Peri-ictal ECG changes in childhood epilepsy: implications for detection systems.

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

[1]Pediatric neurology, University Hospitals Leuven, Belgium
[2]KU Leuven, 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

Word count:

3410

Running title:

Peri-ictal tachycardia in childhood epilepsy.

Key words: seizure, heart rate, tachycardia, childhood epilepsy, seizure detection

Abstract

Introduction

Early detection of seizures could reduce associated morbidity and mortality and improve the quality of life in patients with epilepsy. In this study, the aim is to investigate whether ictal tachycardia is present in focal and generalized epileptic seizures in children. We try to predict in which type of seizures tachycardia can be identified before actual seizure onset.

Methods

ECG segments in 80 seizures were analyzed in time and frequency domain before and after onset of epileptic seizures on EEG. These ECG parameters were analyzed to find the most informative ones that can be used for seizure detection. The algorithm of Leutmezer et al. was used to find the temporal relationship between the change in heart rate and seizure onset.

Results

In time domain the mean RR shows a significant difference before compared to after onset of the seizure in the focal seizures. This can be observed in temporal lobe seizures as well as frontal lobe seizures. Calculation of mean RR interval has a high specificity for detection of ictal heart rate changes. Pre-ictal heart rate changes are observed in 70% of the partial seizures.

Conclusion

Ictal heart rate changes are present only in partial seizures in this childhood epilepsy study. The changes can be observed in temporal lobe seizures as well as frontal lobe seizures. Heart rate changes precede seizure onset in 70% of the focal seizures, making seizure detection and closed loop systems a possible therapeutic alternative in the population of refractory epilepsy in childhood.

Introduction

Epilepsy is a chronic neurological condition characterized by recurrent epileptic seizures. A lot of morbidity and also mortality in epilepsy is due to seizures [1]. The phenomenon sudden unexpected death in epilepsy patients (SUDEP) is the most important epilepsy-related mode of death and is the

leading cause of death in people with chronic uncontrolled epilepsy [2,3] . Apart from SUDEP, mortality and morbidity as a result of seizure-related events eg accidents, drowning,… is frequent. As the occurrence of seizures is unpredictable, much effort is put into trying to predict or early detect seizures. Detection of seizures could be very helpful in the development of warning systems but also in novel treatment strategies. The ultimate goal is to detect seizures and achieve termination of seizure activity through "closed loop" systems [4,5]. This implies early or pre-ictal detection of seizures.

The autonomic nervous system is the control part of the nervous system. The autonomic nervous system has an important representation in the central nervous system and epileptic seizures are often associated with changes in autonomic function [6,7]. These changes can occur at the same time but also before and after the actual seizure onset on EEG. Activation of the central autonomic centers by spreading of epileptic discharges during a seizure is thought to be responsible for the pre-ictal autonomic symptoms. At the time of the clinical seizure, motor activity and stress responses probably contribute to the ictal autonomic symptoms.

Heart rate can be measured relatively easily and is therefore an interesting parameter for long-term monitoring. The peri-ictal heart rate changes can be of use in seizure detection systems, as illustrated in figure 1. Fig 1 In this case, seizures could be identified with the use of ECG alone. Ictal tachycardia is probably the best studied autonomic phenomenon in epilepsy [8,9]. However, most studies on the presence of ictal tachycardia were conducted in adults with refractory temporal lobe seizures as a predominant seizure type[11-19].Table

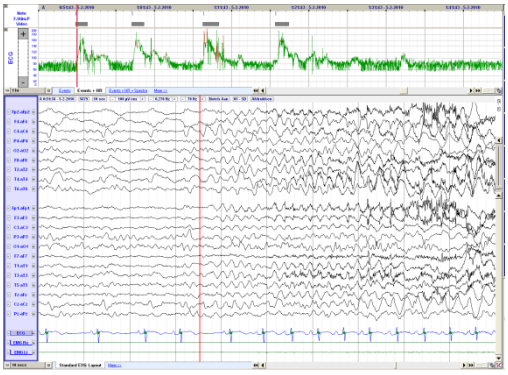


Figure 1

Upper part: heart rate pattern (green line) showing sudden increase in heart rate at the moment of seizure onset (time-scale 1 hour/page)

Lower part: EEG onset of seizure (red line) and accompagnying tachycardia (time-scale 10 sec/page).

In this study, the first aim is to investigate if ictal tachycardia is present in focal and generalized epileptic seizures in children. In the seizures with ictal tachycardia, we will try to define the most sensitive EKG parameter for detection of tachycardia that could be useful in seizure detection systems in the future. A final aim was to better define in which seizure types pre-ictal ECG changes could be identified.

Methods

Seizures were selected retrospectively from patients admitted to the epilepsy clinic UZ Leuven. All patients were admitted for 24 hour video EEG because of refractory epilepsy. Video/EEG recordings were obtained using the 10-20 International System of Electrode Placement. EEG recordings were reviewed by 2 independent EEG specialists. Onset of seizures were annotated based on EEG and video. Lead II ECG was measured simultaneously with a sampling rate of 250 Hz. After preprocessing of the ECG signal, 5 minutes of lead II ECG were extracted, starting 3 minutes before the onset of each seizure. Results were visually inspected to ensure that no QRS-complex was missed.

In the first part of the analysis, data were split into 2 segments: baseline (3 minutes) and ictal (2 minutes). Parameters in time and frequency domain were calculated and compared according to the stardards of the Task Force (Task Force). In time domain we analyzed heart rate for both segments using mean RR interval, standard deviation of all normal to normal intervals (SDNN) reflecting all the cyclic components responsible for variability in the period of recording and the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), estimating high frequency variations in heart rate. Serial autocorrelation was used as another method to show how the samples of the RR interval time series cross-correlate at different time points. In frequency domain power spectra of the RR intervals were calculated. Statistical differences were determined by the Kruskal-Wallis test and $p<0.001$ was considered statistically significant.

Next, we wanted to to identify the most informative ECG parameter to discriminate the data sets before and after the onset of seizures. To find the best predictive features, Kruskal-Wallis was used and features were selected that give a p value < 0.05.

In the last part of the analysis , the algorithm proposed in Leutmezer et al. was used to find the temporal relation of ictal heart rate changes to EEG seizure onset [17]. This method enables dynamic ECG analysis at the transition from the interictal to the ictal state. Using this methodology we can automatically identify heart rate changes that were seizure related. In this way, we can correlate the start of ECG changes with the EEG onset of the seizure and define the temporal relationship.

Results

80 seizures were selected, 40 with focal onset, 40 with generalized onset. Generalized seizures were tonic, tonic-clonic or myoclonic. In the seizures with focal onset, 20 were originating from the frontal lobe and 20 from the temporal lobe.

In the temporal lobe seizures 11 were left sided in onset and 9 right sided.

Mean age of the patients was 9,2 years (range 3-16), male/female ratio was 1.9, 1-3 seizures were selected from a total of 35 patients.

1. *Analysis of ECG segments before and after encephalographic onset of seizure*

In the first part of the analysis, data were split into a baseline segment, before seizure onset on EEG, and an ictal segment, after seizure onset on EEG. In time domain the mean RR decreases after onset of the seizure in the focal seizures. The difference in mean RR is statistically significant ($p<0.001$). SDNN was computed but showed no clear difference, RMSSD indicates a difference between the two segments with $p=0.049$. There were no statistical significant differences observed in the generalized seizures. In frequency domain, no statistical significant differences were observed in the power spectra of both types of seizures.

In the serial autocorrelation coefficient, we have the same findings. Serial autocorrelation shows a significant difference for partial seizures but not for generalized seizures ($p<0.001$).

Figure 2 shows our findings for the 3 groups, frontal lobe seizures, temporal lobe seizures and generalized seizures. Fig 2. In more detail, ictal bradycardia was noted in 5 patients, 3 with temporal lobe seizures and 2 with frontal lobe seizures. All these seizures were left sided in onset.

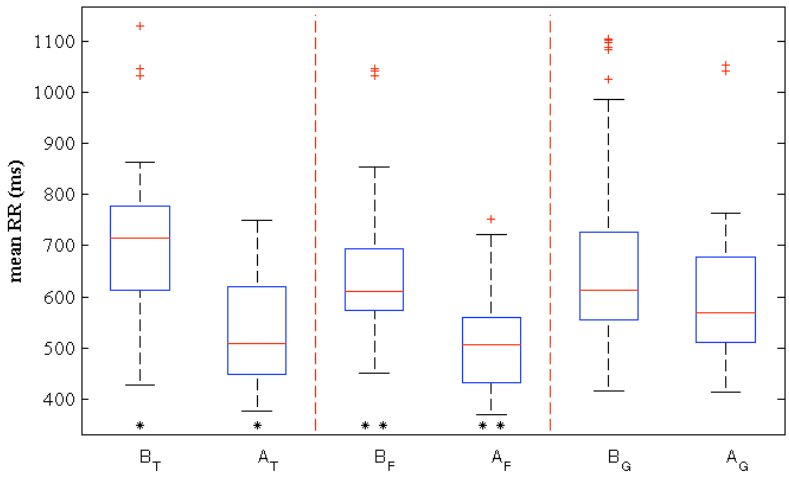


Figure 2: Significant difference in mean RR interval before (B) and after (A) seizures onset in frontal (F) as well as temporal lobe(T) epilepsy. No difference was found in generalized seizures (G).

*p<0.01, **p<0.01

The sets of heart rate parameters that were used for our first analysis (RR, SDNN, RMSSD, serial autocorrelation and power spectra of RR) were compared for sensitivity and specificity in partial seizures.

We examined 3 possible combinations of parameters:

A first set contains all time and frequency domain parameters with a p-value<0.05. A second set combines mean RR interval and serial correlation and RR interval alone is a third possibility. This classification shows that mean RR provides the best specificity whereas a combination of parameters can improve sensitivity in partial seizures. However, important to note is that sensitivity remains low., whatever parameters was included.

features	**sensitivity**	**specificity**
Time and frequency <0.05	0.56	0.91
mean RR and serial correlation	0.31	0.93
mean RR	0.43	0.95

2. *Heart rate changes at the onset of the focal seizures*

In the second part of the analysis we used the algorithm of Leutmezer to find the temporal relationship of ictal heart rate changes to seizure onset on EEG. As the heart rate changes were not present in patients with generalized seizures, we used only the focal seizures for this analysis. We could confirm that the majority of the focal seizures present a typical pattern after use of the algorithm as described by Leutmezer and this pattern is shown in the figure. Figure 3 After identification of the breakpoint in heart rate we compared the onset of the ictal heart rate changes with the onset of the seizure on EEG. In 70% of the focal seizures we found a pre-ictal onset of heart rate changes. 8% showed a pre-ictal bradycardia, 62% showed a pre-ictal tachycardia. Looking at the temporal relationship between the heart rate changes and seizure onset on EEG, we found that the

time lag has a mean of 3.59 seconds (range 0.2-29 seconds). 20% of the focal seizures had an ictal onset of heart rate changes whereas in 10% ECG changes were only noted after EEG onset of the seizure

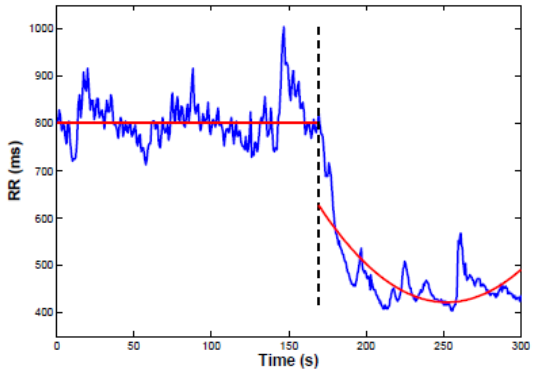


Figure 3: example of significant decrease in RR interval at the onset of the seizure showing the "heart rate breakpoint" at the transition from pre-ictal steady state phase to ictal tachycardia phase according to the algorithm of Leutmezer et al.

Discussion

Higher brain systems have a descending control on autonomic outflow from the brainstem to the heart. The insula and prefrontal cortex are thought to represent the autonomic nervous system at the cortical level and can influence the output of the medullary reflex centers [20,21]. Input from the insula can give rise to an excitatory "pressor" or inhibitory "depressor" response at the cardiac level. There is evidence of a hemispheric specific organisation of this response as shown in the depth electrode studies by Oppenheimer with the pressor response lateralized to the right and depressor response to the left hemisphere [22].

In patients with seizures, epileptic discharges are thought to propagate to the central autonomic network and change or disturb normal autonomic control of vital cardiac functions. This activation of central autonomic nervous system is responsible for the peri-ictal autonomic cardiac symptoms observed in epilepsy patients. As we know heart rate changes can precede the clinical and encephalographic seizure onset, early detection of these changes can have an application in seizure detection systems.

Ictal tachycardia in adults has been reported in up to 100 % of the seizures, taking into account that in most of the studies, focus is on focal seizures alone or more specifically temporal lobe seizures, as

these are the most refractory in adult epilepsy. An overview of the papers on this issue is presented in the table. Table

These results are comparable with the findings in our study. Ictal tachycardia is present in 90% of the children with focal seizures originating from the temporal lobe or frontal lobe. Temporal and frontal lobe structures are anatomically closely interconnected with the central autonomic network, so spreading to these regions are most likely to induce autonomic changes. In generalized seizures there is a trend towards faster heart rate after seizure onset, but difference between the ECG segments before and after seizure onset was not statistically significant.

Looking at the heart rate changes in more detail, we found ictal bradycardia in 5 partial seizures, 3 originating from the temporal lobe and 2 from the frontal lobe. All these seizures were left sided in origin, consistent with the hemispheric specific findings in stimulation studies [22]. These studies show a lateralization with depressor response to the left hemisphere. However, other studies on lateralization showed contradictory results . The pattern of seizure spread, presence of a lesion and hand dominance are probably factors influencing ictal cardiovascular response and explaining in part the different results in previous studies [23-25].

Early detection of seizures is becoming an important issue in epilepsy. Acute changes in heart rate or respiration can be the first manifestation of a seizure. Early detection of seizures is important in the development of closed loop systems. These novel systems aim to abort seizures with immediate therapeutic measures at the onset of the seizure. Therefore, identification of these early autonomic manifestations in seizures can contribute in developing new treatment strategies based on seizure detection for patients with refractory seizures.

From our results we can confirm that ictal heart rate changes can be clearly found in focal seizures in childhood originating from the temporal lobe as well as the frontal lobe, but not in generalized seizures. Due to relatively small sample size, difference between mesial and lateral temporal lobe seizures could not be made. The heart rate changes preceded the seizure onset on EEG in 70% of the cases, making seizure detection and development of closed loop systems a possible therapeutic alternative in refractory focal seizures in childhood. However, in previous reports, sinus tachycardia preceded seizure onset on surface EEG for an average in 18.7 seconds [6,14,17]. In our study population, time lag was only 3.59 seconds, making the time window to react very short.

Calculation of the mean RR has a high specificity (0.95) for detection of seizures. However, we need a combination of more parameters to improve sensitivity which remains quite low(0.43). In addition, in generalized seizures tachycardia alone is not useful for seizure detection. In this subpopulation, a

combination of parameters will improve sensitivity and specificity and the use of for instance accelerometers seems promising [4,26].

Conclusion

Ictal heart rate changes are present in seizures in childhood epilepsy. The changes can be observed in temporal lobe seizures as well as frontal lobe seizures, but not in generalized seizures. Heart rate changes precede seizure onset in 70% of the focal seizures, making seizure detection and closed loop systems a possible therapeutic alternative in childhood epilepsy. However, sensitivity of ECG changes remains low and the time lag between pre-ictal heart rate changes and actual seizure onset is very short.

	Adult/children	Seizure type	Ictal findings	Pre-ictal findings
Marshall et al. 1983	adults	TLE	Ictal tachycardia 64%	
Blumhardt et al. 1986	adults	TLE	Ictal tachycardia 92%	
Keilson et al. 1989	adults	Refractory seizures	Ictal tachycardia 96%	
Galimberti et al. 1996	adults	Partial seizures	Ictal tachycardia 49%	
Schernthaner et al.1999	adults	Partial seizures	Ictal tachycardia 82.5%	Preictal tachycardia 76.1%
Garcia et al. 2001	adults	Partial seizures	Ictal tachycardia 32%	
Zijlmans et al. 2002	adults	Refractory seizures	Ictal tachycardia 73%	Preictal tachycardia 23%
Leutmezer et al. 2003	adults	Most pronounced TLE	Ictal tachycardia 86.9%	
Di Gennaro et al. 2004	adults	TLE	Ictal tachycardia 92%	

Mayer et al. 2004	children	TLE	Ictal tachycardia 98%	Preictal 20/71
Moseley et al. 2011	adults	Refractory seizures	Ictal tachycardia 57%	
Isik et al. 2012	children	Refractory seizures	Ictal tachycardia 100%	

Table Studies on presence of ictal/pre-ictal tachycardia in patients with refractory epilepsy

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)

References

[1] Forsgren L, Hauser WA, Olafsson E, Sander JW, Sillanpää M, Tomson T . Mortality of epilepsy in developed countries: a review. *Epilepsia*. 2005;**46**:18-27.

[2] Tomson T, Nashef L, Ryvlin P Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurology* 2008; **7**:1021–1031.

[3] Devinsky O. Sudden, unexpected death in epilepsy. *New England Jounal of Medicine.* 2011;**365**:1801-1811.

[4] Van de Vel A, Cuppens K, Bonroy B, Milosevic M, Jansen K, Van Huffel S, Vanrumste B, Lagae L, Ceulemans B. Non-EEG seizure-detection systems and potential SUDEP prevention: State of the art. *Seizure*. 2013 Mar 15 [Epub ahead of print]

[5] Iasemidis LD Seizure prediction and its applications. *Neurosurgery Clinics of North America.*2011;**22**:489-506.

[6] Baumgartner C., Lurger S., Leutmezer F. Autonomic symptoms during epileptic seizures. *Epileptic Disorders* 2001;**3**:103-116.

[7] Fogarasi A., Janszky J., Tuxhorn I. Autonomic symptoms during childhood partial epileptic seizures. *Epilepsia* 2006;**47**,584-588

[8] Mayer H., Benninger F., Urak L., Plattner B.,Geldner J., Feucht M. EKG abnormalities in children and adolescents with symptomatic temporal lobe epilepsy. *Neurology* 2004; **63**,324-328.

[9] Işik U, Ayabakan C, Tokel K, Ozek MM. Ictal electrocardiographic changes in children presenting with seizures. *Pediatrics International.*2012;**54**:27-31.

[10] Marshall DW, Westmoreland BF, Sharbrough FW. Ictal tachycardia during temporal lobe seizures. *Mayo Clinic Proceedings* 1983; **58**:443–446.

[11] Blumhardt LD, Smith PE, Owen L. Electrocardiographic accompaniments of temporal lobe epileptic seizures. *Lancet* 1986; **1**:1051–1056.

[12] Keilson MJ, Hauser WA, Magrill JP. Electrocardiographic changes during electrographic seizures. *Archives of Neurology* 1989;**46**:1169-1170.

[13] Galimberti CA, Marchioni E, Barzizza F, Manni R, Sartori I, Tartara A. Partial epileptic seizures of different origin variably affect cardiac rhythm. *Epilepsia* 1996;**37**:742–747.

[14] Schernthaner C, Lindinger G, Potzelberger K, Zeiler K, Baumgartner C. Autonomic epilepsy–the influence of epileptic discharges on heart rate and rhythm. *Wiener Klinische Wochenschrift* 1999;**111**:392–401.

[15] Garcia M, D'Giano C, Estelles S, Leiguarda R, Rabinowicz A. Ictal tachycardia: its discriminating potential between temporal and extratemporal seizure foci. *Seizure* 2001;**10**:415–419.

[16] Zijlmans M, Flanagan D, Gotman J. Heart rate changes and ECG abnormalities during epileptic seizures: prevalence and definition of an objective clinical sign. *Epilepsia* 2002; **43**:847–854.

[17] Leutmezer F, Schernthaner C, Lurger S, Pötzelberger K, Baumgartner C. Electrocardiographic changes at the onset of epileptic seizures. *Epilepsia*. 2003;**44**:348-354.

[18] Di Gennaro G, Quarato PP, Sebastiano F, Esposito V, Onorati P, Grammaldo LG, Meldolesi GN, Mascia A, Falco C, Scoppetta C, Eusebi F, Manfredi M, Cantore G. Ictal heart rate increase precedes EEG discharge in drug-resistant mesial temporal lobe seizures. *Clinical Neurophysiology* 2004;**115**:1169–1177.

[19] Moseley BD, Wirrell EC, Nickels K, Johnson JN, Ackerman MJ, Britton J. Electrocardiographic and oximetric changes during partial complex and generalized seizures. *Epilepsy Research.* 2011;**95**:237-245.

[20] Benarroch E.E. The central autonomic network: functional organisation, dysfunction, and perspective. *Mayo Clinic Proceedings* 1993;**68**:988-1001.

[21] Ostrowsky K., Maglin M., Ryvlin P., Isnard J., Guenot M., Mauguière F. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cerebral Cortex* 2002;**12**:376-385.

[22] Oppenheimer SM, Gelb A, Girvin J.P., Hachinski V.C. Cardiovascular effects of human insular cortex stimulation. *Neurology* 1992;**42**:1727-1732.

[23] Opherc C, Coromilas J, Hirsch LJ Heart rate and ECG changes in 102 seizures: analysis of influencing factors. *Epilepsy Res*earch 2002;**52**:117-127.

[24] Sevcenzu C, Struijk JJ Autonomic alterations and cardiac changes in epilepsy. *Epilepsia* 2010;**51**:725-737.

[25] Saleh Y, Kirchner A, Pauli E, Hilz MJ, Neundörfer B, Stefan H. Temporal lobe epilepsy: effect of focus side on the autonomic regulation of heart rate? *Nervenarzt*. 2000;**71**:477-480.

[26] Beniczky S, Polster T, Kjaer TW, Hjalgrim H. Detection of generalized tonic-clonic seizures by a wireless wrist accelerometer: A prospective, multicenter study. *Epilepsia*. 2013;**54**:e58-61.