous breathing patterns have not been well characterized.

Breathing patterns can be described by way of mean values and variability by a variety of respiratory parameters (Tobin et al., 1983a; Tobin et al., 1988). For example, tachypnoea and hyperventilation represent breathing patterns with increases in respiratory rate and minute ventilation, respectively. On the other hand, irregular (IB) and oscillatory breathing (OB) represent breathing patterns with increases in non-periodic and periodic variations, respectively, as a manifestation of respiratory instability (Bruce and Daubenspeck, 1995). Deviation of either mean values or variability of respiratory parameters from normal levels may reflect that individuals are under pathophysiological conditions and suffer from defects in respiratory control (Tobin et al., 1983b; Loveridge et al., 1984; Brack et al., 2002; Bien et al., 2004). For instance, OB is often associated with diseases such as congestive heart failure (Cherniack and Longobardo, 1973; Tobin and Snyder, 1984; Naughton, 1998; Caruana-Montaldo et al., 2000), neurological disorders (Brown and Plum, 1961; Rout et al., 1971; Cherniack and Longobardo, 1973; North and Jennett, 1974; Tobin and Snyder, 1984; Caruana-Montaldo et al., 2000) and prolonged hyperventilation (Cherniack and Longobardo, 1973), and in some cases, is linked to disease mortality (Rout et al., 1971; Ponikowski et al., 1999; Sin et al., 2000). Since this form of respiratory instability is largely reduced or abolished by inhalation of 100% O_2, factors such as abnormalities in the arterial chemoreceptor mechanism, hypocapnia, hypoxia and heart-to-brain circulatory delay have been suggested to contribute to its development (Longobardo et al., 1966; Naughton, 1998; Ponikowski et al., 1999; Leung and Bradley, 2001).

The objectives of this study were: (1) to characterize the spontaneous breathing patterns in PVS patients; (2) to investigate whether they display respiratory instability and if so; (3) to assess the effects of inhalation of 100% O_2 on their respiratory instability.

2. Materials and methods

2.1. Subjects

Twenty-seven PVS patients from three nursing homes were included in this study over the period 1 January to 30 June 2003 as the experimental group. They all met the following criteria: (1) unaware of self and environment for at least 12 months due to severe brain damage from various etiologies; (2) completely bedridden, not able to take care of themselves and to communicate with other persons; (3) their Glasgow coma scale (Shah, 1999) was $\leq$8 and their Barthel Index Score (Mahoney and Barthel, 1965) was <20; (4) had been able to breathe room air on their own through the tracheostomy tube and free form ventilator support for at least 6 months with acceptable blood gases data; (5) clinically and hemodynamically stable, and having no fever and (6) free from heart failure, pulmonary and renal diseases, and signs of increased intracranial pressure or infection. Another 15 age- and sex-matched normal volunteers were included as the control group during the same study period and were free from cardiopulmonary, neuromuscular and renal diseases, and without histories of smoking and congestive heart failure. These normal volunteers were instructed regarding the study procedure, but were blinded to the study design. For all subjects, sedatives, hypnotics and narcotics were discontinued for at least 8 h prior to the study. Appropriate institutional review board approval was obtained and written informed consent was obtained from the patient's legal guardian and from the control subjects.

2.2. Measurements of physiological parameters

Each recording period of physiological parameters lasted for 30 min. A computerized pulmonary mechanics monitoring system (CO_2SMO + model 8100, Novametrix Medical Systems, CT, USA) was used to create a continuous record of pressure, volume, flow, end-tidal CO_2 ($P_{ET}CO_2$) and oxygen saturation (SpO_2) during respiration. For this purpose, an adult flow and CO_2 sensor were placed at the opening end of the tracheostomy tube of the PVS patients and a CAPNO$_2$ mask^{TM} (Novametrix Medical Systems) was employed for the volunteers. A pulse oximeter sensor was placed on the subject's index finger. The respiratory signals were sampled at 100 Hz, displayed and stored in a computer for later analysis of the breathing patterns. The data acquisition methods for $P_{ET}CO_2$ and SpO_2 were on a single-breath mode and with an averaging time of 2 s, respectively. Arterial blood pressure was measured by a portable, non-invasive device (Baumanometer, W.A. Baum Co. Inc., NY, USA) before and after each recording period.

2.3. Protocol

All subjects were included during the daytime when they were awake and lying on a bed with upper body elevated to a 30° angle. All measurements were performed at least 1 h after consuming a meal. Airway secretions of the PVS patients were suctioned out when necessary. The recording did not start unless patients displayed a stable breathing pattern with low deviation in respiratory parameters. Recordings of physiological parameters were performed for three 30 min periods; the subjects breathed room air first (baseline), then 100% O_2 and then room air again with an elapsed time of 5 min between any two recording periods. At the end of 2nd air-breathing period, if the breathing pattern still had observable differences from baseline breathing pattern, more periods of recording were performed to study the recovery time. During each recording period, the subject's posture and other management procedures were kept the same. The measurement was terminated if subjects had one or more of the following signs of cardiopulmonary distress: tachypnoea (respiratory rate > 35 breaths/min for ≥5 min); hypoxemia (arterial oxygen saturation measured by the pulse oximeter ≤85% for ≥30 s); significant changes in heart rate (heart rate >140 beats/min or a sustained increase or decrease >20% from baseline for ≥1 min); any significant arrhythmia for ≥30 s; agitation, diaphoresis, or anxiety. One day after the inclusion day, an additional measurement was performed for each PVS patient to study the consistency of the displayed breathing pattern. For this purpose, a chest band was placed at the nipple level on the rib cage to continuously measure respiratory movement over a 30 min period using a respiratory inductance plethysmograph (Respigraph; NonInvasive Monitoring Systems, FL, USA) every 2 h over a 24 h period.

2.4. Data analysis

For each subject, data of expired tidal volume (V_T), inspiratory time (T_I), expiratory time (T_E), total breath duration (T_{TOT} or $T_I + T_E$), peak inspiratory flow ($\dot{V}_I$), minute ventilation ($\dot{V}_E$), $P_{ET}CO_2$ and SpO_2 were analyzed on a time-series breath-by-breath basis for each 30 min recording period using Analysis + Respiratory Mechanics Analysis Software (Novametrix Medical Systems), and their average values and coefficients of variation over this period were calculated. Artifacts such as coughing or swallowing were not included in the analysis. Spectral analysis of V_T was modified from that previously reported (Äärimaa and Välimäki, 1988; Ponikowski et al., 1999). In brief, power spectral analysis of the breath-by-breath data was re-sampled at evenly spaced time intervals of 8 ms by a linear interpolation. The mean value of each set of data was subtracted from the time series data to remove the direct current component. A Hanning window in the time domain was used to attenuate the leakage effect. The time series data was appended by zero-valued samples to the size of 262144 (2^{18}) data points. The resulting power spectra have a theoretic resolution of 4.77×10^{-4} Hz. The graph of the power spectrum was smoothed by a moving average filter set at a size of 15. The density values of total power and very-low-frequency (VLF) power were calculated as the integral under the power spectral function with a frequency range between 0.001–0.5 Hz (oscillatory cycle duration = 1000–2 s or 0.06–30 cycles/min) and 0.003–0.04 Hz (oscillatory cycle duration = 333–25 s or 0.18–2.4 cycles/min), respectively. The frequency range of VLF power was chosen to cover the possible range of cycle duration of OB reported previously (Bruce and Daubenspeck,

1995; Hall et al., 1996; Khoo, 1999; Ponikowski et al., 1999).

2.5. Statistical analysis

Categorical variables were analyzed by X^2 or Fisher exact test. Non-parametric comparisons among the three study groups were performed using the Kruskal–Wallis test. The Mann–Whitney test with Bonferroni correction was applied for any pairwise comparison between groups. For comparing the data with or without oxygen inhalation, the Wilcoxon Signed Ranks test was applied. The Pearson product–moment correlation analysis was applied to assess the relationship between changes in V_T and T_I, changes in V_T and T_E, or changes in V_T and $\dot{V}_I$. All data were analyzed with SPSS software (Standard Version 11.0.1, SPSS Inc., IL, USA) and presented as mean ± S.D. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline breathing patterns

In general, the baseline breathing patterns of the 15 normal subjects (the control group) tested were relatively stable (Figs. 1A and 2A). In contrast, 15 of the 27 PVS patients studied exhibited IB with irregular changes in both V_T and T_{TOT} (the PVS-IB group; Figs. 1B and 2B), whereas the other 12 displayed OB (the PVS-OB group; Figs. 1C and 2C). The OB was characterized by cycles of gradually increasing V_T followed by gradually decreasing V_T, leading to regular waxing and waning of ventilation (Figs. 1C and 2C); the minimal V_T of each oscillatory cycle was below 50% of the maximal V_T, as defined previously (North and Jennett, 1974). In these 12 PVS patients, 5 of them had Cheyne–Stokes respiration (OB with apnoea) and the other 7 had periodic breathing (OB without apnoea). In each of the patient displaying OB, T_{TOT}, $\dot{V}_E$ and $P_{ET}CO_2$ also showed cyclic changes, whereas the variations in SpO_2 did not exhibited an oscillatory pattern (Fig. 2C). As a result, the fluctuation of V_T had a positive correlation with those of T_{TOT} and $\dot{V}_E$, and an inverse correlation with that of $P_{ET}CO_2$ (Fig. 2C). Further analysis of the correlation between changes in V_T and T_I, changes in V_T and T_E, and changes in V_T and $\dot{V}_I$ revealed that the PVS-IB group had correlation coefficients of 0.423, 0.432 and 0.580, respectively, whereas the PVS-OB group had correlation coefficients of 0.304, 0.271 and 0.663, respectively. Additional measurements by the respiratory inductance plethysmograph confirmed that the breathing pattern displayed by each PVS patient was consistent during a 24 h period.

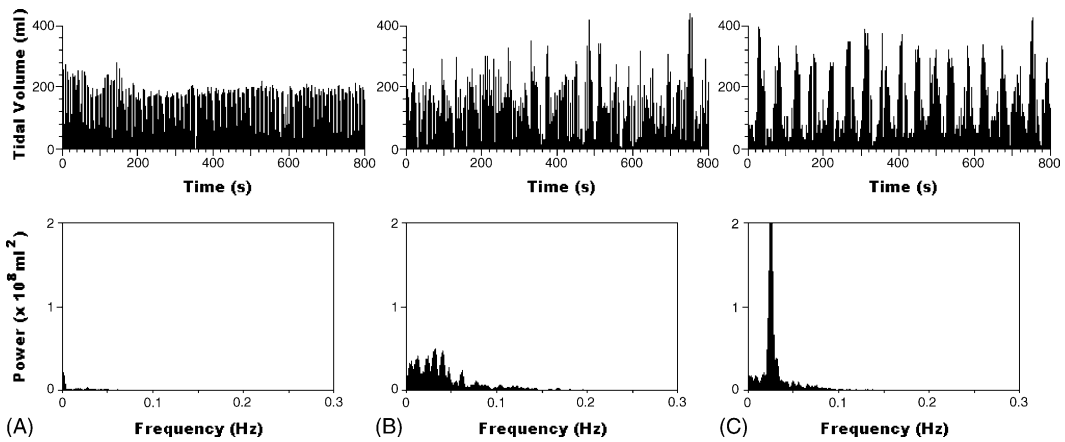

Fig. 1. Tracings and results of spectral analysis of tidal volume in one normal subject (A), 1 patient with persistent vegetative state (PVS) displaying irregular breathing (B) and 1 patient with PSV displaying oscillatory breathing (C). Note that PVS patient has an irregular or oscillatory breathing and this displayed a more variable tidal volume and hence a greater power density, compared to the normal subject. Only the PVS patient with oscillatory breathing had a clear central peak of power in the very-low-frequency band (0.003–0.04 Hz).

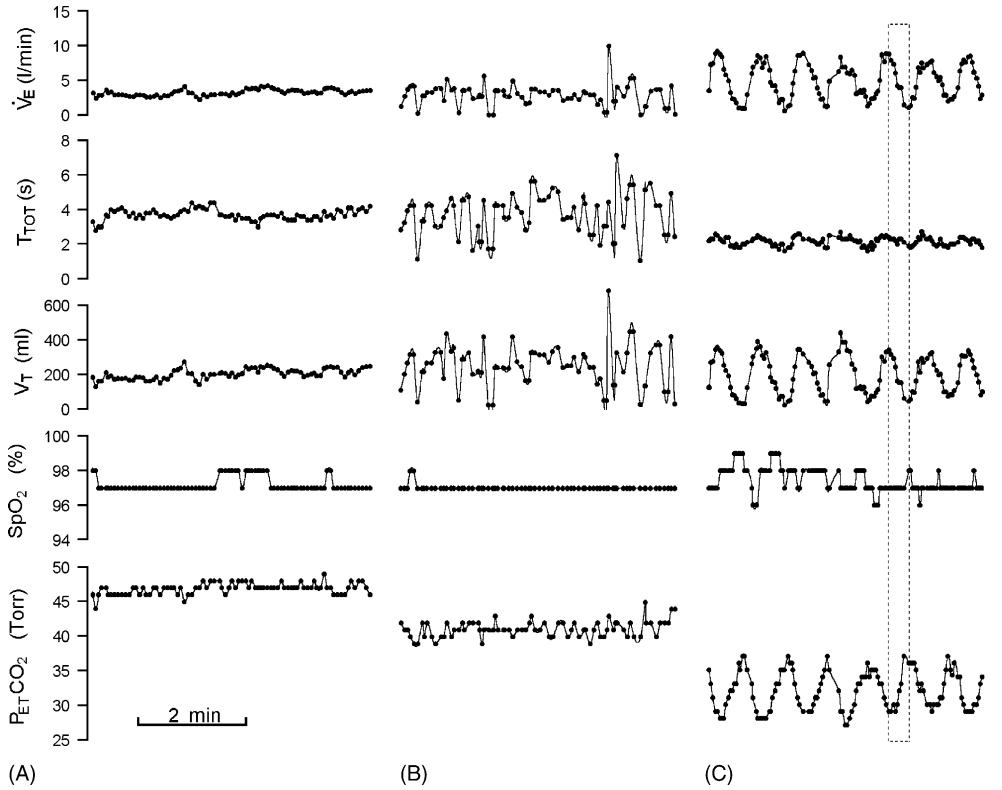

Fig. 2. Five-minute breath-by-breath tracings of minute ventilation ($\dot{V}_E$), total breath duration (T_{TOT}), tidal volume (V_T), arterial O_2 saturation (SpO_2) and end-tidal CO_2 tension ($P_{ET}CO_2$) in one normal subject (A), 1 patient with persistent vegetative state (PVS) displaying irregular breathing (B) and 1 patient with PSV displaying oscillatory breathing (C). Note that the cyclic change in V_T had a positive correlation with those of T_{TOT} and $\dot{V}_E$, and an inverse correlation with that of $P_{ET}CO_2$, but the changes of SpO_2 did not exhibit a cyclic pattern in the PVS patient with oscillatory breathing.

3.2. Subject characteristics

The physical and clinical characteristics of the three study groups are listed in Table 1. As shown, PVS patients had various etiologies. The PVS-OB group had a significantly higher baseline systolic and diastolic blood pressure and a significantly lower $P_{ET}CO_2$, as compared to the control group; these three parameters in the PVS-OB group did not differ from those in the PVS-IB group. Other characteristics did not vary among the three study groups.

3.3. Average values and coefficients of variation

Table 2 shows the average values and coefficients of variation of the four breathing pattern parameters measured in the three study groups. As shown, the differences in average values were minimal among groups. Only the average value of $\dot{V}_I$ in the PVS-OB group was significantly greater than those in the control group. Other pairwise comparisons of average values between any two groups showed no statistical significance. Conversely, coefficients of variation differed in many aspects among the three study groups. Data for V_T, T_{TOT} and $\dot{V}_I$ in the PVS-IB group were significantly greater than the same data for the control group. Furthermore, the data for V_T, T_{TOT}, $\dot{V}_I$ and $\dot{V}_E$ in the PVS-OB group were significantly greater than the data for the control and the PVS-IB groups.

3.4. Spectral analysis

Spectral analysis of the V_T was then employed to further characterize OB and the occurrence of a discrete

Table 1
Physical and clinical characteristics of the three study groups

Study groups	Control (n = 15)	PVS-IB (n = 15)	PVS-OB (n = 12)
Age (years)	61.27 ± 12.56	57.27 ± 15.59	69.25 ± 15.10
Sex (male/female)	8/7	9/6	7/5
BMI (kg/m^2)	22.64 ± 3.08	22.37 ± 2.74	21.95 ± 2.80
Vegetative duration (months)	–	82.60 ± 61.73	74.33 ± 36.13
Glasgow coma scale	Clear	7.33 ± 0.72	7.17 ± 0.83
Tracheostomy tube ID	–	7.13 ± 0.55	7.42 ± 0.90
Systolic blood pressure (mmHg)	116.67 ± 11.57	122.00 ± 21.34	130.17 ± 18.55*
Diastolic blood pressure (mmHg)	69.20 ± 8.27	75.77 ± 13.44	79.33 ± 10.66*
Pulse rate (min^{-1})	71.80 ± 9.36	79.21 ± 11.35	80.84 ± 13.47
Oxygen saturation (%)	96.59 ± 1.39	96.31 ± 1.07	95.32 ± 1.63
End-tidal CO_2 (Torr)	43.13 ± 3.38	39.99 ± 4.38	37.20 ± 5.22*
Etiology of vegetative status, no. (%)			
Cerebrovascular accident	–	6 (40.0)	8 (66.7)
Hypoxic encephalopathy	–	3 (20.0)	3 (25.0)
Head injury	–	3 (20.0)	1 (8.3)
Brain tumor post craniotomy	–	1 (6.7)	–
Senile dementia	–	1 (6.7)	–
Late form of congenital syphilis	–	1 (6.7)	–

Data are mean ± S.D. PVS: persistent vegetative state; PVS-IB: PVS patients with irregular breathing; PVS-OB: PVS patients with oscillatory breathing; BMI: body mass index (body weight in kg body^{-1} height in m^{-2}); ID: internal diameter. Control, normal subjects. Systolic and diastolic blood pressure was measured 3 min before the first 30 min recording period. Data of pulse rate, oxygen saturation and end-tidal CO_2 were mean values averaged over the first 30-min recording period during breathing air.
* $P < 0.017$ vs. the Control group.

well-defined peak in the VLF band (0.003–0.04 Hz) was considered as evidence of OB, as suggested previously (Ponikowski et al., 1999). As shown in Fig. 1, the cyclic change in V_T measured in PVS-OB patients resulted in a greater power density, compared to those of the PVS-IB patients and control subjects. Additionally, the cyclic change in V_T in the PVS-OB patient had a clear central peak of power around 0.025 Hz, whereas the change in V_T in the control subject and PVS-IB patient had no such peak (Fig. 1). As a group, the mean frequency of the central peak of power in the PVS-OB group was 0.021 ± 0.010 Hz (range, 0.035–0.004 Hz;

Table 2
Comparisons of average values and coefficients of variation of breathing pattern parameters measured for the three study groups

Study groups	Control (n = 15)	PVS-IB (n = 15)	PVS-OB (n = 12)
Average values			
Tidal volume (ml)	286 ± 59	235 ± 82	238 ± 48
Total breath duration (s)	3.77 ± 1.01	3.24 ± 0.82	2.93 ± 1.01
Peak inspiratory flow (l/min)	14.81 ± 3.19	16.59 ± 3.96	21.06 ± 5.76*
Minute ventilation (l/min)	4.75 ± 1.34	4.43 ± 1.36	5.16 ± 1.50
Coefficients of variation			
Tidal volume	0.17 ± 0.05	0.28 ± 0.10*	0.54 ± 0.10*,**
Total breath duration	0.12 ± 0.03	0.19 ± 0.08*	0.30 ± 0.12*,**
Peak inspiratory flow	0.15 ± 0.05	0.29 ± 0.09*	0.40 ± 0.08*,**
Minute ventilation	0.12 ± 0.05	0.16 ± 0.05	0.30 ± 0.13*,**

Data are mean ± S.D. PVS: persistent vegetative state; PVS-IB: PVS patients with irregular breathing; PVS-OB: PVS patients with oscillatory breathing. Control, normal subjects. For each parameter, mean value was averaged over the first 30-min recording period during breathing air.
* $P < 0.017$ vs. the Control group.
** $P < 0.017$ vs. PVS-IB group.

$n = 12$), which corresponded to a mean duration of oscillatory cycle of 45 ± 13 s (range, 28–74 s). Both total power (21094 ± 10212 ml^2; $n = 12$) and VLF power (15140 ± 8313 ml^2; $n = 12$) of V_T for the PVS-OB group were significantly greater than those for the PVS-IB (total power, 4212 ± 4293 ml^2; VLF power, 2705 ± 3034 ml^2; $n = 15$) and control groups (total power, 1789 ± 1374 ml^2; VLF power, 992 ± 845 ml^2; $n = 15$). Although the total power and VLF power of V_T in the PVS-IB group were numerically greater than those in the control group, their statistical comparisons did not reach a significant level.

3.5. Effect of O_2 inhalation on breathing patterns

Among the 42 subjects studied, 8 in the control group, 7 in the PVS-IB group and 11 in the PVS-OB group received 100% O_2 inhalation; other normal subjects and the guardians of other PVS patients did not agree to receive this test. O_2 inhalation significantly increased mean SpO_2 in the three study groups, but it did not significantly alter their mean $P_{ET}CO_2$ (Table 3). In general, O_2 inhalation did not affect the breathing pattern in the control group and the IB in the PVS-IB group. As a result, O_2 inhalation did not significantly affect either average values (Fig. 3) or coefficients of variation (Fig. 4) of the four breathing pattern parameters in these two study groups. Contrastingly, O_2 inhalation abolished the OB in the PVS-OB group (Fig. 5); it took <30 s in 9 patients, ∼5 min in 1 patient and ∼10 min in the remaining one for the OB to disappear. As a result, although O_2 inhalation did not significantly affect the average values of the four breathing pattern parameters measured in the PVS-OB groups (Fig. 3), it significantly reduced their coefficients of variation (Fig. 4). The abolition of OB could also be evidenced by the disappearance of the central peak in the VLF band (Fig. 5B) and by the significant reduction of total power and VLF power in the spectral analysis of V_T (Fig. 6). After OB was abolished, each of these patients displayed IB (Fig. 5B), which was sustained during the rest of the O_2 inhalation period. Within 5 min after termination of O_2 inhalation, the increased mean SpO_2 in the three study groups returned to their baseline values (Table 3). However, 4 patients took <5 min for their OB to recover (Fig. 5C), whereas the other 7 patients took 7.5, 8, 20, 35, 45, 155 and 460 min, respectively. As a group, except for the coefficient of variation of V_T, the coefficients of variation for the three other breathing parameters recovered to their baseline levels during the recording period from 5 min to 35 min after termination of O_2 inhalation (Fig. 4).

Table 3
Comparisons of average values of oxygen saturation and end-tidal CO_2 measured during breathing room air, 100% O_2 and room air again for the three study groups

Groups	Normal ($n = 8$)	PVS-IB ($n = 7$)	PVS-OB ($n = 11$)
Oxygen saturation (%)			
Air (baseline)	97.97 ± 0.76	96.03 ± 0.71	95.39 ± 1.69
O_2	99.48 ± 0.44*	99.13 ± 0.50*	99.29 ± 0.52*
5 min after O_2	98.25 ± 1.04	96.71 ± 1.89	97.00 ± 0.77
End-tidal CO_2 (Torr)			
Air (baseline)	44.47 ± 3.91	41.94 ± 3.45	37.15 ± 5.47
O_2	43.70 ± 3.81	40.03 ± 2.65	36.18 ± 6.12
5 min after O_2	44.13 ± 3.41	40.43 ± 3.60	35.64 ± 5.54

Data are mean ± S.D. PVS: persistent vegetative state; PVS-IB: PVS patients with irregular breathing; PVS-OB: PVS patients with oscillatory breathing. Control, normal subjects. Data of Air (baseline) and O_2 are mean values averaged over the 30-min recording period breathing room air and 100% O_2. Data measured 5 min after O_2 are mean values averaged over the first minute recording period breathing room air after termination of O_2 inhalation.

* $P < 0.05$ vs. Air (baseline).

4. Discussion

Results of this study demonstrated that our PVS patients consistently exhibited either IB (56% of the patients studied) or OB (44% of the patients studied). Both groups maintained average values of V_T, T_{TOT}, $\dot{V}_E$ and SpO_2 similar to those of the control group. However, the PVS-OB group, but not the PVS-IB group, displayed a significantly lower average $P_{ET}CO_2$ than that of the control group. Both the IB and the OB groups showed increased respiratory variability as evidenced by the greater coefficients of variation of respiratory parameters measured and by the larger total power of V_T in the spectral analysis, when compared to the control group. Since OB, but not IB, displayed a discrete well-defined peak in the VLF band in the spectral analysis of V_T, the deviations of respiratory variability in IB and OB appear to be due to increases in non-periodic and periodic variations of breathing pattern, respectively. These results indicate that PVS patients were display-

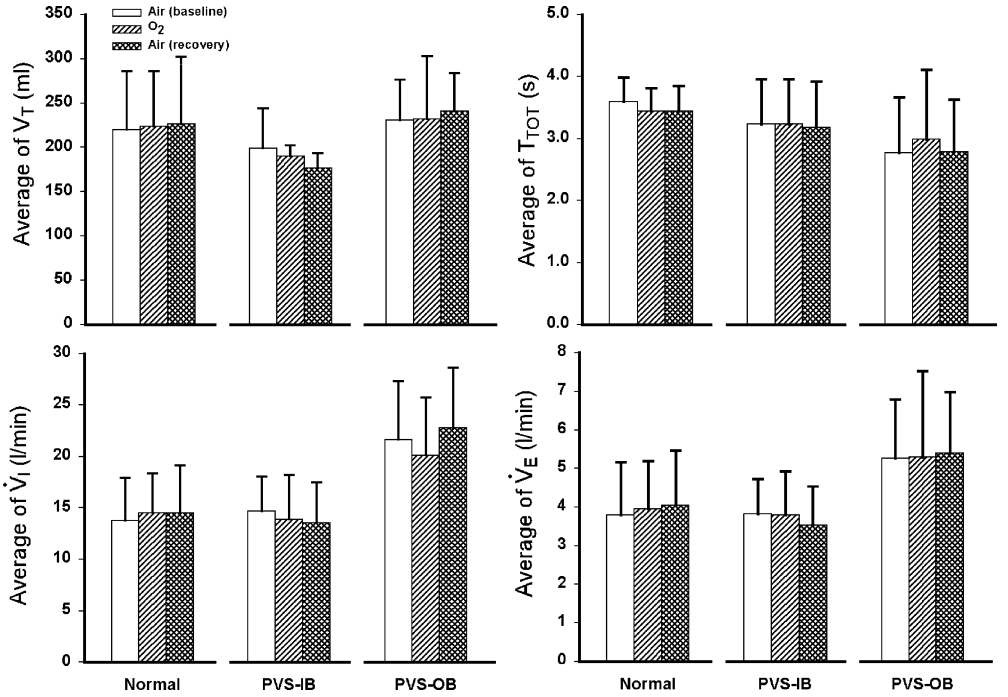

Fig. 3. Average values of tidal volume (V_T), total breath duration (T_{TOT}), peak inspiratory flow ($\dot{V}_I$) and minute ventilation ($\dot{V}_E$) in eight normal subjects, 7 patients with persistent vegetative state (PVS) displaying irregular breathing (PVS-IB) and 11 PVS patients displaying oscillatory breathing (PVS-OB) for three 30-minute periods during breathing air, 100% O_2 and then air again. Five minute elapsed between any two recording periods. The data are mean ± S.D. Note that no significant change in the average values for all four parameters among three experimental conditions in each group was found.

ing two distinct types of abnormal breathing patterns, both of which reflect respiratory instability.

The exact reasons why PVS patients have respiratory instability are not totally understood. The loss of awareness in PVS patients has been shown to result from bilateral damage in the cerebral cortex, intra- and subcortical connections in the cerebral hemispheric white matter, and thalamus (Kinney and Samuels, 1994). Both IB and OB are commonly found in patients with acute brain damage (Rout et al., 1971; North and Jennett, 1974) and have been attributed to damage to the respiratory neurones themselves (Kinney and Samuels, 1994; Zeman, 1997) or the loss of non-specific input from higher centers (Wang et al., 1957). Consequently, the brainstem mechanism and its interaction with suprabulbar mechanisms involved in maintaining respiratory stability are disturbed. Apart from the disturbance of central neural mechanisms, other factors may also contribute to the respiratory instability in PVS patients. For example, in the non-periodic instability, additional respiratory variability may be introduced by modulations from airway meachnoreceptors, peripheral chemoreceptors, or cerebral blood flow (Bruce and Daubenspeck, 1995). In the PVS-IB group, the fluctuation of V_T correlated with $\dot{V}_I$, T_I or T_E, but it was more related to the fluctuation of $\dot{V}_I$ and thus to the change of respiratory drive. It is speculated that the increase in V_T may lead to an increase in T_E via the Hering–Breuer reflex, which contributes to the increased variability observed in the PVS-IB group. Additionally, PVS patients usually have disorders in cerebral blood flow (Gotoh et al., 1969; Kinney and Samuels, 1994; The Multi-Society Task Force on PVS, 1994) and variations in the cerebral blood flow may alter the discharges of central chemoreceptors and thus affect breathing pattern (Bruce and Daubenspeck, 1995). Our PVS patients have been bedridden for >12 months and this may also have possibly altered their pulmonary function. They have received a tracheostomy, which allows them to bypass the upper airways. However, these factors are

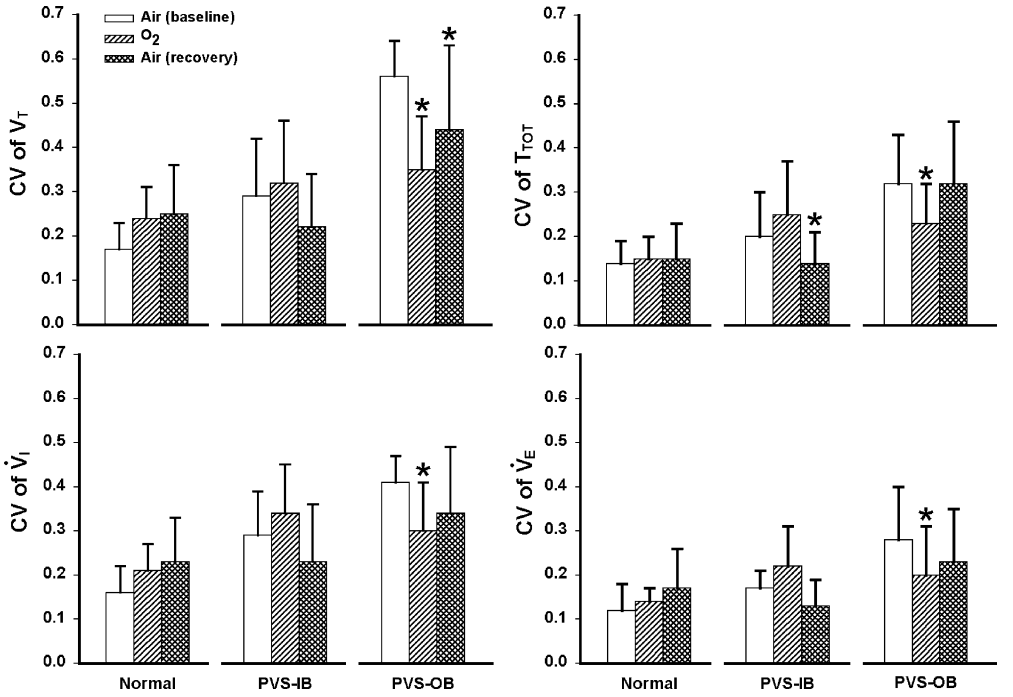

Fig. 4. Coefficients of variation of tidal volume (V_T), total breath duration (T_{TOT}), peak inspiratory flow ($\dot{V}_I$) and minute ventilation ($\dot{V}_E$) in eight normal subjects, 7 patients with persistent vegetative state (PVS) displaying irregular breathing (PVS-IB) and 11 PVS patients displaying oscillatory breathing (PVS-OB) for three 30 min periods during breathing air, 100% O_2 and then air again. Five minute elapsed between any two recording periods. Data are mean ± S.D. Note that O_2 inhalation significantly reduced coefficients of variation of all four parameters in the PVS-OB group, but did not change coefficients of variation of any parameter in other two groups. *$P < 0.05$ vs. baseline data by Wilcoxon Signed Ranks test.

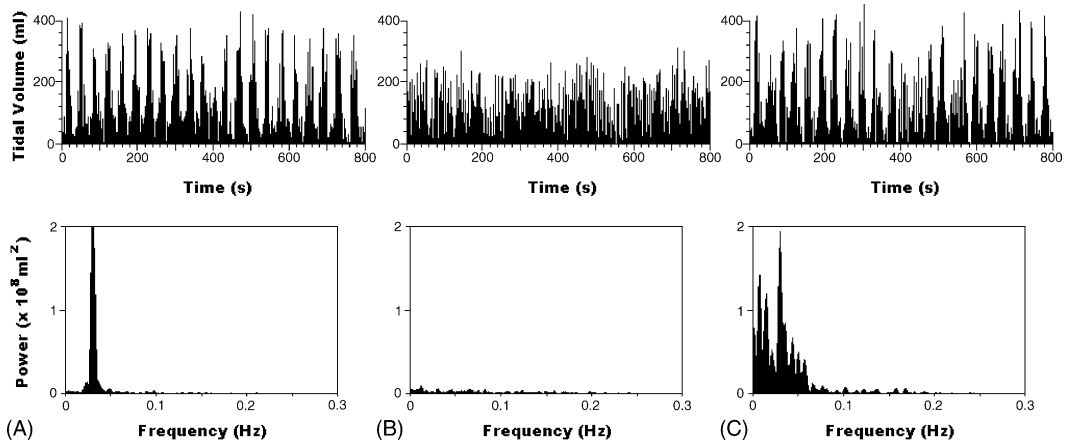

Fig. 5. Tracings and results of spectral analysis of tidal volume in 1 patient with persistent vegetative state patient displaying oscillatory breathing for three periods during breathing air (A), 100% O_2 (B) and then air again (C). Note that the oscillatory breathing and the central peak in the very-low-frequency band, which once had been abolished by inhalation of 100% O_2, returned after withdrawal of O_2.

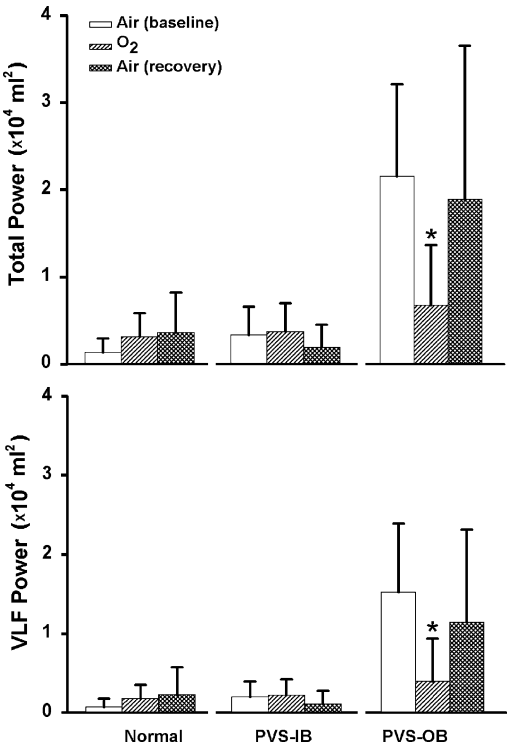

Fig. 6. The effect of 100% O_2 inhalation on total power and the very-low-frequency (VLF) power of tidal volume in eight normal subjects, 7 patients with persistent vegetative state (PVS) displaying irregular breathing (PVS-IB) and 11 PVS patients with oscillatory breathing (PVS-OB). Data are mean ± S.D. *$P < 0.05$ vs. baseline data by Wilcoxon Signed Ranks test.

unlikely to be the cause of IB or OB because deteriorations of pulmonary function (Loveridge et al., 1984; Brack et al., 2002) and bypassed upper airway resistance (Bruce and Daubenspeck, 1995) are known to decrease, but not increase, respiratory variability. If the influence of bypassing upper airway exists, the increased respiratory variability observed in our PVS patients may have been underestimated. In this study, measurements were made through a CAPNO$_2$ mask^{TM} in the volunteer, but through the flow and CO_2 sensors attached to the opening end of the tracheostomy tube in PVS patients. However, this is also unlikely since different apparatus may affect the mean values of breathing pattern parameters (Askanazi et al., 1980; Perez and Tobin, 1985), but not breathing pattern variability (Tobin et al., 1988). Whatever the causes, the IB observed in our PVS patients does not seem to be related to peripheral chemoreceptor function because chemical denervation of these chemoreceptors by the inhalation of 100% O_2 did not affect either the mean values or the variability of the respiratory parameters measured.

Hypoxemia has been suggested as playing a role in producing OB in normal subjects during ascent to high altitude (Lahiri et al., 1983) or inhalation of hypoxic gas mixture (Berssenbrugge et al., 1983), and in patients with idiopathic central sleep apnoea (Hall et al., 1996). In this study, the average value of SpO_2 in our PVS-IB or PVS-OB patients did not statistically differ from, but was numerically smaller than, that of the normal subjects. Due to the nature of the O_2–hemoglobin dissociation relationship, differences in the corresponding PaO_2 values among these three study groups could be very marked. The same reason may also explain why the variations in SpO_2 did not exhibit an oscillatory pattern in the PVS-OB group. Thus, our PVS patients, particularly the PVS-OB group, may be mildly hypoxic as compared to the control group. Several animal studies (Lahiri et al., 1981; Van Beek et al., 1983) have demonstrated that lowing arterial PO_2 levels may increase the carotid body chemoreceptor sensitivity to $PaCO_2$. Accordingly, the increase in the loop gain of peripheral chemoreceptors could contribute to the development of OB, according to the analyses presented by Khoo (2000).

Our PVS-OB patients also had a significantly lower $P_{ET}CO_2$ as compared to the control group. Although their average value of V_E was numerically greater than that in the control group, the difference did not reach a significant level. Both the relatively high $\dot{V}_E$ and a possible low metabolic rate may contribute to the low $P_{ET}CO_2$ in these PVS-OB patients. Their $P_{ET}CO_2$ also showed cyclic changes that had an inverse correlation with V_T or $\dot{V}_E$. Periodic instability of breathing patterns is attributed typically to unstable operation of neurochemical feedback loops (Bruce and Daubenspeck, 1995). For example, patients with neurological disorders who display OB have hyperventilation, increased CO_2 sensitivity and hypocapnia (Heyman et al., 1958; Brown and Plum, 1961). Hypocapnia produced by hyperventilation is well known to play a vital role in the development of OB in other clinical settings (Khoo, 1999). Similar to the situation during sleep (Dempsey and Skatrud, 1988; Khoo, 1999), the loss of the behavioral and non-specific environmental influences

related to consciousness in PVS patients may promote neurochemical control and thus this could become the primary regulatory system of respiration. Furthermore, hypocapnia may possibly reduce the ventilatory contribution from the medullary chemoreceptors and increase the importance and sensitivity of peripheral chemoreceptors in the control of breathing (Khoo, 1999). When these consequences occur, OB may be developed in response to cyclic changes in arterial blood gases and respiratory instability may be promoted due to the relative short time constant of ventilatory responses from the peripheral chemoreceptors (Brown and Plum, 1961; Khoo, 1999). Indeed, spectral analysis of V_T in our PVS-OB patients revealed that the change in V_T had a mean cyclic duration of 45 ± 13 s, which is less than the time constant (60–180 s) of ventilatory responses of the central chemoreceptors (Cunningham et al., 1986). Furthermore, the oscillatory changes in $P_{ET}CO_2$ in our PVS-OB patients may reflect a similar fluctuation of $PaCO_2$ (Gotoh et al., 1969; Wu et al., 2003), which produces periodic stimulation of peripheral chemoreceptors. Patients with neurological disorders who displayed Cheyne–Stokes respiration (OB with apnoea) have been shown to have maximal $PaCO_2$ coinciding with peak $\dot{V}_E$ and near minimal $PaCO_2$ coinciding with beginning apnoea (Brown and Plum, 1961). Thus, a central apnoea may be triggered to produce Cheyne–Stokes respiration (OB with apnoea) in some of our PVS-OB patients if the minimum $PaCO_2$ level fell below the apnoea threshold, while periodic breathing (OB without apnoea) was presented in others if minimal $PaCO_2$ level did not fall below the apnoea threshold. This notion is supported by the present finding that chemical denervation of peripheral chemoreceptors by inhalation of 100% O_2 significantly reduced the respiratory variability of the PVS-OB group, abolished their central peak of power of V_T and prevented their OB. The inhibitory effect of O_2 inhalation on OB in these PVS patients evidently is not related to improvements in hyperventilation and hypocapnia because O_2 inhalation did not alter their mean $P_{ET}CO_2$ and $\dot{V}_E$. The inhibitory effect of O_2 inhalation is presumably due to the result that the loop gain of peripheral chemoreceptors is decreased. This notion is consistent with the view suggested by other investigators who also found that O_2 inhalation attenuated OB in patients with neurological disorders (Brown and Plum, 1961), congestive heart failure (Hanly et al., 1989; Krachman et al., 1999; Ponikowski et al., 1999), or idiopathic central sleep apnoea (Franklin et al., 1997).

A heart-to-brain circulatory delay has also been suggested as playing a role in producing OB in patients with congestive heart failure (Hall et al., 1996; Mortara et al., 1999). Our patients were free from heart failure and the contribution of the heart-to-brain circulatory delay, if any, is unlikely to be cardiogenic. PVS patients usually have disorders in cerebral blood flow and O_2 delivery (Kinney and Samuels, 1994; Zeman, 1997). These disorders may possibly produce mild hypoxia/ischemia stress for the brain tissues, which may disturb the central respiratory controller and this gives rise to OB. In this case, it is also plausible that inhalation of 100% O_2 should improve O_2 delivery to the brain tissues and thereby abolishes OB in our PVS patients. Compared to that of the normal subjects, our PVS-OB patients displayed a higher arterial blood pressure, a result that may be related to increased sympathetic activity (Naughton, 1998). Interestingly, a similar situation has also been reported in congestive heart failure patients with OB (Ponikowski et al., 1997, 1999). The link between increased sympathetic activity and OB is still obscure.

It is not clear why some of our PVS patients displayed IB while others exhibited OB. Comparisons of their physical characteristics such as age, sex, body mass index, vegetative duration, Glasgow coma scale and etiologies of vegetative status show no difference between the PVS-IB and PVS-OB groups. In patients with neurological disorders, IB is linked to infratentorial lesions (Lee et al., 1974; Bassetti et al., 1997) and OB is associated with supratentorial (Heyman et al., 1958; Brown and Plum, 1961; Karp et al., 1961; Bassetti et al., 1997) or infratentorial lesions (Lee et al., 1974; North and Jennett, 1974; Bassetti et al., 1997). Patients with lesions in the medulla and pons have been reported to have higher incidences of IB than OB (North and Jennett, 1974). Therefore, one possibility is that brain lesions disturb breathing in different ways according to the extent and topography of the lesion. On the other hand, our PVS-OB patients displayed IB when OB was abolished by O_2 inhalation and regained OB after removal of O_2 inhalation. In some of the PVS-IB patients, it was noted that their breathing pattern occasionally showed discontinuous, non-uniform cyclic pattern (e.g., Fig. 1B). Therefore, the other possibility is that these two PVS groups have similar pathophys-

iology, but the PVS-OB group has an increased loop gain of peripheral chemoreceptors that is sufficient to produce the oscillatory behavior. Patients with brain damage have an impairment of activation of short-term potentiation (Georgopoulos et al., 1995), a brainstem mechanism that may be important in preventing OB by damping ventilatory responses to cyclic stimuli (Khoo, 1999). This raises the question of whether its absence is a possible reason that can explain the difference in abnormal breathing patterns among PVS patients.

In normal volunteers, hypoxia-induced Cheyne–Stokes respiration during sleep disappeared within 0.3–2 min after O_2 inhalation and returned within 0.5–4 min after withdrawal of O_2 (Berssenbrugge et al., 1983; Lahiri et al., 1983; Anholm et al., 1992; Khoo et al., 1996). In this study, the OB disappeared within 0.5–5 min after O_2 inhalation in nearly all the PVS patients tested. After termination of O_2 inhalation, although SpO_2 quickly returned to the baseline level within 5 min, 5 patients took 7.5–45 min for their OB to slowly recover and the other 2 patients even took 155 and 460 min. The body storage capacity of O_2 is low so the blood and tissue oxygen are expected to return to their baselines within minutes, if not seconds, after termination of O_2 inhalation. The long lasting after-effect of O_2 inhalation in these PVS-OB patients appears to relate to a form of respiratory plasticity, which is known to be a time-dependent adjustment of the central or peripheral control of breathing that results from neurological lesions or intermittent hypoxia (Forster, 2003; Mitchell et al., 2001). The characteristics, time of development and mechanisms of this respiratory plasticity require further investigation.

In conclusions, the results of this study show that PVS patients displayed either IB or OB, both of which reflect respiratory instability. Brain damage, hypocapnia and/or increased loop gain of arterial chemoreceptors may contribute to the pathogenesis of OB, whereas brain damage presumably may be the cause of IB.

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