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Abstract	Purpose: Adequate epileptic seizure detection may have the potential to minimize seizure related complications and improve treatment evaluation. Autonomic changes often precede ictal electroencephalographic discharges and therefore provide a promising tool for timely seizure detection. We reviewed the literature for seizure detection algorithms using autonomic nervous system parameters. Methods: PubMed and Embase databases were systematically searched for original human studies, validating an algorithm for automatic seizure detection using autonomic function alterations. Studies on neonates only and pilot studies without performance data were excluded. Algorithm performance was compared for studies with a similar design (retrospective vs. prospective) reporting both sensitivity and false alarm rate (FAR). Quality assessment was performed using QUADAS-2 and

recently reported quality standards on reporting seizure detection algorithms.

Results: 21 out of 638 studies were included for analysis. Fifteen studies presented a single46 modality algorithm using heart rate variability (n=10) , heart rate (n=4) and QRS morphology 47 (n=1), while six studies assessed multimodal algorithms using various combinations of HR, corrected QT interval, oxygen saturation, electrodermal activity and accelerometry. Most studies had small sample sizes and a short follow-up period. Only two studies performed a prospective validation. A tendency towards a lower FAR was found for retrospectively validated algorithms using multimodal autonomic parameters compared to those using single modalities (mean sensitivity per participant 71-100% vs. 64-96% and mean FAR per participant 0.0-2.4/h vs. 0.7-5.4/h).

Conclusions: The overall quality of studies on seizure detection using autonomic parameters is low. Unimodal autonomic algorithms cannot reach acceptable performance as false alarm rates are still too high. Larger, prospective studies are needed to validate multimodal automatic seizure detection.

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Ictal autonomic changes as a tool for seizure detection

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Abstract

Purpose: Adequate epileptic seizure detection may have the potential to minimize seizure-related complications and improve treatment evaluation. Autonomic changes often precede ictal electroencephalographic discharges and therefore provide a promising tool for timely seizure detection. We reviewed the literature for seizure detection algorithms using autonomic nervous system parameters.

Methods: PubMed and Embase databases were systematically searched for original human studies, validating an algorithm for automatic seizure detection using autonomic function alterations. Studies on neonates only and pilot studies without performance data were excluded. Algorithm performance was compared for studies with a similar design (retrospective vs. prospective) reporting both sensitivity and false alarm rate (FAR). Quality assessment was performed using QUADAS-2 and recently reported quality standards on reporting seizure detection algorithms.

Results: 21 out of 638 studies were included for analysis. Fifteen studies presented a single-modality algorithm using heart rate variability (n=10) , heart rate (n=4) and QRS morphology (n=1), while six studies assessed multimodal algorithms using various combinations of HR, corrected QT interval, oxygen saturation, electrodermal activity and accelerometry. Most studies had small sample sizes and a short follow-up period. Only two studies performed a prospective validation. A tendency towards a lower FAR was found for retrospectively validated algorithms using multimodal autonomic parameters compared to those using single modalities (mean sensitivity per participant 71-100% vs. 64-96% and mean FAR per participant 0.0-2.4/h vs. 0.7-5.4/h).

Conclusions: The overall quality of studies on seizure detection using autonomic parameters is low. Unimodal autonomic algorithms cannot reach acceptable performance as false alarm rates are still too high. Larger, prospective studies are needed to validate multimodal automatic seizure detection.

Key words: Automatic seizure detection; autonomic function(s); autonomic parameter(s); algorithm(s); epilepsy; SUDEP.

Introduction

Epileptic seizures are potentially dangerous as they can lead to complications including injury, status epilepticus and sudden unexpected death in epilepsy (SUDEP).[1] Adequate seizure detection may have the potential to minimize these complications and to ameliorate treatment evaluation as seizures, particularly those at night, are often underreported.[2–5] Detection devices may also help to improve independence and quality of life of people with epilepsy and their caregivers.[3,6]

Several parameters including movement, sound and autonomic nervous system changes can be used to detect seizures. This review focusses on changes in autonomic function, including cardiovascular, respiratory and transpiration changes.[7] Seizures can alter autonomic function particularly if the central autonomic network is involved. The most common expression is sudden increase in sympathetic tone.[7,8] Ictal tachycardia (IT) is a very frequent sign with prevalence rates ranging from 80 to 100%.[9,10] IT is a hallmark of convulsive seizures (i.e. focal to bilateral tonic-clonic as well as generalized tonic-clonic seizures) and also more common in temporal lobe versus extratemporal lobe seizures.[9] Changes in autonomic function can precede ictal electroencephalographic (EEG) discharges by several seconds.[10–12] Pre-ictal tachycardia has an incidence rate of approximately one third of seizures.[13] Autonomic alterations may therefore provide an adequate tool for early seizure detection and facilitate timely interventions. Ictal arrhythmias and desaturations are more common but thought to be self-limiting, while postictal arrhythmias and apneas may lead to SUDEP.[14–17] SUDEP usually occurs several minutes after a convulsive seizure (mean 10 min., range 2-17 min.).[18] Alarming at seizure onset may be sufficient to timely intervene.

We aimed to systematically review different seizure detection algorithms using autonomic function changes.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline.[19]

PubMed and Embase databases were systematically searched through May 2018 for original studies validating an algorithm for automatic seizure detection using heart rate (HR), heart rate variability (HRV), oxygen saturation (SpO2), electrodermal activity (EDA, reflecting changes in transpiration) or a combination of the aforementioned. A sequence of synonyms for 'autonomic variables', 'seizures' and 'detection' were used as search terms.(Supplementary Table 1) Studies were included if they met the following criteria: 1. Human studies; 2. Written in English; 3. Reporting on children or adults with any type of epilepsy; 4. Validating an algorithm for automatic seizure detection using autonomic parameters; 5. Reporting at least one performance measure (sensitivity, positive predictive value (PPV), false alarm rate (FAR) or detection latency (DL)). Studies on neonates only were excluded, because both seizure and autonomic function characteristics differ greatly at this age compared to older age. Pilot studies lacking performance data, as well as conference abstracts and reviews were also excluded.(Figure 1)

One author (AvW) screened all titles and abstracts, and full texts of the remaining studies. For each included article the following parameters were recorded: method of automatic seizure detection, type of autonomic variable, individual characteristics, number and types of seizures analyzed, prospective or retrospective validation, total recording time and performance of the algorithm, including sensitivity, PPV, FAR and DL. We compared performance of algorithms using multimodal autonomic parameters versus those using single modalities, provided that the studies (1) had a similar design (prospective vs. retrospective) and (2) reported both sensitivity and FAR.

Quality of included studies was evaluated using the QUADAS-2.[20] This tool consist of four domains (patient selection, index test, reference standard, and flow & timing) and different signaling questions to assist in judgements about risk of bias and applicability. Additionally, we assessed all included studies according to the recently proposed standards for clinical validation of seizure detection devices (SDDs).[21]

Results

Out of 638 articles identified, 86 studies were selected on the basis of title and abstract. After full text screening, 21 studies were included for further analysis. Most excluded articles lacked validation of a seizure detection algorithm.(See Figure 1) Characteristics of included studies are summarized in Table 1. Most studies (n=15) focused on ictal cardiac changes as a tool for seizure detection algorithms, including HRV (n=10)[8,22–30], HR (n=4)[31–34], and changes in QRS morphology (n=1)[35]. Six studies used multimodal algorithms, including combinations of HR, corrected QT interval (QTc), SpO2, EDA and accelerometry (ACC).[2,36–40] None of the included studies validated an algorithm based on oxygen saturation or EDA alone. Most studies were conducted in adults, but two studies included a pediatric population[23,40] and six studies included both children and adults.[22,25,35–37,39] Fourteen studies prospectively enrolled their participants[8,22,23,26,28,30–33,36-40] yet only two studies prospectively validated their algorithm.[31,33]

Most studies had small sample sizes (median population size 14, IQR 7-26). The number of seizures analyzed per patient tended to be low (median number of seizures per participant 3, IQR 2-7). Total recording time used for validation of the algorithm varied from 7 minutes to 158 hours per person (median recording time per participant 34 hours, IQR 3-86h), but was not specified in two studies. Seizure onset was mostly focal (n=14)[8,22,24–26,28,30,31,33,34,37,39,40,42], focal and generalized in some (n=4)[2,23,35,42] or not specified (n=3)[32,36,38]. All four performance measures (sensitivity, PPV, FAR and DL) were only reported in three out of 21 studies[22,33,39]; eight studies reported three[2,23–25,28,30,31,42], eight studies reported two[8,26,34,36–38,40,43], one study reported one[41] and one study only reported sensitivity and PPV data on part of the subjects.[32]

Heart rate analysis

Heart rate was monitored using single- or multiple lead electrocardiography (ECG) in twelve of eighteen studies.[8,22,23–26,28,32,34-37,42,43] Alternative methods included photoplethysmography (PPG) in a wearable sensor (n=2)[2,30] and an implanted heart rate sensor (AspireSR) (n=2).[31,33]

Heart rate measurement was done using various methods of R-peak detection, including those proposed by Pan and Tompkins[30,41], Kohler[28], Yeh and Wang[22–24] or unspecified

methods.[8,25,26,31–34,42] Some studies applied noise filtering techniques to diminish false R-peak detection, including high- and low-pass noise filters[8,22–24,26,30] or a specific algorithm (Baseline Estimation and Denoising with Sparsity).[42]

One single case study prospectively assessed a HR algorithm using a vagal nerve stimulation (VNS) device with a fixed HR sensitivity threshold.[33] Alarms were generated in case the HR augmentation exceeded 50% of the baseline HR. During the 68 recording hours, 11 out of 12 seizures were detected (sensitivity 92%) together with 128 false alarms (FAR 1.88/h.). A second prospective validation study of the same VNS device compared different HR thresholds (≥20%, ≥40% and ≥60% increase from baseline) in 16 adults with refractory epilepsy.[31] Lower thresholds resulted in higher sensitivity and higher FAR compared to higher thresholds (e.g. sensitivity 59.3% and FAR 7.2/h. for threshold ≥20% vs. sensitivity 18.8% and FAR 0.5/h. for thresholds ≥60%).

Similar effects of varying thresholds (of both the relative HR increase and the duration of HR increase) were reported in two studies on retrospectively validated HR algorithms.[32,34] A follow-up using the same dataset, examined different factors that may influence the probability of seizure detection.[44] The best regression model was created with different variables, including age, gender, etiology, seizure class and years with epilepsy.

Heart rate variability (HRV)

All of the HRV-focused studies performed retrospective validations.[8,22–26,28,30,41,42] Different HRV features were selected and specific feature thresholds were classified as 'ictal' or 'interictal'. Nine out of ten HRV studies applied linear analysis[8,22–25,28,30,41,42], using time domain[22–25,28,30,41,42] and frequency domain[8,25,28,41,42] features. Time domain analysis focusses on the instantaneous HR; the intervals between two normal QRS complexes, abbreviated as 'NN'. Different time domain features, such as the mean NN interval or distribution of NN have been used for seizure detection. Four studies extracted and classified these time domain features using a support vector machine (SVM) classifier and validated the same HRV algorithm in different populations.[22–24,30] The first retrospective study on seventeen people with temporal lobe epilepsy found a mean sensitivity of 83.2% with a FAR of 2.01/h.[22] The second study extracted ECG or PPG data out of three different heart rate sensors worn by eleven adults with temporal lobe epilepsy.[30] The best performance was found using a

wearable ECG device, with a sensitivity of 64% and a FAR of 2.35/h. A third study tested the algorithm in 28 children and showed an overall higher sensitivity (81.3%) with lower FAR (0.75/h).[23] Performance, particularly FAR improved when applying a patient-specific heuristic classifier. The latter was confirmed in the fourth study on data from nineteen people with temporal lobe epilepsy from a pre-existing epilepsy database.[24] The authors also proposed an adaptive seizure detection algorithm and showed similar results with simulated 'real-time' user feedback.

Frequency domain analysis is used to extract the frequency components of the HR signal, each with its own physiological footprint: low-frequency (LF; 0.04-0.15Hz), high frequency (HF; 0.15-0.40Hz), very low frequency (VLF; 0.0001-0.04Hz) and very high frequency (VHF; 0.4-0.5Hz). Different frequencies were identified by power spectral density analysis of HRV in four studies[8,25,28,41] and two studies fastened this process by an efficiency algorithm (Fast Fourier Transform (FFT)).[8,28] The LF/HF ratio was examined in two studies, reflecting the balance of sympathetic and parasympathetic function.[25,41] One of these studies tested a seizure detection algorithm combining both time and frequency domain features on eleven focal seizures upon awakening.[25] Ten out of eleven seizures were detected prior to seizure onset (sensitivity 91%, DL -494 ± 262s.). Another study on seven adults with focal epilepsy using time-frequency analysis of HRV based on a combination of the Matching-Pursuit and Wigner-Ville Distribution algorithm, reported a sensitivity of 96.4% with high FAR (5.4/h.).[42] Combining ECG with EEG algorithms revealed better performance (sensitivity 100%, FAR 1.6/h.).

To assess the dynamic properties of ictal HR changes, non-linear analysis can be applied, for example Lorenz (or Poincaré) plot. This method plots the current R-R interval against the following R-R value. Standard deviations of the transverse (SD1) and longitudinal (SD2) direction of these plots can be calculated and higher ratios of SD2/SD1 reflect increase in sympathetic tone. These ratios can be used in seizure detection algorithms, since an increase in sympathetic tone is often seen during the pre-ictal and early ictal phase. One small retrospective study proposed the 'modified Cardio Sympathetic Index' (mCSI) as a new measure in seizure detection, reflecting the sympathetic tonus.[26] A seizure detection algorithm based on changes in mCSI yielded a sensitivity of 88% in five people with temporal lobe epilepsy (FAR not reported). A larger follow-up study on adults with focal epilepsy

compared frequency domain analysis with Lorenz plot analysis.[8] mCSI appeared more sensitive, but FARs were not reported.

The two remaining studies on HRV combined linear and non-linear analysis.[28,41] The first retrospective study on seven people with focal epilepsy reported an overall sensitivity of 88.3% with a specificity of 86.2% after selecting an optimal performance threshold for each patient.[41] The second study combined time-frequency and Lorenz plot analysis with a second non-linear analysis, named sample entropy.[28] This parameter quantifies regularity and complexity of time series and entropy decreases can be seen during the ictal phase. Combining all these methods together on ECG data from twelve temporal lobe epilepsy patients resulted in overall sensitivity of 94.1% with a FAR of 0.49/h.

Another retrospective study reported two different seizure detection algorithms based on changes in QRS morphology (algorithm 1) and cardiorespiratory interactions (algorithm 2).[35] The first algorithm captures five consecutive QRS complexes, aligns them with respect to the R-peak and assembles them into one QRS matrix. Principal component analysis was used to select different features from this QRS matrix. This process was repeated for every heart beat and resulted in a sensitivity of 89.5-100% for detecting focal onset seizures and 86% for generalized onset seizures. The second algorithm is based on the well-known modulatory effects of respiration on HRV. These cardiorespiratory changes were quantified using phase-rectified Signal Averaging, a methodology used to detect quasi-periodicities in nonstationary signals such as the resampled RR interval time series, and were used for seizure detection. A slightly better performance was achieved by the second algorithm with a sensitivity of 100% for focal onset seizures and 90% for generalized onset seizures. In this study, 10.4-90% of the generated alarms were false and this percentage was lower for the second algorithm.

Combination of autonomic parameters

All multimodal autonomic algorithms were retrospectively validated. A combination of three biosignals, measured by two different devices, were used for seizure detection in a study on ten subjects with focal epilepsy.[2] An algorithm based on a specific seizure pattern of increased HR, decreased SpO2 and increased EDA was able to detect all seizures in six out of ten patients, with a low FAR of 0.015/h. Specific thresholds of HR, QTC and SpO2 were combined in an algorithm tested on a larger study population of 45 people with refractory

epilepsy.[37] Only half of the collected data was used for analysis and a sensitivity of 81-94% was found for focal to bilateral tonic-clonic seizures, while focal seizures without bilateral spreading showed worse performance with a sensitivity of 25-36%. Overall FAR ranged from 0.4-2.4/h.

Three other retrospective validation studies combined EDA and accelerometry (ACC), measured with one device.[38–40] Different classifiers were used to select features of EDA and ACC. The first study tested two machine learning algorithms, the k-nearest neighbor (kNN) and Random Forest classifier. The first classifier achieved the best results with eleven features and was most sensitive for non-motor seizures (sensitivity 97.1%, FAR not reported). The second classifier selected 26 features and showed best performance on motor seizures (sensitivity 90.5%, FAR not reported). A second study used a SVM classifier to extract nineteen features (16 ACC and 3 EDA).[40] Fourteen out of sixteen focal onset seizures with bilateral spread were detected (sensitivity 88%) and FAR was 0.04/h. The same feature set was used in the third study and compared to a larger (40 ACC and 6 EDA) and a reduced (22 ACC and 3 EDA) feature set.[39] Retrospectively tested on 24 children and 45 adults with focal epilepsy, the reduced set showed best performance (sensitivity 94.6%, FAR 0.20/day).

A multicenter study combined HR and ACC measures in 95 people with nocturnal major motor seizures.[36] Data from only 23 patients could be used for retrospective validation of three different algorithms, based on changes in HR, ACC and 'HR or ACC'. Clinically urgent seizures were well detected (sensitivity 71–87%), but FAR was relatively high (2.3-6.3/night) with great variation between subjects.

Quality of included studies

According to the QUADAS-2 criteria, overall quality of included studies was medium-high.(Table 2) Seventeen out of 21 studies were at risk of bias, mainly due to an undefined patient selection process and fitting of the algorithm.[2,8,22–26,30,32,34, 37-43] There were high concerns regarding applicability of the selected patients in three studies, because the population consisted of children only and/or were not well described.[23,25,33] Concerns about applicability of the index test (i.e. the tested algorithm) arose in nine studies, mainly because the algorithm was fitted to one dataset.[2,8,23,25,28,30,32,36,37]

Based on the standards for clinical validation of SDDs proposed by Beniczky and Ryvlin[21], most studies were classified as 'phase 1 proof-of-principle' studies, whereas three were

classified as 'phase 0 initial studies'[34,41,42] and only one as a phase 2 study on a dedicated SDD[31].(Table 3) Seven other studies also tested a dedicated device, but included small population sizes or did not address safety of the device and were therefore classified as phase 1[2,30,33,36,38–40]. Ten studies trained and tested their algorithm on the same dataset[2,8,22,26,32,34,37,40–42] and only four used a predefined algorithm or cut-off values.[30,31,33,36] Eighteen studies used video-EEG as reference standard, the remaining three used EEG or ECoG without video recordings.[34,41,42]

Discussion

The overall quality of studies on seizure detection using autonomic parameters is low. Small population sizes, short follow-up periods and high heterogeneity of studies raises concerns about applicability of the results. Available studies are mainly 'initial' or 'proof-of-principle' studies and lack long term and real-time ambulatory monitoring, which is needed for more reliable performance data and usability outcomes.

HR or HRV based algorithms are most frequently applied, but it is hard to compare the results, due to great variation in detection techniques and lack of reporting on FAR.(Table 4) Additionally, FARs, when mentioned, are high across these studies and exceed acceptable limits for daily practice. We could not compare performance of HR and HRV based algorithms due to variety of the study designs. HRV based algorithms seem attractive given their short detection latency, yet still require prospective validation. HRV is, however, situation dependent and affected by exercise, stress, respiration and sleep stages.[45-47] These confounding factors make it more challenging to distinguish ictal patterns from non-ictal ones, resulting in lower accuracy.[48] Also, similar activation of the autonomic nervous system can occur preceding physiological arousal or other sleep related movements.[49]

Multimodal algorithms might help to lower FARs. A retrospective study on seven children with tonic-clonic seizures validated different unimodal and multimodal algorithms on the same dataset. All combinations of multimodal sensors, including ECG, EMG and ACC, showed at least 75% lower FAR.[50] Studies differentiating their outcome for seizure type showed diverse results, indicating that that different seizure types may require different detection techniques. Multimodal techniques can provide a solution for this problem.[51] Another

solution could be personalization or tailoring of an algorithm. One study group studied two different personalization strategies and calculated the number of seizures required for accurate tailoring.[52] The authors proposed an initialization phase to tailor an existing predefined algorithm to a patient-specific algorithm. Six to eight seizures seemed sufficient to set individual thresholds.[52] Another retrospective multicenter study proposed an automatic adaptive HRV algorithm and tested it on a database of 107 nocturnal seizures from 28 children.[23] After an initialization phase of five seizures, the personalized algorithm resulted in lower FARs compared to the patient-independent algorithm. A follow-up study proposed an adaptive classifier with real-time user feedback, with similar performance, this method might be better accepted in daily practice.[24]

Conclusion

Autonomic function alterations seem to provide an attractive tool for timely seizure detection. Unimodal autonomic algorithms, however, cannot reach acceptable performance: while most algorithms are quite sensitive, false alarm rates are still too high. Multimodal algorithms or personalization of the algorithm are important strategies to improve performance. Larger, prospective, home-based studies with long-term follow-up are needed to validate these methods and to demonstrate the added value of SDDs in clinical care.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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