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Mini review article

HEART RATE VARIABILLITY PROCESSING IN EPILEPSY: THE ROLE IN DETECTION AND PREDICTION OF SEIZURES AND SUDEP

ANALIZA VARIJABILNOSTI SRČANE FREKVENCIJE U EPILEPSIJI: ULOGA U DETEKCIJI I PREDIKCIJI NAPADA I IZNENADNE NEOČEKIVANE SMRTI U EPILEPSIJI

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Abstract

Epilepsy is a very prevalent neurological disorder. The gold standard in diagnosis of epilepsy is the EEG signal recorded during a seizure with characteristic ictal pattern. Automated systems for detection of seizures are a field of intensive research, in an attempt to create a reproducible, observer-independent mechanism for epilepsy diagnosis. Chronic therapy is a cornerstone of the epilepsy treatment, but the possibility to predict seizure onset and, consequently, to act with medications right before the seizure, instead of relying on everyday medications, is considered the holy grail of epilepsy research. Significant element of morbidity and mortality in epilepsy is sudden unexpected death in epilepsy (SUDEP) that occurs in roughly 1% of patients.

Signal analysis techniques for EEG have been a staple in epilepsy research, but recently, with the rise of telemetric systems, heart rate variability (HRV) analysis derived from the ECG signal has been gaining importance. It has been found that perturbations in autonomic nervous system (ANS) regulation occur during, and even up to several minutes before, seizure onset allowing for changes in HRV to act in prediction, as well as detection, of seizures. Also, there is a compelling research exploring the extent of autonomic disbalance during seizures, as well as in the interictal periods in patients at risk for or that have had SUDEP.

The focus of this review is to give a short crossection of research involving the utility HRV has in prediction and detection of seizure onset, as well as determining etiology classification and risk evaluation in SUDEP.

Keywords:
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Sažetak

Epilepsija je izuzetno često neurološko oboljenje. Zlatni standard u dijagnostici epilepsije je signal na elektroencefalografiji (EEG) sa karakterističnim iktalnim promenama, zabeležen u toku napada. Automatizovani sistemi za detekciju napada su značajno polje istraživanja u naporima da se postigne reproducibilna metoda za dijagnostiku epilepsije, nezavisna od različitih interpretacija. Hronična terapija je osnova lečenja epilepsije, ali se mogućnost predikcije napada i davanja terapije u neposrednom preiktalnom periodu smatra svetim gralom istraživanja u epilepsiji. Značajan element mortaliteta i morbiditeta u Epilepsiji je "iznenadna neočekivana smrt u epilepsiji" (*engl. sudden unexpected death in epilepsy,* SUDEP), koja se javlja kod oko 1% pacijenata obolelih od ove bolesti. Metode analize EEG signala su oduvek bile osnova istaživanja, ali je u skorije vreme, posebno sa razvojem telemetrijskih sistema, došlo do porasta značaja analiza "varijabilnosti srčane frekvencije" (*engl. heart rate variabillity,* HRV), izvedenih iz signala elekrokardiograma (EKG). Otkriveno je da su smetnje u regulaciji autonomnog nervnog sistema (ANS) prisutne u toku, a i do više minuta pre početka napada, što omogućava da promene u HRV dobiju ulogu u predikciji i detekciji napada. Postoje i istraživanja koja ukazuju na značajan autonomni disbalans tokom napada, kao i u interiktalnim periodima kod pacijenata koji su pod rizikom ili koji su bili pogođeni SUDEP-om. Cilj ovog istraživanja jeste da da kratak pregled istraživanja koja se tiču uloge HRV u detekciji i predikciji napada, kao i u istraživanjima etiologije klasifikacije i faktora rizika za SUDEP.

Ključne reči:
EEG,
EKG,
HRV,
SUDEP

Introduction

Epilepsy is a very frequent disease in the human population, with prevalence of roughly 1% in the general population (1). Epilepsy is characterised by intermittent hypersynchronous neuronal activity that is manifested as a seizure. This phenomenon can involve neurons from a single cortical region, such as the temporal lobes, that manifest as partial seizures (i.e. temporal lobe epilepsy) or the entire cortex, producing the characteristic Grand-mal tonic-clonic seizures (GTSC) (2). Contemporary epileptology faces different tasks, among which diagnosis, prediction and therapy and prevention of life-threatening outcomes attracts multidisciplinary approach.

The gold standard in diagnosis of epilepsy is the EEG signal recorded during a seizure, as determined by an experienced neurologist based on characteristic spike-wave pattern of the signal, in coordination with the clinical symptoms (3). This technique, however, has its drawbacks. There is a significant amount of inter-observer variability in analysis of the EEG signal, since background noise, muscle and EKG artefacts can mimic the characteristic pattern of epileptic activity. Also, this technique includes the necessity of sometimes multiple days of video-EEG monitoring to document the seizure, which is nor convenient nor cost effective (4).

Another problem in treatment of epilepsy relays in its paroxysmal nature, i.e. the stochastic, unpredictable nature of seizure onset. Chronic therapy with antiepileptic drugs is a cornerstone of the epilepsy treatment, but the possibility to predict seizure onset and consequently to act with medications right before the seizure, instead of relying on everyday medications, is considered the holy grail of epilepsy research (5).

Significant element of morbidity and mortality in epilepsy is sudden unexpected death in epilepsy (SUDEP) that occurs in roughly 1% of patients. As the etiology is still unknown, developing classifiers and detecting patients at risk for SUDEP is of great importance (6). Signal analysis techniques for EEG have been a staple in epilepsy research, but recently, with the rise of telemetric technologies, heart rate variability (HRV) analysis derived from the EKG signal has been gaining importance (7). The HRV is determined by the balance of sympathetic/parasympathetic signalling. It has been found that perturbations in autonomic nervous system (ANS) regulation occur during, and even up to several minutes before seizure onset, allowing for changes in HRV to act in prediction, as well as detection, of seizures (8). Also, there is a compelling research exploring the extent of autonomic disbalance during seizures, as well as in the interictal periods, in patients at risk for or that have had SUDEP (9).

The focus of this review is to give a short crossection of research on the utility of HRV in prediction and detection of seizure onset, as well as determining etiology classification and risk evaluation in SUDEP.

HRV in detection of seizures

Many automated systems for seizures detection have been developed and the most successful studies on these systems report sensitivities reaching 99%. The main problems are false alarms occurring anywhere from 0.25 / h to 1 / h (10,11). Majority of detection protocols have relied on EEG analysis. The main issues with this approach are that it relies on cumbersome equipment and requires significant processing power. This, in turn, hinders potential for long term acquisition of signals and real time analysis significantly lowering the utility of this approach (12). On the other hand, studies using HRV analysis have recently reported excellent results using different approaches, but with significantly lighter

equipment than was previously needed (13). HRV was tested on focal seizures, secondarily generalized seizures and GTSC. Various types of seizures and cortical regions affected influence the ANS differently: for example, ictal tachycardia is more pronounced in seizure activity arising from the right hemisphere (14). Namely, when a right hemispheric focus is the cause of focal seizures, ictal tachycardia was detected in 98.5%, while in GTSC arising from the right hemisphere, it was noted the percentage of 100% (14). A large study by Zijlmans M. from 2002, regarding seizures mostly of temporal lobe (TL) origin, has shown that 73% of focal seizures lead to tachycardia of at least 10 bpm and these seizures occurred in 93% of patients. Additionally, bradycardia of at least 10 bpm was detected in 7% of seizures in the same study. Heart rate changes were most often noted around the start of a seizure and in 23% of the seizures (43% of patients) the heart rate changes preceded both EEG changes and clinical onset (15). On the other hand, a study by van Elmpt W. J. on 10 patients with a total of 104 mixed, mostly myoclonic, tonic and absence seizures, showed heart rate disturbances in only 48.1% of seizures. This is lower than in other studies examined, but it is related to the very short duration and subtle clinical picture of most seizures studied (16). Also, the etiology of changes in heart rate and HRV during seizures was studied by Epstein et al. using subdural and depth electrodes in TL seizures. It was shown that heart rate alterations are dependent on limbic system involvement and that the amount of increase depended on the volume of cerebral structures recruited into a seizure (17). This leads to a conclusion that patient oriented and individualised approach has to be taken into consideration when analysing the utility of HRV in detection of seizures.

HRV in prediction of seizure onset

Detection of seizures is a minor problem when compared to the holy grail of epilepsy research: the prediction of epileptic seizure onset. This problem is of particular importance in refractory epilepsy. Approximately 30% of all patients have refractory epilepsy (18), requiring well-balanced polytherapy or advanced therapeutic options. These patients are candidates for surgery, but even after surgery, the probability of becoming seizure free is anywhere between 35% and 75%, depending on weather the lesion can be detected and the localisation of the lesion (19). As opposed to the traditional chronic treatment, being able to predict a seizure could greatly reduce morbidity caused by the disease: it is possible to imagine accurate prediction enabling patients to get mentally and physically prepared for a seizure, thus reducing the restrictions in life activities for epilepsy patients (20). As previously mentioned it, could even prove possible for medications to be administered acutely in the pre-ictal period and ideally prevent the onset of seizures (21)

As for detection, prediction of seizure onset is traditionally based on detection of EEG changes. One of the studies reporting best results using EEG- based techniques has achieved sensitivity of 97.5%, with a false positive rate of 0.27 per hour (22). Essentially, the problems for EEG - based prediction of seizures remain the same as mentioned for detection. That is one of the reasons HRV is also a promising field of research when it comes to prediction of seizure onset. Behbahani et al. (23) studied pre-ictal HRV in 16 patients, with a total of 170 seizures, in an attempt to predict seizures. An algorithm using frequency and time domain measures of HRV was used to detect changes and rise alarm, when the changes exceeded a predefined threshold. The performance achieved by this algorithm was a sensitivity of 78.59%, with a false positive rate of 0.21 per hour, which is better than a random classifier, but still significantly inferior to EEG - based algorithms. An interesting attempt was done by Fujiwara et al. (24) who used a multivariate process (Multivariate statistical process control - MSPC) to analyze multiple HRV features for seizure prediction. They reported sensitivity of 91% percent with a false positive rate of 0.7 per hour (24). On the other hand, Pavei et al. (25) used a different approach. The HRV was analyzed using Eigen Decomposition of covariance matrices to create input for support vector machine (SVM) based algorithm. A total of 34 seizures from 13 patients were studied. This approach could detect pre-ictal activity from 5 minutes before to just before seizure onset with a sensitivity of 94.1%. Furthermore, the false positive rate was tested on 123.6 h of ECG recordings from non-epilepsy patients. The false positive rate was 0.19 per hour for non-epilepsy and 0.49 per hour in epilepsy patients (25). Vandecasteele et al. did one of the first studies to compare hospital ECG vs. wearable ECG vs. photpletismography (PPG) devices in seizure prediction. Photoplethysmography devices are the nowadays popular wrist watch based heart rate monitors used by athletes and increasingly the general population. The algorithm used in this study was a simple heart rate increase detection system. The sensitivities were respectively 57%, 70%, and 32% with corresponding false alarms occurring 1.92, 2.11 and 1.80 per hour. Thus, it was shown that while detection precision of the PPG device is considerably lower, the wearable ECG device has fully comparable performance to the hospital ECG (26).

In conclusion, it is important to note that, besides ECG and EEG based approaches that are, by far, the most studied and most accurate, there are also those based on accelerometry (ACC), electromyography (EMG) and galvanic skin response (27). Different detection modalities are suitable for different types of seizures and for most patients a personalized approach with combinations of different modalities will probably be the future of seizure prediction (28).

SUDEP and the role of HRV

Sudden unexpected death in epilepsy (SUDEP) accounts for up to 17% of deaths in patients with epilepsy, with a frequency of 1.2 per 1000 patient-years (30). The group with the highest risk for SUDEP are patients suffering from developmental and epileptic

encephalopathies, due to sodium channel (SCN) mutations, in whom the risk is 9.32 per 1000 patient-years (31,32). Numerous risk factors have been identified for SUDEP including: a major association with uncontrolled tonic–clonic seizures, medication noncompliance, epilepsy onset before 16 years, male sex, and duration of epilepsy > 15 years (33). But the largest group of patients at a higher risk for SUDEP are those suffering from drug-resistant epilepsy, in whom the frequency is estimated at 4.2 per 1000 patient-years (34).

Despite the recognition of risk factors for SUDEP, the etiology is still unknown and the stochastic nature of its occurrence creates serious problems in counselling patients and formulating prevention strategies (33). The research in SUDEP can thus be said to have two intertwining paths: providing insight into etiology of SUDEP and finding biomarkers that can predict the onset of SUDEP. Cardiac autonomic dysregulation and thus HRV changes, have so far been implicated in both problems.

From the very beginning of research into SUDEP, it was noted that seizures often cause heart rate and rhythm abnormalities, as well as other changes in the ECG (35,36). As previously noted, the most common abnormality caused by seizures is sinus tachycardia and less often bradycardia (14,15,17) but other, more severe cardiac rhythm and conduction changes have been recognised. Severe bradycardia to asystole, ST-segment and QT-interval abnormalities, bundle branch blocks have all, albeit much more rarely been recognized to occur during seizures (37,38). How these changes lead to SUDEP and can they be the direct cause is still a matter of debate. Different mechanisms have been postulated to explain how lethal arrhythmias could occur. First, excessive stimulation of the heart by the autonomic nervous system during seizures could directly result in fatal arrhythmias (39). Second, repeated excessive stimulation of the heart, such as occur during uncontrolled seizures in drug resistant epilepsy, and could lead to myocardial necrosis, creating a suitable terrain for arrhythmia occurrence in time (40). This was, in fact, corroborated by findings of myocardial fibrosis in post mortem heart samples of patients who suffered from SUDEP (40). Finally, numerous case reports of patients that have died of SUDEP and were followed in the imminent period prior to SUDEP occurrence show progressive disturbances in HRV further corroborating this hypothesis (41-44).

With etiologic mechanisms still unclear, the question of biomarker recognition and risk stratification has more recently become a central point of the SUDEP research (45). This led to the creation of the first SUDEP Risk Inventory (SUDEP-7) in 2011, a risk stratification tool consisting of seven validated risk factors including for SUDEP (46). The SUDEP-7 inventory also included two biomarkers of SUDEP risk: the root mean square differences of successive R–R intervals (RMSSD) and generalized postictal EEG suppression. The RMSSD is a measure of HRV mediated by the vagus nerve and autonomic regulation of the heart. Low HRV as demonstrated by low RMSSD is associated with higher risk for arrhythmias (such as atrial fibrillation), cardiovascular disease and unfavourable outcomes in patients with chronic heart failure (47). The score was validated on 19 subjects with intractable partial seizures, with a mean seizure frequency of 22.8 per month showing that RMSSD is inversely correlated with the SUDEP-7 score ($r = -0.64$, $p = 0.004$) (46). The SUDEP-7 inventory was revised by Novac et al. in 2015, on 25 patients with drug resistant epilepsy again showing a similar correlation of RMSSD and SUDEP-7 score (Pearson $r = -0.45$, $p = 0.027$) (48). Other, less systematic attempts at exploring HRV as a biomarker for SUDEP, have also shown promise. A study of patients with SCN epilepsy vs. non SCN epilepsy has shown significantly greater disturbances of HRV by various HRV measures in SCN patients, lending further proof to the hypothesis of dysautonomia as a factor in SUDEP (49).

Although previously mentioned studies have provided correlative evidence of HRV changes in patients with epilepsy and SUDEP, as of yet, there is no conclusive proof of cause and effect. Further studies will be necessary for establishing this and finding biomarkers to more precisely stratify at risk individuals.

Conclusion

Perturbations in the ANS regulation during, and even up to several minutes before, seizure onset reflects in changes in HRV and could be used to predict, as well as to detect seizures. Also, the ANS disbalance during seizures, as well as in the inter-ictal periods, in patients at risk for or that have had SUDEP, are promising base for utility of HRV in this issue.

Taking into account the summary of recently published studies in the field, it could be concluded that the utility of HRV in prediction and detection of seizure onset, as well as determining etiology classification and risk evaluation in SUDEP has a promising future.

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