Author/s:
Myers, KA;Sivathamboo, S;Perucca, P

Title:
Heart rate variability measurement in epilepsy: How can we move from research to clinical practice?

Date:
2018-12-01

Citation:
Myers, K. A., Sivathamboo, S. & Perucca, P. (2018). Heart rate variability measurement in epilepsy: How can we move from research to clinical practice?. Epilepsia, 59 (12), pp.2169-2178. https://doi.org/10.1111/epi.14587.

Persistent Link:
https://hdl.handle.net/11343/284843

DR. KENNETH ALEXIS MYERS (Orcid ID : 0000-0001-7831-4593)

Article type : Critical Review – Invited Commentary

Critical Review

Heart Rate Variability Measurement in Epilepsy: How Can We Move from Research to Clinical Practice?

Kenneth A. Myers,[1,2] Shobi Sivathamboo,[3,4,5,6] Piero Perucca[3,4,5,6]

(1) Research Institute of the McGill University Health Center, Montreal, Quebec, Canada

(2) Department of Pediatrics, Division of Child Neurology, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada

(3) Department of Medicine (The Royal Melbourne Hospital), The University of Melbourne, Parkville, Victoria

(4) Department of Neurology, The Royal Melbourne Hospital, Parkville, Victoria, Australia

(5) Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Victoria, Australia

(6) Department of Neurology, Alfred Health, Melbourne, Victoria, Australia

Corresponding Author: Dr. Kenneth Myers; Montreal Children's Hospital, McGill University Health Centre Glen Site; 1001 Décarie Blvd; Montreal, PQ; H4A 3J1; Canada; Phone: 514-412-4466; Fax: 514-412-4373; e-mail: kenneth.myers@mcgill.ca.

Running Title: Integrating HRV Into Clinical Practice

Text Pages: 32; Words: 3582; References: 95; Figures: 2; Tables: 0.

Summary

Our objective was to critically evaluate the literature surrounding heart rate variability (HRV) in people with epilepsy, and to make recommendations as to how future research could be directed to facilitate and accelerate integration into clinical practice. We reviewed relevant HRV publications including those involving human subjects with seizures. HRV has been studied in epilepsy patients for over 30 years and, overall, patients with epilepsy display altered interictal HRV suggesting a shift in autonomic balance towards sympathetic dominance. This derangement appears more severe in those with temporal lobe epilepsy and drug-resistant epilepsy. Normal diurnal variation in HRV is also disturbed in at least some people with epilepsy, but this aspect has received less study. Some therapeutic interventions, including vagal nerve stimulation and anti-epileptic medications, may partially normalize altered HRV, but studies in this area are sometimes contradictory. During seizures, the changes in HRV may be complex, but the general trend is towards a further increase in sympathetic overactivity. Research in HRV in people with epilepsy has been limited by inconsistent experimental protocols and studies that are often underpowered. HRV measurement has the potential to aid clinical epilepsy management in several possible ways. HRV may be useful in predicting which patients are likely to benefit from surgical interventions such as vagal nerve stimulation and focal cerebral resection. As well, HRV could eventually have utility as a biomarker of risk for sudden unexpected death in epilepsy. However, at present, the inconsistent measurement protocols used in research are hindering translation into clinical practice. A minimum protocol for HRV evaluation, to be used in all studies involving epilepsy patients, is necessary in order to eventually allow HRV to become a useful tool for clinicians. We propose a straightforward protocol, involving five-minute measurements of root mean square of successive differences in wakefulness and light sleep.

Key Words: Heart rate variability; Sudden unexpected death in epilepsy; Autonomic; Epilepsy; Sympathetic.

Introduction

Heart rate variability (HRV) is the variation in the time interval between consecutive heart beats. Evaluating HRV is useful from a physiologic perspective because HRV reflects the balance between parasympathetic and sympathetic activity in the autonomic nervous system.[1] In general, increases in HRV reflect a shift towards parasympathetic dominance, while decreases indicate relative increases in sympathetic activity (Figure 1). This is, of course, a simplification as the real-world relationships are more complex and nonlinear.[2] In clinical medicine, HRV has been of interest since the late 1970s due to the recognition that lower HRV is predictive of mortality in certain adult populations, including the elderly and those with cardiac disease.[3,4]

Epilepsy is a disease of the brain characterised by an *enduring* predisposition to generate epileptic seizures.[5] There are many different epilepsy phenotypes and a wide spectrum of severity. Altered patterns of HRV have been recognized in people with epilepsy for nearly 25 years.[6] Understanding autonomic function (and dysfunction) in epilepsy is of interest for several reasons. Many seizure types involve rapid changes in autonomic balance, depending on what regions of the brain are involved. In addition, autonomic dysfunction has been hypothesised to contribute towards sudden unexpected death in epilepsy (SUDEP)..

Despite a considerable wealth of research into altered HRV in epilepsy (Figure 2), evaluation of HRV has yet to become a part of the clinical toolbox of clinical epileptology. In this critical review, we discuss published research of HRV in humans with epilepsy, and the path forward to integrating HRV into clinical practice.

Search Strategy and Review Criteria

We searched PubMed up to June 2018, using the following terms: "epilepsy" and "heart rate variability". Only articles published in English were reviewed. We also identified relevant published articles by searching reference lists of retrieved papers and from our own files.

Methods of Evaluation

In cardiac medicine, there are guidelines for evaluation of HRV, first published in 1996.[7] While these can be applied to epilepsy studies to an extent, evaluating HRV in a person who experiences seizures is a more complex endeavour compared to an individual with primary cardiac pathology. In patients with epilepsy, HRV can be assessed between seizures (interictal), during seizures (ictal), before seizures (pre-ictal), after seizures (post-ictal), or over a long period of time which may or may not include seizures (e.g. 24-hour Holter monitor).

In addition, there are a number of options for specific outcome measures, including time domain parameters (e.g. root mean square of successive differences (RMSSD), standard deviation of R-R interval (SDNN), and percentage of consecutive R-R intervals differing by more than 50 milliseconds (pNN50)) and frequency domain parameters (very low frequency (VLF) power, low frequency (LF) power, high frequency (HF) power, and LF/HF ratio).[7]

Time domain metrics are convenient because calculation is straightforward and can be performed using basic spreadsheet software programs. SDNN is simply the standard deviation of R-R intervals over a period of time. SDNN reflects all components which contribute to variability but is partially dependent on the period of time over which measurements are made. For this reason, SDNN measures obtained from different durations should not be compared (i.e. the SDNN calculated from a 5-minute recording should not be compared to a 24-hour recording). RMSSD and pNN50 are all more dependent on short-term changes in heart rate and thus reflect primarily high frequency variation.[7]

Frequency domain parameters require more elaborate algorithmic calculation, which in most cases involve fast Fourier transform. However, methods of calculation are less standardized. From this spectral analysis, HF power, LF power, and LF/HF ratio can be determined. There is also a very low frequency (VLF) component, but the physiological significance of this is less clear.[7] LF and HF can be expressed in absolute power (ms^2) or in normalized units (nu; the proportion of the power to the total power minus the VLF component).[7] Spectral analysis has been reported to allow separation of autonomic components, with the LF band primarily thought to represent cardiac sympathetic drive, and HF band parasympathetic (vagal) outflow.[7] However, there is more recent evidence that LF/HF ratio is not a reliable surrogate measure of autonomic balance.[8]

In general, there has been considerable variation in the experimental approaches taken to assess HRV in epilepsy, which may partially explain the contradictory findings between some of the studies discussed hereafter.

Interictal HRV Patterns in Different Epilepsy Types

Temporal Lobe Epilepsy

The majority of epilepsy HRV research has involved study of adult patients with temporal lobe epilepsy (TLE). This population is a logical choice because seizures in TLE commonly have autonomic features, including tachycardia, bradycardia and sweating. When compared to healthy, age-matched controls, most studies found that awake and 24-hour HRV measures are

lower, including variance, HF, LF and LF/HF ratio, suggesting a shift towards sympathetic dominance.[9,10] One study found that with hyperventilation, an exaggerated sympathetic response was seen in patients with mesial TLE when compared to controls.[11]

Autonomic derangements appear to be more severe in patients with refractory seizures and/or with hippocampal sclerosis.[12,13] Over time, the derangements can vary, with worsening correlating with acute deteriorations,[14] but also progressive worsening over time.[15] Notably, the results of one study suggested that more severe HRV derangement was predictive of a poorer outcome following resective surgery.[16]

Although the vast majority of studies have involved adult patients, one study compared ten children with TLE to ten with absence epilepsy, as well as ten healthy controls.[17] That study examined awake HRV from a 5-minute recording, and performed only frequency domain analysis. No significant differences were found between patients with TLE and controls; however, the number of patients studied was relatively small and standard time domain outcome measures were not evaluated.

Generalized Epilepsy

In adults with generalized epilepsy, the overall evidence indicates that HRV is also abnormal. Findings indicating an interictal shift towards sympathetic dominance have been reported for adult patients with juvenile myoclonic epilepsy[10] and epilepsy with generalized tonic-clonic seizures;[18] however, the degree of derangement tends to be milder than observed with TLE. One study of a relatively small cohort of drug-naïve genetic generalized epilepsy patients did not find statistically significant differences in HRV when compared to controls.[19]

In children with generalized epilepsy, the same patterns have generally been observed.[20,21] The previously mentioned study of Varon et al[17] found that in children with absence epilepsy, heart rate was higher and entropy measures different, suggesting autonomic dysfunction in those with absence seizures.

Epileptic Spasms

HRV has been studied in patients with epileptic spasms in infancy, with two studies reporting findings indicating a shift towards sympathetic dominance,[22,23] and one no significant differences other than lower heart rate in slow wave sleep.[24] A fourth study examined HRV in sleep only, finding increased LF component.[25] Following treatment, there is a shift towards recovery of parasympathetic function.[22,23,25]

Dravet Syndrome

Three studies have examined HRV in patients with Dravet syndrome (DS). Two studies found that HRV values from 24-hour Holter monitors were decreased in patients with DS when compared to healthy controls.[26,27] In fact, patients with DS appear to have extremely depressed parasympathetic function, even amongst the general epilepsy population. Delogu et al found that HRV values from 24-hour Holter were lower even when compared to a group of patients with other forms of epilepsy. A more recent study evaluated 5-minute periods in wakefulness and sleep, and found that patients with DS had lower awake HRV values than patients with other drug-resistant epilepsy.[28]

Lennox-Gastaut Syndrome

There is a single case report of a patient with Lennox-Gastaut syndrome who had severely depressed HRV at baseline, which improved following implantation of a vagal nerve stimulator.[29]

Frontal Lobe Epilepsy

One study comparing patients with frontal lobe epilepsy to healthy controls found faster heart rate and increased HF power in the epilepsy patients, suggesting a shift towards sympathetic dominance in this population as well.[30]

Hot Water Epilepsy

A study using 5-minute awake ECG recordings found a shift towards sympathetic dominance, evidenced by increased LF, LF/HF ratio, and decreased RMSSD and HF.[31]

Non-Specific Epilepsy

There have been a number of studies of interictal HRV in more heterogeneous adult epilepsy populations. Most have reported trends indicating a shift towards sympathetic dominance,[32-34] though some failed to find statistically significant differences.[35] In similarly designed studies of pediatric patients, the same patterns are typically seen, though children with drug-resistant epilepsy often have more severe derangements.[36-39]

Psychogenic Non-Epileptic Seizures

One last epilepsy-related area of study that merits discussion is patients with psychogenic non-epileptic seizures (PNES). PNES are clinical events that may resemble epileptic seizures; however, there is no EEG abnormality and the events are presumed to be manifestations of underlying psychological stress. Interestingly, individuals with PNES (but no epilepsy) also have lower interictal HRV than controls.[40,41] One study found that interictal HRV was not significantly different in PNES patients and those with epilepsy.[40] These findings raise the question – are HRV abnormalities in epilepsy related to the underlying pathology of the disease, or are they more a reflection of the psychological stress of having epilepsy?

Effects of Treatment on Interictal HRV

The effects of various anti-epileptic therapies on HRV have been investigated. Some, such as vagal nerve stimulation (VNS), have a fairly clear physiological hypothesis by which they might exert effects. In other cases, such as anti-epileptic drugs, it is unclear if the treatment has a direct effect on the autonomic nervous system, or if effects on HRV occur secondary to improved epilepsy control.

Vagal Nerve Stimulation

The effects of VNS on HRV have been intensely studied, as direct stimulation of the vagal nerve appears to be an obvious strategy by which to modulate autonomic balance. When studied acutely, examining the differences in HRV when the stimulator is on versus off, the LF:HF peak ratio was reported to be lower when the stimulator is on in a single patient case study,[42] while two other studies reported no significant differences in HRV measures across patients, suggesting considerable interindividual variability.[43,44]

When studying interictal HRV before and after implantation, a number of studies reported findings indicating a shift back towards increased parasympathetic activity with VNS;[29,45-47] with a similar shift noted in healthy subjects stimulated using transcutaneous VNS.[48] However, multiple other studies failed to find a statistically significant difference before and after VNS treatment.[49-52] One study reported that VNS actually decreased HRV.[53] Another study reported only a blunting of day-to-night changes in the power of LF and HF components 36 months after treatment initiation.[54] Some of the studies also reported differences in outcomes other than traditional HRV measures, such as T wave alternans, a different measure of cardiac electrical stability[46,51] or reversal of abnormal heart rate complexity.[55]

One possible explanation for the variability in results is that different studies used different time points for evaluation and, while the response may be present as early as 6 months, the effects are not necessarily sustained.[45] Additionally, the choice of right versus left vagal nerve stimulation may be important; studies incorporating sodium amytal injections have suggested that HRV is primarily driven by the right hemisphere.[56,57] Interestingly, recent data has suggested that the degree of HRV derangement could predict the likelihood of clinical response to VNS.[58,59]

Effects of Anti-Epileptic Drug Treatment

A number of studies have investigated the effects of drug treatment on abnormal HRV in epilepsy. In some cases, such as the already-discussed West syndrome, there are multiple studies with data that generally agrees that there is HRV improvement following treatment initiation.[22,23,25] In epilepsy with older childhood onset, autonomic balance also appears to partially normalize following treatment initiation as well.[36,38]

However, in adult studies the findings have been less consistent. One study reported that HRV became even lower in adults with epilepsy following initiation of carbamazepine.[60] A number of studies have examined the effects of weaning medication in adults, including the rapid tapering that typically occurs during epilepsy monitoring unit admissions. Here, results were conflicting: two studies found that rapid weans led to acute decreases in HRV, though one study only reviewed sleep activity;[61,62] the third study found instead no significant differences.[63] One study

examined more typical, gentle outpatient medication weans, and found that HRV actually appeared to improve after weaning medication in this manner.[64]

Surgical Resection

Two studies examined HRV before and after resective surgery in patients with TLE: both found that there was no change in HRV post-operatively.[65,66] HRV could have utility in pre-surgical work-up, however, as one study found that patients with more severe HRV derangements pre-operatively had poorer surgical outcomes.[16]

Wake-Sleep Differences

Relatively few studies have examined the relationship between HRV in sleep and wakefulness in epilepsy; this is surprising given that the autonomic balance has obvious diurnal variation. Parasympathetic activity progressively increases with deeper stages of sleep, with a shift back towards sympathetic dominance during rapid eye movement sleep.[67] There is considerable evidence that diurnal patterns of HRV are deranged in patients with epilepsy; however, the exact nature of the derangement is not completely clear.

One study of patients with generalized epilepsy found that there was an exaggerated shift towards parasympathetic dominance in sleep.[68] In contrast, two studies published by the same group found a blunting of the normal parasympathetic shift in sleep.[52,69] Finally, another study found no difference in sleep:awake HRV ratios between patients with epilepsy and controls; however, that study used only nocturnal versus daytime HRV from Holter monitor recordings, and did not actually confirm the arousal state of the patients at the time of the HRV period analysed.[70]

A number of studies have specifically looked at HRV during sleep alone. One study compared children with focal epilepsy to healthy controls, and found that epilepsy patients had lower HRV in sleep.[71] Another study examined only an aspect of the cyclic alternating pattern in sleep, in patients with sleep-related hypermotor epilepsy, with results suggesting a shift towards sympathetic dominance.[72] Finally, one research group examined HRV around the time of sleep

apneas in patients with both TLE and juvenile myoclonic epilepsy, finding that both groups displayed a lack of the normal autonomic response to a sleep apnea event.[73,74]

Peri-Ictal Patterns

There have been a great number of studies which have examined peri-ictal changes in HRV, and these will not be discussed in detail here. Although the results are not completely consistent, the general theme is that there is a further increase in sympathetic dominance during virtually all types of seizures, most dramatic in temporal lobe and generalized tonic-clonic seizures.[75-77] The post-ictal changes can be long-lasting, demonstrated in one study which found that tonic-clonic seizures were associated with decreases in time domain metrics of HRV which lasted up to 5-6 hours.[78]

In many cases, these studies have been conducted with the goal of developing seizure prediction devices; the observation of HRV changes prior to clinical seizure onset suggests this could be useful.[79] In addition, some studies have found subtle differences when comparing ictal HRV in epileptic seizures and PNES,[80,81] however the wide interindividual variability suggests that at this point HRV would not be a useful tool in differentiating the two event types.

SUDEP

SUDEP is the leading cause of death in several epilepsy populations, and in the United States is the second leading neurological cause of total years of potential life lost after stroke.[82,83] SUDEP is defined as a "sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause for death."[84] The strongest risk factor for SUDEP are the presence, but more importantly, the frequency of uncontrolled tonic-clonic seizures.[85,86] Other risk factors comprise of not being seizure free for 1-5 years and not adding an antiepileptic drug when medically refractory.[85]

One of the primary reasons for the enthusiasm for investigation of HRV in epilepsy is the potential to better understand SUDEP. This entity is thought to at least partially relate to

autonomic dysfunction, and three studies have shown correlation of SUDEP risk factors with more severely deranged HRV,[34,87,88] though a third did not find a significant correlation.[33] Postictal EEG suppression may potentially be a biomarker of SUDEP,[89] and in one study was associated with decreased HF power.[90] However, these findings were not confirmed in another larger study.[91]

A more direct link between SUDEP and altered HRV was recently reported in a study that retrospectively evaluated HRV in patients with drug-resistant epilepsy, half of whom had sodium channel mutations; those with sodium channel mutations who went on to suffer SUDEP were found to have more extreme HRV derangements, with low HRV in wakefulness and extremely high or low sleep:awake HRV ratios.[28] An earlier study with a similar design but fewer patients reported no difference between patients suffering SUDEP and others with epilepsy, though the method of analysis of the results was subsequently questioned.[92,93]

Finally, there have been several studies of acute and subacute HRV changes in individual cases of sudden death in patients with seizures. Jeppesen et al described an adult patient with drug-resistant epilepsy due to a focal cortical dysplasia who died while admitted to hospital; they found an increase in parasympathetic activity in the hours and days leading up to death.[94] Myers et al described a child with a chromosomal disorder and febrile seizures, who suffered sudden unexpected death during continuous EEG monitoring; in that case, HRV was extremely low in the hours prior to death, but eight minutes prior to death there was a dramatic spike in HRV indicating a sudden parasympathetic shift.[95]

Discussion

Over 25 years of study of HRV in epilepsy, we have learned a considerable amount. Across different forms of epilepsy, interictal HRV is consistently lower, demonstrating a shift towards sympathetic dominance. These abnormalities are most severe in patients with drug-resistant epilepsy, as well as those with other risk factors for SUDEP. Treatment of seizures can have a positive effect on deranged HRV; but does not seem to completely normalize autonomic dysfunction. Unfortunately, HRV epilepsy research is presently limited by inconsistent methodology between different research groups, which makes inter-study comparisons difficult.

Often, confounding factors such as age, sex, medications and co-morbid medical conditions, are not properly accounted for. Furthermore, many studies involve small numbers of patients and are underpowered.

The lack of a standardized protocol for measurement and reporting of HRV in epilepsy patients is currently limiting the use of HRV as a clinical biomarker for people with epilepsy. Solving this problem is crucial, as studies have suggested HRV could be useful in predicting the success of resective epilepsy surgeries, as well as determining which candidates are most likely to benefit from VNS. HRV might even eventually become useful as a biomarker of SUDEP risk.

While there are guidelines for HRV measurement from cardiology associations,[7] these do not translate well to people with epilepsy. A 24-hour Holter monitor does not allow for accurate evaluation of sleep versus awake HRV, and diurnal variations in HRV may have considerable relevance for people with seizures. Furthermore, HRV over a 24-hour period could be increased or decreased considerably by a patient's seizure frequency during that period. Instead, a standardized minimum protocol for HRV more appropriate for epilepsy patients is necessary. With that in mind, we propose the following outcome measures be the primary values reported in all epilepsy studies involving interictal HRV:

(1) 5-minute Awake RMSSD: RMSSD measured over a 5-minute period during which the patient is awake and alert, and resting comfortably.
(2) 5-minute Sleep RMSSD: RMSSD measured over a 5-minute period during which the patient is in stage N1 or N2 sleep.
(3) Sleep:Awake RMSSD ratio: Sleep RMSSD divided by awake RMSSD.
* Given that seizures are associated with acute changes to HRV, we recommend when selecting five-minute epochs, these are: (a) at least 8 hours after the last tonic-clonic seizure; (b) at least 1 hour after the last known clinical (excluding tonic-clonic seizures), subclinical, electrographic seizure; and (c) at least 1 hour before the next clinical seizure.

Additionally, minimal clinical data should be collected and reported, including: age, sex, medications, epilepsy syndrome, seizure type(s), and co-morbid medical conditions.

This protocol has several advantages. For one, these values can be recorded during most routine EEG studies, and in fact the ECG data may be extracted from the EEG recording itself, allowing for retrospective data collection. Furthermore, the use of a time domain parameter simplifies the method of analysis, avoiding pitfalls due to variations in the Fourier transform protocols necessary for frequency domain analysis. It is true that RMSSD is primarily a measure of short term variation in heart rate; however, this is all that is necessary when evaluating over a relatively brief 5-minute period. Other measures, including SDNN, pNN50, 24-hour HRV and frequency domain measures, can still be described of course, but the above minimal protocol should be reported in all studies of interictal HRV in epilepsy populations. With this approach, we hope that HRV epilepsy studies will move forward in a manner that will facilitate an ultimate jump from research to clinical practice.

Acknowledgements

KAM receives research support from the Research Institute of the McGill University Health Centre, Citizens United for Research in Epilepsy and dravetCanada. SS is supported by a NHMRC Program Grant to Professor Terence J. O'Brien (##APP1091593), and a Ball Grant from The Royal Melbourne Hospital Neuroscience Foundation. PP is supported by the Bridging Postdoctoral Fellowship (BPF) from Monash University (BPF18-0114)

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure Statement

KAM has received a grant from dravetCanada for a research project related to heart rate variability in patients with Dravet syndrome.

Key Point Box

- Interictal heart rate variability studies suggest sympathetic overactivity occurs in most forms of epilepsy.
- Autonomic dysregulation appears to be most severe in those with temporal lobe epilepsy and drug-resistant epilepsy.
- Heart rate variability has potential clinical applications, including predicting response to certain therapies and as a SUDEP risk biomarker.
- Heart rate variability research in epilepsy has been limited by the lack of consistently-used protocols.
- For heart rate variability measurements to be successfully integrated into clinical practice, a standardized evaluation protocol is needed.

Figure Legends

Figure 1: Heart rate variability is a surrogate measure of autonomic nervous system balance. Increased heart rate variability indicates a shift towards parasympathetic dominance, while lower heart rate variability is seen in times of high sympathetic output.

Figure 2: The number of Pubmed-indexed papers related to heart rate variability and epilepsy per year, with publication dates between 1990 and 2017. Data generated by a Pubmed search for "heart rate variability epilepsy" performed on 14-July-2018.

References

[1] Katona PG, Jih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. J Appl Physiol 1975; 39: 801-805.

[2] Goldberger JJ, Challapalli S, Tung R, et al. Relationship of heart rate variability to parasympathetic effect. Circulation 2001; 103: 1977-1983.

[3] Tsuji H, Venditti FJ, Jr., Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation 1994; 90: 878-883.

[4] Wolf MM, Varigos GA, Hunt D, et al. Sinus arrhythmia in acute myocardial infarction. Med J Aust 1978; 2: 52-53.

[5] Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014; 55: 475-482.

[6] Frysinger RC, Engel J, Harper RM. Interictal heart rate patterns in partial seizure disorders. Neurology 1993; 43: 2136-2139.

[7] Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996; 93: 1043-1065.

[8] Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front Physiol 2013; 4: 26.

[9] Massetani R, Strata G, Galli R, et al. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability. Epilepsia 1997; 38: 363-369.

[10] Tomson T, Ericson M, Ihrman C, et al. Heart rate variability in patients with epilepsy. Epilepsy Res 1998; 30: 77-83.

[11] Assenza G, Mecarelli O, Tombini M, et al. Hyperventilation induces sympathetic overactivation in mesial temporal epilepsy. Epilepsy Res 2015; 110: 221-227.

[12] Ansakorpi H, Korpelainen JT, Huikuri HV, et al. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2002; 72: 26-30.

[13] Ansakorpi H, Korpelainen JT, Tanskanen P, et al. Cardiovascular regulation and hippocampal sclerosis. Epilepsia 2004; 45: 933-939.

[14] Toichi M, Murai T, Sengoku A, et al. Interictal change in cardiac autonomic function associated with EEG abnormalities and clinical symptoms: a longitudinal study following

acute deterioration in two patients with temporal lobe epilepsy. Psychiatry Clin Neurosci 1998; 52: 499-505.

[15] Suorsa E, Korpelainen JT, Ansakorpi H, et al. Heart rate dynamics in temporal lobe epilepsy-A long-term follow-up study. Epilepsy Res 2011; 93: 80-83.

[16] Persson H, Kumlien E, Ericson M, et al. Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy. Neurology 2005; 65: 1021-1025.

[17] Varon C, Montalto A, Jansen K, et al. Interictal cardiorespiratory variability in temporal lobe and absence epilepsy in childhood. Physiol Meas 2015; 36: 845-856.

[18] Mativo P, Anjum J, Pradhan C, et al. Study of cardiac autonomic function in drug-naive, newly diagnosed epilepsy patients. Epileptic Disord 2010; 12: 212-216.

[19] Kilinc O, Cincin A, Pehlivan A, et al. Assessment of Time and Frequency Domain Parameters of Heart Rate Variability and Interictal Cardiac Rhythm Abnormalities in Drug-naïve Patients with Idiopathic Generalized Epilepsy. J Epilepsy Res 2016; 6: 22-27.

[20] Harnod T, Yang CC, Hsin YL, et al. Heart rate variability in children with refractory generalized epilepsy. Seizure 2008; 17: 297-301.

[21] El-Sayed HL, Kotby AA, Tomoum HY, et al. Non-invasive assessment of cardioregulatory autonomic functions in children with epilepsy. Acta Neurol Scand 2007; 115: 377-384.

[22] Gencpinar P, Kocabas A, Duman Ö, et al. Cardiac Autonomic Dysfunction in Patients With Infantile Spasm and the Effect of Adrenocorticotropic Hormone Treatment. J Child Neurol 2016; 31: 134-137.

[23] Møller MM, Høgenhaven H, Uldall P, et al. Heart rate variability in infants with West syndrome. Seizure 2015; 27: 10-15.

[24] Jansen K, Vandeput S, Van Huffel S, et al. Cardiac autonomic dysfunction in West syndrome. Epilepsy Res 2012; 102: 167-172.

[25] Hattori A, Hayano J, Fujimoto S, et al. Cardiac vagal activation by adrenocorticotropic hormone treatment in infants with West syndrome. Tohoku J Exp Med 2007; 211: 133-139.

[26] Delogu AB, Spinelli A, Battaglia D, et al. Electrical and autonomic cardiac function in patients with Dravet syndrome. Epilepsia 2011; 52 Suppl 2: 55-58.

[27] Ergul Y, Ekici B, Tatli B, et al. QT and P wave dispersion and heart rate variability in patients with Dravet syndrome. Acta Neurol Belg 2013; 113: 161-166.

[28] Myers KA, Bello-Espinosa LE, Symonds JD, et al. Heart rate variability in epilepsy: A potential biomarker of sudden unexpected death in epilepsy risk. Epilepsia 2018;

[29] Koenig SA, Longin E, Bell N, et al. Vagus nerve stimulation improves severely impaired heart rate variability in a patient with Lennox-Gastaut-Syndrome. Seizure 2008; 17: 469-472.

[30] Harnod T, Yang CC, Hsin YL, et al. Heart rate variability in patients with frontal lobe epilepsy. Seizure 2009; 18: 21-25.

[31] Meghana A, Sathyaprabha TN, Sinha S, et al. Cardiac autonomic dysfunction in drug naive hot water epilepsy. Seizure 2012; 21: 706-710.

[32] Goit RK, Jha SK, Pant BN. Alteration of cardiac autonomic function in patients with newly diagnosed epilepsy. Physiol Rep 2016; 4:

[33] Baysal-Kirac L, Serbest NG, Sahin E, et al. Analysis of heart rate variability and risk factors for SUDEP in patients with drug-resistant epilepsy. Epilepsy Behav 2017; 71: 60-64.

[34] Drake ME, Jr., Andrews JM, Castleberry CM. Electrophysiologic assessment of autonomic function in epilepsy. Seizure 1998; 7: 91-96.

[35] Persson H, Ericson M, Tomson T. Heart rate variability in patients with untreated epilepsy. Seizure 2007; 16: 504-508.

[36] Hallioglu O, Okuyaz C, Mert E, et al. Effects of antiepileptic drug therapy on heart rate variability in children with epilepsy. Epilepsy Res 2008; 79: 49-54.

[37] El Shorbagy HH, Elsayed MA, Kamal NM, et al. Heart-type fatty acid-binding protein as a predictor of cardiac ischemia in intractable seizures in children. J Pediatr Neurosci 2016; 11: 175-181.

[38] El-Rashidy OF, Shatla RH, Youssef OI, et al. Cardiac autonomic balance in children with epilepsy: value of antiepileptic drugs. Pediatr Neurol 2015; 52: 419-423.

[39] Kolsal E, Serdaroglu A, Cilsal E, et al. Can heart rate variability in children with epilepsy be used to predict seizures? Seizure 2014; 23: 357-362.

[40] Ponnusamy A, Marques JL, Reuber M. Heart rate variability measures as biomarkers in patients with psychogenic nonepileptic seizures: potential and limitations. Epilepsy Behav 2011; 22: 685-691.

[41] Bakvis P, Roelofs K, Kuyk J, et al. Trauma, stress, and preconscious threat processing in patients with psychogenic nonepileptic seizures. Epilepsia 2009; 50: 1001-1011.

[42] Kamath MV, Upton AR, Talalla A, et al. Effect of vagal nerve electrostimulation on the power spectrum of heart rate variability in man. Pacing Clin Electrophysiol 1992; 15: 235-243.

[43] Setty AB, Vaughn BV, Quint SR, et al. Heart period variability during vagal nerve stimulation. Seizure 1998; 7: 213-217.

[44] Frei MG, Osorio I. Left vagus nerve stimulation with the neurocybernetic prosthesis has complex effects on heart rate and on its variability in humans. Epilepsia 2001; 42: 1007-1016.

[45] Hirfanoglu T, Serdaroglu A, Cetin I, et al. Effects of vagus nerve stimulation on heart rate variability in children with epilepsy. Epilepsy Behav 2018; 81: 33-40.

[46] Schomer AC, Nearing BD, Schachter SC, et al. Vagus nerve stimulation reduces cardiac electrical instability assessed by quantitative T-wave alternans analysis in patients with drug-resistant focal epilepsy. Epilepsia 2014; 55: 1996-2002.

[47] Pruvost M, Zaaimi B, Grebe R, et al. Cardiorespiratory effects induced by vagus nerve stimulation in epileptic children. Med Biol Eng Comput 2006; 44: 338-347.

[48] Clancy JA, Mary DA, Witte KK, et al. Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. Brain Stimul 2014; 7: 871-877.

[49] Barone L, Colicchio G, Policicchio D, et al. Effect of vagal nerve stimulation on systemic inflammation and cardiac autonomic function in patients with refractory epilepsy. Neuroimmunomodulation 2007; 14: 331-336.

[50] Garamendi-Ruiz I, Gómez-Esteban JC. Cardiovascular autonomic effects of vagus nerve stimulation. Clin Auton Res 2017;

[51] Verrier RL, Nearing BD, Olin B, et al. Baseline elevation and reduction in cardiac electrical instability assessed by quantitative T-wave alternans in patients with drug-resistant epilepsy treated with vagus nerve stimulation in the AspireSR E-36 trial. Epilepsy Behav 2016; 62: 85-89.

[52] Ronkainen E, Korpelainen JT, Heikkinen E, et al. Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation treatment: a one-year follow-up study. Epilepsia 2006; 47: 556-562.

[53] Jansen K, Vandeput S, Milosevic M, et al. Autonomic effects of refractory epilepsy on heart rate variability in children: influence of intermittent vagus nerve stimulation. Dev Med Child Neurol 2011; 53: 1143-1149.

[54] Galli R, Limbruno U, Pizzanelli C, et al. Analysis of RR variability in drug-resistant epilepsy patients chronically treated with vagus nerve stimulation. Auton Neurosci 2003; 107: 52-59.

[55] Liu H, Yang Z, Meng F, et al. Chronic vagus nerve stimulation reverses heart rhythm complexity in patients with drug-resistant epilepsy: An assessment with multiscale entropy analysis. Epilepsy Behav 2018; 83: 168-174.

[56] Yoon BW, Morillo CA, Cechetto DF, et al. Cerebral hemispheric lateralization in cardiac autonomic control. Arch Neurol 1997; 54: 741-744.

[57] Ahern GL, Sollers JJ, Lane RD, et al. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital test. Epilepsia 2001; 42: 912-921.

[58] Liu HY, Yang Z, Meng FG, et al. Preoperative Heart Rate Variability as Predictors of Vagus Nerve Stimulation Outcome in Patients with Drug-resistant Epilepsy. Sci Rep 2018; 8: 3856.

[59] Liu H, Yang Z, Huang L, et al. Heart-rate variability indices as predictors of the response to vagus nerve stimulation in patients with drug-resistant epilepsy. Epilepsia 2017; 58: 1015-1022.

[60] Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. Epilepsy Res 2003; 57: 69-75.

[61] Kenneback G, Ericson M, Tomson T, et al. Changes in arrhythmia profile and heart rate variability during abrupt withdrawal of antiepileptic drugs. Implications for sudden death. Seizure 1997; 6: 369-375.

[62] Hennessy MJ, Tighe MG, Binnie CD, et al. Sudden withdrawal of carbamazepine increases cardiac sympathetic activity in sleep. Neurology 2001; 57: 1650-1654.

[63] Stefani M, Arima H, Mohamed A. Withdrawal of anti-epileptic medications during video EEG monitoring does not alter ECG parameters or HRV. Epilepsy Res 2013; 106: 222-229.

[64] Lossius MI, Erikssen JE, Mowinckel P, et al. Changes in autonomic cardiac control in patients with epilepsy after discontinuation of antiepileptic drugs: a randomized controlled withdrawal study. Eur J Neurol 2007; 14: 1022-1028.

[65] Dericioglu N, Demirci M, Cataltepe O, et al. Heart rate variability remains reduced and sympathetic tone elevated after temporal lobe epilepsy surgery. Seizure 2013; 22: 713-718.

[66] Persson H, Kumlien E, Ericson M, et al. No apparent effect of surgery for temporal lobe epilepsy on heart rate variability. Epilepsy Res 2006; 70: 127-132.

[67] Boudreau P, Yeh WH, Dumont GA, et al. Circadian variation of heart rate variability across sleep stages. Sleep 2013; 36: 1919-1928.

[68] Sivakumar SS, Namath AG, Tuxhorn IE, et al. Decreased heart rate and enhanced sinus arrhythmia during interictal sleep demonstrate autonomic imbalance in generalized epilepsy. J Neurophysiol 2016; 115: 1988-1999.

[69] Ronkainen E, Ansakorpi H, Huikuri HV, et al. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2005; 76: 1382-1386.

[70] Persson H, Kumlien E, Ericson M, et al. Circadian variation in heart-rate variability in localization-related epilepsy. Epilepsia 2007; 48: 917-922.

[71] Ferri R, Curzi-Dascalova L, Arzimanoglou A, et al. Heart rate variability during sleep in children with partial epilepsy. J Sleep Res 2002; 11: 153-160.

[72] Dorantes G, Mendez M, Alba A, et al. Heart rate variability in cyclic alternating pattern during sleep in healthy and Nocturnal Front Lobe Epilepsy patients. Conf Proc IEEE Eng Med Biol Soc 2015; 2015: 5944-5947.

[73] Nayak C, Sinha S, Nagappa M, et al. Lack of heart rate variability during apnea in patients with juvenile myoclonic epilepsy (JME). Sleep Breath 2015; 19: 1175-1183.

[74] Nayak CS, Sinha S, Nagappa M, et al. Lack of heart rate variability during sleep-related apnea in patients with temporal lobe epilepsy (TLE)-an indirect marker of SUDEP? Sleep Breath 2017; 21: 163-172.

[75] Jeppesen J, Beniczky S, Fuglsang-Frederiksen A, et al. Detection of epileptic-seizures by means of power spectrum analysis of heart rate variability: a pilot study. Technol Health Care 2010; 18: 417-426.

[76] Brotherstone R, McLellan A. Parasympathetic alteration during sub-clinical seizures. Seizure 2012; 21: 391-398.

[77] Surges R, Scott CA, Walker MC. Enhanced QT shortening and persistent tachycardia after generalized seizures. Neurology 2010; 74: 421-426.

[78] Toth V, Hejjel L, Fogarasi A, et al. Periictal heart rate variability analysis suggests long-term postictal autonomic disturbance in epilepsy. Eur J Neurol 2010; 17: 780-787.

[79] Behbahani S, Dabanloo NJ, Nasrabadi AM, et al. Pre-ictal heart rate variability assessment of epileptic seizures by means of linear and non-linear analyses. Anadolu Kardiyol Derg 2013; 13: 797-803.

[80] Jeppesen J, Beniczky S, Johansen P, et al. Comparing maximum autonomic activity of psychogenic non-epileptic seizures and epileptic seizures using heart rate variability. Seizure 2016; 37: 13-19.

[81] Ponnusamy A, Marques JL, Reuber M. Comparison of heart rate variability parameters during complex partial seizures and psychogenic nonepileptic seizures. Epilepsia 2012; 53: 1314-1321.

[82] Devinsky O, Hesdorffer DC, Thurman DJ, et al. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol 2016; 15: 1075-1088.

[83] Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia 2014; 55: 1479-1485.

[84] Nashef L, So EL, Ryvlin P, et al. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012; 53: 227-233.

[85] Harden C, Tomson T, Gloss D, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2017; 88: 1674-1680.

[86] Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011; 52: 1150-1159.

[87] Novak JL, Miller PR, Markovic D, et al. Risk Assessment for Sudden Death in Epilepsy: The SUDEP-7 Inventory. Front Neurol 2015; 6: 252.

[88] DeGiorgio CM, Miller P, Meymandi S, et al. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 Inventory. Epilepsy Behav 2010; 19: 78-81.

[89] Lhatoo SD, Faulkner HJ, Dembny K, et al. An electroclinical case-control study of sudden unexpected death in epilepsy. Ann Neurol 2010; 68: 787-796.

[90] Poh MZ, Loddenkemper T, Reinsberger C, et al. Autonomic changes with seizures correlate with postictal EEG suppression. Neurology 2012; 78: 1868-1876.

[91] Lamberts RJ, Laranjo S, Kalitzin SN, et al. Postictal generalized EEG suppression is not associated with periictal cardiac autonomic instability in people with convulsive seizures. Epilepsia 2013; 54: 523-529.

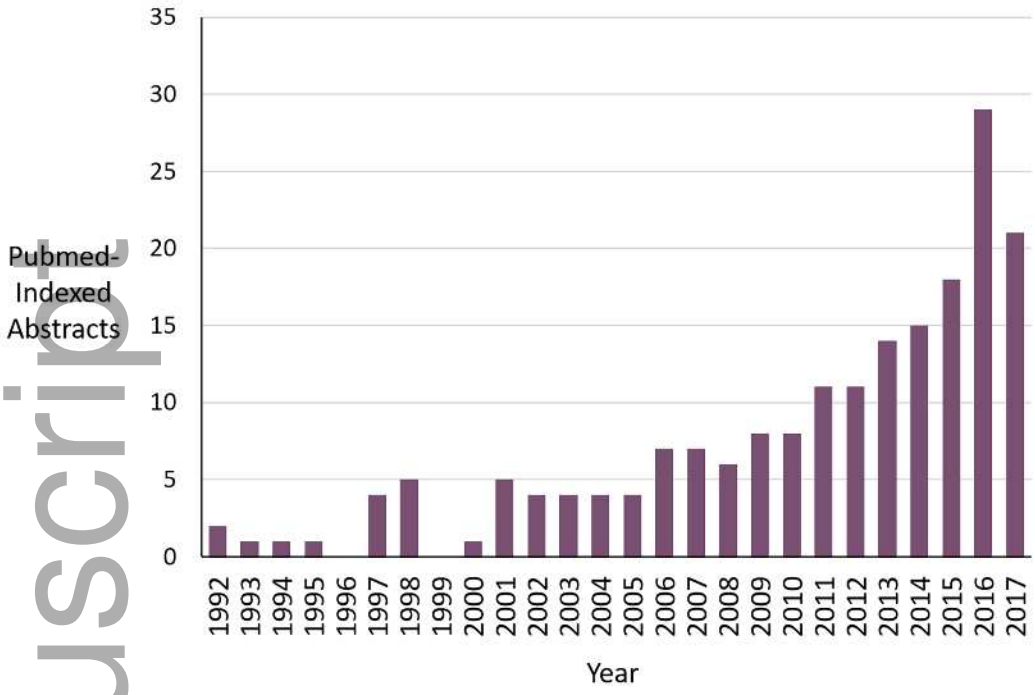
[92] Surges R, Henneberger C, Adjei P, et al. Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy? Epilepsy Res 2009; 87: 277-280.

[93] DeGiorgio CM, DeGiorgio AC. SUDEP and heart rate variability. Epilepsy Res 2010; 90: 309-310; author reply 311-302.

[94] Jeppesen J, Fuglsang-Frederiksen A, Brugada R, et al. Heart rate variability analysis indicates preictal parasympathetic overdrive preceding seizure-induced cardiac dysrhythmias leading to sudden unexpected death in a patient with epilepsy. Epilepsia 2014; 55: e67-71.

[95] Myers KA, McPherson RE, Clegg R, et al. Sudden Death After Febrile Seizure Case Report: Cerebral Suppression Precedes Severe Bradycardia. Pediatrics 2017; 140:

epi_14587_f1.tif



epi_14587_f2.tif