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

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ABSTRACT

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

Electrocardiogram segments in 80 seizures were analyzed in time and frequency domains before and after the 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. [17] was used to find the temporal relationship between the change in heart rate and seizure onset.

In the time domain, the mean RR shows a significant difference before compared to after onset of the seizure in 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.

Preictal heart rate changes are observed in 70% of the partial seizures.

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 in 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 children with refractory epilepsy.

1. Introduction

Epilepsy is a chronic neurological condition characterized by recurrent epileptic seizures. There is a threefold increase in mortality in people with epilepsy compared to the general population [1]. The phenomenon of sudden unexpected death in epilepsy (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 (e.g., accidents and drowning) are frequent. As the occurrence of seizures is unpredictable, much research is put into prediction or early detection of seizures. Detection of seizures could be very helpful not only 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 preictal 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 not only 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 periictal autonomic symptoms. At the time of the clinical seizure, motor activity and stress responses probably contribute to the ictal autonomic symptoms.

Heart rate is easy to measure and is therefore a useful parameter for long-term monitoring. The periictal heart rate changes can be of use in seizure detection systems, as illustrated in Fig. 1. In this case, seizures could be identified with the use of ECG alone. Ictal tachycardia is 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 [10–19] (Table 1).

In this study, the first aim was to investigate if ictal tachycardia is present in focal and generalized epileptic seizures in children. In the seizures with ictal tachycardia, we endeavored to define the most sensitive

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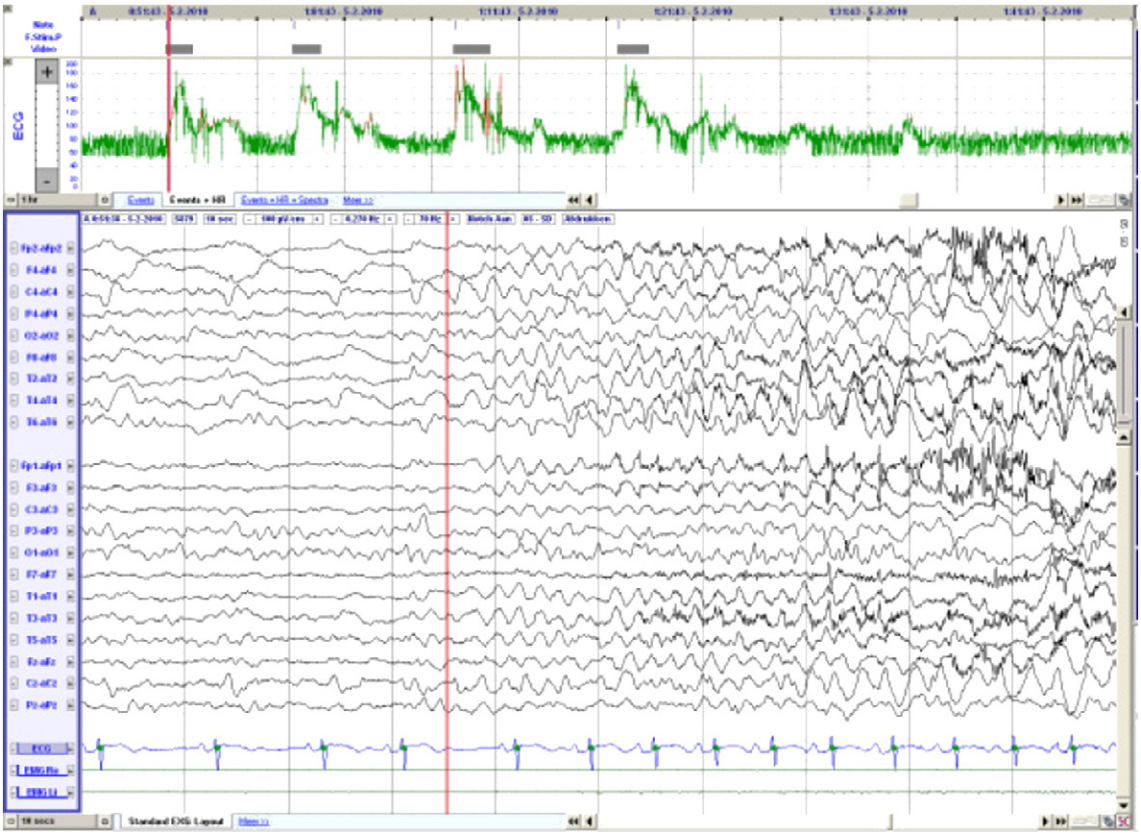

Fig. 1. Upper part: heart rate pattern (green line) showing sudden increase in heart rate at the moment of seizure onset (time scale: 1 h/page). Lower part: EEG onset of seizure (red line) and accompanying tachycardia (time scale: 10 s/page).

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 ictal ECG changes could be identified before onset of the seizure on the scalp EEG.

2. Methods

Seizures were selected retrospectively from patients admitted to the epilepsy clinic of UZ Leuven. All patients were admitted for 24-hour video-EEG because of refractory epilepsy. Scalp-EEG recordings were obtained using the 10–20 international system of electrode placement. The EEG recordings were reviewed by 2 independent EEG specialists. The onset of seizures was 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 min of lead II ECG was extracted, starting 3 min 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 min) and ictal (2 min). Parameters in the time and frequency domains were calculated. In the time domain, we analyzed the 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 the frequency domain, the 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.

Table 1
Studies on the presence of ictal/preictal tachycardia in patients with refractory epilepsy.

	Adults/children	Seizure type	Ictal findings	Preictal findings
Marshall et al. [10]	Adults	TLE	Ictal tachycardia 64%	
Blumhardt et al. [11]	Adults	TLE	Ictal tachycardia 92%	
Keilson et al. [12]	Adults	Refractory seizures	Ictal tachycardia 96%	
Galimberti et al. [13]	Adults	Partial seizures	Ictal tachycardia 49%	
Schernthaner et al. [14]	Adults	Partial seizures	Ictal tachycardia 82.5%	Preictal tachycardia 76.1%
Garcia et al. [15]	Adults	Partial seizures	Ictal tachycardia 32%	
Zijlmans et al. [16]	Adults	Refractory seizures	Ictal tachycardia 73%	Preictal tachycardia 23%
Leutmezer et al. [17]	Adults	Most pronounced TLE	Ictal tachycardia 86.9%	
Di Gennaro et al. [18]	Adults	TLE	Ictal tachycardia 92%	
Mayer et al. [8]	Children	TLE	Ictal tachycardia 98%	Preictal tachycardia 20/71
Moseley et al. [19]	Adults	Refractory seizures	Ictal tachycardia 57%	
Işik et al. [9]	Children	Refractory seizures	Ictal tachycardia 100%	

Next, we wanted 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 on scalp recordings and define the temporal relationship.

3. Results

Eighty seizures were selected: 40 with focal onset and 40 with generalized onset. Generalized seizures were tonic, tonic–clonic, or myoclonic. In the seizures with focal onset, 20 originated from the frontal lobe and 20 from the temporal lobe.

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

The mean age of the patients was 9.2 years (range: 3–16), the male/female ratio was 1:9, and 1–3 seizures/patient were selected from a total of 35 patients. There were no patients receiving drugs with chronotropic action.

3.1. 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 the time domain, the mean RR decreases after the onset of the seizure in the focal seizures. The mean differences in RR interval after seizure onset were 172 +/− 137 ms in the temporal lobe seizures and 112 +/− 131 ms in the frontal lobe seizures. The difference in mean RR is statistically significant ($p < 0.001$). Standard deviation of all normal-to-normal intervals was computed but showed no clear difference, while RMSSD indicated a difference between the two segments with $p = 0.049$. There were no statistically significant differences observed in the generalized seizures. In the frequency domain, no statistically 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 showed a significant difference for partial seizures but not for generalized seizures ($p < 0.001$).

Fig. 2 shows our findings for the 3 groups: frontal lobe seizures, temporal lobe seizures, and generalized seizures. 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.

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.

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

3.2. Heart rate changes at the onset of the focal seizures

In the second part of the analysis, we used the algorithm of Leutmezer et al. [17] 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 et al. [17] and this pattern is shown in Fig. 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 scalp EEG. In 70% of the focal seizures, we found a preictal onset of heart rate changes. Eight percent showed a preictal bradycardia, while 62% showed a preictal tachycardia. Looking at the temporal relationship between the heart rate changes and seizure onset on EEG, we found that the time lag had a mean of 3.59 s (range: 0.2–29 s). Twenty percent 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.

4. 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

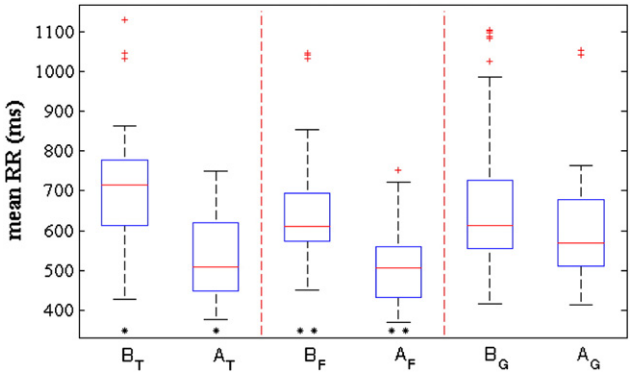

Fig. 2. Significant difference in mean RR interval before (B) and after (A) seizure onset in frontal (F) as well as temporal lobe (T) epilepsy. No difference was found in generalized seizures (G). *p < 0.01, **p < 0.01.

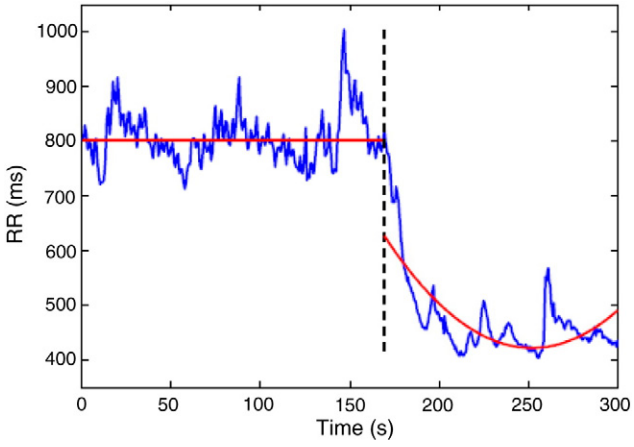

Fig. 3. Example of significant decrease in RR interval at the onset of the seizure showing the "heart rate breakpoint" at the transition from the preictal steady state phase to the ictal tachycardia phase according to the algorithm of Leutmezer et al.

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 organization of this response as shown in the depth electrode studies by Oppenheimer et al. 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 the central autonomic nervous system is responsible for the periictal autonomic cardiac symptoms observed in patients with epilepsy. As we know, heart rate changes can precede clinical and encephalographic seizure onset, and 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, the 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 Table 1.

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 is most likely to induce autonomic changes. In generalized seizures, there is a trend towards faster heart rate after seizure onset, but the 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. Because of the relatively small sample size, the difference between mesial and lateral temporal lobe seizures could not be determined. 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 of 18.7 s [6,14,17]. In our study population, the time lag was only 3.59 s, making the time window to react very short.

Calculation of the mean RR revealed 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].

5. 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 preictal heart rate changes and actual seizure onset is very short.

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