Sleep and Pathological Wakefulness at Time of Liberation from Mechanical Ventilation (SLEEWE): A Prospective Multicenter Physiological Study

Martin Dres[1,2], Magdy Younes[3,4], Nuttapol Rittayamai[1,5], Tetyana Kendzerska[6], Irene Telias[1], Domenico Luca Grieco[1], Tai Pham[1], Detajin Junhasavasdikul[1], Edmond Chau[1], Sangeeta Mehta[8,11], M. Elizabeth Wilcox[9,11], Richard Leung[7], Xavier Drouot[10], Laurent Brochard[1,11]*

[1]Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada
[2]AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine intensive – Réanimation (*Département "R3S"*), F-75013, Paris, France
[3]YRT Ltd, Winnipeg, Manitoba, Canada
[4]Sleep Disorders Centre, Winnipeg, Manitoba, Canada
[5]Division of Respiratory Diseases and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[6]Division of Respirology, the Ottawa Hospital Research Institute, Ottawa, Canada
[7]Respirology and Sleep laboratory, St Michael's Hospital, Toronto
[8]Intensive Care Unit, Mount Sinai Hospital, Toronto, Canada
[9]Department of Medicine (Critical Care), Toronto Western Hospital, Toronto
[10]CHU de Poitiers, Neurophysiologie clinique et Explorations fonctionnelles, Poitiers, France
[11]Interdepartmental Division of Critical Care Medicine, University of Toronto, Canada

Address for correspondence
Laurent Brochard
Medical and Surgical Intensive Care Unit
St Michael's Hospital
209 Victoria Street, 4th Floor, Room 4-079, Toronto, ON M5B 1T8
Toronto, Canada
E-mail: BrochardL@smh.ca
Phone: +1 416 864 5686

**Deputy Editor, AJRCCM (participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works)*

Authors' contributions:

MD, NR, RL and LB designed the study. MD coordinated the study. MD, IT, DLG, TP, EC, SM, MEW, DJ and LB were responsible for patient screening, enrolment and follow-up. MD, MY, XD and LB analysed the data. XD, MY and TK scored PSG. MD, MY and LB wrote the manuscript. All authors had full access to all of the study data, contributed to drafting the manuscript or critically revised it for important intellectual content, approved the final version of the manuscript, and took responsibility for the integrity of the data and the accuracy of the data analysis.

Funding:

MD was supported by The French Intensive Care Society (SRLF bourse de mobilité 2015); The 2015 Short Term Fellowship program of the European Respiratory Society; The 2015 Bernhard Dräger Award for advanced treatment of ARF of the European Society of Intensive Care Medicine; The Assistance Publique Hôpitaux de Paris; The Fondation pour la Recherche Médicale (FDM 20150734498) and by MitacsGlobalink Sorbonne Universités. LB holds the Keenan Chair in Critical Care and Acute Respiratory Failure.

Running head: Pathological wakefulness and separation from mechanical ventilation

Descriptor number: 4.13 Ventilation: Non-Invasive/Long-Term/Weaning.

Word count: 4042

This article has an online data supplement, which is accessible from this issue's online table of contents.

Conflict of interest: Martin Dres received personal fees from Pulsion Medical System and Lungpacer. Laurent Brochard's laboratory has research contracts with Covidien (PAV), Air Liquide (CPR), Philips (equipment for sleep), Fisher Paykel (high flow therapy). Magdy Younes is the inventor of the ORP technology and receives royalties and consultation fees from Cerebra Health, the exclusive licensee of the technology. Nuttapol Rittayamai received a grant from his home institution in Thailand. The other authors have no conflict of interest relevant to this study.

At a glance commentary

Scientific Knowledge on the Subject:

Critically ill patients can develop EEG abnormalities in the intensive care unit. The impact of these abnormalities at the time of liberation from mechanical ventilation is poorly established. We conducted standard polysomnography and calculated the odds ratio product (ORP), which is a continuous index evaluating sleep depth, 15 hours before a spontaneous breathing trial (SBT) in patients deemed ready to attempt liberation from mechanical ventilation.

What this Study Adds to the Field:

Abnormal patterns of sleep and wakefulness were highly prevalent and sleep scoring by conventional criteria did not differ between patients with successful and failed SBT. By contrast, the level of wakefulness, as assessed by the ORP, was significantly higher in patients with successful SBT. Poor correlation between sleep depth in right vs. left hemispheres predicted SBT failure.

Abstract

Background

Abnormal patterns of sleep and wakefulness exist in mechanically ventilated patients.

This study, The Effect of Sleep Disruption on the Outcome of Weaning from Mechanical Ventilation Study, aimed at investigating polysomnographic indexes as well as a continuous index evaluating sleep depth, the odds ratio product (ORP), to determine whether abnormal sleep or wakefulness are associated with the outcome of spontaneous breathing trials (SBT).

Methods

Mechanically ventilated patients at three sites were enrolled if an SBT was planned the subsequent day. Electroencephalogram was recorded using a portable sleep diagnostic device 15 hours prior to SBT. ORP was calculated from the power of 4 electroencephalogram frequency bands relative to each other: it ranges from full wakefulness (2.5) to deep sleep (0). Correlation between right and left hemispheres ORP (R/L) was calculated.

Results

Among 44 patients enrolled, 37 had technically adequate signals: eleven (30%) passed the SBT and were extubated, 8 (21%) passed the SBT but were not deemed clinically ready for extubation, and 18 (49%) failed the SBT. Pathological wake or atypical sleep were highly prevalent but distribution of classical sleep stages was similar between groups. The mean ORP and the proportion of time that the ORP was >2.2 were higher in extubated patients compared to the other groups ($P<0.05$). R/L ORP was significantly lower in patients who failed the SBT and the area under the ROC curve of R/L ORP to predict failure was 0.91 (95% CI 0.75–0.98).

Conclusion

Patients who pass an SBT and are extubated reach higher levels of wakefulness as indicated by ORP, suggesting abnormal wakefulness in others. Hemispheric ORP correlation is much poorer in patients who fail a SBT.

Keywords: weaning, delirium, sedation, extubation, mechanical ventilation

Introduction

Patients under mechanical ventilation in the intensive care unit (ICU) present a variety of electroencephalographic (EEG) abnormalities both during wakefulness and sleep (1–3). Excessive sleep fragmentation, reduced REM sleep and loss of normal circadian rhythm are consistent across studies, suggesting frequent sleep deprivation (3–5). The EEG during behaviorally-confirmed wakefulness is often abnormal in ICU patients, with an increase in slow wave activity (seen during sleep in outpatients) and decrease in activity of higher frequencies that characterize wakefulness (1,3,6,7). This pattern has been called “pathological wakefulness”. Patients with pathological wakefulness also often show atypical EEG patterns during sleep with marked reduction in EEG spindles and K complexes that help differentiate different stages of non-REM sleep; this is referred to as “atypical sleep” (6). Accordingly, in many ICU patients, it is difficult to distinguish wakefulness from sleep from the EEG alone using the standard rules (7). The high prevalence of sleep loss/disruption in these patients, and the fact that similar EEG changes are observed with experimental sleep deprivation (8, 9),suggest that sleep loss is an important contributing factor to these EEG abnormalities (10).

A recent study found that weaning time is longer in difficult-to-wean patients who have atypical sleep than in those who display normal sleep patterns (11). Reasons for failing a spontaneous breathing trial (SBT) are multifactorial (12, 13). Sleep deprivation may be a risk

factor for weaning-failure since it can reduce ventilatory responses to hypoxemia (14) and decrease respiratory muscle endurance (15), impair immune responses (16, 17), cardiovascular responses (18), neuroendocrine and metabolic function (19, 20), neurocognitive function (21), and increase the incidence of delirium (22, 23).

In this study we evaluated the EEG of mechanically ventilated ICU patients during a 15-hour period preceding a SBT. We hypothesized that patients with atypical Sleep or pathological wakefulness were more likely to fail an SBT. In addition to conventional scoring, we used a digital scoring system (24, 25) that produces a number of EEG markers (Odds Ratio Product (ORP) and spindle characteristics) that are relevant to identify pathological wakefulness and atypical sleep as well as possible cerebral pathology (24). ORP is a continuous index of sleep depth that ranges from 0 (very deep sleep) to 2.5 (full wakefulness. ORP is derived from the relation of powers in different EEG frequencies to each other (24). ORP is highly correlated with arousability (24) and is therefore a valid index of sleep depth. One of its advantages is that it can distinguish between different levels of wakefulness since the awake range extends from 2.5 (full wakefulness) to ≈1.8 (epochs still scored wake but contain some sleep features). This would make it particularly useful for identifying Pathological Wakefulness in which wake EEG contains some sleep features. In such cases, ORP during wakefulness would be closer to 1.8 than to 2.5.

The rationale for this study is that over a prolonged period of observation (15 hours) an individual who is neither sleep-deprived nor pathologically obtunded should have both sleep periods and ORP levels close to 2.5 present over the period of recording.

Methods

We conducted a prospective multicenter physiological study (SLEEWE; clinicaltrials.gov identifier NCT02464735) between January 2016 and May 2017 in three ICUs of three hospitals affiliated to the University of Toronto. The study received approval by local Research Ethics Board (REB# 15-142) and was registered (NCT02464735). Patients and/or next of kin gave consent before being included.

Patients

Intubated, mechanically ventilated patients were eligible for inclusion when a SBT was planned by the clinical team for subsequent day. Exclusion criterion was impaired consciousness with Glasgow Coma Scale $\leq$ 8T.

Sleep assessment

Sleep was monitored using a portable monitor (Alice PDx diagnostic system, Philips Respironics) and included two central EEG electrodes, right and left electrooculography electrodes, submental electromyography electrodes and electrocardiography electrodes, from 5:00 pm to 8:00 am. Sleep assessment was performed off-line using manual and digital techniques. These methods are described in detail in the online supplement. Briefly:

- Sleep recordings were manually scored, first quickly after the recording and second by a sleep specialist with experience in ICU tracings (TK and XD) blinded to patient's status. The 2007 American Academy of Sleep Medicine (AASM) rules were applied (26). When typical wake and sleep EEG patterns were absent, sleep was scored using the alternative classification, including pathological wakefulness and atypical sleep (6).
- ORP was continuously quantified (MY, who was also blinded to patient status and weaning outcome) (See online supplement for details). In six of the 37 patients the

EEG signals were technically unacceptable for this type of analysis. In the remaining 31 patients the following ORP-derived indices were calculated:

- Average ORP over the entire 15 h total recording time.
- Percent of total recording time with ORP >1.5, >2.0, and >2.2.
- Intra-class correlation coefficient between ORP in the right and left hemispheres (R/L ORP). Normally, sleep depth changes in parallel in both hemispheres and the intra-class correlation for right vs. left ORP across the night is typically between 0.9 and 1.0. Lower values indicate regional differences in sleep depth which would suggest disruption of the normal processes that coordinate sleep throughout the brain.

In addition to ORP-related variables we also calculated density of spindles (number per minute when ORP was <1.5 with no rapid eye movements, indicating likely non-REM sleep).

Weaning protocol

A daily screening was performed each afternoon and patients that were anticipated to undergo an SBT the morning after were included. The morning following the sleep assessment, if patient met the readiness-to-wean criteria, an SBT was performed. Criteria to undergo SBT the following day were: SpO_2 ≥ 92% on FiO_2 ≤0.5 and positive end-expiratory pressure ≤8 cmH2O, and low/no doses of vasopressors. SBT with common policy is standard practice in all three ICUs (27) and SBT was done on the ventilator with no pressure assist of any kind (28). SBT lasted up to 60 minutes. Success/failure of the SBT was determined by the clinical team based on predefined criteria (29). Likewise, the decision for extubation after successful SBT was made by the ICU team independently from the study.

Clinical data collection

Demographic data, comorbidities, admission diagnosis, Sequential Organ Failure Assessment (SOFA) score upon admission and enrolment, duration of MV upon and after enrolment, ICU and hospital stay were recorded. Blood pressure, heart rate, respiratory rate, SpO_2, blood gases, analgesic and sedative medications, mode of ventilation and ventilator settings were recorded at the time the polysomnography was started, at 8:00 am the next day, and during the SBT. Neurological function was assessed twice daily by measuring the Richmond Agitation Sedation Scale (RASS) and the Confusion Assessment Method (CAM-ICU) score.

Study design

Polysomnography was set up at 5:00 PM. A trained investigator positioned the electrodes and checked correct recording with a laptop equipped with dedicated software (Sleepware G3, Philips Respironics). The following morning, the SBT was performed, usually between 8:00 and 9:00 am.

Statistical analyses

Continuous variables are presented with means and standard deviation (SD), whereas categorical variables are summarized using proportions and 95% confidence intervals (CI). Normality of the distribution was checked by using the Kolmogorov-Smirnov test. We initially sought to compare patients who passed vs. failed SBT, but decided to separate the patients into three groups: those who failed the SBT, those who passed but were not extubated and those who passed the SBT and were extubated (SBT failure, SBT success without extubation, and SBT success with extubation). The groups were discriminated based on 1) a recent large observational study on weaning from mechanical ventilation which found that less than 60% of patients passing an SBT are extubated on the same day (30, 31); 2) the distinction between the SBT which detects the ability to be separated from the ventilator and the extubation

criteria (32) and 3) the clinical practice in the 3 centres. The main comparisons were made among the three groups (failed SBT, successful SBT with extubation and successful without extubation). We also report in the supplement the comparisons between patients who passed the SBT *versus* those who failed the SBT. For sample size calculation, we assumed a success/failure rate of the SBT of 55%/45% and planned to have a minimum of 15 patients per group. We also anticipated a dropout rate of approximately 20% due to technical problems, and thus planned to enroll 42 patients from the three sites.

Comparisons of proportions were made using Fisher exact tests. Continuous variables were compared by analysis of variance, paired test or unpaired test as appropriate. Receiver Operating Characteristic (ROC) curves were constructed to evaluate the ability of R/L ORP to predict SBT success. Sensitivity, specificity and area under the ROC curve (AUC-ROC) were calculated. A p value < 0.05 was considered significant

Results

A total of 44 patients were enrolled and 37 had acceptable quality of polysomnography recordings. Patients' characteristics are shown in Table 1. The most common reason for intubation was acute respiratory failure (49%). At enrollment, patients had been ventilated for 6 ± 4 days and had a SOFA score of 8 ± 4. On the day of polysomnography, RASS was 0 ± 1 and delirium was present in 5 patients (14%).

SBT was successful in 19 patients (51%), 11 being extubated and 8 deemed not ready for extubation by the clinical team, and was unsuccessful in 18 (49%). Reasons for SBT failure and for not extubating those who passed are given in Table E1.

Characteristics of the patients and weaning outcome

Patients who failed SBT had a shorter duration of ICU stay compared to their counterparts (Tables 1 and E2). RASS was similar between all groups and delirium was slightly but not significantly higher in patients who passed the spontaneous breathing trial (5/19 vs. 0/18). Clinical variables at the time of the SBT did not differ.

Sleep characteristics and weaning outcome

Conventional and alternative visual polysomnography scoring:

Sleep duration and sleep quality during the night before SBT based on conventional and alternative assessment of polysomnography are presented in Tables 2 and E3. Pathologic wakefulness and atypical sleep were frequent but did not significantly differ across groups. Pathological wakefulness and atypical sleep, as previously defined (6), were present in 39% and 55% in patients who failed the SBT, 50% and 50% in patients who passed the SBT and were not extubated, and 27% and 27% respectively in patients who passed the SBT. As a consequence, only 61% of the patients could be scored according to classical stages. Total sleep time based on this analysis was found to be shorter in patients who failed the SBT. When

scorable, distribution of stages 3, REM-sleep and fragmentation index did not differ between groups.

ORP analysis

ORP analysis was possible in only 31 of the 37 enrolled patients. Figures 1 and E1 shows EEG tracings in seven 30-second epochs, representing different levels of wakefulness and sleep in a patient with normal EEG patterns; note that the average ORP in each reflects the visual differences between the seven strips. There was no correlation between the mean ORP in the first third of the recording and the RASS measured at the start of the recording (Figure E2).

ORP-derived indices prior to SBT showed significant differences between groups (Table 2). Patients who were successfully extubated had higher average ORP during total recording time and more time with ORP>2.0 and >2.2 than in the other two groups (Table 2). Figures 2 and E3 show the probability of successful SBT in relation to time spent above specified ORP levels. There was no significant difference among groups in spindle density.

R/L ORP ranged from 0 to 0.97 (0.68±0.24). Figure 3 shows three examples spanning the entire spectrum and Figure 4 shows examples of EEG tracings with discrepancy between right and left ORP. Average R/L ORP was significantly lower in patients who failed the SBT as compared to their counterparts (Figures 5 and E4). When comparing SBT failure vs. all SBT success, R/L ORP was 0.54±0.26 vs. 0.80±0.15 respectively (p=0.006). The area under the ROC curve of R/L ORP to predict failure of SBT was 0.91 (95% CI 0.75–0.98). A R/L ORP value >0.70 predicted successful SBT with a sensitivity of 85% (95% CI, 56–98%) and a specificity of 88% (95% CI, 62–98%). Interestingly, there was a non-linear relation between R/L ORP and % of time spent above specified ORP levels. Figure 6 shows the relation between time >2.2 and R/L ORP.

Discussion

This study investigated quality and quantity of sleep using conventional sleep scoring guidelines and an index (ORP) that measures where brain state lies on a continuous scale between full wakefulness and deep sleep, in the 15 hours preceding SBT in patients clinically deemed ready for attempting to terminate mechanical ventilation. The high prevalence of stages referred to as pathological wakefulness or atypical sleep made the classical scoring of sleep of limited value and the distribution of sleep stages did not differ. By contrast, the degree of wakefulness was clearly lower in patients who failed the SBT based on ORP assessment. The two main findings are that the likelihood of success of SBT and extubation is highly correlated with the fraction of monitoring time spent in full wakefulness (ORP >2.2), and that a poor correlation between sleep depth in the right and left brain hemispheres predicts SBT failure. The group who passed SBT and was extubated was the only one characterized by both high hemispheric correlation and full wakefulness.

Identification of abnormal wakefulness:

Identification of pathological wakefulness, the presence of sleep features in the EEG during confirmed wakefulness, has been technically difficult. So far, identification of this state required simultaneous direct observation of the patient (to establish behavioral wakefulness) while monitoring the EEG for presence of slow activity typically associated with sleep (6,7). Since direct observation over extended periods is not feasible, it is not possible to determine whether such pattern, if present, represents the situation throughout wakefulness or transient sleepiness during few minutes of observation, which may be normal. Furthermore, identification of excessive slow activity in the EEG requires specialised expertise that is not readily available in the ICU.

ORP can distinguish between different levels of wakefulness (Figures 1A-1C) and has been observed to decrease during wakefulness following sleep restriction (33) and during sleep deprivation studies (34). Full wakefulness is typically associated with ORP>2.2 (Figure 1A). In this study 23/31 patients (74%) spent < 10 minutes out of 15 hours, with ORP >2.2. For a perspective, ambulatory patients spend ≈10% of an 8 hour nocturnal study with ORP >2.2 (24). Obviously, if a normal ambulatory subject were monitored for 15 hours, the percentage of time spent with ORP >2.2 would be close to 50% since the balance of time (7 hours) would be mostly wake time. Only 4 patients (14%) approached this level of full wakefulness and all passed the SBT. Thus, the vast majority of patients in this study had some degree of obtundation or abnormal or incomplete wakefulness most of the time they were awake.

Whereas the EEG pattern of pathological wakefulness is consistent with sleep deprivation (1) it may also be observed with other encephalopathies (35). This possibility is, less likely, however, given that the patients were deemed ready for termination of ventilation and their RASS score was consistently showing an awake state.

Wakefulness and Liberation from Mechanical Ventilation:

The current study demonstrated that success of SBT and subsequent extubation are directly correlated with time spent with full wakefulness (Figure 2). Yet, the reasons for SBT failure were primarily respiratory failure and desaturation (Table E1). Assuming that an abnormal wakefulness is related to sleep deprivation, and given that sleep deprivation is known to depress ventilatory responses to CO_2 and hypoxia and reduce respiratory muscle endurance (14, 15), one could speculate that sleep deprivation contributed to SBT failure through failure to respond to hypoxemia/hypercapnia, resulting in desaturation without distress (8 of 18 patients who failed, Table E1), or through impaired diaphragm endurance (15), which would result in respiratory distress with or without desaturation (8 of the 18

patients who failed). An adequate response to the load requires intact responses to CO_2 and hypoxia and reasonable respiratory muscle endurance.

A significant proportion of patients (8/19, 42%) who passed SBT were not extubated since they were deemed not ready by the clinical team. This finding is in line with a recent epidemiological study conducted in France where only 58% of the patients who passed the SBT were actually extubated (30). In fact, that these patients had more abnormal wakefulness than those extubated in our study (lower ORP levels; Table 2) suggests that the decision to delay extubation had biological grounds.

Abnormal sleep and liberation from mechanical ventilation:

Recently, Thille et al. reported a longer duration of weaning in patients with atypical sleep (11). Our results add support to their findings that abnormal EEG patterns influence clinical outcome in ICU patients. However, when we used the same techniques they used to identify patients with Atypical Sleep we found no differences between the three patient groups (Table 2, Sleep Quality by alternative criteria).

There are several reasons the alternate methods they used were not discriminating in our study. First, they studied patients who already failed SBT. Their patients may have had more severe abnormalities capable of being identified by less sensitive techniques. Second, the main diagnostic features of atypical sleep are visual absence of spindles and K complexes (6). Agreement between manual scorers in spindle detection is poor (36, 37). Furthermore, determining that spindles are *completely* absent is problematic as it requires careful inspection of each epoch in the recording. Accordingly, lack of significant differences in number of patients with *absent* spindles in our study (Table 2, Sleep Quality) and presence of such differences in Thille's study may reflect differences in manual scoring (11). Last, as in

most sleep studies in the ICU, they selected non sedated patients, being off sedation since several days.

We used an automatic validated (Warby S, personal communications) spindle detector. Despite a stated absence of spindles by visual inspection in more than half the patients (Table 2) none of the patients had complete absence of spindles with digital analysis. Spindle density was not significantly different among the 3 groups (p=0.15, table 2). However, it was significantly higher in the extubated patients than in the other two groups combined (0.59±0.56 min^{-1} vs. 0.27±0.33 min^{-1}, p=0.03). It must be noted that spindle density was markedly depressed in all three groups relative to the values obtained with the same digital detector in non-ICU patients (2.65±1.62 min^{-1} per EEG channel). The highest spindle density in the current study was 1.56 min^{-1}, well below the average in non-ICU patients. Given that spindles are involved in memory consolidation (38), it is tempting to speculate that spindle suppression in ICU patients is a mechanism aimed at reducing memory of the unpleasant experiences encountered in this environment. Whether such suppression is protective against future psychopathology is debatable (39, 40).

Correlation between Sleep Depth in the Two Hemispheres:

This is the first time that agreement in sleep depth between right and left hemispheres was examined in ICU patients. This correlation has been observed in hundreds of non-ICU polysomnographic studies both in normal subjects and in patients with chronic sleep disorders (M. Younes, unpublished observation). R/L ORP intra-class correlation in non-ICU patients is only rarely below 0.90. Accordingly, finding that R/L ORP was <0.7 in nearly half the patients (Figure 5) is remarkable and highly significant. Moreover, the fact that R/L ORP predicted success or failure of SBT (area under the ROC curve =0.91), and that patients with values <0.7 spent little/no time with ORP >2.2 while in all patients who spent >11% of the time with

normal wakefulness R/L ORP was normal, further emphasise the importance of this finding and suggest that it is a feature that develops with extreme pathological wakefulness.

That R/L correlation may be relevant to success of SBT was coincidental. When ORP was introduced in the clinical sleep laboratory of the author who developed ORP (MY) it was noted that in occasional patients there was, at times, marked difference between ORP in the left and right hemispheres. This tool was developed and added to a battery of new EEG biomarkers he developed to help research to identify their significance (e.g. alpha intrusion index, spindle characteristics…etc.). Other than the current findings, there is no prior literature on its association with clinical disorders but its use in research is just beginning.

Although it is not possible at present to determine why SBT failure and poor R/L correlation are associated the finding that a poor correlation is associated with severe pathological wakefulness (Figure 6) suggests a possible link. As discussed previously, pathological wakefulness in the ICU setting is likely the result of sleep deprivation. Sleep deprivation may increase the risk of SBT failure through its negative effect on ventilatory responses and respiratory muscle endurance. To the extent that poor R/L correlation reflects more severe sleep deprivation, SBT failure when R/L correlation is poor may simply be a reflection of more severe respiratory control abnormalities.

Poor R/L correlation is a form of regional differences in sleep (i.e. some parts of the brain are asleep while others are awake). This form of sleep, often called unihemispheric sleep, is widely utilized by dolphins and related mammals (41) as well as by birds (42) when operating under physiological conditions that require long periods without sleep. It is possible that this primitive adaptive mechanism is reactivated in humans under conditions where natural sleep is deemed by the individual to be unsafe.

When discrepancies are present, spectral analysis typically shows one EEG having slightly higher power in the beta frequency (>14Hz) and lower power in the slow frequency (<7 Hz). As illustrated in figure 4, which shows tracings from some of the most outliers in the ORP scatter plots (arrows in figure 3), the difference in visual appearance of the two EEG signals when discrepancies exist, is too subtle to detect by the naked eye unless it is very large. Accordingly, such an abnormality can only be detected through digital analysis.

Clinical Implications:

1) Together, the current study and the previous study by Thille et al. (11) clearly indicate that EEG abnormalities are an important risk factor for failure to wean. Given that patients who fail weaning contribute disproportionately to cost of ICU care and to morbidity and mortality(30), studies are clearly needed to determine why these abnormalities develop (sleep deprivation, metabolic factors, drugs…) and how to prevent them.

2) Our study is hypothesis generating and the current findings suggest that EEG monitoring throughout the ICU admission could allow early detection of pathological wakefulness so that measures can be taken to mitigate its progression. Unless research studies point to other etiologies, we suggest that appearance of pathological wakefulness strongly suggest sleep deprivation and measures should be taken to ensure adequate sleep.

3) Visual inspection of the EEG is not sufficient to detect the EEG abnormalities of pathological wakefulness (Figure 4).

4) That all patients with severe pathological wakefulness, including those with the most severe form (<2% time with ORP >2.2 and R/L ORP <0.7), scored 0±1 on RASS, indicates that RASS score is quite insensitive for detecting pathological wakefulness.

Strengths and limits:

This study is the first to report the use of a new method that allows continuous measuring of sleep depth in the ICU. In addition, this study was conducted in three ICUs from three different hospitals. Assessment of PSG and ORP derived indices was made off-line by sleep specialists (TK, XD and MY) blinded to patients' conditions and SBT outcomes. This study has also limitations including intrinsic limitations of the classical sleep scoring process. Assessment of hemispheric EEG correlation with the R/L ORP was not correlated with specific neurological investigation but there were no clinical grounds to suspect the presence of primary brain disease.

Conclusion

Our findings indicate that quantifying abnormal wakefulness and hemispheric EEG correlation are feasible and potentially helpful at the bedside to identify patients not ready to be weaned from the ventilator. It also underlines a need for studies to determine the reasons for these EEG abnormalities and how to avoid them. Time during full or normal wakefulness (as assessed by ORP) was higher in patients who passed SBT and were extubated, and hemispheric EEG correlation was much poorer in patients who failed SBT.

Acknowledgments

We would like to deeply thank the nurses and respiratory therapists at the three different ICUS who were essential in the success of this project, as well as the research coordinators at the three sites, especially Kurtis Salway, Gyan Sandhu, Jennifer Hodder and Sumesh Shah. Special thanks also to Orla Smith, Jenny Gu and Carolyn Campbell for a great

help in the overall organization, to Unmesh Edke for enrolling patients and for the attending physicians for supporting the study.

We thank Philips for providing the devices for the study.

References

1. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. *Chest* 2000;117:809–818.

2. Gabor JY, Cooper AB, Crombach SA, Lee B, Kadikar N, Bettger HE, Hanly PJ. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med* 2003;167:708–715.

3. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 2001;163:451–457.

4. Elliott R, McKinley S, Cistulli P, Fien M. Characterisation of sleep in intensive care using 24-hour polysomnography: an observational study. *Crit Care* 2013;17:R46.

5. Friese RS, Diaz-Arrastia R, McBride D, Frankel H, Gentilello LM. Quantity and quality of sleep in the surgical intensive care unit: are our patients sleeping? *J Trauma* 2007;63:1210–1214.

6. Drouot X, Roche-Campo F, Thille AW, Cabello B, Galia F, Margarit L, d'Ortho M-P, Brochard L. A new classification for sleep analysis in critically ill patients. *Sleep Med* 2012;13:7–14.

7. Watson PL, Pandharipande P, Gehlbach BK, Thompson JL, Shintani AK, Dittus BS, Bernard GR, Malow BA, Ely EW. Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. *Crit Care Med* 2013;41:1958–1967.

8. Naitoh P, Kales A, Kollar EJ, Smith JC, Jacobson A. Electroencephalographic activity after prolonged sleep loss. *Electroencephalogr Clin Neurophysiol* 1969;27:2–11.

9. Olbrich E, Landolt HP, Achermann P. Effect of prolonged wakefulness on

electroencephalographic oscillatory activity during sleep. *J Sleep Res* 2014;23:253–260.

10. Younes M. To sleep: perchance to ditch the ventilator. *Eur Respir J* 2018;51:.

11. Thille AW, Reynaud F, Marie D, Barrau S, Rousseau L, Rault C, Diaz V, Meurice J-C, Coudroy R, Frat J-P, Robert R, Drouot X. Impact of sleep alterations on weaning duration in mechanically ventilated patients: a prospective study. *Eur Respir J* 2018;51:.

12. McConville JF, Kress JP. Weaning patients from the ventilator. *N Engl J Med* 2012;367:2233–2239.

13. Dres M, Demoule A. Diaphragm dysfunction during weaning from mechanical ventilation: an underestimated phenomenon with clinical implications. *Crit Care* 2018;22:73.

14. White DP, Douglas NJ, Pickett CK, Zwillich CW, Weil JV. Sleep deprivation and the control of ventilation. *Am Rev Respir Dis* 1983;128:984–986.

15. Chen HI, Tang YR. Sleep loss impairs inspiratory muscle endurance. *Am Rev Respir Dis* 1989;140:907–909.

16. Bryant PA, Trinder J, Curtis N. Sick and tired: Does sleep have a vital role in the immune system? *Nat Rev Immunol* 2004;4:457–467.

17. Faraut B, Boudjeltia KZ, Vanhamme L, Kerkhofs M. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. *Sleep Med Rev* 2012;16:137–149.

18. Khan MS, Aouad R. The Effects of Insomnia and Sleep Loss on Cardiovascular Disease. *Sleep Med Clin* 2017;12:167–177.

19. Davies SK, Ang JE, Revell VL, Holmes B, Mann A, Robertson FP, Cui N, Middleton B, Ackermann K, Kayser M, Thumser AE, Raynaud FI, Skene DJ. Effect of sleep deprivation on the human metabolome. *Proc Natl Acad Sci U S A* 2014;111:10761–10766.

20. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine

function. *Lancet* 1999;354:1435–1439.

21. Bonnet MH. Acute sleep deprivation. *Princ Pract Sleep Med*, Kryger MH, Roth T, Dement WC, eds. Philadelphia: Elsevier Saunders; 2005. p. 51–66.

22. Babkoff H, Sing HC, Thorne DR, Genser SG, Hegge FW. Perceptual distortions and hallucinations reported during the course of sleep deprivation. *Percept Mot Skills* 1989;68:787–798.

23. Roche Campo F, Drouot X, Thille AW, Galia F, Cabello B, d'Ortho M-P, Brochard L. Poor sleep quality is associated with late noninvasive ventilation failure in patients with acute hypercapnic respiratory failure. *Crit Care Med* 2010;38:477–485.

24. Younes M, Ostrowski M, Soiferman M, Younes H, Younes M, Raneri J, Hanly P. Odds ratio product of sleep EEG as a continuous measure of sleep state. *Sleep* 2015;38:641–654.

25. Malhotra A, Younes M, Kuna ST, Benca R, Kushida CA, Walsh J, Hanlon A, Staley B, Pack AI, Pien GW. Performance of an automated polysomnography scoring system versus computer-assisted manual scoring. *Sleep* 2013;36:573–582.

26. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, Troester MT, Vaughn BV. AASM Scoring Manual Updates for 2017 (Version 2.4). *J Clin Sleep Med* 2017;13:665–666.

27. Goligher EC, Detsky ME, Sklar MC, Campbell VT, Greco P, Amaral ACKB, Ferguson ND, Brochard LJ. Rethinking Inspiratory Pressure Augmentation in Spontaneous Breathing Trials. *Chest* 2017;151:1399–1400.

28. Sklar MC, Burns K, Rittayamai N, Lanys A, Rauseo M, Chen L, Dres M, Chen G-Q, Goligher EC, Adhikari NKJ, Brochard L, Friedrich JO. Effort to Breathe with Various Spontaneous Breathing Trial Techniques. A Physiologic Meta-analysis. *Am J Respir Crit Care Med* 2017;195:1477–1485.

29. Boles J-M, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H,

Stanchina M, Vieillard-Baron A, Welte T. Weaning from mechanical ventilation. *Eur Respir J* 2007;29:1033–1056.

30. Béduneau G, Pham T, Schortgen F, Piquilloud L, Zogheib E, Jonas M, Grelon F, Runge I, Nicolas Terzi null, Grangé S, Barberet G, Guitard P-G, Frat J-P, Constan A, Chretien J-M, Mancebo J, Mercat A, Richard J-CM, Brochard L, WIND (Weaning according to a New Definition) Study Group and the REVA Network ‡. Epidemiology of Weaning Outcome according to a New Definition. The WIND Study. *Am J Respir Crit Care Med* 2017;195:772–783.

31. MacIntyre N. Another Look at Outcomes from Mechanical Ventilation. *Am J Respir Crit Care Med* 2017;195:710–711.

32. Thille AW, Richard J-CM, Brochard L. The decision to extubate in the intensive care unit. *Am J Respir Crit Care Med* 2013;187:1294–1302.

33. PK Schweitzer, Griffin K, Younes M, Walsh J. Assessment of sleep depth and propensity during sleep restriction using the Odds Ratio Product. *Sleep* 2018;A57-58.

34. Tanayapong P, Maislin G, Staley B, Pack F, Pack AI, Younes M. Odd Ratio Product : a measure of sleep homeostasis following prolonged wakefulness. 2018;41:A83.

35. Sutter R, Kaplan PW, Valença M, De Marchis GM. EEG for Diagnosis and Prognosis of Acute Nonhypoxic Encephalopathy: History and Current Evidence. *J Clin Neurophysiol* 2015;32:456–464.

36. Warby SC, Wendt SL, Welinder P, Munk EGS, Carrillo O, Sorensen HBD, Jennum P, Peppard PE, Perona P, Mignot E. Sleep-spindle detection: crowdsourcing and evaluating performance of experts, non-experts and automated methods. *Nat Methods* 2014;11:385–392.

37. Wendt SL, Welinder P, Sorensen HBD, Peppard PE, Jennum P, Perona P, Mignot E, Warby SC. Inter-expert and intra-expert reliability in sleep spindle scoring. *Clin Neurophysiol*

2015;126:1548–1556.

38. Clawson BC, Durkin J, Aton SJ. Form and Function of Sleep Spindles across the Lifespan. *Neural Plast* 2016;2016:6936381.

39. Schelling G, Stoll C, Haller M, Briegel J, Manert W, Hummel T, Lenhart A, Heyduck M, Polasek J, Meier M, Preuss U, Bullinger M, Schüffel W, Peter K. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. *Crit Care Med* 1998;26:651–659.

40. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. *Crit Care Med* 2001;29:573–580.

41. Lyamin OI, Manger PR, Ridgway SH, Mukhametov LM, Siegel JM. Cetacean sleep: an unusual form of mammalian sleep. *Neurosci Biobehav Rev* 2008;32:1451–1484.

42. Rattenborg NC, Lima SL, Amlaner CJ. Half-awake to the risk of predation. *Nature* 1999;397:397–398.

Figure legends

Figure 1. EEG traces (C3) representing progression from full wakefulness (Panel A) to deep sleep (stage N3, panel G) in a patient from this study who had normal EEG patterns, and the corresponding average ORP values (average of the ten 3-second values in the 30-second epoch). Note that the top 3 panels meet the guidelines of wake epochs even though their visual appearance differs substantially. The ORP values reflect the gradual transition from full wakefulness (Panel A) to stage 1 (Panel D). Note also that panels E and F are both scored stage N2 despite the marked difference in appearance. Again, ORP reflects the gradual deepening of sleep within stage N2. Arrows point to EEG spindles. Horizontal bars in panel D identify sections with wake pattern (high frequency dominance). A more detailed legend is available in the online supplement (**Figure E2**).

Figure 2. Probability of successful spontaneous breathing trial according to the percentage of total recording time (TRT) spent above odds ratio product (ORP) >2.2. Patients were sorted according to % of TRT spent with ORP >1.5, >2.0 and >2.2. Each series was divided into 3 ≈equal aliquots (lowest 10, middle 10 and highest 11). % total recording time spent with ORP >1.5 ranged 0-98%. When the threshold was raised to %time spent above 2.2 (full wakefulness) the probability of success was 0 in the lower third (%<0.8), 20% in the middle third (% 0.8-4.0) and 65% for the highest third (% >4.0). See also Figure E3 for more details.

Figure 3. TOP: Scatter plots of the relation between odds ratio product (ORP) in the right and left hemispheres across total recording time in 3 patients. Each dot represents the results in a single 30-second epoch. A) From the patient with the best correlation (intra-class correlation (ICC) =0.97). B) From a patient with very poor correlation (ICC=0.12). C) From a patient with

intermediate correlation (ICC=0.62). The bottom panels show the time course of the difference between the two sides. Grey lines are consecutive epoch by epoch differences. Black lines are 10-minute moving average of the individual epoch differences. Arrows identify the individual 30-second epochs shown in **Figure 4**.

Figure 4. Tracings illustrating the visual appearance of the left and right central EEG derivations (C3 and C4) in 5 epochs with large differences between ORP (odds-ratio-product) of the two sides. ORP values are listed to the right of the panels. Panels A-D are from the patient in panel B of figure 3 and their locations are indicated by the arrows in the scatter plot of Figure 3B. Panel E is from the patient in figure 3C. Note that except when the difference between the two ORP values is very large (panels A and B) it is very difficult to visually appreciate the presence of major discrepancy between the right and left signals. The epoch in panel A could not be scored.

Figure 5. Intra-class correlation between Odds Ratio Product (ORP) of the right and left hemispheres (R/L ORP ICC) in patients who failed the spontaneous breathing trial (SBT), who passed and were not extubated and who passed and were extubated.

Figure 6. Relation between percent of total recording time spent with odds ratio product (ORP) >2.2 and intra-class correlation between ORP values in the right and left hemispheres (R/L ORP ICC). When % total recording time was 0, it was changed to 0.1 to allow logarithmic regression. Patients who spent >11% time with ORP >2.2 (n=7) had invariably high R/L ORP ICC (0.89±0.08) whereas patients who had an R/L ORP ICC<0.70 (n= 14; ICC=0.49±0.19) invariably had very little time with ORP>2.2 (%time >2.2 = 2.7±3.4%).

Table 1. Characteristics of the patients

	Failed SBT	Passed SBT		Overall p
		No Extubation	Extubation	
	n=18	n=8	n=11	
At ICU admission				
Male, *n (%)*	11 (61)	7 (88)	6 (55)	0.29
Body mass index, $kg.m^{-2}$	30 ± 10	26 ± 4	31 ± 5	0.47
APACHE 2	21 ± 9	17± 10	26 ± 7	0.10
Main reason for intubation, *n (%)*				
Acute respiratory failure	11 (61)	3 (37)	4 (36)	0.84
Acute respiratory distress syndrome	7 (39)	3 (37)	4 (36)	0.99
Coma	2 (11)	3 (26)	2 (18)	0.29
Cardiac arrest	1 (6)	0 (0)	1 (9)	0.62
Post-surgery	2 (11)	2 (37)	2 (18)	0.55
Other	2 (11)	0 (0)	2 (18)	0.45
At time of enrollment				
Length of ICU stay, *days*	4.4 ± 3.2	5.0 ± 2.5	10.4 ± 8.6 *	0.01
SOFA score	6 ± 3	8 ± 3	7± 3	0.32
Treatment regimens, *n (%)*				
Continuous sedative infusion	7(39)	2 (37)	8 (73)	0.08
Continuous analgesic infusion	5 (28)	5 (63)	5 (45)	0.23
Neurologic assessment				
RASS	1 ± 1	0 ± 2	0 ± 1	0.26
CAM-ICU positive, *n (%)*	0 (0)	2 (25)	3 (27)	0.06
Arterial blood gases				
$PaCO_2$, *mmHg*	44 ± 12	39± 9	35 ± 6	0.10
PaO_2/FiO_2 ratio	249 ± 73	219 ± 79	282 ± 90	0.36
At time of SBT				
Systolic arterial pressure, *mmHg*	133 ± 22	141 ± 22	126 ± 22	0.47
Diastolic arterial pressure, *mmHg*	65 ± 14	68 ± 14	65 ± 6	0.88
Heart rate, min^{-1}	90 ± 18	84 ± 12	88 ± 15	0.75
Respiratory rate, min^{-1}	25 ± 7	21 ± 7	21 ± 4	0.29
SpO_2, *%*	96 ± 3	97± 2	96 ± 2	0.51

* versus “Failed SBT” (one-way ANOVA)

SBT: spontaneous breathing trial; ICU: intensive care unit; SOFA: sequential organ failure assessment; RASS: Richmond agitation sedation scale; CAM-ICU: Confusion Assessment Method for the ICU; $PaCO_2$: Partial tension in carbon dioxide; PaO2: Partial tension in oxygen; FiO_2: inspired fraction in oxygen

Table 2. Sleep characteristics the night before the spontaneous breathing trial

	Failed SBT	Passed SBT		Overall p
		No extubation	Extubation	
	18	8	11	
Sleep quantity (Conventional criteria)				
Duration of PSG, *min*	753 ± 219	781 ± 116	875 ± 22	0.16
Total sleep time, *min*	187 ± 125	366 ± 189	260 ± 195	0.05
Total sleep time, *%*	22 ± 16	46 ± 20	30 ± 22	0.02
Wake min, *min*	455 ± 182	385 ± 165	530 ± 242	0.31
Classical scoring possible	8	4	7	
Sleep stage 1, *%*	18 ± 9	14 ± 17	15 ± 9	0.84
Sleep stage 2, *%*	51 ± 21	57 ± 21	59 ± 17	0.76
Sleep stage 3, *%*	26 ± 27	27 ± 31	20 ± 15	0.85
Rapid eye movement stage, *%*	3 ± 4	2 ± 2	6 ± 6	0.29
Arousal and micro-awaking, h^{-1}	34 ± 12	26 ± 19	36 ± 18	0.57
Sleep quality (Alternative criteria)				
Pathologic wakefulness, *n (%)*	7 (39)	4 (50)	3 (27)	0.59
Atypical sleep, *n (%)*	10 (56)	4 (50)	3 (27)	0.32
Abnormal sleep EEG pattern, *n (%)*	9 (50)	4 (50)	4 (36)	0.75
Absence of spindles, *n (%)*	12 (66)	4 (50)	4 (36)	0.27
Digitally-derived indices				
n	15	7	9	
Av ORP	1.12 ± 0.40*	0.91 ± 0.32*	1.5 ± 0.40	0.02
Time ORP >2.2, % *Total Recording Time*	3.8 ± 6.2*	6 ± 13	18 ± 18	0.03
Time ORP >2.0, % *Total Recording Time*	9.1 ± 11.4*	8 ± 15*	31 ± 26	0.01
Time ORP >1.5, *% Total Recording Time*	29 ± 27*	18 ± 18*	55 ± 28	0.02
R/L ORP ICC	0.54 ± 0.26*£	0.80 ± 0.15	0.80 ± 0.16	<0.01
Awakening index, h^{-1}	9 ± 7	7 ± 6	19 ± 19	0.07
Spindle Density (minute^{-1})	0.30 ± 0.34	0.21 ± 0.32	0.59 ± 0.56	0.15

* versus “Passed SBT with extubation”

£ versus “Passed SBT without extubation”

PSG: polysomnography; EEG: electroencephalogram; SBT: spontaneous breathing trial; ORP: odds ratio product; REM: rapid eye movement stage; ICC: intra-class correlation coefficient; R/L: right/left ratio; TST: total sleep time

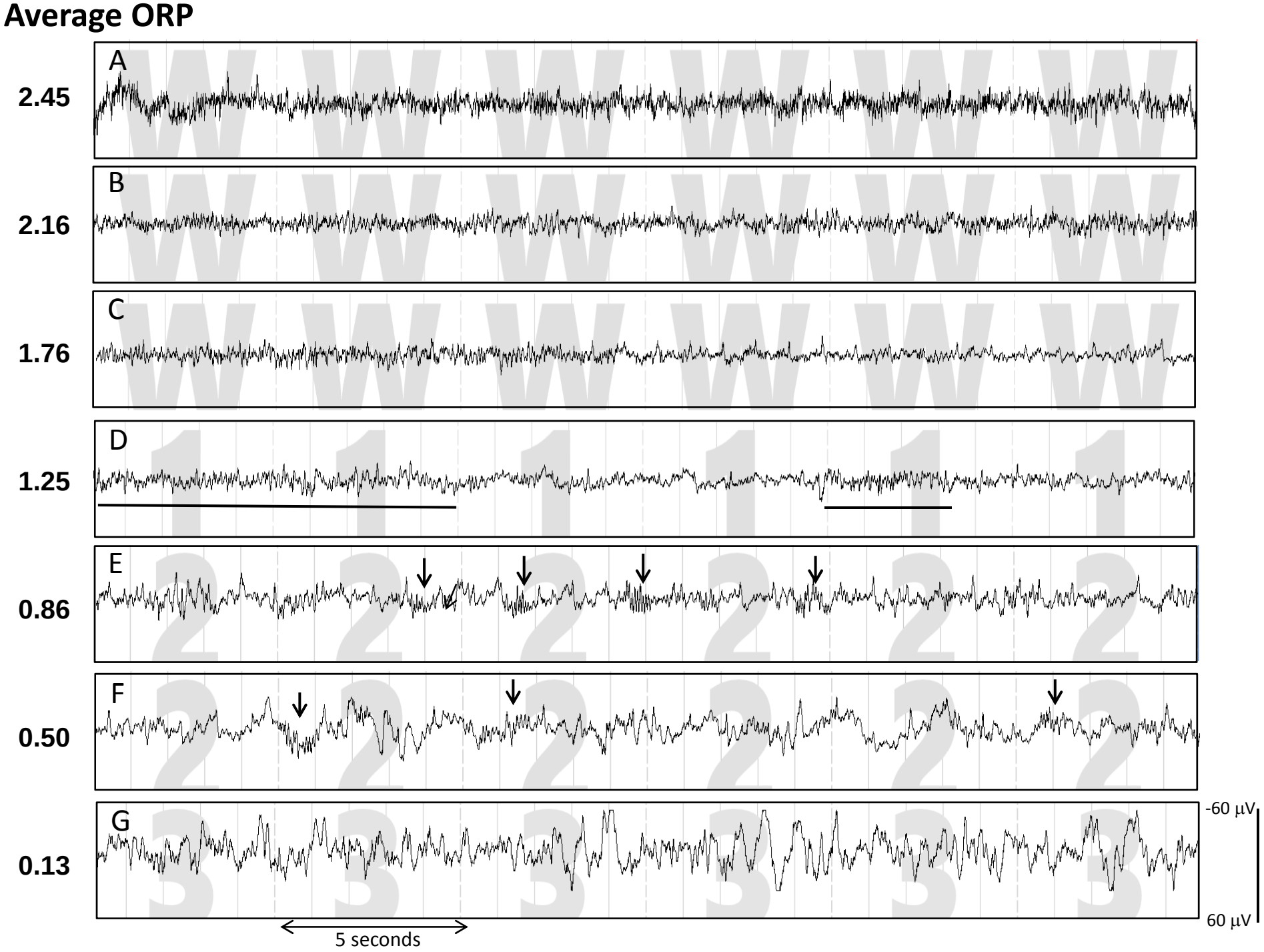

Average ORP
2.45
A
2.16
B
1.76
C
1.25
D
0.86
E
0.50
F
0.13
G
-60 µV
60 µV
5 seconds

Figure 1

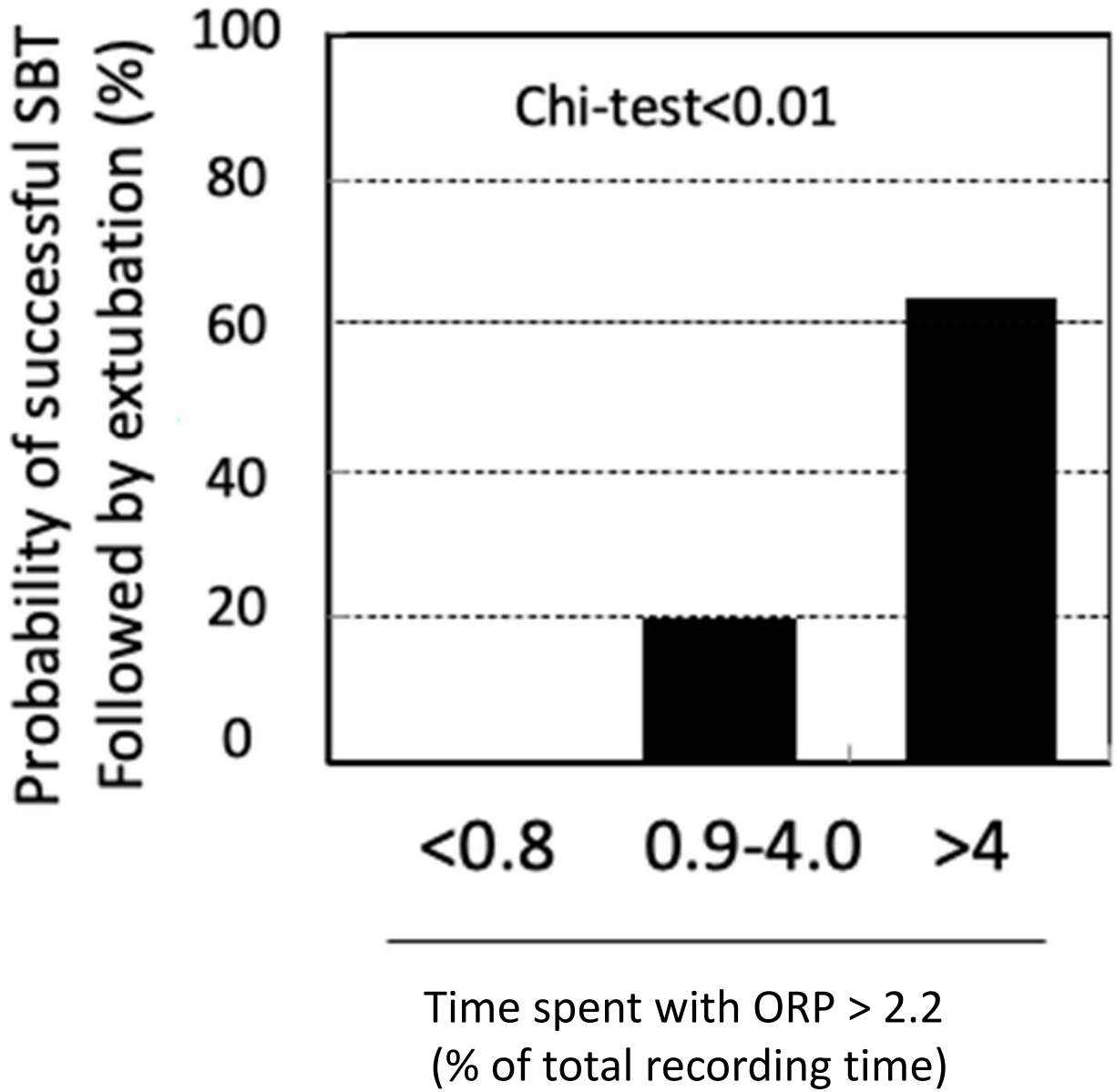

Probability of successful SBT
Followed by extubation (%)
100
80
60
40
20
0
Chi-test<0.01
<0.8
0.9-4.0
>4
Time spent with ORP > 2.2
(% of total recording time)

Figure 2

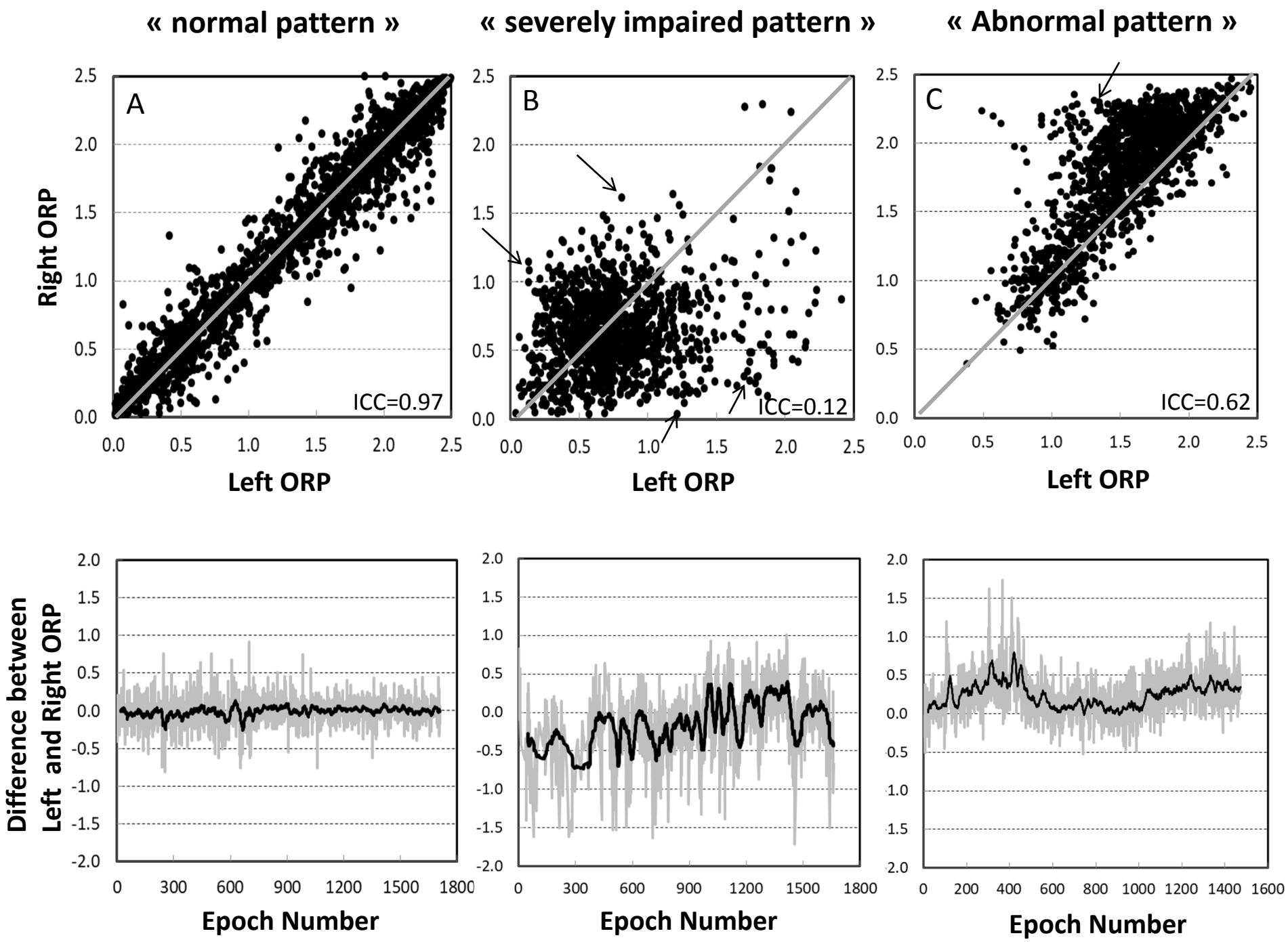

« normal pattern »
« severely impaired pattern »
« Abnormal pattern »
A
B
C
Right ORP
Left ORP
ICC=0.97
ICC=0.12
ICC=0.62
Difference between Left and Right ORP
Epoch Number

Figure 3

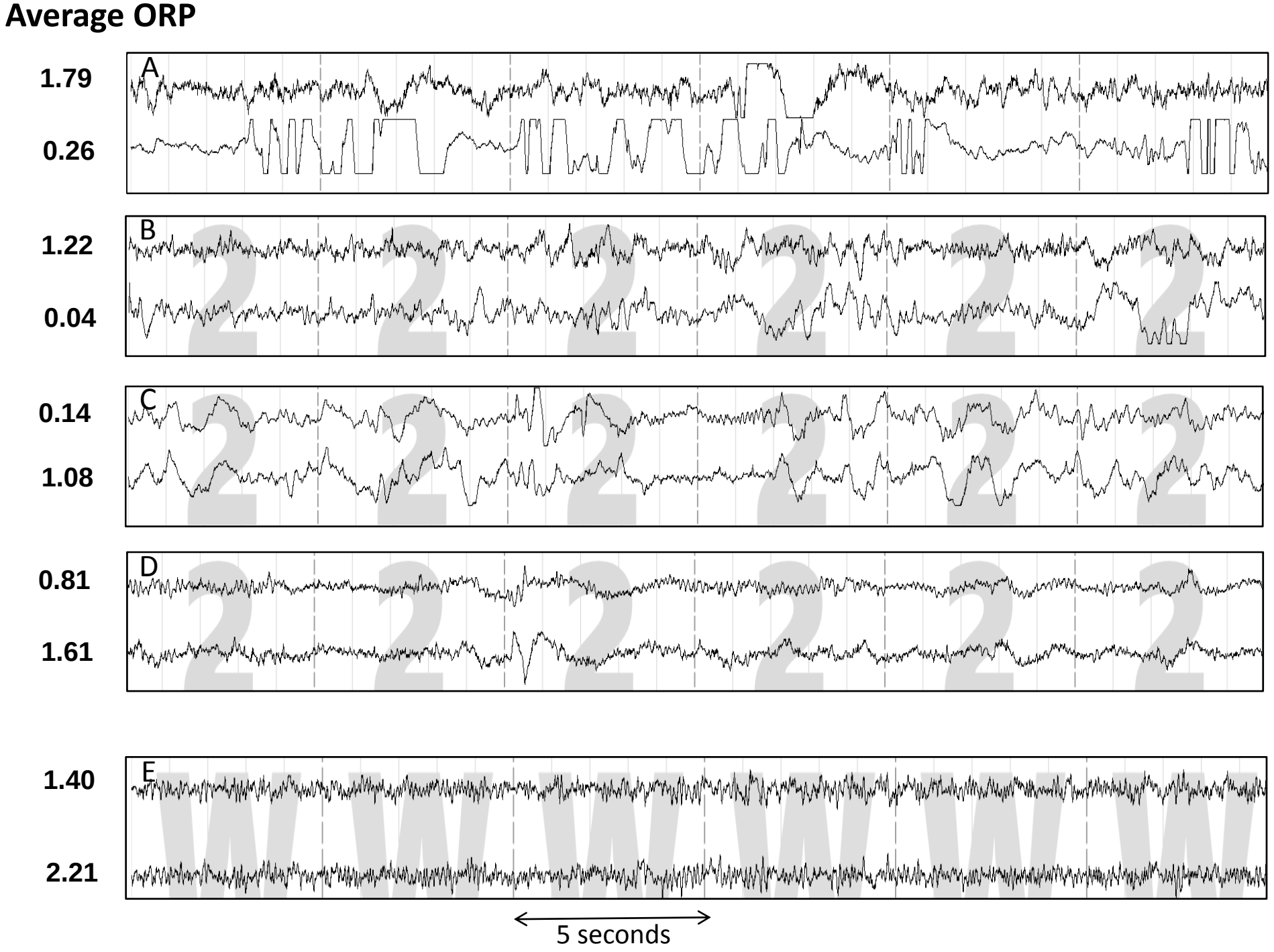

Average ORP
1.79
A
0.26
1.22
B
0.04
0.14
C
1.08
0.81
D
1.61
1.40
E
2.21
5 seconds

Figure 4

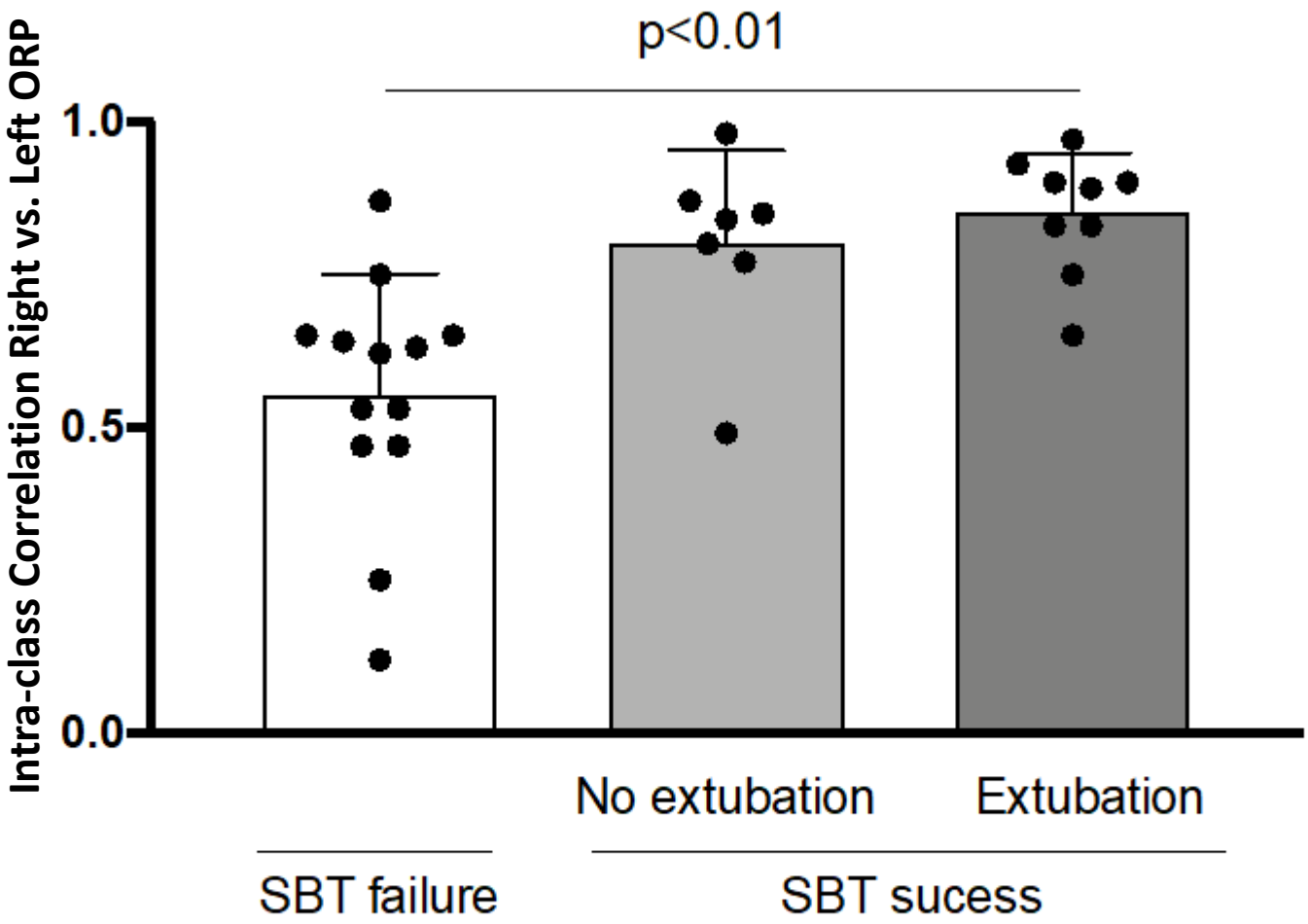

p<0.01
Intra-class Correlation Right vs. Left ORP
1.0
0.5
0.0
No extubation
Extubation
SBT failure
SBT sucess

Figure 5

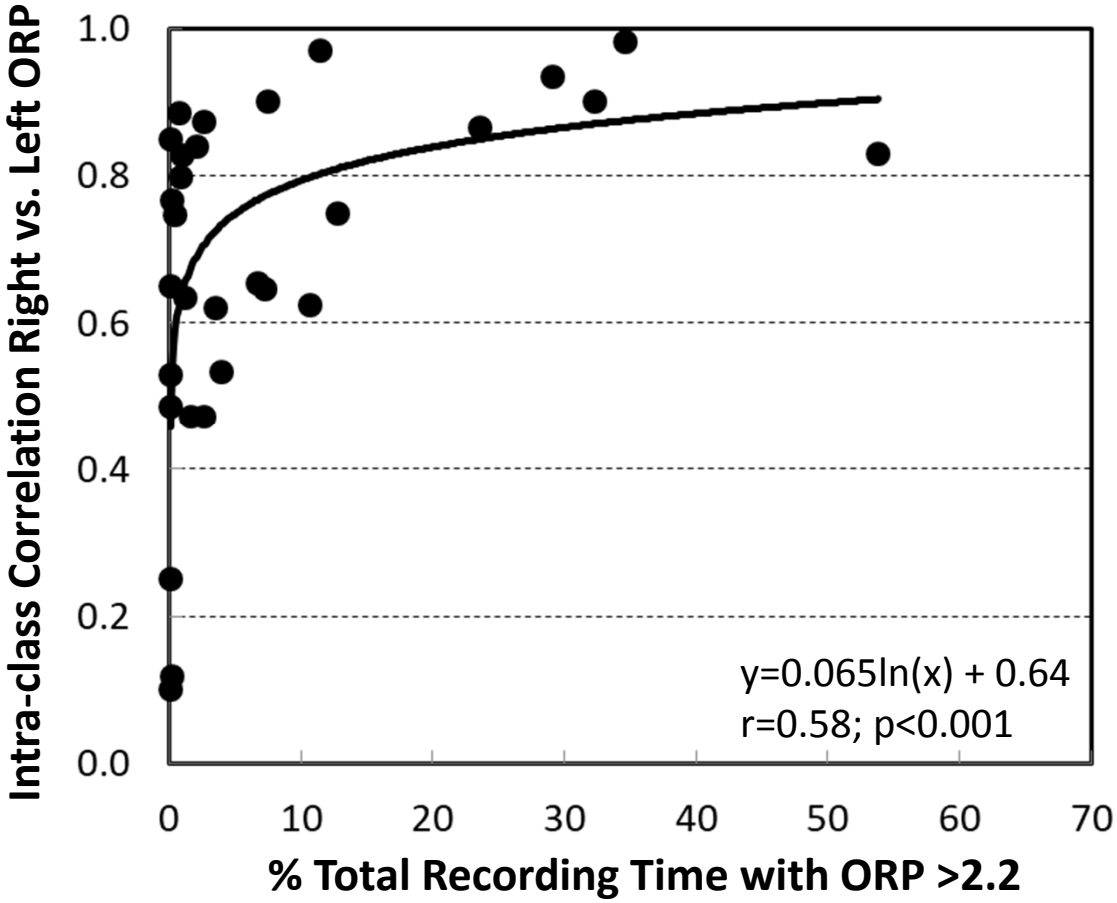

Intra-class Correlation Right vs. Left ORP
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
% Total Recording Time with ORP >2.2
y=0.065ln(x) + 0.64
r=0.58; p<0.001

Figure 6

Sleep and Pathological Wakefulness at Time of Liberation from Mechanical Ventilation (SLEEWE): A Prospective Multicenter Physiological Study

Martin Dres, Magdy Younes, Nuttapol Rittayamai, Tetyana Kendzerska, Irene Telias,

Domenico Luca Grieco, Tai Pham, Detajin Junhasavasdikul, Edmond Chau, Sangeeta Mehta,

Elizabeth Wilcox, Richard Leung, Xavier Drouot, Laurent Brochard

Online supplement

Methods

Weaning protocol

Per ICU policies, we perform SBTs at an early stage, corresponding to a low pre-test probability of successful patients ready for extubation (close to 50%). Consequently, we have a high proportion of patients who formally "pass" the SBT from a physiological standpoint, but are not deemed ready for extubation based on the physician's or clinical team's judgment. This is consistent with a recent large observational study on weaning, which found that of all patients passing an SBT, only 58% were immediately extubated (1). We thought it was important to identify all groups of patients, and describe patients who passed the SBT and are extubated, patients who passed SBT but were not extubated and patients who failed.

Sleep assessment

First, sleep recordings were manually scored by two sleep specialists blinded to patient's status. In a first attempt, 2007 American Academy of Sleep Medicine rules were used to score PSGs from the channel with the best EEG signal quality (C4 or C3) (2). When typical wake and sleep EEG patterns were absent, sleep was scored using the alternative classification, including pathological wakefulness and abnormal sleep (3). In this classification, only 2 states are identified based on EEG, EOG and EMG patterns. An epoch of wake (i.e. with high electromyographic activity and eye movements) was classified as pathological wakefulness if the dominant frequency of the background EEG was below 7Hz or if no frequency peak could be identified on a frequency spectrum. If peak frequency was above 7Hz and attenuated by eyes opening, the epoch was classified as normal wake. An epoch of sleep (i.e. with delta waves occupying more than 20% of the epoch) was classified as atypical sleep when usual EEG landmarks of sleep stage N2 (i.e. sleep spindles or K-complexes) were absent

from the onset of the sleep episode. Sleep fragmentation was defined as the sum of arousals and awakenings per hour of sleep. Results were expressed in minutes and % of total sleep time. Duration of rapid eye movement (REM) sleep and non-REM sleep stages including deep sleep was assessed using the standard criteria of the 2007 American Academy of Sleep Medicine (2).

Second, sleep depth was continuously quantified by computing the odds ratio product (ORP). Detailed description of the method has been reported elsewhere (4). Briefly, power spectrum of EEG is determined in 3-second epochs and divided into delta, theta, alpha-sigma, and beta frequency bands. The power in each frequency band is assigned a value from 0 to 9 based on its location within the entire range of powers in that band encountered in clinical sleep studies. Each 3-second epoch is then assigned a 4-digit number that reflects the relative power in the 4 frequency ranges (10,000 possible patterns). For example, pattern “8257” denotes a segment with high delta and beta powers, low theta power and average alpha power. Probability of each pattern occurring in 30-s epochs staged awake is determined, resulting in a continuous probability value from 0% to 100%. This is divided by 40 (% of epochs staged awake) producing the odds ratio product (ORP), with a range of 0–2.5. ORP< 1.0 predicts sleep (1.0=light sleep and ORP<0.5= deep sleep) and ORP 2.0 to 2.5 predicts wakefulness with > 95% accuracy in both cases, while range 1.0 to 2.0 represents unstable sleep (4).

The investigator who performed the ORP analysis (MY) was blinded to patients’ clinical status or outcome of the SBT. In six of the 37 patients the EEG signals were technically unacceptable for this type of analysis. In the remaining 31 patients the following ORP-derived indices were calculated:

- Average ORP over the entire 15 h total recording time.

- Percent of total recording time ORP was >1.5, >2.0, and >2.2.
- Correlation between sleep depth (ORP) in the right and left hemispheres (R/L): Intra-class correlation coefficient was determined for the relation between ORP in C3 and ORP in C4 obtained in each 30-second epoch with two valid EEG signals within total recording time.
- In addition to ORP-related variables we also calculated the density of spindles (# per minute when ORP was <1.5 with no rapid eye movements, indicating non-REM sleep).

References

1. Béduneau G, Pham T, Schortgen F, Piquilloud L, Zogheib E, Jonas M, Grelon F, Runge I, Nicolas Terzi null, Grangé S, Barberet G, Guitard P-G, Frat J-P, Constan A, Chretien J-M, Mancebo J, Mercat A, Richard J-CM, Brochard L, WIND (Weaning according to a New Definition) Study Group and the REVA (Réseau Européen de Recherche en Ventilation Artificielle) Network ‡. Epidemiology of Weaning Outcome according to a New Definition. The WIND Study. *Am J Respir Crit Care Med* 2017;195:772–783.

2. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, Troester MT, Vaughn BV. AASM Scoring Manual Updates for 2017 (Version 2.4). *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med* 2017;13:665–666.

3. Drouot X, Roche-Campo F, Thille AW, Cabello B, Galia F, Margarit L, d'Ortho M-P, Brochard L. A new classification for sleep analysis in critically ill patients. *Sleep Med* 2012;13:7–14.

4. Younes M, Ostrowski M, Soiferman M, Younes H, Younes M, Raneri J, Hanly P. Odds ratio product of sleep EEG as a continuous measure of sleep state. *Sleep* 2015;38:641–654.

Tables

Table E1. Reasons of failure of the spontaneous breathing trial and reasons of delayed extubated while patients succeed the spontaneous breathing trial and average ORP.

Patients	Criteria of SBT failure*	Average ORP
1	Respiratory failure	0.48
2	Undocumented	N/A
3	Hypertension and desaturation	0.74
4	Respiratory failure	1.05
5	Respiratory failure	N/A
6	Agitation, Respiratory failure	1.12
7	Respiratory failure	1.66
8	Respiratory failure	N/A
9	Decreased level of consciousness and desaturation	1.44
10	Desaturation	1.29
11	Weak cough	0.70
12	Desaturation	1.12
13	Desaturation	1.71
14	Abundant secretions and weak cough	0.67
15	Decreased level of consciousness	1.63
16	Decreased level of consciousness	0.83
17	Respiratory failure	0.87
18	Decreased level of consciousness	1.04
Patients	**Reasons for no extubation**	**Average ORP**
1	Undocumented	1.49
2	Decreased level of consciousness	0.47
3	Abundant secretions and weak cough	0.71
4	Decreased level of consciousness	0.69
5	No cuff leaks	N/A
6	Weak cough	1.15
7	Decreased level of consciousness	1.43
8	No cuff leaks	0.90

*Hypertension was defined as a systolic blood pressure higher than 180 mmHg.
*Respiratory failure was defined as a respiratory rate higher than 35/min and labored work of breathing.
*Desaturation was defined as a SpO_2 lower than 90%.

Table E2. Characteristics of the patients at inclusion (successful spontaneous breathing trial vs. failed spontaneous breathing trial).

	Failed SBT n=18	**Passed SBT n=19**	**P**
At admission			
Male, *n (%)*	11 (61)	13 (68)	0.97
Body mass index, $kg.m^{-2}$	30 ± 10	29 ± 5	0.76
APACHE 2	21 ± 9	22 (17 – 28)	0.76
Main reason for intubation, *n (%)*			
Acute respiratory failure	11 (61)	7 (37)	0.52
Acute respiratory distress syndrome	7 (39)	7 (36)	0.99
Coma	2 (11)	5 (26)	0.40
Cardiac arrest	1 (6)	1 (5)	0.60
Post-surgery	2 (11)	4 (21)	0.99
Other	2 (11)	2 (11)	0.99
At enrollment			
Length of ICU stay, *days*	4.4 ± 3.2	10.4 ± 8.6	0.03
SOFA score	6 ± 3	7± 3	0.36
Treatment regimens, n (%)			
Continuous sedative infusion	7(39)	10 (53)	0.51
Continuous analgesic infusion	5 (28)	10 (53)	0.18
Neurologic assessment			
RASS	1 ± 1	0 ± 1	0.07
CAM-ICU positive, *n (%)*	0 (0)	5 (26)	0.02
Arterial blood gases			
$PaCO_2$, *mmHg*	44 ± 12	37 ± 11	0.09
PaO_2/FiO_2 ratio	249 ± 73	261 ± 108	0.87

SBT: spontaneous breathing trial; ICU: intensive care unit; SOFA: sequential organ failure assessment; RASS: Richmond agitation sedation scale; CAM-ICU: Confusion Assessment Method for the ICU; $PaCO_2$: Partial tension of carbon dioxide; PaO2: Partial tension of oxygen; FiO_2: inspired fraction of oxygen.

Table E3. Sleep characteristics the night before the spontaneous breathing trial (2 groups)

	Failed SBT n=18	Passed SBT n=19	P
Sleep quantity			
Duration of PSG, *min*	753 ± 219	836 ± 88	0.14
Total sleep time, *min*	187 ± 125	305 ± 195	0.05
Total sleep time, *%*	23 ± 16	37 ± 22	0.01
Wake min, *min*	455 ± 182	469 ± 220	0.02
EEG background, *Hz*	7 ± 2	8 ± 2	0.48
Sleep stage 1, *%*	18 ± 9	15 ± 12	0.56
Sleep stage 2, *%*	51 ± 22	58 ± 17	0.46
Sleep stage 3, *%*	27 ± 27	22 ± 21	0.76
Rapid eyes movement stage, *%*	3 ± 5	4 ± 5	0.65
Arousal and micro-awaking, h^{-1}	34 ± 12	32 ± 18	0.77
Sleep quality			
Pathologic wakefulness, *n (%)*	7 (39)	7 (37)	0.99
Atypical sleep, *n (%)*	10 (55)	7 (37)	0.33
Abnormal sleep EEG pattern, *n (%)*	9 (50)	8 (42)	0.74
Presence of spindles, *n (%)*	6 (33)*	11 (58)	0.04
ORP derived indices			
Av ORP	1.1 ± 0.4	1.3 ± 0.5	0.25
Time ORP >2.2, *% TRT*	3.8 ± 6.2*	12.2 ± 16.3	0.04
Time ORP >2.0, *% TRT*	9.1 ± 11.4*	20.7 ± 24.2	0.05
Time ORP >1.5, *% TRT*	29 ± 27	38.7±30.9	0.19
R/L ORP, ICC	0.54 ± 0.26*	0.80 ± 0.15	<0.01
Awakening index, h^{-1}	9 ± 7	14 ± 15	0.27
Spindle Density (minute^{-1})	0.30±0.34	0.43±0.50	0.21

PSG: polysomnography; EEG: electroencephalogram; SBT: spontaneous breathing trial; ORP: odds ratio product; REM: rapid eye movement stage; R/L ORP ICC: intra-class correlation coefficient of right vs. left ORP; TST: total sleep time. *, significantly lower than in the success group

Legend of Figures

Figure E1. EEG traces (C3) representing progression from full wakefulness (Panel A) to deep sleep (stage N3, panel G) in a patient from this study who had normal EEG patterns, and the corresponding average ORP values (average of the ten 3-second values in the 30-second epoch). Note that the top 3 panels meet the guidelines of wake epochs even though their visual appearance differs substantially. Panel A represents full wakefulness with dominant high frequency rhythm throughout. At 2.45, ORP is near the maximum level. In panel B the high frequency activity is less intense and some slower frequency rhythm is briefly interspersed within the epoch. The epoch still meets the standard criteria of wake (more than 15 seconds with high frequency rhythm (8)). ORP is, however, lower at 2.16. Epoch C began with a wake pattern but there was considerable rhythm slowing in the last ≈12 seconds. ORP is considerably lower (1.76) but the epoch still meets the wake criteria. In panel D the sections with dominant high frequency rhythm (horizontal bars) total <15 seconds and the stage in now NREM 1. ORP is lower still (1.25). Note also that panels E and F are both scored stage N2 despite the marked difference in appearance. In panel E there is no longer any wake pattern and spindles appear (arrows). Stage is now NREM 2 and ORP is further reduced. Panel F has more prominent slow wave activity but there are not enough delta waves to qualify for stage NREM 3 sleep. The epoch is still scored NREM 2 even though it is clearly deeper sleep than epoch E. ORP, however, reflects this difference (0.50 vs.0.86). Finally, (panel G), the patient has several delta waves and the epoch qualifies for stage NREM 3. ORP is near the bottom of the ORP scale (0.13).

Figure E2. Correlation between the ORP and the Richmond Agitation-Sedation Scale (RASS) (Pearson r=0.03 [95% -0.40 – 0.46], p=0.87).

Figure E3. Probability of successful spontaneous breathing trial according to the percentage of total recording time (TRT) spent above specified odds ratio product (ORP). Patients were sorted according to % of TRT spent with ORP >1.5, >2.0 and >2.2. Each series was divided into 3 ≈equal aliquots (lowest 10, middle 10 and highest 11). % total recording time spent with ORP >1.5 ranged 0-98%. One third of patients spent <10% above 1.5. Of these only one (10%) passed SBT (Figure 2A). % time >1.5 ranged 10-45% in the middle third of patients. Three of these 10 patients (30%) passed SBT (Figure 2A). Of the remaining 11 patients with % time >45% 5 passed SBT (45%). The middle panel shows the results when %time ORP >2.0 was used instead. None of the ten patients with the lowest % passed SBT (Figure 2B). For the third of patients in the middle (range 2-15% TRT >2.0) and the highest (> 15% TRT >2.0) groups the probability of success was 30% and 55%, respectively. When the threshold was raised to %time spent above 2.2 (full wakefulness) the probability of success was 0 in the lower third (%<0.8), 20% in the middle third (% 0.8-4.0) and 65% for the highest third (% >4.0) (Figure 2C).

Figure E4. Intra-class correlation between right and left hemispheres Odds Ratio Product (ORP) in patients who passed and who failed the spontaneous breathing trial (SBT).

Figure E1.

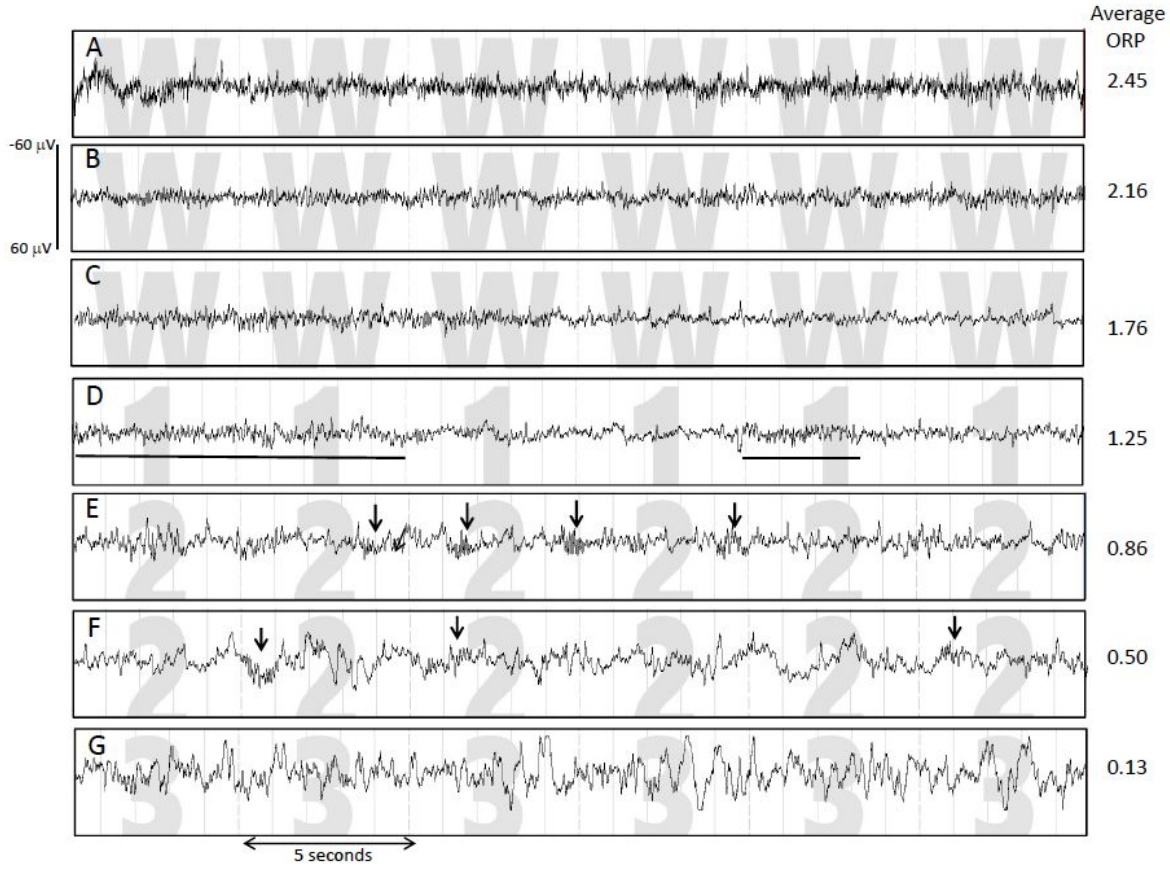

Average
ORP
A
2.45
-60 μV
B
2.16
60 μV
C
1.76
D
1.25
E
0.86
F
0.50
G
0.13
5 seconds

Figure E2.

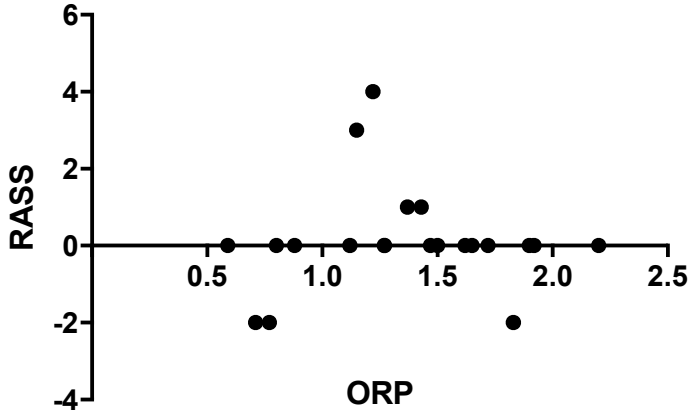


Figure E3

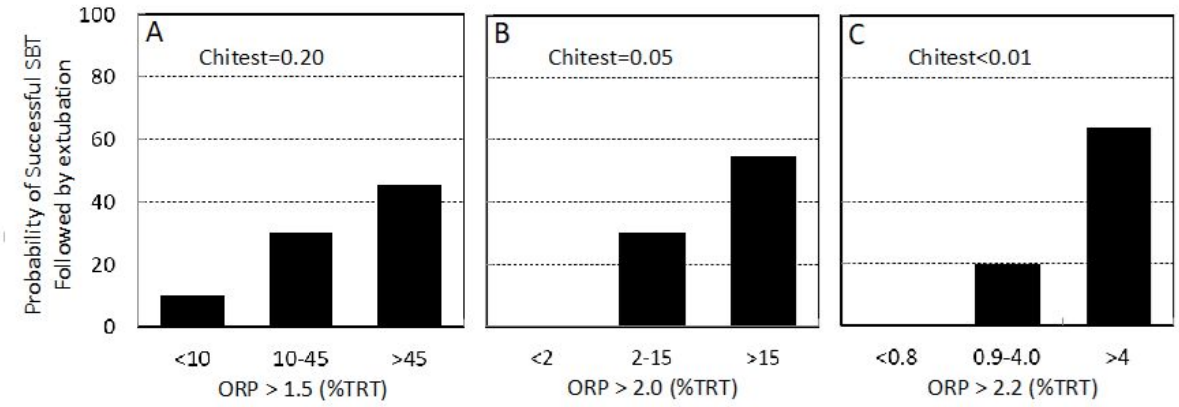
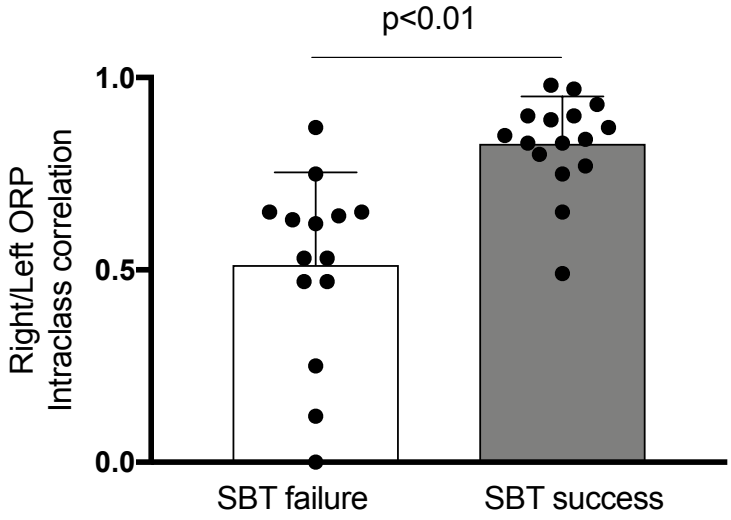

Probability of Successful SBT Followed by extubation
100
80
60
40
20
0
A
Chitest=0.20
<10
10-45
>45
ORP > 1.5 (%TRT)
B
Chitest=0.05
<2
2-15
>15
ORP > 2.0 (%TRT)
C
Chitest<0.01
<0.8
0.9-4.0
>4
ORP > 2.2 (%TRT)

Figure E4.


p<0.01
1.0
0.5
0.0
Right/Left ORP
Intraclass correlation
SBT failure
SBT success