Sleep and Breathing (2019) 23:433–438
https://doi.org/10.1007/s11325-018-1699-2

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Reliability of autonomic activations as surrogates of cortical arousals in ventilated patients affected by amyotrophic lateral sclerosis

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Received: 12 March 2018 / Revised: 26 June 2018 / Accepted: 12 July 2018 / Published online: 24 July 2018

Abstract

Purpose The study aims to evaluate the performance of autonomic activations as a tool to assess sleep fragmentation and to recognize hypopneas in patients with amyotrophic lateral sclerosis (ALS) under non-invasive mechanical ventilation and secondarily, to evaluate, in patients with the same disease, the relationship between disruption of autonomic nervous system (ANS) activity and the usefulness of the autonomic activations as surrogates of cortical arousals.

Methods Sixteen ALS patients underwent simultaneous polysomnography and portable cardiorespiratory monitoring (PM). On the polysomnography, standard rules were used for scoring arousals and respiratory events. On the PM, autonomic arousals were scored as ≥ 15% heart rate (HR) increase with a ≥ 35% pulse wave amplitude (PWA) reduction, HR increase ≥ 20%, or PWA decrease ≥ 40%. Nocturnal HR variability was analyzed in the ALS patients and in 11 control subjects as an index of ANS activity.

Results Synchronized epoch by epoch analysis of the polysomnography and PM recordings showed that only 31.0 (22.5–58.7)% cortical and 36.1 (20.5–47.2)% autonomic arousals were associated with one another. Among hypopneas scored at polysomnography, 71.7% were associated with a cortical arousal but not with a desaturation. On average, HR variability in ALS showed signs of depressed ANS activity that was particularly evident in the patients where the cortical arousals exceeded the autonomic ones.

Conclusions In ventilated ALS patients, autonomic activations may hardly have a role as surrogates of cortical arousals for assessment of sleep fragmentation and for respiratory scoring. Depression of ANS activity may be related to their poor performance.

Keywords Autonomic arousals · Autonomic nervous system · Amyotrophic lateral sclerosis · Heart rate variability · Portable monitoring

Introduction

Poor sleep quality and sleep fragmentation have been described in patients with neuromuscular diseases, including amyotrophic lateral sclerosis (ALS). In these patients, several factors may cause an increase of arousals, such as pain, cramps, and respiratory disorders [1]. Mechanical ventilation minimizes respiratory disorders but may not be enough to ensure a sufficient improvement of perceived sleep quality [2]. Cortical arousals detected during polysomnography (PSG) are an important component of sleep architecture and are taken into account to objectively evaluate sleep quality. Correctly identifying arousals and understanding their possible causes could help to reduce sleep fragmentation and to improve sleep satisfaction. Recent studies have demonstrated that an accurate titration of noninvasive ventilation (NIV) by PSG is necessary to improve sleep quality of ALS patients [3, 4].

According to current rules, cortical arousals are also essential to recognize some respiratory events that otherwise would remain undetected, i.e., hypopneas that are not associated with oxygen desaturation but with cortical arousals [5]. However, PSG is burdensome for some ALS patients, especially those at an advanced stage of the disease. Therefore, in clinical

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practice, cardiorespiratory portable monitoring (PM) is often used instead of PSG [6], but it does not provide information on cortical arousals.

Cortical arousals are generally associated with withdrawal of vagal activity and activation of the sympathetic nervous system, resulting in heart rate (HR) augmentation, vasoconstriction, and blood pressure rise. These manifestations have been indicated as autonomic arousals [7].

Recently, PM devices using autonomic activations as potential surrogates of cortical arousals have been introduced on the market [8, 9]. In patients with obstructive sleep apnea, several attempts have been done to replace cortical arousals with different manifestations of autonomic activation, both to assess sleep fragmentation and to improve recognition of respiratory events [10–14]. Whether in ALS autonomic activations may be used as surrogates of cortical arousals is unknown. In fact, ALS is associated with variably disrupted autonomic activity [15], and little is known about autonomic activations during sleep in this disease.

In this study, we simultaneously performed full night PSG and PM recordings in patients with ALS who received NIV. We used a PM device with a software that automatically scores autonomic arousals based on predefined threshold changes in pulse wave amplitude (PWA) and HR, and evaluated the relationship between cortical arousals, manually scored on the PSG according to standard criteria, and autonomic arousals as scored by the PM device. Besides, in order to evaluate autonomic nervous system (ANS) activity of the patients, we compared their nocturnal HR variability with nocturnal HR variability in control subjects. The aims of this study were: to evaluate performance of autonomic activations as a tool to assess sleep fragmentation and to recognize hypopneas; to assess the relationship between ANS activity disruption and the usefulness of the autonomic activations as surrogates of cortical arousals.

Methods

Twenty long-term ventilator users, with ALS, were enrolled between October 2014 and December 2015. All patients used the same ventilator model (Astral™150, ResMed Europe). They were ventilated only at night and were adapted to NIV. Two subjects received assisted volume-controlled ventilation, and the other ones received assisted pressure-controlled ventilation. A 2-cm H_2O positive end-expiratory pressure (PEEP) was given to one patient only. Nine subjects suffered from arterial hypertension. Two of them were taking beta-blockers and the other ones were taking ACE inhibitors or angiotensin receptor blockers. Patients with major mental disorders or cardiac arrhythmias were not included. The recruited patients were submitted to a routine baseline respiratory function evaluation, including measurements of forced vital capacity, maximal inspiratory pressure, maximal expiratory pressure (Vmax22, Sensormedics, Yorba Linda, CA, USA), and morning arterial blood gases and acid–base balance (ABG; BGE IL, Lexington, MA, USA). The study was approved by the local ethics committee and all subjects gave informed consent.

Nocturnal monitoring included simultaneous all-night PSG, PM, and transcutaneous CO_2 ($PtcCO_2$) recordings.

Full PSG (SomnoLab 2 AASM, Weinmann, Hamburg, Germany) was performed according to standard methods as a part of a routine follow-up control. Three unipolar electroencephalogram signals (one frontal, one central, and one occipital), right and left electro-oculograms, and chin electromyogram were recorded for conventional sleep staging. The other recorded signals included airflow and mask pressure detected by pneumotacographs, thoracic and abdominal movements, oxyhemoglobin saturation (SpO_2), HR, snoring, body position, and electrocardiogram (ECG).

PM was performed by means of a device (Somnocheck Micro, Weinmann, Hamburg, Germany) equipped with and a fingertip photoplethysmographic sensor. SpO_2, HR, and PWA were detected by means of the photoplethysmographic sensor.

$PtcCO_2$ was recorded with a SenTec Digital Monitor (software version SMB SW-V04.03). The V-Sign™ Sensor was applied to the earlobe with a dedicated Ear Clip (SenTec AG, Therwil, Switzerland).

On the PSG, sleep and cortical arousals were scored according to the 2007 American Academy of Sleep Medicine criteria [16]. Arousals occurring at termination of respiratory events were classified as respiratory arousals. Total sleep time (TST), sleep efficiency (defined as TST/total recording time × 100), and duration of each sleep stage as percent of the TST were calculated. Arousal index was calculated as number of arousals per hour of TST. The following respiratory events were manually scored: apneas, defined as complete cessation of airflow for at least 10 s, and hypopneas, defined as ≥ 50% reductions in respiratory airflow lasting ≥ 10 s, accompanied by a ≥ 3% SpO_2 decrease or an arousal. Apnea/hypopnea index (AHI) was calculated as total number of apneas and hypopneas/h of TST. The following SpO_2 parameters were measured in the sleep time: mean SpO_2, lowest SpO_2, time spent with $SpO_2 < 90\%$ ($T < 90$), and oxygen desaturation index (ODI), defined as ≥ 3% SpO_2 falls/h of sleep time.

On the PM recording, time free from artifacts was analyzed. Autonomic arousals were automatically scored when one of the following criteria was fulfilled: a ≥ 15% increase in HR in association with a ≥ 35% decrease in PWA, a HR increase by ≥ 20%, or a PWA decrease by ≥ 40% [17]. Then, in each patient, an epoch-by-epoch comparison of the PSG and PM recording was performed to evaluate percentages of associated and independently occurring cortical and autonomic arousals.

The $PtcCO_2$ device was calibrated before and at the end of each recording to automatically perform drift correction, when necessary, and to improve interpretation of the $PtcCO_2$ values. Mean $PtcCO_2$ and maximum $PtcCO_2$ were automatically calculated after manual elimination of artifacts.

HR variability (HRV) analysis was performed in the patients with ALS and in 11 age- and gender-matched control subjects with suspected obstructive sleep apnea (OSA) who had shown an AHI < 5 at PSG. All control subjects were healthy, apart two of them who were hypertensive and were treated by diuretics or angiotensin receptor blockers.

The ECG signal acquired during PSG was digitized at a sampling rate of 256 Hz, and was visually inspected and corrected for ectopic beats. The data were entered into Kubios HRV analysis software (version 2.0; Department of Applied Physics, University of Eastern Finland). The analysis was performed by mathematical and linear statistical models in the time and frequency domains.

Overall HRV was evaluated by standard deviation of all RR intervals (SDNN), and by RR triangular index (RRTI). As indices of parasympathetic activity, root mean square of the differences between consecutive RR intervals (RMSSD) and mean hourly rate of changes in consecutive normal sinus intervals > 50 ms (pNN50) were calculated in the time domain [18]. In addition, fast Fourier transform was used for analysis in the frequency domain: high frequencies (HF; 0.15–0.4 Hz), as an index of parasympathetic outflow, low frequencies (LF; 0.04–0.15 Hz), that reflect both sympathetic and parasympathetic influences, and LF/HF ratio were calculated [19].

Statistical analysis

Data were expressed as mean ± SD, or as median [IQR]. Agreement between cortical and autonomic arousal scores in each subject was evaluated by Bland-Altman analysis, and differences in arousals number were tested by Wilcoxon test. Data obtained by HRV data in the patients were compared with those in control subjects by unpaired Student's *t* test or Mann-Whitney *U* test, as appropriate, and were tested for linear correlation with individual differences between cortical and autonomic arousals. A two-tailed *p* value < 0.05 was taken to indicate statistical significance. Statistical analysis was performed using MedCalc for Windows (version 16.8.4; MedCalc Software, Maria Kerke, Belgium).

Results

Of the 20 patients initially enrolled, 4 were eliminated (2 due to EEG and 2 to flow artifacts or signal loss). Sixteen patients remained. Their clinical characteristics are presented in Table 1.

Table 1 Demographics and respiratory function of the included patients

Age (years)	64.5 ± 7.0
Sex	4 F/12 M
BMI (kg/m^2)	25.2 ± 5.2
Disease duration (years)	3.4 ± 1.8
FVC (percent predicted)	55.1 ± 19.3
FVC (L)	1.7 ± 0.8
MIP (cm H_2O)	31.7 ± 19.3
MEP (cm H_2O)	39.4 ± 21.4
PaO_2 (mmHg)	73.5 ± 9.4
$PaCO_2$ (mmHg)	44.6 ± 6.5
pH	7.41 ± 0.0
HCO_3^- (mEq/L)	28.6 ± 2.5

Data are expressed as mean ± SD. Blood gases were measured during room air breathing

BMI body mass index, FVC forced vital capacity, MIP maximal static mouth inspiratory pressure, MEP maximal static mouth expiratory pressure, PaO_2 partial arterial oxygen pressure, PCO_2 partial arterial carbon dioxide pressure, HCO_3^- plasma bicarbonates

Polysomnography data are shown in Table 2. Among hypopneas, 71.7% were associated with a cortical arousal, but not with a desaturation; 23.9% were associated only to oxygen desaturation; and 4.3% were associated to both a cortical arousal and an oxygen desaturation.

Table 2 Polysomnography data

TST (min)	336.3 ± 60.8
SE (%)	75.1 ± 13.2
N1 (%)	35.8 ± 20.1
N2 (%)	48.7 ± 18.9
N3 (%)	2.6 (0.0–13.0)
REM (%)	8.1 ± 7.6
AHI (n/h)	0.8 (0.0–15.3)
Arousal index (n/h)	16.8 (13.9–20.3)
SpO_2m (mmHg)	93.2 ± 1.9
ODI (n/h)	1.5 (0.2–5.9)
T < 90 (min)	8.2 (0.0–13.3)
Mean $PtcCO_2$ (mmHg)	38.3 ± 5.1
Maximum $PtcCO_2$ (mmHg)	46.2 ± 5.0

Data are expressed as mean ± SD or as median (interquartile range)

TST total sleep time, SE sleep efficiency, N1 non-REM stage 1, N2 non-REM stage 2, N3 non-REM stage 3, R REM stage, AHI total number of apneas and hypopneas per hour of sleep, RDI total number of respiratory events per hours of sleep, SpO_2m mean nocturnal arterial oxygen saturation, ODI number of oxygen desaturations ≥ 4% per hour of sleep, *T* < 90 time spent with SpO_2 below 90%, $PtcCO_2$ transcutaneous carbon dioxide pressure

Table 3 Number of cortical and autonomic arousals, and their association

Total cortical arousals (*n*)	Total cortical arousals associated with an autonomic arousal (%)	Respiratory cortical arousals (*n*)	Respiratory cortical arousals associated with an autonomic arousal (%)	Autonomic arousals (*n*)	Autonomic arousals associated with a cortical arousal (%)
101.1 (75.4–121.2)	31.0 (22.5–58.7)	21.1 (11.6–57.6)	14.2 (0.0–28.4)	86.4 (42.4–159.2)	36.1 (20.5–47.2)

In the whole patients' sample, the average number of total cortical and autonomic arousals did not differ ($p = 0.93$) but, intraindividually, most of both kinds of events occurred independently of each other. Similarly, most cortical respiratory arousals were not associated with an autonomic arousal (Table 3). In addition, there was a poor agreement between the number of cortical and autonomic arousals in each patient (Fig. 1).

Results of HRV analysis are shown in Table 4. Control subjects did not differ in age and sex from ALS patients (57.8 ± 10.9 vs 64.5 ± 7.0 years, $p = 0.06$, and 3 females/11 subjects vs 4 females/16 subjects, $p = 0.89$, controls vs ALS, respectively). They slept for 330.6 ± 55.3 and had a sleep efficiency of 67.9 ± 13.2, with 24.3 ± 10.0% stage N1, 51.0 ± 6.9% stage N2, 11.0 ± 6.7 stage N3, 13.3 ± 7.6% stage R, and 16.6 ± 4.4 arousal index. All recordings included > 90% pure beat signal. Most HRV parameters differed significantly between ALS patients and controls, demonstrating a depressed ANS function in the patients. In the patients, the difference between number of cortical and autonomic arousals was negatively correlated with RRTI and RMSSD (Fig. 2).

Discussion

The most important finding of this study was that in mechanically ventilated patients with ALS, there was a high discrepancy between cortical arousals and the autonomic arousals scored on HR and PWA changes. Hypopneas were more often associated to cortical arousals than to oxygen desaturations. On average, both sympathetic and parasympathetic modulations of nocturnal HRV were lower in the patients than in control subjects. Patients with lower indices of autonomic modulation showed more cortical than autonomic arousals whereas those with higher indices showed more autonomic arousals but, in all patients, most of the two types of arousal occurred independently of each other. Therefore, nocturnal autonomic activations affecting cardiovascular activity do not appear adequate surrogates of cortical arousals in patients with ALS.

In different populations, autonomic activations during sleep have been demonstrated to be correlated to EEG activations, although in an imperfect fashion. In healthy subjects, increasing strength of arousals was associated with progressively larger HR changes [20]. In patients referred to sleep centers for suspected sleep-disordered breathing, PWA drops ≥ 20% were associated with an augmentation in EEG power

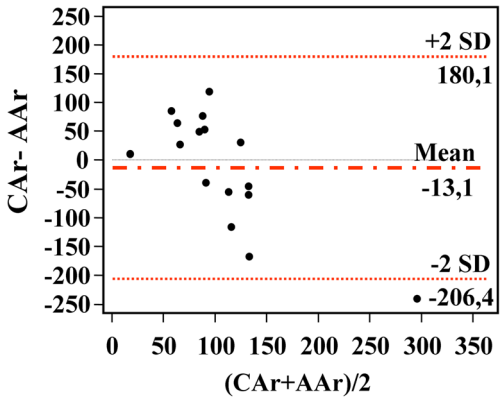

Fig. 1 Bland-Altman plot for comparison between number of cortical arousals scored on polysomnography and autonomic arousals scored on portable cardiorespiratory monitoring. CAr cortical arousals, AAr autonomic arousals

Table 4 Analysis of heart rate variability

	ALS (*n* = 16)	Controls (*n* = 11)	*p*
Time domain analysis			
RR (ms)	780 ± 140.7	980.3 ± 115.4	0.0007
SDNN	31.4 ± 17.0	51.0 ± 12.3	0.003
	26.9 (18.6–41.7)	50.0 (40.4–56.9)	0.004
RMSSD (ms)	36.3 ± 21.5	45.3 ± 13.5	0.23
	35.3 (17.2–45.6)	44.2 (35.1–54.1)	0.15
RRTI (ms)	5.3 ± 2.5	10.2 ± 3.8	0.0004
	4.1 (3.4–6.9)	9.3 (7.9–11.5)	0.001
pNN50 (%)	8.7 ± 7.8	16.6 ± 9.6	0.02
	7.0 (2.0–14.4)	17.1 (9.8–21.9)	0.02
Frequency domain analysis			
LF (ms^2)	513.6 ± 576.0	1057 ± 436.2	0.01
	335.0 (104.0–787.5)	953.0 (727.2–1263.7)	0.006
HF (ms^2)	428.6 ± 521.3	673.9 ± 397.8	0.20
	171.5 (76.5–655.5)	561.0 (394.7–820.7)	0.05
LF/HF	1.5 ± 1.1	1.6 ± 0.5	0.81
	1.0 (0.8–2.2)	1.8 (1.2–2.0)	0.29

Data are presented as mean ± SD and median (interquartile range)

RR mean R-R interval duration, SDNN standard deviation of all R-R intervals, RMSSD root mean square of the differences between successive RR intervals, RRTI RR triangular index, integral of the sample density distribution of R-R intervals divided by the maximum of the density distribution, pNN50 percentage of number of R-R intervals lasting less than 50 ms, LF low frequencies, HF high frequencies, LF/HF low/high frequency ratio

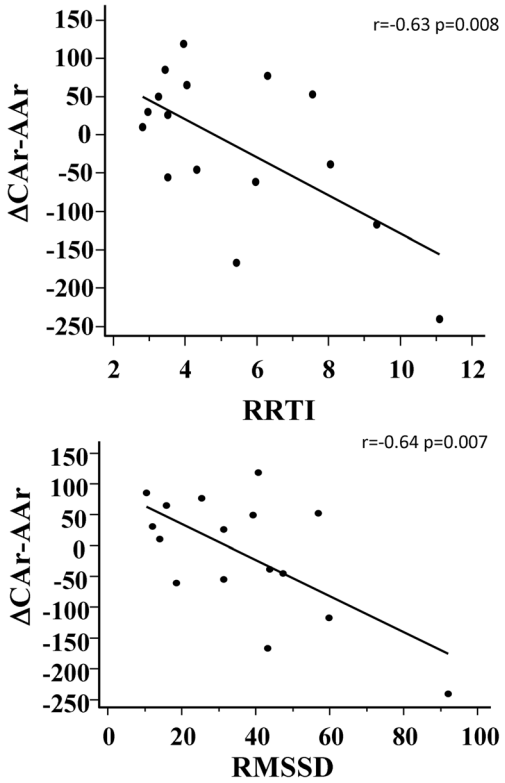

Fig. 2 Correlations of heart rate variability indices with the difference between the number of cortical and autonomic arousals in the patients. RRTI RR triangular index, RMSSD root mean square of the differences between consecutive RR intervals

density, although that did not always fulfill standard criteria for cortical arousals [8]. In a study on patients with obesity hypoventilation syndrome under NIV, PWA drops ≥ 30% had high sensitivity and positive predictive value, although low specificity and negative predictive value, for cortical arousals [21]. In patients with different types of sleep disorders, indices of HR variability reflected the degree of sleep fragmentation [22]. To our knowledge, no study has explored how cortical arousals correlate to autonomic activations in ALS, and if such activations may be considered surrogates of cortical arousals to evaluate sleep fragmentation and to score respiratory events. In our ALS patients, we found that autonomic and cortical arousals were largely independent. Furthermore, a large number of hypopneic events could not be identified without cortical arousal scoring. Thus, the autonomic arousals did not demonstrate useful either to assess sleep fragmentation or to score respiratory events.

Then, we tried to explore if the poor performance of the autonomic arousals could be related to ANS activity. In fact, a decrease in sympathetic activity may account for a reduction in vasomotor activity as assessed by pulse wave amplitude changes. The literature has shown various types and degrees of autonomic dysfunction in patients with ALS, which could be explained by interindividual differences or by different degrees of advancement of the disease. Some studies have shown a reduced cardiovagal modulation [23, 24]. Other studies described a hyperactivity of the sympathetic nervous system as an early feature of the disease, and sympathetic hypoactivity in the late stages of the disease [25]. Indeed, a high heterogeneity in muscle sympathetic nerve activity (MSNA) was found in ALS, as some patients showed an abnormally high MSNA at rest and others a normal resting MSNA [26]. Some ALS patients do not have a sympathetic skin response, which supports the view that deterioration of sympathetic function is part of the disease process [27, 28]. In our ALS subjects, HRV analysis revealed that average autonomic HR modulation was lower than in control subjects, but with large interindividual differences. Indices of autonomic modulation were correlated to the difference between cortical and autonomic arousals. That could suggest that each ALS patient requires a different threshold of autonomic phenomena to score an autonomic arousal, and that a fixed criterion for scoring autonomic arousals for all ALS patients is not appropriate. However, we found that even if autonomic arousals were more common when autonomic modulation was better preserved, in all subjects a majority of each type of arousal was not associated with the other one. Then, any change in threshold for definition of autonomic arousals would not substantially improve the performance of autonomic activations in the assessment of nocturnal recordings in this category of patients.

This study has some limitations. Some patients were taking drugs potentially influencing autonomic activity. However, we intentionally chose this approach because we were interested to evaluate patients in real life. Besides, our patients were under NIV so that the results of this study may not perfectly fit non-ventilated patients. In a previous work, in ALS patients, we observed that positive expiratory pressure (PEEP) altered autonomic balance [29]. Additionally, in patients with obesity hypoventilation syndrome, other authors observed that changing the NIV back-up rate may influence outcomes of PWA analysis in the identification of autonomic arousals [21]. Further studies performed before and after NIV, or under different modalities of NIV, may better clarify if in ALS patients the role of autonomic activations as sign of arousal may change in relationship to treatment.

In conclusion, in ventilated ALS patients, the use of autonomic activations as sign of arousal responses is of little, if any, clinical utility, and methods to improve information from PM recordings to estimate sleep fragmentation and to score respiratory events that are not associated with oxygen desaturations may hardly rely on autonomic phenomena. Nocturnal autonomic modulation of HR is variably altered in ALS. Autonomic reactivity may partly account for the large discrepancy between cortical and autonomic arousals in ALS patients, although autonomic events could occur randomly, and may hardly be interpreted as sign of arousal.

Acknowledgments The authors gratefully acknowledge Valentina Massa, Flavia Armato, Fabio Artisi, and Corrado D'Urso for their technical contribution and for the help in the management of patients and in collecting data.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the ethics committee "Palermo 2 Azienda Ospedaliera Villa Sofia-Cervello". All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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