Early respiratory dysfunction as a biomarker for epileptic encephalopathy.

Katrien Jansen, MD[1], Carolina Varon[2,3], Sabine Van Huffel, PhD[2,3], Lieven Lagae, MD, PhD[1]

[1]Pediatric neurology, University Hospitals Leuven, Belgium
[2]KULeuven, Department of Electrical Engineering-ESAT, SCD-SISTA, Leuven, Belgium
[3]iMinds Future Health Department, Leuven, Belgium

Corresponding author

Lieven Lagae
Department of Pediatric Neurology
University Hospitals Leuven
Herestraat 49, 3000 Leuven, Belgium
Tel +32 16 343845
Fax +32 16 343842
e-mail: lieven.lagae@uzleuven.be

key words:
autonomic, ECG, epileptic spasms, respiration, West syndrome

word count

Abstract

Objectives

West syndrome is an epileptic encephalopathy starting in infancy with almost continuous interictal epileptic activity, so-called hypsarrhytmia pattern, and therefore is an interesting model for investigating the effect of interictal epileptic activity on autonomic function. It is known that autonomic dysfunction contributes to morbidity and mortality in epilepsy. Our aim is to investigate the effect of interictal epileptic activity in West syndrome on respiratory control.

Materials and methods

Interictal single-lead ECG signals were extracted from 24 hour video-EEG recordings in 10 children suffering from West syndrome and 14 control subjects. RR interval time series were calculated and respiration was derived from the ECG signal. ECG-derived respiration (EDR) signals were computed and time and frequency domain parameters were extracted to characterize the respiration pattern.

Results

In time domain, the standard deviation of the EDR signal is significantly lower in patients with West syndrome compared to control subjects. This finding is an indication of a less variable respiratory rate.

In frequency domain we analysed the mean power spectrum for the EDR. In patients with West syndrome there is more activity at the lower frequencies considered to be a risk factor for apneas. Secondly, there is an attenuated peak at the higher frequency band where normal respiratory rate is to be found, indicating an abnormal breathing pattern.

Conclusions

Our results show that there is a clear dysfunction in autonomic respiratory control in patients with West syndrome, in between the typical ictal epileptic spasms, compared to control subjects. Respiration is more fixed and contains a higher risk for apneas.

Introduction

Epilepsy and seizures have a profound effect on the central autonomic nervous system (1). During seizures, acute changes in heart rate and/or respiration can occur when ictal epileptic activity directly affects autonomic control centers. In addition, interictal discharges can also have a long-term effect on autonomic function. In patients with longlasting or refractory epilepsy, chronic dysfunction of autonomic cardiac control has already been demonstrated by several authors (2-4). In those patients autonomic alterations are evaluated by monitoring heart rate variability. However, little is known of the effect of epilepsy on other autonomic functions such as respiration. Respiratory dysfunction could be another risk factor for morbidity and mortality in patients with epilepsy (5).

West syndrome is an age-dependent epileptic syndrome characterized by epileptic spasms, hypsarrhythmia on the EEG and arrest or regression in psychomotor development. It is an epileptic encephalopathy starting in infancy with typically continuous interictal epileptic activity and therefore it is an interesting model for investigating the effect of interictal epileptic activity on autonomic function (6). Ictal repiratory changes, during the epileptic spasms, are thought to be due to involvement of central respiratory control centers. However, little is known of the effect of interictal epileptic activity on the central respiratory centers. The goal of this study was to investigate the effect of interictal epileptic activity on respiratory control in an early epileptic encephalopathy.

Material and methods

Single-lead ECG signals were obtained from 24 hour video EEG recordings in children suffering from West syndrome and in control subjects. Inclusion criteria were presentation with epileptic spasms and hypsarrhythmia on the EEG. Only interictal data outside the periods of infantile spasms were used. EEG, ECG and simultaneous video recordings were evaluated by 2 independent EEG specialists. Control subjects were referred to the epilepsy clinic for non-epileptic sleep myoclonus and had normal EEG findings. Control subjects were age matched at the moment of EEG evaluation to take into account age-dependent differences.

Lead II ECG recordings were collected with a sampling frequency of 250 Hz. The respiration signal was derived from the ECG by the methodology of Widjaja et al. by means of kernel principal component analysis (7). Respiration changes the ECG signal due to a mechanical

interaction: the volume changes in the lungs during respiration alter the electrical impedance. The changing position of the electrodes with respect to the heart change the morphology of the heart beats in the ECG signal. Due to these interactions, it is feasible to derive a reliable respiratory signal from the ECG, termed ECG-derived respiration (EDR). First of all, the ECG signal was divided into segments of one minute of duration. Next, the R-peaks were detected using a modified Pan-Tompkins algorithm, where artifacts were detected and eliminated. The positions of these R-peaks lead to the computation of the RR interval time series and to the estimation of the EDR signals. After following this procedure, each minute was characterized by a set of time and frequency domain attributes. The parameters extracted from the EDR signals were in time domain the mean EDR and standard deviation of EDR (std). The mean EDR displays the mean respiratory rate, the standard deviation of EDR is indicative for the variability of the respiratory rate. In frequency domain spectral components were defined as low frequency (LF) between 0.04 - 0.2Hz and high frequency (HF) between 0.2 – 0.1Hz components. The components in the LF band are indicative for slower breathing frequencies and apneic events, whereas the components in the HF band include the normal respiratory rate for age and the faster breathing frequencies. Differences between minutes of control and West subjects were evaluated using the Mann-Whitney U-test, where p-values lower than 0.05 were considered statistically significant.

Results

Ten patients with infantile spasms at presentation were included and 14 control subjects. The mean age at onset of epilepsy was 6 months (range 4-9 months). The mean age at the moment of EEG evaluation was 8 months (range 5-11 months). All patient had MRI evaluation to exclude anatomical lesions which could contribute to respiratory dysregulation and none showed brainstem abnormalities. Neurometabolic screening showed no important underlying disease and specifically no sign of mitochondrial disease in all patients. Patients' characteristics and treatment at the moment of evaluation are shown in the table. ECG data were obtained for a mean duration of 14 hours (range 10-22 hours) during continuous monitoring. Both sleep and wake data were included during these hours to exclude the effect of state on respiratory control. All subjects had still uncontrolled spasms but only data inbetween seizures were used. Anti-epileptic treatment was already started in 7 subjects, 3 subjects were evaluated before any treatment. None of the subjects received ACTH. The delay between onset of West syndrome and EEG/ECG evaluation is mentioned in the table.

The first available EEG was used as we wanted to focus on the early effects of the interictal discharges on respiratory function.

Significant differences between West patients and control subjects were observed in both time and frequency domains.

In time domain, there was no significant difference in the mean EDR. However, the standard deviation of EDR was significantly lower in patients with West syndrome compared to control subjects indicating less variability in respiratory rate ($p=0.02$) (Fig 1A). In frequency domain, the mean power spectrum of the respiratory signals of West patients indicates more activity at lower frequencies in the LF band ($p=0.004$) and less activity at the higher amplitude components in the HF band ($p=0.04$) compared to controls (Fig 1B and C). These high frequency components correspond to normal respiratory rates and are attenuated in patients with West syndrome. Figure 2 shows the mean power spectra for controls and West subjects, and the 25 and 75 percentiles determine the variation intervals. The attenuated peak at the normal respiratory rate in the HF band is clearly visualized.

Discussion

The autonomic system is in charge of maintaining homeostasis in the body. Inadequate autonomic control is a risk factor for health eg after myocardial infarction (8). A well-functioning autonomic system is also of importance in many inborn survival systems or auto-resuscitation triggered by vagal or sympathetic activity. The defence systems against hypoxia and asphyxia seem even more important in very young children and possibly fail in infants with ALTE or SIDS (9-10). Seizures are reported in up to 25 % of the infants presenting with an acute life threatening event, illustrating the important impact a seizure disorder can have on normal autonomic control in young children(11).

Normal respiration is mediated through the hypothalamus and brain stem autonomic nuclei. The ventrolateral medulla generates the respiratory rhythm, with influences of nucleus ambiguous and influences from higher brain systems eg prefrontal cortex or insula. Acute respiratory compromise has already been documented during seizures and is probably due to direct involvement of these respiratory centers in seizure activity. This can be involvement at a cortical level or discharges in the respiratory centers of the brainstem (5-12). In patients with epilepsy, interictal epileptic activity also induces alterations in autonomic control centers. These changes are best discernible in the cardiovascular system and seem to evolve with time, being more severe in refractory or long-term epilepsy. This is illustrated in a study

by Sathyaprabha et al. This study showed that the longer the duration of epilepsy, the more severe the autonomic changes (13). The described autonomic alterations could be of importance as one of the pathophysiological mechanisms in sudden unexplained death in epilepsy patients (SUDEP) (14).

In this study, we used West syndrome as a model of a short term but severe epileptic encephalopathy with almost continuous interictal epileptic activity, the so-called hypsarrythmia pattern. In these patients, we already described in a previous study autonomic cardiovascular alterations that were seen after a relatively short disease course (15). Now we wanted to focus on respiratory control.

In our data clear differences in autonomic control between patients with West syndrome and control subjects are observed in time and frequency domain parameters. Standard deviation of respiration is lower in patients with West syndrome. This could indicate that respiration is less variable in patients with West syndrome and therefore less adaptable in acute situations, compared to controls. This is of importance because continuous adjustment of respiration is expected according to the needs of the moment. In frequency domain there is more activity at the lower frequencies in patients with West syndrome and less activity at the normal respiratory rate range. This indicates a loss of respiratory rate at the normal frequencies corrected for age and a high amount of very slow respiratory rate or apneic events.

These results show that there is a clear difference in autonomic respiratory control in patients with West syndrome compared to control subjects. Respiration is more fixed, contains more slow components or apneas and there is a loss of respiration at the expected frequency corrected for age. Whether these findings predispose patients with West syndrome to SUDEP or epilepsy related mortality in the course of their disease needs further study.

We did consider the effect of the differences in delay between onset of infantile spasms and EEG evaluation as well as the potential effect of medication on our results. Therefore we looked at the results of the 3 subjects who were included immediately after onset of epileptic spasms and received no medication (patient 6,8 and 9 in the table and blue dots in fig 1 A, B and C). The dysfunction in respiratory control of this small subgroup is even more pronounced in 2 of the 3 subjects as can be seen in fig 1 A,B and C . This suggests that the presence of interictal spikes influences the function of the respiratory network very early. This finding is very different from the cardiovascular anomalies that are only present after a longer disease course. One hypothesis could be that the respiratory control system is more vulnerable to continuous interictal spikes compared to the cardiovascular system. In this respect, a dysfunctional respiratory control could be considered as an early biomarker in

epileptic encephalopathy. Whether the differences we find between the cardiovascular en respiratory system are only due to a longer lasting presence of spikes or whether the systems are in different ways influenced by the epileptogenesis in the developing brain remains to be studied however.

In conclusion we demonstrated in the current study the loss of normal autonomic control of respiration in patients with West syndrome, already very early on in the disease. We hypothesize that normal respiratory control and arousal mechanisms are disturbed by the epileptic encephalopathy very early, in contrast with cardiac autonomic dysfunction.

Acknowledgements

This research was supported by: Research Council KUL: GOA MaNet, PFV/10/002 (OPTEC), IDO 08/013 Autism, several PhD/postdoc \& fellow grants; Flemish Government: FWO: PhD/postdoc grants, projects: G.0427.10N (Integrated EEG-fMRI), G.0108.11 (Compressed Sensing) G.0869.12N (Tumor imaging); IWT: TBM070713-Accelero, TBM070706-IOTA3, TBM080658-MRI (EEG-fMRI), TBM110697-NeoGuard, PhD Grants; IBBT; Flanders Care: Demonstratieproject Tele-Rehab III (2012-2014); Belgian Federal Science Policy Office: IUAP P7/ (DYSCO, `Dynamical systems, control and optimization', 2012-2017); ESA AO-PGPF-01, PRODEX (CardioControl) C4000103224; EU: RECAP 209G within INTERREG IVB NWE programme, EU HIP Trial FP7-HEALTH/ 2007-2013 (n° 260777)

Conflicts of interest

The authors have no conflicts of interest

Tables and figures

case nr	age at onset (months)	sex (male/female)	treatment at the time of EEG	etiology	age at EEG evaluation (months)
1	5	F	vigabatrin	symptomatic: ACM infarct	7
2	4	M	clonazepam	unknown etiology	11
3	6	M	valproate	unknown etiology	6
4	5	F	vigabatrin	unknown etiology	6
5	7	F	vigabatrin,	unknown etiology	9

			valproate		
6	9	M	none	trisomy 21	10
7	4	M	valproate, topiramate	tuberous sclerosis	10
8	9	M	none	unknown etiology	9
9	5	F	none	unknown etiology	5
10	7	F	vigabatrin	Mowat-Wilson	7

Table

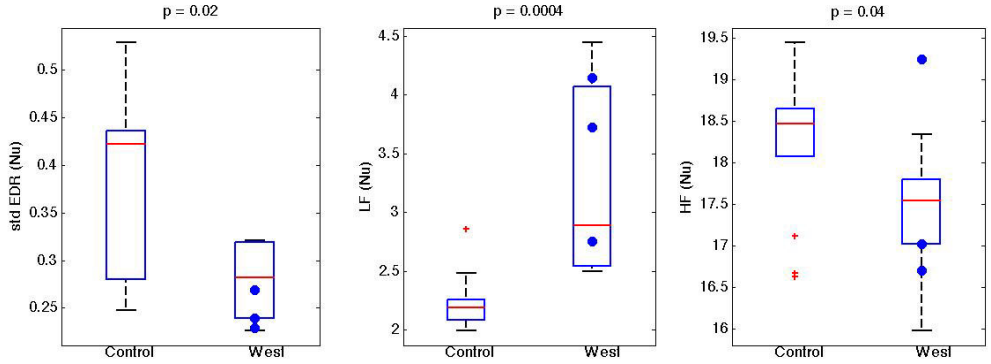


Figure 1

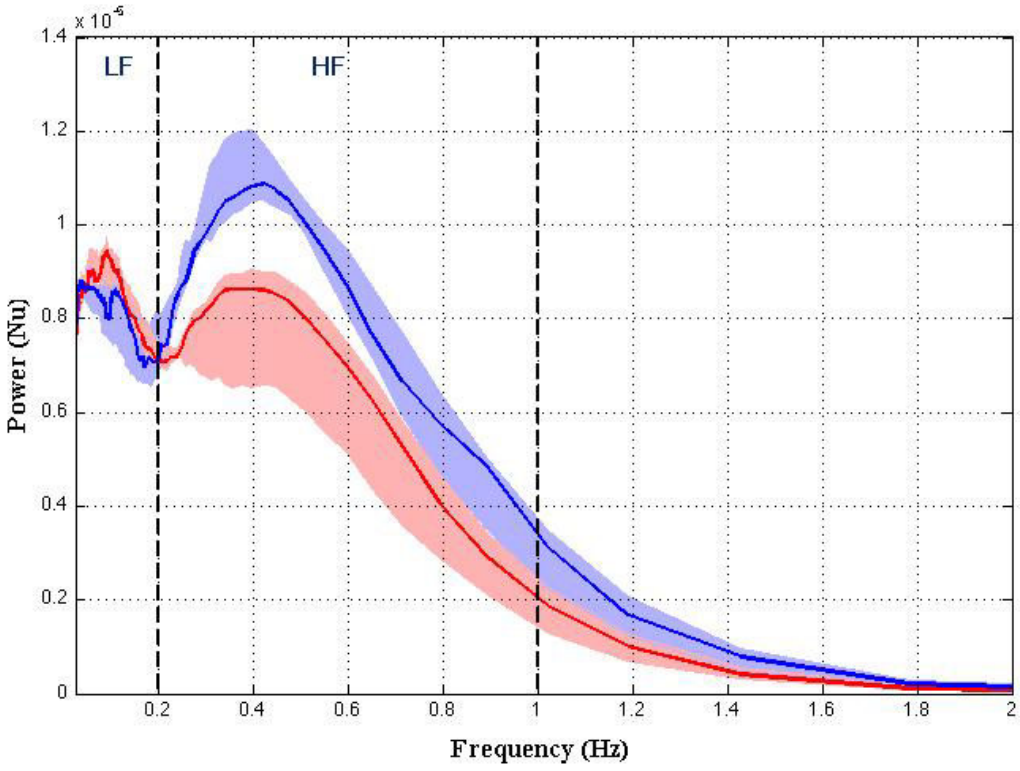


Figure 2

References

1. BAUMGARTNER C , LURGER S , LEUTMEZER F Autonomic symptoms during epileptic seizures. Epileptic Disord. 2001;**3**:103-16

2. CHRONI E, SIRROU V, TRACHANI E, SAKELLAROPOULOS GC, POLYCHRONOPOULOS P Interictal alterations of cardiovagal function in chronic epilepsy. Epilepsy Res. 2008;**83**:117-23

3. JANSEN K, VANDEPUT S, MILOSEVIC M et al. Autonomic effects of refractory epilepsy on heart rate variability. Influence of intermittent vagus nerve stimulation. Dev Med Child Neurol 2011;**53**:1143-9

4. HARNOD T, YANG CCH, HSIN YL, SHIEH KR, WANG PJ, KUO TB Heart rate variability in children with refractory generalized epilepsy. Seizure 2008;**17**:297-301

5. BATEMAN LM, LI CS, SEYAL M Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. http://www.ncbi.nlm.nih.gov/pubmed/18952672 Brain 2008;**131**:3239-45

6. COMMISION ON PEDIATRIC EPILEPSY OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY Workshop on infantile spasms 1992. Epilepsia 1992;**33**:1955

7. WIDJAJA ., VARON ., CAICEDO DORADO A, SUYKENS JAK, AND VAN HUFFEL S Application of Kernel Principal Component Analysis for Single Lead ECG-Derived Respiration, IEEE Transactions on Biomedical Engineering, 2012;**59**:1169-76

8. BUCCELLETTI E, GILARDI E, SCAINI E et al. Heart rate variability and myocardial infarction: systematic literature review and metanalysis. Eur Rev Med Pharmacol Sci 2009;**13**:299-307

9. FRANCO P, SZLIWOWSKI H, DRAMAIX M, KAHN A Polysomnographic study of the autonomic nervous system in potential victims of sudden infant death syndrome. Clin Auton Res. 1998;**8**:243-9

10. EDNER A, KATZ-SALAMON M, LAGERCRANTZ H, ERICSON M, MILERAD J. Heart rate variability in infants with apparent life-threatening events. Acta Paediatr. 2000;**89**:1326-9

11. MCGOVERN MC, SMITH MBH Causes of apparent life threatening events in infants: a systematic review Arch Dis Child 2004;**89**:1043-8

12. O'REGAN ME, BROWN JK Abnormalities in cardiac and respiratory function observed during seizures in childhood. Developmental Medicine and Child Neurology. 2005;**47**: 4-9

13. SATHYAPRABHA TN, SATISHCHANDRA P, NETRAVATHI K, SINHA S, THENNARASU K, RAJU TR. Cardiac autonomic dysfunctions in chronic refractory epilepsy. Epilepsy Res 2006;**72**,49-56

14. TOMSON T, NASHEF L, RYVLIN P Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurology 2008; **7**:1021–31

15. JANSEN K, VANDEPUT S, VAN HUFFEL S, LAGAE L Cardiac autonomic dysfunction in West syndrome. Epilepsy Res 2012; [Epub ahead of print]

Legends

Table: patient characteristics

Figure 1 Differences in time and frequency parameters computed from the ECG derived respiration. Au stands for arbitrary units. Blue dots indicate patients without treatment with anti-epileptic drugs at the time of EEG/ECG.

Figure 2 Normalized mean power spectra for West (red) and controls (blue). The shaded areas indicate the intervals of variation and they correspond to the 25 and 75 percentiles. Reduced peaks at the respiratory frequencies are observed for the West patients. Nu stands for normalized units.