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INVITED REVIEW / DAVETLİ DERLEME

A review of significant research on epileptic seizure detection and prediction using heart rate variability

Kalp hızı değişkenliğini kullanarak epilepsi nöbetlerinin saptanması ve öngörüsü üzerine önemli bir araştırmanın gözden geçirilmesi

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Summary– Epilepsy is a brain disorder that many people struggle with all over the world. Despite extensive research, epilepsy is still an important challenge without a clear solution. There may be confusion about providing a specific approach due to the variety of epileptic seizures and the effectiveness in different environmental conditions. Some patients with epilepsy undergo treatment through medication or surgery. Epileptic patients suffer from unpredictable conditions that may occur at any moment. Given the origins of these seizures, researchers have focused on predicting epileptic seizures via electroencephalogram (EEG). The results indicate some success in this regard. This success led to a focus on optimizing these methods and the evaluation of epilepsy seizure prediction through other vital signals. Both sympathetic and parasympathetic inhibitory effects are undeniable during epileptic seizures. This conflict is visible in the change in heart rate. In recent years several investigations have focused on a behavioral study of heart rate changes before the seizures. The results have led to the development of algorithms for classifying and predicting epileptic seizures using the electrocardiogram (ECG) and the more distinct heart rate variability (HRV). This article presents an overview of seizure detection and prediction methods and discusses their potential to improve the quality of life of epileptic patients.

Özet– Epilepsi tüm dünyada birçok kişinin mücadele ettiği bir beyin rahatsızlığıdır. Yaygın araştırmalara rağmen, kesin çözümü olmayan zor bir rahatsızlık olarak epilepsi önemini kaybetmemiştir. Spesifik bir yaklaşım sunmadaki kafa karışıklığı epilepsi nöbetlerinin çeşitliliğine ve farklı çevresel koşullardaki etkinliğine bağlı olabilir. Epilepsi hastalarının bir bölümü ilaç veya ameliyat ile tedavi edilir. Ancak epilepsi hastaları her an oluşabilen öngörülemez durumlardan rahatsız olabilir. Bu nöbetlerin kökenleri belli olduğuna göre araştırmacılar elektroensefalogramla (EEG) epilepsi nöbetlerinin öngörülmesine odaklanmıştır. Sonuçlar bu açıdan bazı başarılar da göstermektedir. Aynı başarı bu yöntemlerin optimizasyonuna ve hatta diğer yaşamsal belirtiler yoluyla epilepsi öngörüsünün değerlendirilmesine odaklanmaya yol açmıştır. Diğer taraftan epilepsi nöbetleri sırasında sempatik ve parasempatik inhibitör etkiler yadsınamaz. Bu uyuşmazlığın ortaya çıkışı kalp hızındaki değişikliktir. Son yıllarda birkaç araştırmada nöbetler öncesinde kalp hızındaki değişiklikleri davranışsal açıdan incelenmesine başlanmıştır. Kabul edilebilir sonuçlar elektrokardiyogram (EKG) ve açıkçası kalp hızındaki değişkenliği (KHD) kullanarak epilepsi nöbetlerini sınıflandıran ve öngören algoritmaların oluşmasıyla neticelenmiştir. Bu makale nöbetlerin saptanması ve öngörülmesine ilişkin yöntemleri sunmakta ve onların epilepsi hastalarında yaşam kalitesini iyileştirme potansiyelini tartışmaktadır.

Epilepsy is a brain disorder that leads to abnormal messages sent by neurons: the regular patterns of neuronal activity are impaired, which can cause strange sensations, seizures, muscular cramps, and loss of consciousness.

The International League Against Epilepsy (ILAE) has developed new terms for a better description and classification of seizure types.[1] The purpose of such a revision was to denominate seizures more accurately, making it less confusing and more descriptive. In this recent report, there are 3 criteria for deciding on the type of epileptic seizure. The first criterion is the onset of the seizure. The localization of the seizure in the brain might represent what will occur during the seizure, and the symptoms likely to be seen can be predicted. The second criterion is the level of aware-

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ness of the patient, which can indicate the type of the seizure. Finally, the third criterion is the presence of movement during the seizure.

In the new classification based on the ILAE criteria, there are some changes in the clusters of epileptic seizures; for example, partial seizures are now known as focal seizures. The terms dyscognitive, simple partial, complex partial (CP) and secondarily generalized (SG) have been eliminated. Atonic, clonic, epileptic spasms, myoclonic and tonic seizure can be of either focal or generalized onset. The new classification does not make significant changes, but allows for greater flexibility in naming seizure types. Given that these changes were just made in 2017, in this article, we have to identify the types of epileptic seizures discussed based on the previous classifications.

Abbreviations:

ANS	*Autonomic nervous system*
ApEn	*Approximate entropy*
CP	*Complex partial*
DFA	*Detrended fluctuation analysis*
ECG	*Electrocardiogram*
EEG	*Electroencephalogram*
FP/h	*False positive per hour*
GTCS	*Generalized tonic-clonic seizures*
HF	*High frequency*
HR	*Heart rate*
HRV	*Heart rate variability*
ILAE	*International League Against Epilepsy*
IT	*Intervention time*
LF	*Low frequency*
pNN50	*Number of RR intervals differing by >50 milliseconds from the adjacent interval divided by the total number of all RR intervals*
PPG	*Photoplethysmography*
PSD	*Power spectral density*
RMSSD	*Root mean square of successive NN interval differences*
RRI	*RR Interval*
SDANN	*Standard deviation of mean NN intervals in 5-minute recordings*
SDNN	*Standard deviation of normal to normal RR intervals*
SG	*Secondarily generalized*
SOP	*Seizure occurrence period*
SVM	*Support vector machines*
VLF	*Very low frequency*

In many patients, seizures can only be controlled with prescribed medications. Patients with uncontrolled seizures usually suffer from anxiety due to the unstable conditions. This fact should not be ignored: seizure prediction has excellent potential for improving quality of life in such patients. The patient with knowledge of the seizure occurrence period (SOP) can at least avoid hazardous situations that may endanger life, such as being on a busy street or in a swimming pool. Also, an awareness of seizure onset can provide the possibility of prescribing a variety of treatments rather than simply long-term drug treatment, which has neurological and peripheral side effects. Treatment may be necessary only in the interval before the seizure.

Research on predicting epileptic seizures using an electroencephalogram (EEG) has been underway for a long time. As the origin of epilepsy is the brain, different systems throughout the body can be affected. A large part of the basic research on predicting epileptic seizures has been dedicated to examining the effects of epilepsy on central nervous system function.[2–5] The results have demonstrated that heart rate variability (HRV) is a good indicator of autonomic nervous system function and arousal.[6] It can be measured as fluctuation of the RR interval (RRI).

Several reports of heart rate (HR) changes before seizures drew particular attention to the potential of HRV in epileptic seizure prediction. Moreover, the drawbacks of daily EEG recordings and noise effects on this signal confirm that an alternative or a combination method is needed. Therefore, in recent years, along with brain-based methods, means of predicting seizures using HRV were also initiated. In this manuscript, the current detection and prediction algorithms for epileptic seizures based on HRV are described. An overview of these algorithms can efficiently identify their strengths and potential in solving the problems of epileptic patients and help provide individualized care.

HRV Analysis

Various approaches, which include linear and non-linear methods, have been proposed in cardiac research for HRV processing. Sometimes the use of 1 method can be enough to help us recognize the phenomenon. However, there are other cases where it becomes necessary to examine the subject from different aspects to extract the actual dynamics accurately. In essence, the complexity of the event leads us toward choosing the appropriate method.

Linear HRV Analysis

Two principal common linear analyses of HRV include time domain analysis, representing circulation system activity, and frequency domain analysis, which reports the sympathovagal balance of the autonomic nervous system (ANS).

Time Domain Analysis

The first step in this analysis is the detection of QRS complexes, and particularly the R wave, which has the highest amplitude. The features related to changes in HRV over time are as follows:

The total number of heartbeats; mean of RRI; SDNN (standard deviation of normal to normal RR intervals); SDANN (standard deviation of mean NN intervals in 5 min recordings); pNN50 (the number of adjacent RR intervals which differ by more than 50 milliseconds divided by the total number of RR intervals); and RMSSD (root mean square of successive NN interval differences). It is obvious that the examination of time characteristics cannot reflect changes in the HRV signal adequately. Therefore, frequency domain analyses can be helpful in identifying additional changes.

Frequency Domain Analysis

Along with the observations used in time domain analysis, frequency domain analysis enables a precise assessment of autonomic function and spectral composition of temporal variations in the autonomically modulated cardiac rhythm. Frequency domain analysis involves power spectral density (PSD) of HRV. The resulting spectrum is divided into 3 routine bands: the very low frequency (VLF) band from 0.003–0.04 Hz, the low frequency (LF) band from 0.04–0.15 Hz, and the high frequency (HF) band between 0.15 Hz and 0.4 Hz.[7,8]

Previous studies have reported that VLF spectral power is associated with long-term regulatory mechanisms. LF spectral power is a marker of sympathetic modulation on the heart and some parasympathetic influences related to the respiratory system, HF is related to parasympathetic activity mainly caused by respiratory sinus arrhythmia, and the LF/HF ratio is an indication of the balance between sympathetic and parasympathetic systems.[9–12]

Non-linear Methods

Non-linear indices include the power law exponent, which describes the nature of correlations of single frequencies in a time series,[12] and approximate entropy (ApEn), which reflects the degree of irregularity in a series of data. Smaller values indicate greater regularity, while higher values convey more randomness and system complexity.[13] Detrended fluctuation analysis (DFA), which makes a distinction between the internal variations generated by complex systems and variations caused by environmental or other external stimuli.[14]

Another non-linear method for HRV analysis is the Poincaré plot, which used the ellipse-fitting technique. The minor ellipse axis is identical to the standard deviation SD1 and represents the short-term variability of HRV.[15,16] The major axis, the standard deviation SD2, represents long-term variability. The SD1/SD2 ratio represents heart activity.

Effects of Epilepsy On HRV

HRV alteration in the pre-ictal period has been reported before. Depending on the type of epilepsy, these changes may include tachycardia, and alteration of lateralization and the location of the seizures. Novak et al.[17] investigated HRV before, during, and after partial seizures using time-frequency mapping in patients with temporal lobe epilepsy. They found autonomic imbalance and tachycardia in the pre-ictal phase of CP seizures. Spectral power at respiratory frequencies fell rapidly in the period 30 seconds before the seizure. In other words, parasympathetic withdrawal occurred approximately 30 seconds before the seizure and sympathetic activity peaks at seizure onset. Delamont et al.[18] investigated a continuous index of cardiac parasympathetic activity in patients with CP and complex partial with SG seizures. The mean cardiac parasympathetic activity was elevated in the pre-ictal phase, while CP seizures did not show any significant change. It seems that pre-ictal elevation of cardiac parasympathetic activity could be used as a marker for SG seizures. Di Gennaro et al.[19] reported that the HR of patients with mesial and lateral temporal lobe epilepsy increased before seizure onset. Jeppesen et al.[20] used HRV spectrum analysis in patients with focal epilepsy and demonstrated suppressed parasympathetic activity and vagal tone drop prior to and during epileptic seizures. Nilsen et al.[21] reported an elevated HR before partial seizure onset in SG seizures. Behbahani et al.[22] found significant changes in the time-frequency and Poincaré parameters of HRV in 5 minutes before the seizure.

Behbahani et al.[23] analyzed HRV during 5-minute segments in age-matched populations. The patients included males (n=12) and females (n=12), ranging from 41 to 65 years of age. HF and LF components of HRV and Poincaré parameters of HR time were considered. The mean HR markedly differed between gender groups in both right- and left-sided seizures. The HF and the LF/HF ratio increased in the pre-ictal phase of both the male and female groups, but the men demonstrated a greater increase, especially in right-sided seizures. The SD2/SD1 ratio of the pre-ictal phase was greater in males than in females. HF, which is an indication of parasympathetic activity, was greater in females with both right and left-sided seizures, while men showed a sudden increase in sympathetic activity in the pre-ictal phase.

Detection of Epileptic Seizures Based On HRV

As previously stated, epileptic seizures are often accompanied by changes in various autonomic functions, and particularly HR. In past decades, many researchers have used ECG and HRV signals to detect epileptic seizures. Although success in detecting seizures does not guarantee that they can be predicted, it confirms that there are some features that can distinguish seizures. Regardless of the elements used in these algorithms to detect seizures, they apparently have 2 main stages: feature extraction and classification (Fig. 1).

Jeppesen et al.[20] considered 6 seizures experienced by 6 patients with temporal lobe epilepsy (4 females and 2 males). Three intervals were chosen for HRV analysis: 25 to 30 minutes pre-seizure, 30 seconds to 5 minutes post seizure onset, and 30 minute non-seizure sessions. Frequency domain analysis includes LF, HF, LF/HF, LF/(LF+HF) and reciprocal HF-power measurements. The results show that reciprocal HF-power peaks between 10 seconds pre-seizure and 24 seconds post-seizure. A significant difference between a seizure and non-seizure session were not seen in the other features of the analysis. High reciprocal HF-power peaks suggest suppressed parasympathetic activity just around seizure-onset time.

Evrengül et al.[24] analyzed both the frequency and time domain parameters of HRV in 43 patients with generalized tonic-clonic seizures (GTCS) and a sex-matched control group using no medications. In the time domain analysis, the SDNN, SDANN, and HRV triangular index, pNN50, and RMSSD were considered. The patients demonstrated higher values in the time domain features compared with the control group. In the frequency domain analysis, the spectral measures of HRV showed a reduction in HF values and an increase in low LF values. Moreover, a significant increase was observed in the LF/HF. The results confirmed an increase in the sympathetic control of HR in epilepsy patients with GTCS, which could lead to tachyarrhythmia in epileptic patients.

Ponnusamy et al.[25] reported their results of a study of 26 patients with medically refractory temporal lobe epilepsy and 24 sex-matched patients with psychogenic non-epileptic seizures. Time and frequency domain parameters, including LF, HF, SDNN, and RMSSD were extracted. Moreover, the cardiovagal index, cardio-sympathetic index, and ApEn were calculated. The results showed a significant difference between ictal HRV measures during epileptic and non-epileptic seizures. The cardio-sympathetic index was higher in epileptic seizures. The RR interval, LF, HF, and RMSSD were significantly lower during epileptic seizures. Furthermore, a significant difference was recorded in the mean value of ApEn and LF in the ictal phase versus the interictal phase. This research confirms other results, which show greater ANS activation in epileptic seizures.

Malarvili et al.[26] assessed the HRV of 6 seizure and 4 non-seizure events of 64 seconds in 5 newborns as a tool for seizure detection. The characteristics examined were LF, mid-frequency band (0.07–0.15 Hz), and HF. Based on the results, a conditional moment of HRV, the mean/central frequency in the LF, and the variance in the HF can be used to discriminate the neonatal seizure.

Malarvili et al.[27] also investigated the use of HRV for automatic newborn seizure detection. A set of time-frequency features from the neonatal HRV of 8 newborns was extracted. The algorithm achieved 85.7% sensitivity and 84.6% specificity.

Leutmezer et al.[28] assessed ECG changes during 145 seizures recorded with a scalp EEG in 58 patients who underwent video-EEG monitoring. Consecutive RRIs were analyzed with a newly developed mathematical method for a total of 90 seconds.

Behbahani et al.[29] analyzed the effects of epilepsy on the autonomic control of the heart in the ictal phase

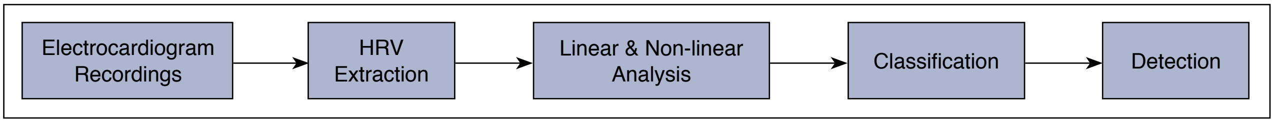

Figure 1. Epileptic seizure detection algorithm based on heart rate variability (HRV).

of 2 types of epileptic seizures with SG and CP. A total of 96 SG and 110 complex partial seizures were included. A 5-minute period of HRV was randomly selected to represent both seizure-free and seizure activity in both groups. Time and frequency domain analysis and nonlinear parameters extracted from the HRV data showed an increase in sympathetic activity in the ictal phase of both SG and CP seizures that significantly differed from seizure-free segments. The mean HR, LF/HF, and the SD2/SD1 ratio of SG had a higher value compared with CP. This research demonstrated that there are significant differences between the autonomic behaviors of CP and SG subjects. In addition, SG seizures show more sympathetic activity in comparison with CP seizures.

Behbahani et al.[30] proposed an algorithm to detect epileptic seizures based on HRV. They used time and frequency domain analysis, as well as nonlinear features, such as the input of an artificial neural network. A multilayer perceptron neural network was used as a classifier. The results demonstrated a sensitivity, specificity, and accuracy of 88.66%, 90%, and 88.33%, respectively, in SG seizures, and 83.33%, 86.11%, and 84.72%, respectively, in CP events.

In addition, Behbahani et al.[31] assessed HRV with a 5-minute duration in 170 seizures that occurred in 16 patients, comprising 86 left-sided and 84 right-sided focus seizures. Time and frequency domain indices and Poincaré parameters of HRV were computed. Support vector machines (SVMs) were used to classify epileptic and non-epileptic signals. The accuracy rates for right-sided and left-sided focus seizures were 86.74% and 79.41%, respectively. This research indicated that patients with right-sided focus epilepsy demonstrated a greater reduction in parasympathetic activity and a greater increase in sympathetic activity. Moreover, the results suggested that the lateralization of seizure onset might have different influences on HR changes.

Shamim et al.[32] proposed a new technique to detect seizures in epileptic patients using the ECG signal. Multiple domain parameters were used: mobility, complexity, mean of absolute deviation of fast Fourier transform coefficients, and spectral entropy. An SVM classifier was used based on a linear threshold for classification. The classification result revealed 94.2% accuracy, 84.1% sensitivity, and 94.5% specificity; the proposed algorithm detected epileptic seizures efficiently.

Malarvili et al.[26] presented their results based on of time frequency analysis to compare the performance of various time frequency distributions applied to HRV to detect non-seizure and seizure activity in newborns. The time frequency distributions included the Wigner-Ville spectrogram, the Choi-Williams distribution function, and the Modified B distribution. The results showed that the Modified B distribution outperformed other distributions regarding time frequency resolution, cross-term suppression and in the ability to represent the neonatal HRV signals of non-seizure and seizure, which are closely spaced components in the time frequency domain.

Moridani et al.[33] studied the HRV of 11 patients. Time and frequency domain parameters of RRI, mean HR, HF, LF, and LF/HF were considered. Poincaré plot features were examined. HRV signals were divided into segments with a 5-minute duration. In each segment, linear and nonlinear features were extracted. During the ictal phase, the mean HR, LF/HF, and SD2/SD1 ratio were significantly increased while the RR intervals were significantly decreased. The proposed algorithm detected seizures with 88.3% sensitivity and 86.2% specificity.

Prediction of Epileptic Seizures Based On HRV

Although the use of HRV to detect epileptic seizures has emerged among EEG-based methods, the algorithms that use HRV to predict are limited. Hirotsugu et al.[34] proposed an HRV-based epileptic seizure prediction algorithm utilizing multivariate statistical process control technology. Various HRV features were derived from the RRI interictal and pre-ictal period. The result of applying the proposed method to clinical data demonstrated that seizures could be detected at least 1 minute before the seizure occurred, which emphasized the possibility of realizing an HRV-based seizure prediction method.

Behbahani et al.[35] analyzed the HRV of 16 epileptic patients and 170 seizures to predict the occurrence of seizures based on the dynamic changes of HRV during the pre-ictal period. Time and frequency domain features were computed for consecutive time windows with a length of 5 minutes. An adaptive decision threshold method was used to raise alarms. Predictions were made when selected features exceeded the decision thresholds. For the seizure occurrence period (SOP) of 4:30 minutes and intervention time

(IT) of 110 seconds, the presented algorithm achieved a sensitivity of 78.59% with a false positive per hour (FP/h) rate of 0.21, which indicated that the system was superior to the random predictor.

Pavei et al.[36] presented a new methodology for the prediction of epileptic seizures using HRV signals. Eigendecomposition of HRV parameter covariance matrices was used to create an input for the SVM classifier. A total of 34 seizures from 12 patients, involving 55.2 hours of inter-ictal ECG recordings were analyzed. Moreover, 123.6 hours of ECG data from healthy subjects were used to test the FP/h. The proposed approach detected seizures from 5 minutes before to just before onset with a sensitivity of 94.1%. The FP/h was 0.49 in patients with epilepsy and 0.19 in healthy subjects.

Vandecasteele et al.[37] compared the performance of 2 wearable devices based on ECG and photoplethysmography (PPG) to predict epileptic seizure. This algorithm classified seizures by HR features using the HR increase. The algorithm was applied to 11 patients suffering from temporal lobe seizures. The sensitivity of the wearable ECG device and the wearable PPG device was 70% and 32%, respectively, with a corresponding FP/h of 2.11 and 1.80. The seizure detection performance using the PPG device was considerably lower than that of the wearable ECG device.

Conclusion

Experiencing an epileptic seizure is frightening for the patient and their relatives. Finding a way to predict and prognosticate these events for the patient has repeatedly been raised in epilepsy-related research. It should be noted that the prediction of epileptic seizures should not terminate to the loss of privacy and lack of comfort at night. In addition to the effectiveness of the prediction algorithm, psychological aspects must also be considered.

Psychological considerations can be viewed from a variety of perspectives. Patients with such diseases are often overwhelmed by these conditions that they may be unable to control at any moment. Insensitivity can contribute to undermining the confidence of patients, which can lead to the patients withdrawing from the community. Assuming that the algorithms provided to predict epileptic seizures based on EEG were working successfully, individuals who have been confronted with their particular circumstances have been told to wear a predesigned cap with recording electrodes for online EEG monitoring. Clearly, such a method jeopardizes the privacy of epileptic individuals and people may ridicule them. Too many false alarms are another reason for patient reluctance to use such methods, as they lose their confidence.

Addressing these issues and their complexities will require the continuation of research to find an algorithm that can provide a sufficient compromise of performance, reliability, and privacy. It seems that the prediction of epileptic seizures using HRV can significantly resolve the problems of permanent recording, noise, and privacy. Anyone can use Holter monitoring and wearable sensors to measure long-term RRI without special skills and with a cost of less than $100.[40] However, we should not forget that the brain is the origin of epileptic seizures. The heart is the second organ affected by seizures, and it cannot be expected that the predictive results with this method of the brain.

When comparing the prediction of epileptic seizures using EEG and ECG signals, it is important to note that brain-based research started years ago and is now in the optimization phase. In other words, these investigations do not seek to establish the possibility of prediction based on EEG. Instead, they are exploring ways to optimize the main parameters for predicting epileptic seizures, including SOP, IT, sensitivity, and FP/h. What is considered a benchmark of for success in these studies is the ability of algorithms to increase the SOP, IT, and sensitivity, as well as decreasing the FP/h. One of the challenges facing the HRV-based algorithms is to distinguish between conditions that lead to changes in HR. The features that are used to distinguish between modes, such as excitement, exercising, walking, etc. can be very useful in increasing the accuracy and success of these algorithms.

HRV-based research on epileptic seizure prediction is not synchronous with EEG-based studies. Much of the research has been done to support the hypothesis that epileptic seizures can be predicted using the HRV. Therefore, the results obtained in this field are still not comparable with EEG-based algorithms and still have great potential for optimization. Indeed, further studies are needed to increase the sensitivity of prediction as well as other mentioned parameters to acquire patient trust. The review of all these studies shows that the most critical point is to provide a successful algorithm that can restore patient comfort. The collaboration of engineers, doctors, and practitioners is useful in providing a proper strategy for detection, classification, and prediction of epileptic seizures. In the course of the prediction of seizures, we can find more suitable methods for controlling, and possibly treating patients.

This article was a presentation of the significant and most recent research concerned with the detection and prediction of epileptic seizures using HRV signals. The primary goal of this review was to assist researchers in the field of ECG signal processing to understand the available methods and encourage their use as well as EEG-based algorithms in order to find a better approach to prediction.

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