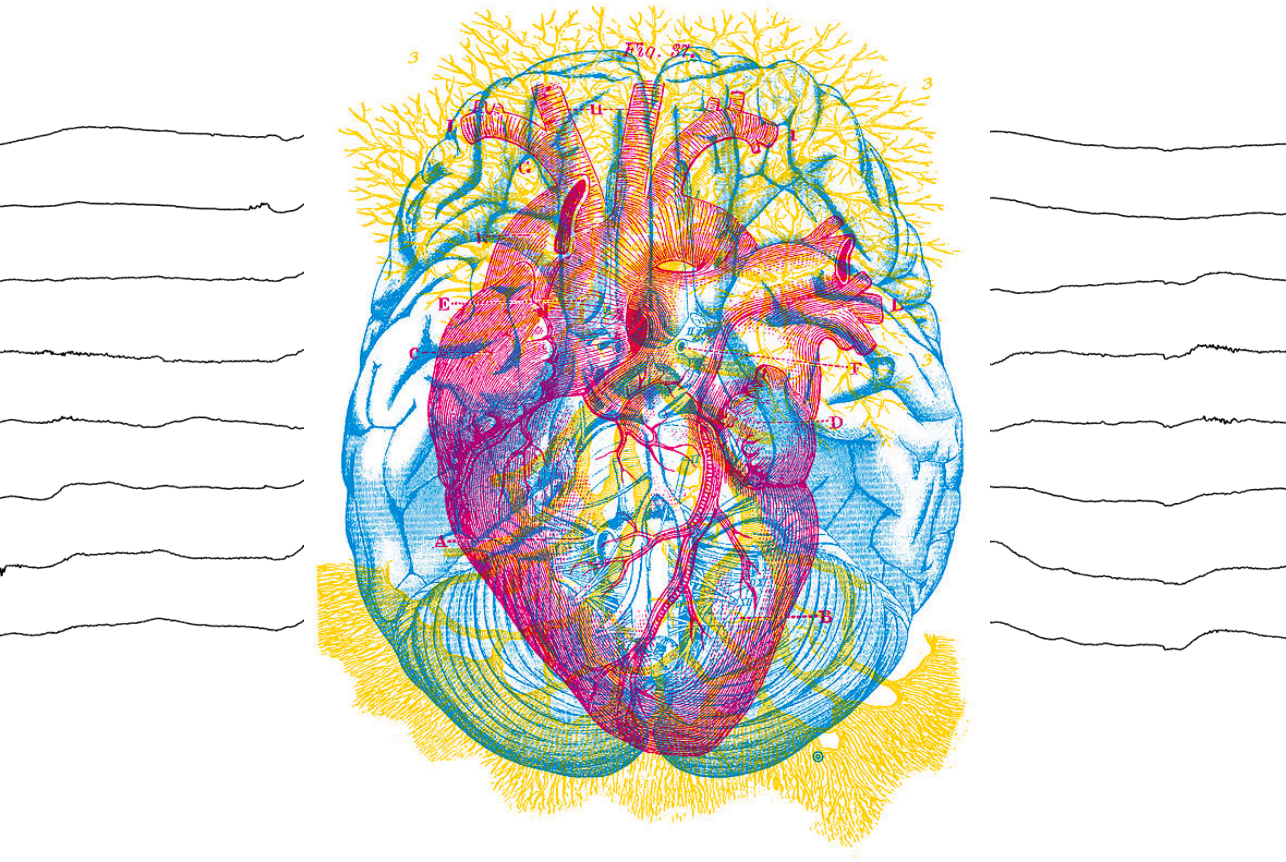
Epilepsy and cardiac arrhythmias: understanding and prevention of SUDEP



Marije van der Lende

Epilepsy and cardiac arrhythmias: understanding and prevention of SUDEP

Marije van der Lende

ISBN: 978-94-6380-521-6

Cover design: Afbeelding 'Heart Brain' © Gary Grayson, opmaak Marije van der Lende
Layout and printed by: Proefschriftmaken.nl

Epilepsy and cardiac arrhythmias: understanding and prevention of SUDEP

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 16 oktober 2019
klokke 15:00 uur

door
Marije van der Lende

geboren te Delft
in 1987

Promotor:
Prof. dr. J.G. van Dijk

Co-promotor:
Dr. R.D. Thijs

Promotiecommissie:
Prof. dr. K. Zeppenfeld
Prof. J.W. Sander, MD, PhD, FRCP, University College London
Dr. R. Surges, University of Bonn Medical Center

Contents

CHAPTER 1

General introduction and aims of the thesis

Sudden unexpected death in epilepsy (SUDEP) is the most tragic consequence of epilepsy. It is more common in younger adults and it is the most frequent cause of direct epilepsy-related premature mortality. As most victims of SUDEP are of young age, of all neurological diseases, second only to stroke, most productive life years are lost due to SUDEP.[1] The cause of SUDEP remains unknown. Multiple risk factors have yet been uncovered, but effective preventative strategies are still lacking.

Definition

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in people with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus. The most important criterium for the condition is postmortem examination, to exclude other causes of sudden death such as myocardial infarction or pulmonary embolism. When postmortem examination has not been done, the death is classified as probable SUDEP.[2] 'Possible SUDEP' is used when there is a competitive cause of death, for example when someone aspirated during a seizure. The term 'SUDEP plus' refers to the situation when another preexistent condition might have contributed to the death, but no primary cause of death due to this condition is found in postmortem examination (for example coronary atherosclerosis without signs of an infarction).[2]

Epidemiology

People with epilepsy have a 2-3 time higher risk of early death compared to the general population.[3] The risk of sudden death in young people with epilepsy is even 24 times higher.[4] This is predominantly due to SUDEP. More people with epilepsy die from SUDEP than, for example, from status epilepticus or injuries.[3] SUDEP incidence differs depending on the study population. In the general population, incidence numbers of 0,1 – 0,4 per 1000 person years have been reported.[5, 6] Incidence, however, increases with epilepsy severity. In cohorts of people with epilepsy in tertiary referral centers, incidence rises to 1,2 - 5,9 per 1000 person years. For epilepsy surgery candidates, incidence may be as high as 6,3 – 9,3 per 1000 person years.[5, 6] A recent meta-analysis showed an average SUDEP risk of 0,22 per 1000 person years for children and 1,2 per 1000 person years for adults.[7] As epilepsy is a chronic condition, SUDEP risk can amount to 12% in children with refractory epilepsy after 40 years follow-up.[8] Most studies reported a peak in the SUDEP incidence for those aged between 15 and 30 years,[4, 8-10] yet a recent survey demonstrated similar incidences across different age groups.[11] The SUDEP incidence in the Netherlands is yet unknown, but in the United Kingdom there are 500 – 1000 SUDEP cases every year.[12]

Circumstances

SUDEP usually occurs at night (58%) and without any witnesses (86%).[13] Victims are mostly found dead in or near their bed, often with signs of a seizure like a tongue bite and urine incontinence.[14] Most victims are found in the prone position (73%).[15] The strong association

between SUDEP and sleep may be explained by the interaction with environmental factors prone position and the absence of a witness. The few available witness reports all describe victims having a convulsive seizure, followed by labored breathing and cyanosis.[16]

Risk factors

Case control studies have identified multiple SUDEP risk factors. Having frequent tonic clonic seizures is the most important risk factor.[17] The more tonic clonic seizures a person has, the higher the SUDEP risk: compared to people without tonic clonic seizures, people with 1-2 tonic clonic seizures have a 5-time higher risk and people with more than three have a 15-time higher risk of SUDEP.[18] Having nocturnal seizures seems to be an independent risk factor, but this needs confirmation.[13] SUDEP risk seems lower for people with nocturnal supervision.[19] Other (weaker) risk factors include: having an intellectual disability, usage of lamotrigine in people with generalized epilepsies,[18] usage of multiple anti-epileptic drugs,[18] usage of anxiolytic drugs, using no anti-epileptic drugs (most likely a delay in diagnosis or dying from SUDEP after one of the first seizures), having extratemporal epilepsy and being male.[7] Using multiple antiepileptic drugs is likely a marker of epilepsy severity.[7, 17] Usage of lamotrigine in generalized genetic epilepsy is also most likely an indirect effect as this drug is often chosen in women because of its minimal teratogen effects, while it not always as effective as valproic acid.[20]

Pathophysiology

SUDEP pathophysiology is poorly understood. VideoEEG recordings of SUDEP victims have helped to increase our understanding of SUDEP pathophysiology, yet it should be kept in mind that these data were obtained in a highly selected population of candidates for epilepsy surgery. The acclaimed MORTEMUS-study analyzed videoEEG recordings of eleven people dying of SUDEP. A similar pattern was seen in all victims: all had a tonic clonic seizure with focal onset, usually starting from sleep. After the seizure ended the EEG turned flat (a phenomenon called 'postictal generalized EEG suppression').[21] Within three minutes this was followed by transient apneas, bradycardias and asystoles with a terminal asystole within 11 minutes.[22] This typical pattern of faltering heartbeat and breathing has been reproduced in animal studies of KCNA1-knock-out mice:[23] seizures provoked by topical application of 4aminopyridine to the cortex led to a slow, negative direct current potential shift in the dorsal medulla, which controls cardiorespiratory function, causing EEG suppression, apnea, bradycardia, and asystole, similar to the events seen in SUDEP.

Asystoles are part of SUDEP pathophysiology. Little is yet known about prevalence of asystole in the ictal and postictal phase. Retrospective studies indicated a low prevalence rate of ictal asystole: 0,27% of people with epilepsy admitted for videoEEG recordings.[24] Higher prevalence rates have been reported in long-term studies using implantable loop recorders. One study reported after two-year follow-up, that four out of 19 people

with epilepsy (21%) had bradycardias or periods of asystole with subsequent permanent pacemaker insertion,[25] while another study reported asystole in only one out of 19 people and no pacemaker insertions.[26] The yield of long term ECG recordings in a large cohort of people with refractory epilepsy still needs to be determined.

Preventing SUDEP

There is a direct link between the frequency of tonic clonic seizures and SUDEP risk.[18] Reducing the number of tonic clonic seizures, therefore, is the best way to lower SUDEP risk. A meta-analysis of drug trials showed SUDEP incidence was over seven times higher in the placebo group compared to the treatment group.[27]

Effective treatments to prevent SUDEP are currently unavailable.[28] The strong association with sleep and lack of a witness suggests that nocturnal supervision could play preventive role.[13, 29] One case control study demonstrated that SUDEP cases less often had a roommate or a listening device compared to the controls.[19] All 14 deaths in a cohort study on children with severe epilepsy and learning disabilities, occurred while the students were not under the supervision of the school.[30] To confirm nocturnal supervision can reduce SUDEP risk, further research is needed.

Aims and outline of this thesis

This thesis focuses on two aspects of SUDEP: (1) the role of arrhythmias to understand its pathophysiology and (2) the role of supervision to potentially improve preventative measures. In chapter two, I will focus on all possible mechanisms of association between epilepsy and cardiovascular conditions, including causal associations, shared risk factors and those resulting from epilepsy or its treatment. In chapter three, I will present a systematic literature search to determine the full spectrum of all cardiac arrhythmias to occur during or after epileptic seizures. I will pay special attention to the timing of arrhythmias (ictal versus postictal) as this seems crucial to understand its relation to SUDEP. In chapter four, I will address the conflicting reports on long-term ECG recordings in epilepsy and the potential of postictal arrhythmias as a SUDEP biomarker by reporting a large-scale multi-centre trial.

To evaluate the potentially protective role of nocturnal supervision I will present the results of an audit at a residential department in chapter five. In this study I assess the impact of continuous video monitoring on the detection of nocturnal seizures. In chapter 6 I will present a SUDEP case control study. In this study I ascertain the effects of nocturnal seizures and nocturnal supervision on SUDEP risk in a cohort of people with epilepsy and an intellectual disability living in residential care.

Chapter 7 and 8 provide a summary of this thesis and discuss future perspectives in English and Dutch.

References

1. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia 2014;55:1479-1485.
2. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;53:227-233.
3. Hitiris N, Mohanraj R, Norrie J, Brodie MJ. Mortality in epilepsy. Epilepsy & behavior : E&B 2007;10:363-376.
4. Ficker DM, So EL, Shen WK, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology 1998;51:1270-1274.
5. Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. Nature reviews Neurology 2009;5:492-504.
6. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. Lancet (London, England) 2011;378:2028-2038.
7. 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.
8. Sillanpaa M, Shinnar S. Long-term mortality in childhood-onset epilepsy. The New England journal of medicine 2010;363:2522-2529.
9. Tellez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. Epilepsy research 2005;65:101-115.
10. Walczak TS, Leppik IE, D'Amelio M, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 2001;56:519-525.
11. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study. Neurology 2017;89:170-177.
12. Hanna NJ, Black M, Sander JW, et al. National Sentinel Clinical Audit of Epilepsy-Related Death. Londen: The Stationery Office 2002.
13. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. Epilepsia 2012;53:253-257.
14. Nashef L, Garner S, Sander JW, Fish DR, Shorvon SD. Circumstances of death in sudden death in epilepsy: interviews of bereaved relatives. Journal of neurology, neurosurgery, and psychiatry 1998;64:349-352.
15. Liebenthal JA, Wu S, Rose S, Ebersole JS, Tao JX. Association of prone position with sudden unexpected death in epilepsy. Neurology 2015;84:703-709.
16. Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. Journal of neurology, neurosurgery, and psychiatry 2000;68:211-213.
17. Hesdorffer DC, Tomson T, Benn E, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia 2012;53:249-252.

18. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52:1150-1159.
19. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005;64:1131-1133.
20. Tomson T, Hirsch LJ, Friedman D, et al. Sudden unexpected death in epilepsy in lamotrigine randomized-controlled trials. Epilepsia 2013;54:135-140.
21. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Annals of neurology 2010;68:787-796.
22. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. The Lancet Neurology 2013;12:966-977.
23. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. Science translational medicine 2015;7:282ra246.
24. Schuele SU, Bermeo AC, Alexopoulos AV, et al. Video-electrographic and clinical features in patients with ictal asystole. Neurology 2007;69:434-441.
25. Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. Lancet (London, England) 2004;364:2212-2219.
26. Nei M, Sperling MR, Mintzer S, Ho RT. Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. Epilepsia 2012;53:e137-140.
27. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. The Lancet Neurology 2011;10:961-968.
28. Maguire MJ, Jackson CF, Marson AG, Nolan SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). The Cochrane database of systematic reviews 2016;7:CD011792.
29. Ali A, Wu S, Issa NP, et al. Association of sleep with sudden unexpected death in epilepsy. Epilepsy & behavior : E&B 2017;76:1-6.
30. Nashef L, Fish DR, Garner S, Sander JW, Shorvon SD. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. Epilepsia 1995;36:1187-1194.

CHAPTER 2

2

The heart of epilepsy: current views and future concepts

S. Shmuely[1,2] | M. van der Lende[1,3] | R.J. Lamberts[1] | J.W. Sander[1,2] | R.D. Thijs[1,2,3]

[1] Stichting Epilepsie Instellingen Nederland - SEIN, Heemstede, the Netherlands

[2] NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG and Epilepsy Society, Bucks SL9 0RJ, UK

[3] Department of Neurology, LUMC Leiden University Medical Centre, Leiden, the Netherlands

Seizure. 2017 Jan;44:176-183.

Abstract

Cardiovascular (CV) comorbidities are common in people with epilepsy. Several mechanisms explain why these conditions tend to co-exist including causal associations, shared risk factors and those resulting from epilepsy or its treatment

Various arrhythmias occurring during and after seizures have been described. Ictal asystole is the most common cause. The converse phenomenon, arrhythmias causing seizures, appears extremely rare and has only been reported in children following cardioinihibitory syncope. Arrhythmias in epilepsy may not only result from seizure activity but also from a shared genetic susceptibility. Various cardiac and epilepsy genes could be implicated but firm evidence is still lacking. Several antiepileptic drugs (AEDs) triggering conduction abnormalities can also explain the co-existence of arrhythmias in epilepsy.

Epidemiological studies have consistently shown that people with epilepsy have a higher prevalence of structural cardiac disease and a poorer CV risk profile than those without epilepsy. Shared CV risk factors, genetics and etiological factors can account for a significant part of the relationship between epilepsy and structural cardiac disease. Seizure activity may cause transient myocardial ischaemia and the Takotsubo syndrome. Additionally, certain AEDs may themselves negatively affect CV risk profile in epilepsy.

Here we discuss the fascinating borderland of epilepsy and cardiovascular conditions. The review focuses on epidemiology, clinical presentations and possible mechanisms for shared pathophysiology. It concludes with a discussion of future developments and a call for validated screening instruments and guidelines aiding the early identification and treatment of CV comorbidity in epilepsy.

Introduction

Well over 100 years ago, the occurrence of asystole during the course of an epileptic seizure was described: "He uttered a cry and was seen to be rubbing his hands together. His pulse was immediately examined for but was not palpable".[1] Since then numerous associations between epilepsy and CV conditions have been identified, including this classical example of ictal asystole.

Co-existing conditions form an important part of the overall burden of epilepsy.[2-5] Several mechanisms of association between epilepsy and comorbid conditions have been described: associations can be explained by cause or effect, a shared risk factor may cause both conditions, or the mechanism of the association is unknown or spurious (i.e. coincidental) (Figure 1).[3,5]

This review serves to discuss the fascinating borderland between epileptology and cardiology and focuses on the major developments over the last 25 years and on future developments. We use the comorbidity framework (Figure 1)[3] to review all cardiac conditions known, and alleged, to be linked to epilepsy. Associations with cardiac arrhythmias are discussed first, followed by an overview of all structural cardiac conditions related to epilepsy.

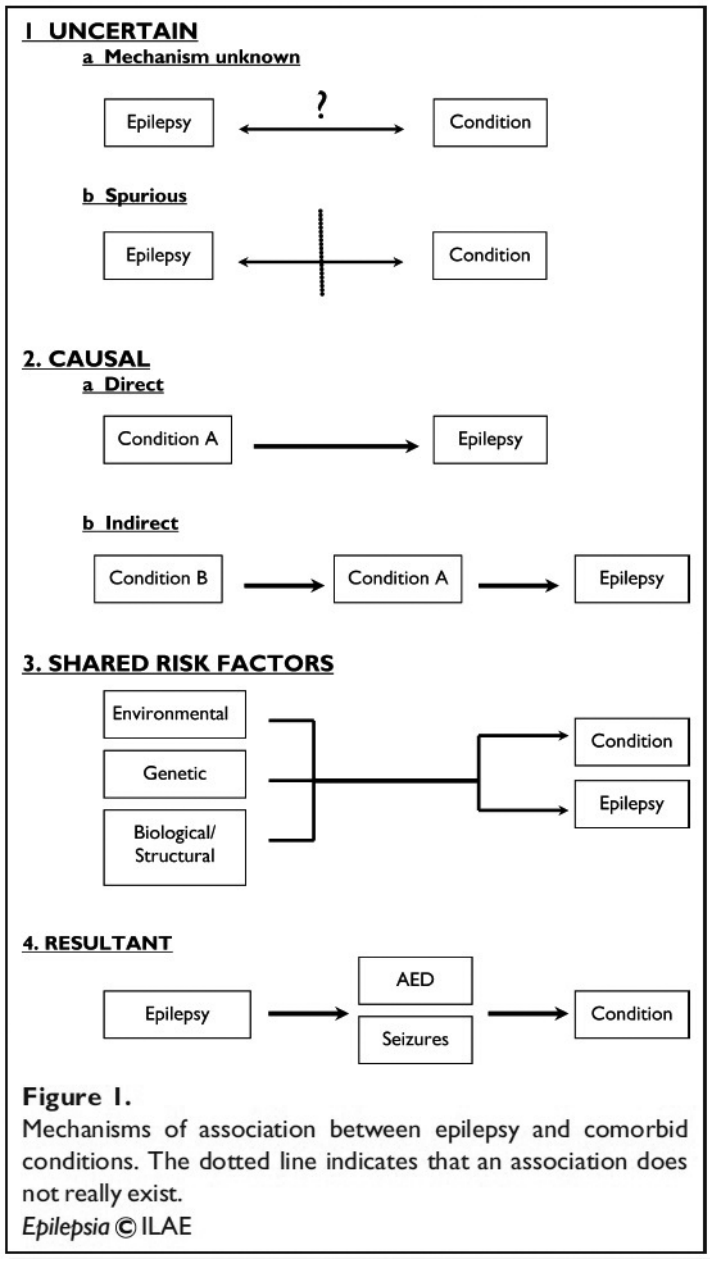


Figure 1. Mechanisms of association between epilepsy and comorbid conditions.

Figure originates from Gaitatzis et al., 2012.[3]

Epilepsy and cardiac arrhythmias

Various arrhythmias have been described, occurring during (ictal) or after (postictal) seizures. Sinus tachycardia is the most common ictal pattern, seen in up to 80% of all seizures[6] and in 82% of people with epilepsy,[7] but usually without symptoms. The most frequent clinically relevant arrhythmia is ictal asystole, occurring in 0.318% (95% CI 0.316% to 0.320%) of people with refractory focal epilepsy admitted for video-EEG.[8] Ictal asystole, bradycardia and AV block predominantly occur in people with temporal lobe epilepsy (Table 1).[8] Clinically, ictal asystole is characterised by sudden loss of tone during a dyscognitive seizure.[9] The circulatory pattern resembles vasovagal syncope with a transient, progressive and self-limiting slowing of the heart rate and decrease of blood pressure.[9-11] For many years, ictal asystole was thought to be a possible mechanism underlying sudden unexpected death in epilepsy (SUDEP). This appears to be unlikely: all but one reported case so far of ictal asystole were self-limiting.[8] In this one case successful resuscitation was started after 44 seconds of asystole and the event was classified as near-SUDEP.[12] The longest ictal asystole reported so far, however, lasted 96 seconds and appeared self-limiting.[13] Whether an event is classified as near-SUDEP or not will depend on interventions of medical personnel: prompt resuscitation in response to ictal asystole will likely lead to more classified as near-SUDEP cases. While there are no reports of fatal ictal asystole, it remains debatable whether ictal asystole can cause SUDEP.

The precise mechanism of ictal asystole is unknown. It may result from epileptic activity directly stimulating the central autonomic networks.[6, 14] For example, focal stimulation of parts of the limbic system (i.e. amygdala, cingulate gyrus) may provoke asystole.[6, 15-17] Alternatively, seizure-induced fear and catecholamine release[18] may evoke a vasovagal response causing cardioinhibition and vasodilation.[19]

Ictal asystole is assumed to be self-limiting, but may cause falls and injuries due to seizure-induced syncope.[20] Proper trials are lacking but retrospective studies suggest that improving seizure control may prevent ictal asystole.[21-23] It also seems advisable to withdraw negative inotropic drugs and to consider the implantation of a loop recorder to monitor possible future events in individuals in whom ictal asystole has been noted. If the asystolic episodes persist, cardiac pacemaker implantation should be considered to reduce the risk of trauma.[20, 21, 23, 24]

In contrast to ictal asystole, postictal asystole is less common, associated with convulsive rather than focal (temporal lobe) seizures and has a higher fatality rate: 7 of 13 reported postictal asystole cases died from SUDEP.[8] All fatal cases had a convulsive seizure with immediate postictal generalised EEG suppression and a stuttering course of transient apnoea and asystole resulting in a terminal apnoea followed by a terminal asystole.[25]

The mechanism underlying this sequence of postictal EEG suppression, apnoea, and terminal asystole has not yet been elucidated. Excessive inhibition causing brainstem depression might play a role.[26] Recent work in two animal models (mice carrying mutations in the *KCNA1* gene or the *SCN1A* gene) demonstrated that seizures initiated by direct cortical stimulation may evoke a spreading depression causing brain stem inhibition and cardiorespiratory collapse.[27]

Another rare (post)ictal arrhythmia is ventricular tachycardia/ventricular fibrillation (VT/VF). So far three cases of postictal VT/VF leading to (near) SUDEP have been reported.[8] All VT/VF occurred directly following a convulsive seizure. No cardiac lesions were found in the case reports. There may be a publication bias, however, as cases with seizure-triggered VT/VF and cardiac lesions may not qualify as SUDEP and thus may be less likely to be reported. The mechanism of seizure-induced VT/VF is unclear. Convulsive seizures may exert proarrhythmogenic effects by triggering the sympathetic nervous system, as reflected by the peak in catecholamines and electrodermal activity.[18, 28] At the same time, convulsive seizures may increase cardiac oxygen deprivation by inducing sinus tachycardia[7] and respiratory impairment causing hypoxemia.[29] It has also been found that ECG-markers of sudden cardiac death such as QTc-lengthening and/or shortening, [30, 31] and T-wave alternans are more prevalent[23] during and after convulsive seizures. The various factors might interact as seizure-related cardiac repolarization abnormalities appeared more frequent in seizures with ictal hypoxemia compared to those without.[32]

Though seizure-induced VT/VF appears to be rare, a prospective community-based study of out-of-hospital cardiac arrests due to ECG-documented VT/VF showed that VT/VF risk in those with epilepsy was three times as high as the general population.[33] A further analysis of those cases with epilepsy and VT/VF showed that most were not seizure-related, but rather occurred in the context of either pre-existing heart disease or as the immediate result of an acute myocardial infarction.[34] Pre-existing heart disease was a stronger predictor for VT/VF in people with epilepsy than markers of epilepsy severity. In a minority of cases, however, VT/VF was unexplained and a diagnosis of (near) SUDEP was established. It thus appears that sudden cardiac arrest and SUDEP are partially overlapping disease entities.
The increased risk of non-seizure related VF/VT episodes in people epilepsy may be explained by high cardiovascular comorbidity.[3, 35] People with epilepsy may have a propensity for sudden cardiac death as reduced heart rate variability, a measure of cardiac sympathovagal balance that is also a risk marker of sudden cardiac death, progressively worsens over time in people with refractory, but not in those with well-controlled, epilepsy.[36] In addition, other markers of sudden cardiac death such as early repolarization pattern and QTc-prolongation are more frequently found in the interictal ECGs of people with epilepsy than in those without epilepsy.[37]

Seizure related arrhythmia	Reported in n cases	Associated seizure types	Reported in n cases	EEG seizure onset	Reported in n cases	SUDEP association
Ictal asystole	103	99% FDS 1% FAS	97	46% LT 31% RT 13% BT 10% Other	80	Unlikely
Postictal asystole	13	85% fbCS 15% FDS	13	20% LT 60% RT 20% Other	10	Likely, accompanied or preceded by PGES/apnea[25]
Ictal bradycardia	25	100% FDS	8	52% LT 38% RT 10% Other	21	Unlikely
Ictal AV Block	11	90% FDS 10% FAS	10	73% LT 18% BT 10% Other	11	Unlikely
Postictal AV Block	2	100% fbCS	2	100% RT	1	Unlikely
Atrial Fibrillation	13	46% GTCS 46% fbCS 8% FDS	13	33% LT 33% Gen 33% Non loc	3	Unlikely
(Post)ictal ventricular fibrillation	3	100% GTCS	3	Insufficient data	0	Probable, but in a minority of cases

Table 1. Reported (post)ictal cardiac arrhythmias.

FDS focal dyscognitive seizure; FAS focal autonomic seizure; fbCS focal seizure evolving to bilateral convulsive seizure; GTCS generalised tonic clonic seizure; LT left temporal; RT right temporal; BT bitemporal; Gen generalised; Non loc non-localising; PGES postictal generalized EEG suppression; *in people with refractory focal epilepsy admitted for a vEEG recording. For more details see van der Lende et al., 2016.[8]

Another mechanism explaining the association between arrhythmias and epilepsy is a shared genetic risk factor. A rapidly increasing number of genes potentially linking epilepsy to cardiac arrhythmias has been identified. Here we discuss some relevant examples; starting with the genes predominantly known for their cardiac functions and then the 'epilepsy genes'.

Several genetic ion channel mutations are thought to be expressed in the brain as well as in the heart, and might thus cause seizures and cardiac arrhythmias. The first reported genetic link between epilepsy and cardiac arrhythmias was the discovery of cardiac sodium channel gene *SCN5A* in the brain.[38] Subsequently, more pathogenic variants in the long QT (LQT) gene family (i.e. *KCNQ1*, *KCNH2* and *SCN5A*) were associated with

a "seizure phenotype" (e.g. self-reported diagnosis of epilepsy and AED use).[39-44] Mice models indicated that other, non-LQT, cardiac channelopathy genes including *RYR2* (associated with catecholaminergic polymorphic ventricular tachycardia),[45] and *HCN1-4*[46, 47] potentially predispose to epilepsy.

Several postmortem studies suggest that the LQT and non-LQT cardiac gene mutations are more common in SUDEP victims.[48-50] As ictal recordings are lacking, it remains questionable whether the fatal events were caused by arrhythmias. The same applies to the identification of 'epilepsy genes' in the post-mortem cohorts.[48, 49] These mutations could be markers explaining epilepsy severity or a genetically mediated liability to fatal seizures. In certain epilepsy syndromes, SUDEP risk seems particularly high.

The most recognized example is the Dravet syndrome (DS), a severe epilepsy syndrome with high premature mortality, caused by SCN1A mutation.[51] In mutant *SCN1A* knock-out mice, postictal bradycardia and seizure-triggered ventricular fibrillation were recorded before a death resembling SUDEP.[52, 53] In DS subjects, markers associated with the risk of sudden cardiac death (decreased HRV and increased QT-dispersion) have been found.[54-55] Ictal proof is, however, lacking and is the subject of an ongoing study (ClinicalTrials.gov Identifier: NCT02415686).

Other less well studied examples of 'epilepsy genes' possibly mediating SUDEP risk include *KCNA1* and *SCN8A*. *KCNA1* is expressed in the vagal nerve as well as in the brain, and is associated with seizures, cardiac arrhythmias, vagal hyperexcitability and premature death in *KCNA1* null mice.[56] Mutations in this gene were found in a SUDEP case with epileptic encephalopathy and suspected cardiac arrhythmias.[57]

A novel pathogenic SCN8A mutation was identified through whole-genome sequencing in a family affected by epileptic encephalopathy and SUDEP.[58] Before then, SCN8A mutations had only been linked to epilepsy in mice.[59] The SCN8A gene encodes a sodium channel that is expressed in heart and brain of mice and rats, and plays a role in excitation-contraction coupling, action potential propagation and pacemaking.[60, 61]

We previously discussed how seizures may cause arrhythmias. Whether the converse phenomenon exists is a subject of controversy. The major complication is the fact that syncopal events are easily mistaken for epilepsy. Misdiagnosis of epilepsy is common, with reported rates of false positives of up to 71%, and syncope is the most misdiagnosed condition. Rates of misdiagnosis of epilepsy vary from 23% in a community-based study of people with a primary diagnosis of epilepsy,[62] to 42% in a group of people with seemingly refractory epilepsy.[63] Which is understandable as various symptoms and signs are seen in both conditions.[11, 63-65] Notably, jerking movements or signs indicative of cerebral standstill

(complete flattening of the EEG) such as roving eye movements or stertorous breathing[11] are often interpreted as signs specific to epilepsy. Consequently, most seemingly overlapping presentations turn out not to be an isolated phenomenon of either syncope or epilepsy, if a proper investigation is performed (e.g. ictal recording of video, heart rate, blood pressure and EEG). Two large scale surveys of up to 2000 tilt-table tests failed to identify any adult case with syncopal-induced seizures.[66, 67] In children, however, a few cases have been reported with a cardioinhibitory reflex syncope followed by video-EEG documented clonic seizures.[68-70] The reason why this phenomenon only appears to affect children is unknown. It may be that the seizure threshold is lower in children (paralleling febrile seizures that also peak in childhood). Alternatively, the depth of cerebral anoxia may be more profound in children as reflected by prolonged asystolic spells. For clinical management it is important to stress that syncope-induced seizures are extremely rare and probably only affect children. The diagnosis requires an ictal video-EEG recording.

Several AEDs, particularly those with sodium blocking properties are known to trigger conduction abnormalities or arrhythmias.[71] Atrioventricular (AV) conduction is the most frequent reported complication. ST changes, Brugada-like patterns, atrial fibrillation and QTc prolongation have also been reported but the association with AED treatment is less well established.[72-86] Most clinically relevant arrhythmias were related to AED overdose. Carbamazepine is, however, known to cause AV conduction blocks at low levels; this is almost exclusively reported in elderly women.[77, 79, 87] Rapid administration of phenytoin may also cause sinus arrest and hypotension; elderly people and those with pre-existing heart disease seem most vulnerable to these adverse effects. IV administration should, therefore, be undertaken slowly, with continuous cardiac monitoring.[76, 83, 86, 88] The above-mentioned AED effects do not seem to play a role in ictal arrhythmias. Nevertheless, it is important to take these effects into consideration in the selection of an AED and to monitor adverse effects closely especially in elderly people and those with cardiovascular comorbidities (Table 2).

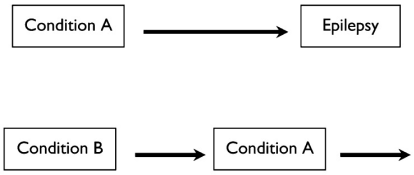
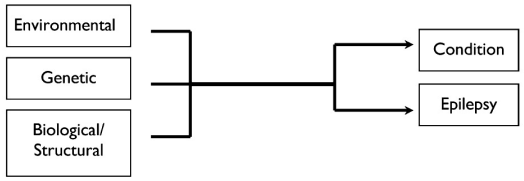
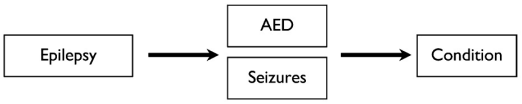
Mechanisms of association	Conditions
Causal 	Arrhythmias → Seizures
Shared risk factor 	Genetics → Epilepsy and arrhythmias - Important 'heart genes': *KCNQ1, KCNH2, SCN5A, RYR2* - Important 'epilepsy genes': *SCN1A, KCNA1, SCN8A*
Resultant 	AED → Arrhythmias - Particularly carbamazepine, phenytoin and lacosamide Seizures → Arrhythmias - Ictal: tachycardia, asystole, bradycardia and AV block. - Postictal: asystole, AV block, atrial flutter or fibrillation and ventricular fibrillation.

Table 2. Putative mechanisms of associations between epilepsy and cardiac arrhythmias.

HRV heart rate variability; VT ventricular tachycardia; VF ventricular fibrillation; AED antiepileptic drugs.

Epilepsy and structural cardiac conditions

Epidemiological studies have consistently shown that people with epilepsy have a higher prevalence of structural cardiac disease than those without epilepsy.[4, 5, 89-92] Cardiovascular disease seems to be a significant contributor to the increased mortality in people with epilepsy, compared with the general population.[93-95]

Shared cardiovascular risk factors can account for the relationship between epilepsy and heart disease, in addition to shared genetics and etiological factors. People with a history of epilepsy are more likely to be obese, physically inactive, and current smokers[90] and have a worse cardiovascular risk profile (i.e. hypertension, hypercholesterolemia, diabetes mellitus, stroke/TIA) than the general population.[35, 90, 96, 97] Unsurprisingly, people with epilepsy have higher rates of fatal and nonfatal cardio- and cerebrovascular disease than controls (mortality ratios up to 5.3 and morbidity ratio up to 7).[35, 98, 99] The presence of cardiovascular disease (e.g. congestive heart failure and cardiac arrhythmias) was also associated with higher mortality risk in people with epilepsy.[100]

Epilepsy treatment can also contribute to a poorer cardiovascular risk profile in epilepsy. Use of the enzyme-inducing AEDs phenytoin or carbamazepine may lead to elevated serological vascular risk markers (e.g. total cholesterol, LDL, homocysteine), and, thus, result in accelerated atherosclerosis.[101-104] Certain AEDs (e.g. valproic acid, carbamazepine) are also known to cause weight gain and increase the risk of developing non-alcoholic fatty liver disease and metabolic syndrome, leading to further deterioration of the cardiovascular risk profile.[102]

The co-occurrence of epilepsy and (congenital) heart disease, often accompanied by intellectual disability, may result from a multiple malformation syndrome: genetic defects may affect the development of both heart and brain, or abnormal cardiovascular function may lead to poor (intrauterine) brain growth.[105]

CV disease can sometimes (indirectly) cause epilepsy through a predisposition to stroke.[106, 107] Stroke is a common risk factor for epilepsy and accounts for about a third of newly diagnosed seizures in people over the age of 60 years.[107, 110] In particular, those with ischemic events with cortical involvement, cerebral hemorrhage (i.e. primary hemorrhage or hemorrhagic transformation of ischemic stroke) and early post-stroke seizures, have an increased risk of post-stroke epilepsy.[107]

Seizure activity may not only induce arrhythmias but may also lead to structural cardiac changes.[71, 111-113] Epileptic seizures have been reported to provoke cardiac ischaemia via both acute and chronic effects on the heart (e.g. impaired heart rate variability, cardiac fibrosis, ST-segment depression and increased heart rate).[71, 114] Transient myocardial ischaemia as indicated by ST-segment depression, was reported in a small-scale study in 40% of all 15 seizures.[114] Another study, however, failed to demonstrate troponin increases, suggesting that the reported ST changes do not usually cause myocardial damage.[115]

Seizures are the second most frequent CNS condition known to induce the cardiomyopathy known as Takotsubo syndrome (TTS).[116] TTS mimics myocardial infarction clinically,

electrocardiographically and chemically.[117] It is characterized by acute onset of chest pain and dyspnoea, sometimes concomitant with palpitations, tiredness, oedema, fever, syncope, anxiety, nausea or vomiting.[116] The seizure type that most frequently causes TTS is the generalized tonic-clonic seizure.[118, 119] Seizures most likely trigger TTS by the stress-induced release of catecholamines.[120] This abundant catecholamine release may be a contributing factor in fatal status epilepticus.[121] A relationship between TTS and SUDEP, however, does not appear likely.[116]

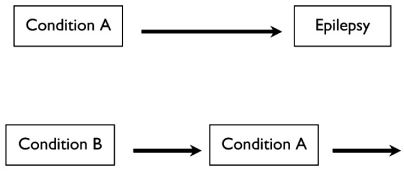
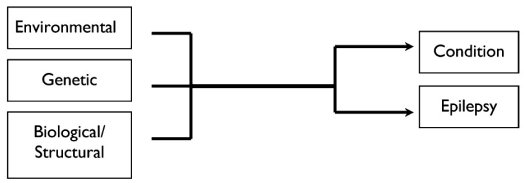
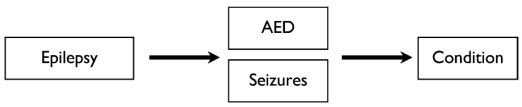
Mechanisms of association	Conditions
Causal 	Cardiac conditions, e.g. embolism and congenital cardiac abnormalities → Stroke
Shared risk factor 	Genetic → Malformation of cortical and cardiac development Shared cardiovascular risk factors → Stroke
Resultant 	AED → Arteriosclerosis AED → Weight gain, non-alcoholic fatty liver disease and metabolic syndrome Seizures → Transient myocardial ischaemia Seizures → Seizure-triggered Takotsubo syndrome (TTS)

Table 3. Putative mechanisms of associations between epilepsy and structural cardiac disease.

AED antiepileptic drugs; TTS, Takotsubo syndrome.

Future concepts

Significant progress has been made since the publication of Russel's case history: the complex interrelationship between epilepsy and cardiac conditions has been explored widely and this review aimed to capture all major discoveries made in this field (Table 2 and 3). Many discoveries of coexisting conditions were made by serendipity, and underlying mechanisms are yet to be uncovered. Treatment regimens are consequently often speculative and lack a personalized approach involving all comorbid conditions. As comorbidity gains recognition we now need to become better at noticing these symptom patterns. Today a substantial gap still remains between the specialties, but as we are now becoming aware of all overlapping syndromes epileptologists will increasingly need to improve their cardiac skills. Pattern recognition can be fostered by incorporating validated screening instruments and guidelines, aiding the early identification and treatment of cardiovascular comorbidity in epilepsy. Concomitantly, a fundamental change in the way clinicians think of epilepsy is crucial.

Epilepsy will soon be viewed as a collection of individual disorders that share a phenotype of an abnormal tendency for unprovoked epileptic seizures. The number of rare epilepsy syndromes with cardiac phenotypes will increase substantially. Epilepsy will be seen as a symptom-complex, and all comorbidities, even the most inconspicuous, should be considered as part of the stratification and phenotyping in people with epilepsy. Cardiovascular comorbidities will provide insight into common mechanisms for epilepsy and give a window into common genetic predispositions. They may also provide important diagnostic clues. Channelopathies, for example, are increasingly identified in people with epilepsy. Genetic factors may explain both the epilepsy and the comorbid disorder(s), even in people with sporadic epilepsies.[122] Genome wide scanning will be widely available and drive the paradigm shift in epilepsy. Certain genes might be identified as contributing to SUDEP,[48, 49] potentially allowing the development of individualised risk prevention strategies. Another major contributor to early identification of overlapping syndromes will be the development of new non-invasive tools to record heart function at home. The miniaturisation of sensors will favour long-term home-based recordings thus aiding the early identification of cardiac arrhythmias.

Advances in seizure detection will likely take off. ECG alone will help to detect a wide variety of seizures but lacks specificity. Combining ECG with other modalities including an accelerometry and electrodermal activity will likely improve accuracy and facilitate the widespread use of seizure detection devices in those with refractory epilepsy.[123, 124]

Another unmet need relates to the treatment of epilepsy: many AEDs have proarrhythmogenic and arteriosclerogenic effects. Though non-pharmacological options exist, drug therapy is still the mainstay of epilepsy treatment and other options are usually

only explored after AEDs have failed to successfully control seizures.[125] Many new AEDs have been launched in the last two decades, but have failed to improve the burden of side effects or substantially change prognosis for seizure control.[126, 127] With improved understanding of epileptogenesis, epigenetic determinants and pharmacogenomics comes the hope for better, disease-modifying or even curative pharmacological and non-pharmacological treatment strategies. Until then, comorbidity should be considered when prescribing AEDs.

The incorporation of neurocardiology into the paroxysmal spectrum will require a critical review of the epilepsy services. We need to validate new instruments to screen for cardiovascular conditions. Modern non-invasive long-term ECG devices may help screen for cardiac conditions and a cardiologist should review any relevant abnormalities. In cases where there is a relevant family history or abnormal ECG findings, a specialist cardiac assessment should be done. Identification and adequate treatment of cardiovascular disorders in epilepsy should therefore be an important part of epilepsy management.

Particular attention should be given to modifiable risk factors such as smoking, obesity, sedentary lifestyle, high cholesterol and hypertension. Physicians should screen for these risk factors in people with epilepsy, provide general health information and if necessary adjust AED treatment. Further studies are needed to improve risk profiling, thus allowing for screening in high risk individuals (with, for example, implantable loop recorders) and targeted interventions (e.g. defibrillators).

References

1. Russell AE. Cessation of the pulse during the onset of epileptic fits, with remarks on the mechanism of fits. Lancet 1906;168:152–4.
2. Forsgren L. Prevalence of epilepsy in adults in northern Sweden. Epilepsia. 1992;33(3):450-8. Epub 1992/05/01.
3. Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: a weighty but often unrecognized burden. Epilepsia. 2012;53(8):1282-93. Epub 2012/06/14.
4. Kadima N KR, Zack M, Helmers S. Comorbidity in adults with epilepsy--United States, 2010. MMWR Morb Mortal Wkly Rep. 2013;62(43):849-53. Epub 2013/11/01.
5. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. Lancet Neurol. 2016;15(1):106-15. Epub 2015/11/10.
6. Sevcencu C, Struijk JJ. Autonomic alterations and cardiac changes in epilepsy. Epilepsia. 2010;51(5):725-37. Epub 2010/01/14.
7. Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure. 2014;23(7):496-505. Epub 2014/04/05.
8. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. J Neurol Neurosurg Psychiatry. 2016;87(1):69-74. Epub 2015/06/04.
9. Schuele SU, Bermeo AC, Alexopoulos AV, Locatelli ER, Burgess RC, Dinner DS, et al. Video-electrographic and clinical features in patients with ictal asystole. Neurology. 2007;69(5):434-41. Epub 2007/08/01.
10. Tinuper P, Bisulli F, Cerullo A, Carcangiu R, Marini C, Pierangeli G, et al. Ictal bradycardia in partial epileptic seizures: Autonomic investigation in three cases and literature review. Brain. 2001;124(Pt 12):2361-71. Epub 2001/11/10.
11. van Dijk JG, Thijs RD, van Zwet E, Tannemaat MR, van Niekerk J, Benditt DG, et al. The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes. Brain. 2014;137(Pt 2):576-85. Epub 2013/12/18.
12. Lanz M, Oehl B, Brandt A, Schulze-Bonhage A. Seizure induced cardiac asystole in epilepsy patients undergoing long term video-EEG monitoring. Seizure. 2011;20(2):167-72. Epub 2010/12/25.
13. Chaila E BJ, Tirupathi S, Delanty N. Ictal bradycardia and asystole associated with intractable epilepsy: a case series. Br J Cardiol 2010;17:245–8.
14. Leung H, Kwan P, Elger CE. Finding the missing link between ictal bradyarrhythmia, ictal asystole, and sudden unexpected death in epilepsy. Epilepsy Behav. 2006;9(1):19-30. Epub 2006/07/01.
15. Altenmuller DM, Zehender M, Schulze-Bonhage A. High-grade atrioventricular block triggered by spontaneous and stimulation-induced epileptic activity in the left temporal lobe. Epilepsia. 2004;45(12):1640-4. Epub 2004/12/02.
16. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992;42(9):1727-32. Epub 1992/09/01.

17. Pool JL, Ransohoff J. Autonomic effects on stimulating rostral portion of cingulate gyri in man. J Neurophysiol. 1949;12(6):385-92. Epub 1949/11/01.
18. Simon RP, Aminoff MJ, Benowitz NL. Changes in plasma catecholamines after tonic-clonic seizures. Neurology. 1984;34(2):255-7. Epub 1984/02/01.
19. Nilsson D, Sutton R, Melander O, Fedorowski A. Spontaneous vs nitroglycerin-induced vasovagal reflex on head-up tilt: Are there neuroendocrine differences? Heart Rhythm. 2016;13(8):1674-8. Epub 2016/07/28.
20. Moseley BD, Ghearing GR, Munger TM, Britton JW. The treatment of ictal asystole with cardiac pacing. Epilepsia. 2011;52(4):e16-e9.
21. Bestawros M, Darbar D, Arain A, Abou-Khalil B, Plummer D, Dupont WD, et al. Ictal asystole and ictal syncope: insights into clinical management. Circ Arrhythm Electrophysiol. 2015;8(1):159-64. Epub 2014/11/14.
22. Kohno R, Abe H, Akamatsu N, Benditt DG. Long-Term Follow-Up of Ictal Asystole in Temporal Lobe Epilepsy: Is Permanent Pacemaker Therapy Needed? J Cardiovasc Electrophysiol. 2016;27(8):930-6. Epub 2016/05/14.
23. Strzelczyk A, Cenusa M, Bauer S, Hamer HM, Mothersill IW, Grunwald T, et al. Management and long-term outcome in patients presenting with ictal asystole or bradycardia. Epilepsia. 2011;52(6):1160-7.
24. Duplyakov D, Golovina G, Lyukshina N, Surkova E, Elger CE, Surges R. Syncope, seizure-induced bradycardia and asystole: two cases and review of clinical and pathophysiological features. Seizure. 2014;23(7):506-11. Epub 2014/04/01.
25. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol. 2013;12(10):966-77. Epub 2013/09/10.
26. Massey CA, Sowers LP, Dlouhy BJ, Richerson GB. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. Nat Rev Neurol. 2014;10(5):271-82. Epub 2014/04/23.
27. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. Sci Transl Med. 2015;7(282):282ra46. Epub 2015/04/10.
28. Poh MZ, Loddenkemper T, Swenson NC, Goyal S, Madsen JR, Picard RW. Continuous monitoring of electrodermal activity during epileptic seizures using a wearable sensor. Conf Proc IEEE Eng Med Biol Soc. 2010;2010:4415-8. Epub 2010/11/26.
29. Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. Brain. 2008;131(Pt 12):3239-45. Epub 2008/10/28.
30. Surges R, Adjei P, Kallis C, Erhuero J, Scott CA, Bell GS, et al. Pathologic cardiac repolarization in pharmacoresistant epilepsy and its potential role in sudden unexpected death in epilepsy: a case-control study. Epilepsia. 2010;51(2):233-42.
31. Surges R, Scott CA, Walker MC. Enhanced QT shortening and persistent tachycardia after generalized seizures. Neurology. 2010;74(5):421-6.

32. Seyal M, Pascual F, Lee CY, Li CS, Bateman LM. Seizure-related cardiac repolarization abnormalities are associated with ictal hypoxemia. Epilepsia. 2011;52(11):2105-11. Epub 2011/09/13.
33. Bardai A, Lamberts RJ, Blom MT, Spanjaart AM, Berdowski J, van der Staal SR, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. PLoS One. 2012;7(8):e42749.
34. Lamberts RJ, Blom MT, Wassenaar M, Bardai A, Leijten FS, de Haan GJ, et al. Sudden cardiac arrest in people with epilepsy in the community: Circumstances and risk factors. Neurology. 2015;85(3):212-8. Epub 2015/06/21.
35. Gaitatzis A, Carroll K, Majeed A, J WS. The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia. 2004;45(12):1613-22. Epub 2004/12/02.
36. Suorsa E, Korpelainen JT, Ansakorpi H, Huikuri HV, Suorsa V, Myllyla VV, et al. Heart rate dynamics in temporal lobe epilepsy-A long-term follow-up study. Epilepsy Res. 2011;93(1):80-3. Epub 2010/11/26.
37. Lamberts RJ, Blom MT, Novy J, Belluzzo M, Seldenrijk A, Penninx BW, et al. Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. J Neurol Neurosurg Psychiatry. 2015;86(3):309-13. Epub 2014/06/21.
38. Hartmann HA, Colom LV, Sutherland ML, Noebels JL. Selective localization of cardiac SCN5A sodium channels in limbic regions of rat brain. Nat Neurosci. 1999;2(7):593-5. Epub 1999/07/15.
39. Anderson JH, Bos JM, Cascino GD, Ackerman MJ. Prevalence and spectrum of electroencephalogram-identified epileptiform activity among patients with long QT syndrome. Heart Rhythm. 2014;11(1):53-7. Epub 2013/10/10.
40. Auerbach DS, McNitt S, Gross RA, Zareba W, Dirksen RT, Moss AJ. Genetic biomarkers for the risk of seizures in long QT syndrome. Neurology. 2016. Epub 2016/07/29.
41. Aurlien D, Leren TP, Tauboll E, Gjerstad L. New SCN5A mutation in a SUDEP victim with idiopathic epilepsy. Seizure. 2009;18(2):158-60. Epub 2008/08/30.
42. Heron SE, Hernandez M, Edwards C, Edkins E, Jansen FE, Scheffer IE, et al. Neonatal seizures and long QT syndrome: a cardiocerebral channelopathy? Epilepsia. 2010;51(2):293-6. Epub 2009/10/30.
43. Keller DI, Grenier J, Christe G, Dubouloz F, Osswald S, Brink M, et al. Characterization of novel KCNH2 mutations in type 2 long QT syndrome manifesting as seizures. Can J Cardiol. 2009;25(8):455-62. Epub 2009/08/12.
44. Partemi S, Cestele S, Pezzella M, Campuzano O, Paravidino R, Pascali VL, et al. Loss-of-function KCNH2 mutation in a family with long QT syndrome, epilepsy, and sudden death. Epilepsia. 2013;54(8):e112-6. Epub 2013/08/01.
45. Lehnart SE, Mongillo M, Bellinger A, Lindegger N, Chen BX, Hsueh W, et al. Leaky Ca2+ release channel/ryanodine receptor 2 causes seizures and sudden cardiac death in mice. J Clin Invest. 2008;118(6):2230-45. Epub 2008/05/17.
46. Benarroch EE. HCN channels: function and clinical implications. Neurology. 2013;80(3):304-10. Epub 2013/01/16.

47. Ludwig A, Budde T, Stieber J, Moosmang S, Wahl C, Holthoff K, et al. Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. EMBO J. 2003;22(2):216-24. Epub 2003/01/07.
48. Bagnall RD, Crompton DE, Petrovski S, Lam L, Cutmore C, Garry SI, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. Ann Neurol. 2016;79(4):522-34. Epub 2015/12/26.
49. Leu C, Balestrini S, Maher B, Hernandez-Hernandez L, Gormley P, Hamalainen E, et al. Genome-wide Polygenic Burden of Rare Deleterious Variants in Sudden Unexpected Death in Epilepsy. EBioMedicine. 2015;2(9):1063-70. Epub 2015/10/27.
50. Tu E, Waterhouse L, Duflou J, Bagnall RD, Semsarian C. Genetic analysis of hyperpolarization-activated cyclic nucleotide-gated cation channels in sudden unexpected death in epilepsy cases. Brain Pathol. 2011;21(6):692-8. Epub 2011/05/28.
51. Shmuely S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: a review. Epilepsy Behav. In Press.
52. Auerbach DS, Jones J, Clawson BC, Offord J, Lenk GM, Ogiwara I, et al. Altered cardiac electrophysiology and SUDEP in a model of Dravet syndrome. PLoS One. 2013;8(10):e77843. Epub 2013/10/25.
53. Kalume F, Westenbroek RE, Cheah CS, Yu FH, Oakley JC, Scheuer T, et al. Sudden unexpected death in a mouse model of Dravet syndrome. J Clin Invest. 2013;123(4):1798-808. Epub 2013/03/26.
54. Delogu AB, Spinelli A, Battaglia D, Dravet C, De Nisco A, Saracino A, et al. Electrical and autonomic cardiac function in patients with Dravet syndrome. Epilepsia. 2011;52 Suppl 2:55-8. Epub 2011/04/08.
55. Ergul Y, Ekici B, Tatli B, Nisli K, Ozmen M. QT and P wave dispersion and heart rate variability in patients with Dravet syndrome. Acta Neurol Belg. 2013;113(2):161-6. Epub 2012/10/16.
56. Glasscock E, Yoo JW, Chen TT, Klassen TL, Noebels JL. Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy. J Neurosci. 2010;30(15):5167-75. Epub 2010/04/16.
57. Klassen TL, Bomben VC, Patel A, Drabek J, Chen TT, Gu W, et al. High-resolution molecular genomic autopsy reveals complex sudden unexpected death in epilepsy risk profile. Epilepsia. 2014;55(2):e6-12. Epub 2014/01/01.
58. Veeramah KR, O'Brien JE, Meisler MH, Cheng X, Dib-Hajj SD, Waxman SG, et al. De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. Am J Hum Genet. 2012;90(3):502-10. Epub 2012/03/01.
59. Papale LA, Beyer B, Jones JM, Sharkey LM, Tufik S, Epstein M, et al. Heterozygous mutations of the voltage-gated sodium channel SCN8A are associated with spike-wave discharges and absence epilepsy in mice. Hum Mol Genet. 2009;18(9):1633-41. Epub 2009/03/04.

60. Du Y, Huang X, Wang T, Han K, Zhang J, Xi Y, et al. Downregulation of neuronal sodium channel subunits Nav1.1 and Nav1.6 in the sinoatrial node from volume-overloaded heart failure rat. Pflugers Arch. 2007;454(3):451-9. Epub 2007/02/03.
61. Noujaim SF, Kaur K, Milstein M, Jones JM, Furspan P, Jiang D, et al. A null mutation of the neuronal sodium channel NaV1.6 disrupts action potential propagation and excitation-contraction coupling in the mouse heart. FASEB J. 2012;26(1):63-72. Epub 2011/09/29.
62. Scheepers B, Clough P, Pickles C. The misdiagnosis of epilepsy: findings of a population study. Seizure. 1998;7(5):403-6. Epub 1998/11/10.
63. Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. J Am Coll Cardiol. 2000;36(1):181-4. Epub 2000/07/18.
64. Grubb BP, Gerard G, Roush K, Temesy-Armos P, Elliott L, Hahn H, et al. Differentiation of convulsive syncope and epilepsy with head-up tilt testing. Ann Intern Med. 1991;115(11):871-6. Epub 1991/12/01.
65. Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. Ann Neurol. 1994;36(2):233-7. Epub 1994/08/01.
66. Blad H, Lamberts RJ, van Dijk GJ, Thijs RD. Tilt-induced vasovagal syncope and psychogenic pseudosyncope: Overlapping clinical entities. Neurology. 2015;85(23):2006-10. Epub 2015/11/13.
67. Mathias CJ, Deguchi K, Schatz I. Observations on recurrent syncope and presyncope in 641 patients. Lancet. 2001;357(9253):348-53. Epub 2001/02/24.
68. Battaglia A, Guerrini R, Gastaut H. Epileptic seizures induced by syncopal attacks. Journal of Epilepsy 1989;2:137-45.
69. Horrocks IA, Nechay A, Stephenson JB, Zuberi SM. Anoxic-epileptic seizures: observational study of epileptic seizures induced by syncopes. Arch Dis Child. 2005;90(12):1283-7. Epub 2005/09/15.
70. Stephenson J, Breningstall G, Steer C, Kirkpatrick M, Horrocks I, Nechay A, et al. Anoxic-epileptic seizures: home video recordings of epileptic seizures induced by syncopes. Epileptic Disord. 2004;6(1):15-9. Epub 2004/04/13.
71. Schuele SU. Effects of seizures on cardiac function. Journal of Clinical Neurophysiology. 2009;26(5):302-8.
72. Al Aloul B, Adabag AS, Houghland MA, Tholakanahalli V. Brugada pattern electrocardiogram associated with supratherapeutic phenytoin levels and the risk of sudden death. Pacing Clin Electrophysiol. 2007;30(5):713-5. Epub 2007/04/28.
73. DeGiorgio CM. Atrial flutter/atrial fibrillation associated with lacosamide for partial seizures. Epilepsy and Behavior. 2010;18(3):322-4.
74. El-Menyar A, Khan M, Al Suwaidi J, Eljerjawy E, Asaad N. Oxcarbazepine-induced resistant ventricular fibrillation in an apparently healthy young man. Am J Emerg Med. 2011;29(6):693 e1-3. Epub 2010/08/17.
75. Feldman AE, Gidal BE. QTc prolongation by antiepileptic drugs and the risk of torsade de pointes in patients with epilepsy. Epilepsy Behav. 2013;26(3):421-6. Epub 2012/12/12.

76. Guldiken B, Remi J, Noachtar S. Cardiovascular adverse effects of phenytoin. J Neurol. 2016;263(5):861-70. Epub 2015/12/10.
77. Ide A, Kamijo Y. Intermittent complete atrioventricular block after long term low-dose carbamazepine therapy with a serum concentration less than the therapeutic level. InternMed. 2007;46(9):627-9.
78. Ishizue N, Niwano S, Saito M, Fukaya H, Nakamura H, Igarashi T, et al. Polytherapy with sodium channel-blocking antiepileptic drugs is associated with arrhythmogenic ST-T abnormality in patients with epilepsy. Seizure. 2016;40:81-7. Epub 2016/07/03.
79. Kasarskis EJ, Kuo CS, Berger R, Nelson KR. Carbamazepine-induced cardiac dysfunction. Characterization of two distinct clinical syndromes. Arch Intern Med. 1992;152(1):186-91. Epub 1992/01/01.
80. Kaufman KR, Velez AE, Wong S, Mani R. Low-dose lacosamide-induced atrial fibrillation: Case analysis with literature review. Epilepsy Behav Case Rep. 2013;1:22-5. Epub 2013/01/01.
81. Krause LU, Brodowski KO, Kellinghaus C. Atrioventricular block following lacosamide intoxication. Epilepsy Behav. 2011;20(4):725-7. Epub 2011/03/18.
82. Nizam A, Mylavarapu K, Thomas D, Briskin K, Wu B, Saluja D, et al. Lacosamide-induced second-degree atrioventricular block in a patient with partial epilepsy. Epilepsia. 2011;52(10):e153-5. Epub 2011/08/02.
83. Randazzo DN, Ciccone A, Schweitzer P, Winters SL. Complete atrioventricular block with ventricular asystole following infusion of intravenous phenytoin. J Electrocardiol. 1995;28(2):157-9. Epub 1995/04/01.
84. Strimel WJ, Woodruff A, Cheung P, Kirmani BF, Stephen Huang SK. Brugada-like electrocardiographic pattern induced by lamotrigine toxicity. Clin Neuropharmacol. 2010;33(5):265-7. Epub 2010/09/25.
85. Swe T, Bhattarai B, Dufresne A. Type 1 Brugada pattern ECG due to supra-therapeutic phenytoin level. BMJ Case Rep. 2016;2016. Epub 2016/06/30.
86. Zoneraich S, Zoneraich O, Siegel J. Sudden death following intravenous sodium diphenylhydantoin. Am Heart J. 1976;91(3):375-7. Epub 1976/03/01.
87. Takayanagi K, Hisauchi I, Watanabe J, Maekawa Y, Fujito T, Sakai Y, et al. Carbamazepine-induced sinus node dysfunction and atrioventricular block in elderly women. JpnHeart J. 1998;39(4):469-79.
88. DeToledo JC, Lowe MR, Rabinstein A, Villaviza N. Cardiac arrest after fast intravenous infusion of phenytoin mistaken for fosphenytoin. Epilepsia. 2001;42(2):288. Epub 2001/03/10.
89. Elliott JO, Lu B, Shneker B, Charyton C, Layne Moore J. Comorbidity, health screening, and quality of life among persons with a history of epilepsy. Epilepsy Behav. 2009;14(1):125-9. Epub 2008/11/06.
90. Kobau R, Zahran H, Thurman DJ, Zack MM, Henry TR, Schachter SC, et al. Epilepsy surveillance among adults--19 States, Behavioral Risk Factor Surveillance System, 2005. MMWR Surveill Summ. 2008;57(6):1-20. Epub 2008/08/08.

91. Strine TW, Kobau R, Chapman DP, Thurman DJ, Price P, Balluz LS. Psychological distress, comorbidities, and health behaviors among U.S. adults with seizures: results from the 2002 National Health Interview Survey. Epilepsia. 2005;46(7):1133-9. Epub 2005/07/20.
92. Tellez-Zenteno JF, Matijevic S, Wiebe S. Somatic comorbidity of epilepsy in the general population in Canada. Epilepsia. 2005;46(12):1955-62. Epub 2006/01/06.
93. Ding D, Wang W, Wu J, Ma G, Dai X, Yang B, et al. Premature mortality in people with epilepsy in rural China: a prospective study. Lancet Neurol. 2006;5(10):823-7. Epub 2006/09/22.
94. Janszky I, Hallqvist J, Tomson T, Ahlbom A, Mukamal KJ, Ahnve S. Increased risk and worse prognosis of myocardial infarction in patients with prior hospitalization for epilepsy--the Stockholm Heart Epidemiology Program. Brain. 2009;132(Pt 10):2798-804. Epub 2009/09/01.
95. Neligan A, Bell GS, Johnson AL, Goodridge DM, Shorvon SD, Sander JW. The long-term risk of premature mortality in people with epilepsy. Brain. 2011;134(Pt 2):388-95. Epub 2011/02/01.
96. (CDC) CfDCaP. Comorbidity in adults with epilepsy--United States, 2010. MMWR Morb Mortal Wkly Rep. 2013;62(43):849-53. Epub 2013/11/01.
97. Elliott JO, Moore JL, Lu B. Health status and behavioral risk factors among persons with epilepsy in Ohio based on the 2006 Behavioral Risk Factor Surveillance System. Epilepsy Behav. 2008;12(3):434-44. Epub 2008/01/08.
98. Cockerell OC, Johnson AL, Sander JW, Hart YM, Goodridge DM, Shorvon SD. Mortality from epilepsy: results from a prospective population-based study. Lancet. 1994;344(8927):918-21. Epub 1994/10/01.
99. Nilsson L, Tomson T, Farahmand BY, Diwan V, Persson PG. Cause-specific mortality in epilepsy: a cohort study of more than 9,000 patients once hospitalized for epilepsy. Epilepsia. 1997;38(10):1062-8. Epub 1998/05/14.
100. St Germaine-Smith C, Liu M, Quan H, Wiebe S, Jette N. Development of an epilepsy-specific risk adjustment comorbidity index. Epilepsia. 2011;52(12):2161-7. Epub 2011/10/19.
101. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? Epilepsia. 2013;54(1):11-27. Epub 2012/09/29.
102. Katsiki N, Mikhailidis DP, Nair DR. The effects of antiepileptic drugs on vascular risk factors: a narrative review. Seizure. 2014;23(9):677-84. Epub 2014/07/17.
103. Lopinto-Khoury C, Mintzer S. Antiepileptic drugs and markers of vascular risk. Curr Treat Options Neurol. 2010;12(4):300-8. Epub 2010/09/16.
104. Mintzer S, Skidmore CT, Abidin CJ, Morales MC, Chervoneva I, Capuzzi DM, et al. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. Ann Neurol. 2009;65(4):448-56. Epub 2009/03/20.
105. Miller G, Vogel H. Structural evidence of injury or malformation in the brains of children with congenital heart disease. Semin Pediatr Neurol. 1999;6(1):20-6. Epub 1999/03/31.
106. Attar H, Sachdeva A, Sundararajan S. Cardioembolic Stroke in Adults With a History of Congenital Heart Disease. Stroke. 2016;47(5):e79-81. Epub 2016/04/14.

107. Ferlazzo E, Gasparini S, Beghi E, Sueri C, Russo E, Leo A, et al. Epilepsy in cerebrovascular diseases: Review of experimental and clinical data with meta-analysis of risk factors. Epilepsia. 2016;57(8):1205-14. Epub 2016/07/07.
108. Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. Stroke. 2004;35(7):1769-75. Epub 2004/05/29.
109. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia. 1996;37(3):224-9. Epub 1996/03/01.
110. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993;34(3):453-68. Epub 1993/05/01.
111. Natelson BH, Suarez RV, Terrence CF, Turizo R. Patients with epilepsy who die suddenly have cardiac disease. Arch Neurol. 1998;55(6):857-60. Epub 1998/06/17.
112. Nei M, Sperling MR, Mintzer S, Ho RT. Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. Epilepsia. 2012;53(8):e137-e40.
113. Tigaran S, Molgaard H, McClelland R, Dam M, Jaffe AS. Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients. Neurology. 2003;60(3):492-5. Epub 2003/02/13.
114. S PCT, Dalager-Pedersen S, Baandrup U, Dam M, Vesterby-Charles A. Sudden unexpected death in epilepsy: is death by seizures a cardiac disease? Am J Forensic Med Pathol. 2005;26(2):99-105. Epub 2005/05/18.
115. Woodruff BK, Britton JW, Tigaran S, Cascino GD, Burritt MF, McConnell JP, et al. Cardiac troponin levels following monitored epileptic seizures. Neurology. 2003;60(10):1690-2. Epub 2003/05/29.
116. Finsterer J, Wahbi K. CNS disease triggering Takotsubo stress cardiomyopathy. Int J Cardiol. 2014;177(2):322-9. Epub 2014/09/13.
117. Finsterer J, Bersano A. Seizure-triggered Takotsubo syndrome rarely causes SUDEP. Seizure. 2015;31:84-7. Epub 2015/09/13.
118. Le Ven F, Pennec PY, Timsit S, Blanc JJ. Takotsubo syndrome associated with seizures: an underestimated cause of sudden death in epilepsy? Int J Cardiol. 2011;146(3):475-9. Epub 2011/01/05.
119. Lemke DM, Hussain SI, Wolfe TJ, Torbey MA, Lynch JR, Carlin A, et al. Takotsubo cardiomyopathy associated with seizures. Neurocrit Care. 2008;9(1):112-7. Epub 2008/03/19.
120. Szardien S, Mollmann H, Willmer M, Akashi YJ, Hamm CW, Nef HM. Mechanisms of stress (takotsubo) cardiomyopathy. Heart Fail Clin. 2013;9(2):197-205, ix. Epub 2013/04/09.
121. Manno EM, Pfeifer EA, Cascino GD, Noe KH, Wijdicks EF. Cardiac pathology in status epilepticus. Ann Neurol. 2005;58(6):954-7. Epub 2005/10/22.
122. Kasperaviciute D, Catarino CB, Chinthapalli K, Clayton LM, Thom M, Martinian L, et al. Uncovering genomic causes of co-morbidity in epilepsy: gene-driven phenotypic characterization of rare microdeletions. PLoS One. 2011;6(8):e23182. Epub 2011/08/23.

123. Ulate-Campos A, Coughlin F, Gainza-Lein M, Fernandez IS, Pearl PL, Loddenkemper T. Automated seizure detection systems and their effectiveness for each type of seizure. Seizure. 2016;40:88-101. Epub 2016/07/05.
124. van Andel J, Thijs RD, de Weerd A, Arends J, Leijten F. Non-EEG based ambulatory seizure detection designed for home use: What is available and how will it influence epilepsy care? Epilepsy Behav. 2016;57(Pt A):82-9. Epub 2016/03/02.
125. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. Lancet. 2006;367(9516):1087-100. Epub 2006/04/04.
126. Loscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia. 2011;52(4):657-78. Epub 2011/03/24.
127. Wassenaar M, van Heijl I, Leijten FS, van der Linden P, Uijl SG, Egberts AC, et al. Treatment of epilepsy in daily clinical practice: have outcomes improved over the past 10 years? J Neurol. 2013;260(11):2736-43. Epub 2013/07/31.

CHAPTER 3

3

Cardiac arrhythmias during or after epileptic seizures

Marije van der Lende[1,2] | Rainer Surges[3] | Josemir W. Sander[1,4] | Roland D Thijs[1,2,4]

[1] Stichting Epilepsie Instellingen Nederland (SEIN), Achterweg 5, 2103 SW, Heemstede, The Netherlands

[2] Department of Neurology, Leiden University Medical Center (LUMC), Albinusdreef 2, 2333 ZA, Leiden, The Netherlands

[3] Department of Epileptology, University of Bonn Medical Center, Sigmund-Freud Str 25, 53127, Bonn, Germany

[4] NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical & Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N 3BG, and Epilepsy Society, Chalfont St Peter, SL9 0RJ, UK

J Neurol Neurosurg Psychiatry. 2016 Jan;87(1):69-74.

Abstract

Objective Seizure-related cardiac arrhythmias are frequently reported and have been implicated as potential pathomechanisms of Sudden Unexpected Death in Epilepsy (SUDEP). We attempted to identify clinical profiles associated with various (post)ictal cardiac arrhythmias.

Design We conducted a systematic search from the first date available to July 2013 on the combination of two terms: "cardiac arrhythmias" and "epilepsy". Databases searched were PubMed, Embase (OVID version), Web of Science and COCHRANE Library. We attempted to identify all case reports and case series.

Results We identified seven distinct patterns of (post)ictal cardiac arrhythmias: ictal asystole (103 cases), postictal asystole (13 cases), ictal bradycardia (25 cases), ictal AV-conduction block (11 cases), postictal AV-conduction block (2 cases), (post)ictal atrial flutter/atrial fibrillation (14 cases) and postictal ventricular fibrillation (3 cases). Ictal asystole had a mean prevalence of 0.318% (95% confidence interval 0.316-0.320) in people with refractory epilepsy who underwent video-EEG monitoring. Ictal asystole, bradycardia and AV-conduction block were self-limiting in all but one case and seen during focal dyscognitive seizures. Seizure onset was mostly temporal (91%) without consistent lateralization. Postictal arrhythmias were mostly found following convulsive seizures and often associated with (near) SUDEP.

Conclusion The contrasting clinical profiles of ictal and postictal arrhythmias suggest different pathomechanisms. Postictal rather than ictal arrhythmias seem of greater importance to the pathophysiology of SUDEP.

Introduction

The occurrence of asystole during the course of an epileptic seizure was described well over 100 years ago: "He uttered a cry and was seen to be rubbing his hands together. His pulse was immediately examined for but was not palpable."[1] Since then various ictal cardiac arrhythmias have been reported and it has been acknowledged that seizures can influence cardiovascular control.

Sinus tachycardia is the most common cardiac consequence of epileptic seizures and may occur in up to 80% of seizures.[2] It may be associated with palpitations, but not with clinical signs such as syncope. Of all clinically relevant ictal arrhythmias, ictal asystole has gained much attention as it may cause syncope and subsequent falls, fractures and traffic accidents.[3] Ictal asystole and rarer ictal arrhythmias have also been suggested as a potential pathomechanism for Sudden Unexpected Death in Epilepsy (SUDEP).

As most information derives from single case reports and case series, our view on ictal arrhythmias still remains fragmented.

We systematically reviewed the literature to identify the full spectrum of clinically relevant (post) ictal cardiac arrhythmias attempting to unveil clinical profiles associated with each arrhythmia.

Methods

We performed a systematic review from the first date available to July 2013 and searched PubMed, Embase (OVID version), Web of Science and the COCHRANE Library. We used subject queries taking into account the terminological differences between these databases. Queries consisted of the combination of two terms: "cardiac arrhythmias" and "epilepsy". Various synonyms and related terms for all subjects were used (for exact search strategy, see appendix A).

One author (MvdL) screened all titles and abstracts for case series and case reports on ictal cardiac arrhythmias. Articles relating to cardiac arrhythmias mistaken for epileptic seizures, medication-induced arrhythmias, animal studies, interictal cardiac arrhythmias, and sinus tachycardia were excluded.

Full texts of all remaining articles were screened. We selected all those with data on individual cases of the following arrhythmias: asystole, bradycardia, atrioventricular conduction block, postictal atrioventricular conduction block, atrial fibrillation/flutter, ventricular tachycardia/fibrillation and pre-excitation syndromes including Wolff-

Parkinson-White. For each individual case we recorded whether the onset was in the pre-ictal, ictal or postictal phase. Asystole was defined as an R-R interval of > 3 seconds. Bradycardia was defined as a heart rate under the 1st centile of a normal heart rate frequency in beats per minute.[4]

Reviews were screened to find additional cases. We also reviewed articles from our personal archives. Only cases with simultaneous video-EEG (vEEG) recordings were included, apart from arrhythmias with fewer than five identified case reports with vEEG. For each case the following variables were collected: age, gender, type of epilepsy, duration of epilepsy, seizure frequency, number and type of anti-epileptic drugs taken, handedness, brain MRI, seizure type associated with cardiac arrhythmia, duration of arrhythmia, time between seizure onset and arrhythmia, localization of seizure onset, cardiac history, pacemaker implantation. Data from individual cases were collected into databases for each arrhythmia. To determine the prevalence of ictal asystole we combined individual data from similar studies.

Results

One thousand, one hundred sixty-seven articles were identified and after titles and abstracts were reviewed, we excluded 989. After 178 full text articles were reviewed, 65 reporting 162 cases with (post) ictal arrhythmias were included. (Appendix B). No pre-ictal cardiac arrhythmias were identified.

Bradycardia

Asystole

After exclusion of thirteen cases without vEEG data, 126 cases of asystole were included (14 case series; 43 case reports), 103 with ictal and 13 with postictal onset.

Ictal asystole

Prevalence data were reported in seven cases series. Asystole was defined as an R-R interval of > 3 seconds in two case series and an R-R interval of > 4 seconds in one case series. The remaining four case series did not provide a definition of asystole. The mean prevalence of ictal asystole in all people admitted for a vEEG recording (including those without epilepsy) was 0.177% (95% confidence interval (CI): 0.177-0.178).[5, 6] The mean prevalence of ictal asystole in all people with refractory focal epilepsy admitted for a vEEG recording was 0.318% (95% CI: 0.316-0.320).[7-11]

Ictal asystole was only reported in people with focal epilepsy (Table 1). Most ictal asystole occurred during the course of a focal dyscognitive seizure (formally known as a complex

	Ictal asystole n=103	Reported in *n* cases	Post-ictal asystole n=13	Reported in *n* cases
Age (years)	44 (16.3)	101	34 (11.7)	13
Gender	51% male	101	46% male	13
Type of epilepsy	100% focal	89	100% focal	12
Epilepsy duration (years)	15 (5-30)	60	8 (2-21)	11
Seizure frequency (per month)	4 (1-10)	25		
AED	No AED 13%	84		
	Monotherapy 27%			
	Polytherapy 60%			
Normal MRI	50%	64	17%	6
Right-handed	92%	36		
Seizure duration prior to asystole (sec)	24 (13-35)	47	187 (71-276)	8
Time between seizure offset and start asystole (sec)			90 (20-158)	10
Seizure type at onset of asystole	99% FDS	96	85% fbCS	13
	1% FAS	1	15% FDS	
Evolving to bilateral convulsive seizure after onset of asystole	7%	90	Not applicable	
Duration asystole (sec)	19 (10-26)	96	24 (7-60)	6
EEG seizure onset (n)	LT/LFT 37 (35/2)	80	LT/LFT 2 (2/0)	10
	RT/RFT 25 (23/2)		RT/RFT 6 (5/1)	
	BT 10		BF 1	
	LH 3		Ri par 1	
	Non-lat 3			
	RH 1			
	RO 1			
PGES before asystole	Not applicable		70%	10
Apnea before asystole			100%	8
Pacemaker implanted	88%	50	50%	4

Table 1. (Post)ictal asystole

Results are presented as percentiles, mean (SD) or median (25th-75th percentile)
AED Anti-epileptic drugs, FDS focal dyscognitive seizure, FAS focal autonomic seizure, fbCS focal seizure evolving to bilateral convulsive seizure, LT left temporal, LFT left frontotemporal, RT right temporal, RFT right frontotemporal, BT bitemporal, BF bifrontal, LH left hemisphere, ri par right parietal, non-lat non-laterizing, RH right hemisphere, RO right occipital, PGES postictal generalized EEG suppression

partial seizure) on average starting 30 seconds after seizure onset. The mean duration of ictal asystole was 20 seconds (range 3-96). The seizure onset zone was reported in 78% of the cases and was temporal in 90% without consistent lateralization.

All ictal asystoles were self-limiting, except in one subject where resuscitation was started after 44 seconds of cardiac arrest. This event was labeled as near-SUDEP.

Postictal asystole

Most postictal asystole was seen after a focal seizure evolving to a bilateral convulsive seizure and had a mean duration of 30 seconds (Table 1). Most postictal asystoles were preceded by postictal generalized EEG suppression (PGES). Seven of thirteen people died of (probable) SUDEP.

Ictal bradycardia

Twenty-five vEEG cases of ictal bradycardia without asystole were identified. Characteristics of ictal bradycardia cases were similar to those with ictal asystole. Ictal bradycardia was only reported in people with focal epilepsy during focal dyscognitive seizures. Seizure onset was predominantly temporal. (Table 2)

Ictal AV-conduction block

We found eleven cases of ictal AV-conduction block: nine complete AV-blocks and two second degree AV-blocks. In five cases complete ictal AV block was followed by a cardiac standstill; these cases were also included in the ictal asystole section. A pre-existent conduction block (left bundle or right bundle branch block) was reported in two of eleven cases. All had focal epilepsy. All ictal AV block occurred during non-convulsive seizures. Seizure onset was never lateralized primarily in the right hemisphere. (Table 3)

Postictal AV-conduction block

Two cases of postictal AV blocks were found; both were preceded by a focal seizure evolving to a bilateral convulsive seizure.

Tachycardia

No cases with ictal AV nodal tachycardia, AV reentry tachycardia or pre-excitation syndromes such as Wolff-Parkinson-White were identified.

Atrial Flutter / Atrial Fibrillation

14 cases of (post)ictal atrial fibrillation (n=13) or atrial flutter (n=1) were found. Only three subjects had an ictal vEEG recording: one ictal atrial fibrillation (AF) during a focal dyscognitive seizure and two cases of postictal AF after convulsive seizures; two of these cases later died of definite SUDEP.

The remaining 11 cases without vEEG had AF after a possible convulsive seizure, usually persisting for several hours. Because of the lack of ictal proof, these cases are discussed separately. (Table 4)

	Ictal bradycardia n=25	Reported in *n* cases
Age (years)	48 (22.5)	20
Gender	55% male	20
Type of epilepsy	100% focal	21
Epilepsy duration (years)	5 (0-9)	10
AED	No AED 22%	9
	Monotherapy 44%	
	Polytherapy 33%	
Normal MRI	38%	13
Right-handed	60%	5
Seizure duration prior to bradycardia (sec)	25 (11-39)	9
Seizure type at onset of bradycardia	100% FDS	8
EEG seizure onset (n)	LT/LFT 11 (8/3)	21
	RT/RFT 8 (7/1)	
	T 1	
	L par occ 1	
Pacemaker implantation	3 (37%)	8

Table 2. Ictal bradycardia

Results are presented as percentiles, mean (SD) or median (25th-75th percentile)
FDS focal dyscognitive seizure, LT left temporal, LFT left frontotemporal, T temporal, L par occ left parieto-occipital, sGTCS secondary generalized tonic clonic seizure

	Ictal AV conduction block (n=11)	Reported in *n* cases	Postictal AV conduction block (n=2)	Reported in *n* cases
Age (years)	49 (12)	11	30 and 56	2
Gender	20% male	10	1 male, 1 female	2
Type of epilepsy	100% focal	10	focal	1
Epilepsy duration (years)	23 (11-31)	5	39	1
Seizure type	90% FDS	10	100% fbCS	2
	10% FAS			
EEG seizure onset (n)	LT/LFT 8 (7/1)	11	RT	1
	BT = 2			
	Left insula = 1			
Pacemaker implanted	100%	5	100%	1

Table 3. (Post) Ictal AV block

Results are presented as percentiles, mean (SD) or median (25th-75th percentile)
FDS focal dyscognitive seizure, fbCS focal seizure evolving to bilateral convulsive seizure, FAS focal autonomic seizure, LT left temporal, LFT left frontotemporal, RT right temporal, BT bitemporal

	(Post) ictal AF with vEEG (*n*=3)	Reported in *n* cases	(Post) ictal AF without vEEG (*n*=10)	Reported in *n* cases
Age (years)	22, 34	2	37 (16)	10
Gender		0	90% male	10
Type of epilepsy	2 focal epilepsy, 1 GGE	3	5 focal epilepsy, 3 GGE	8
Epilepsy duration (years)	6, 34	2	7 (0-25) SD 10.3	7
Seizure frequency	1/year, 1/week	2	3/year, 3/week	2
Seizure type	1 GTCS, 1 fbCS, 1 FDS	3	50% fbCS, 50% GTCS	10
Start of AF in postictal phase	2	3		
Duration of AF	10 sec, 55sec, >110sec	3	1.5 – 25 hours	9
Normal MRI		0	57%	7
Cardiac history	0%	2	14%	7
EEG seizure onset	Non loc, LT, Gen	3		0

Table 4. (Post)Ictal atrial fibrillation

Results are presented as percentiles, mean (SD) or median (25th-75th percentile)
AF atrial fibrillation, GTCS generalized tonic clonic seizure, fbCS focal seizure evolving to bilateral convulsive seizure, FDS focal dyscognitive seizure, GGE genetic generalized epilepsy, non loc non localizing, LT left temporal, Gen generalised

Ventricular Fibrillation

Three cases of postictal VF were identified; one without vEEG. In all three cases VF was preceded by a convulsive seizure and CPR was initiated: two were classified as near SUDEP and one as definite SUDEP.

One individual was known to have a first-degree AV block, but none had major VT/VF risk factors.

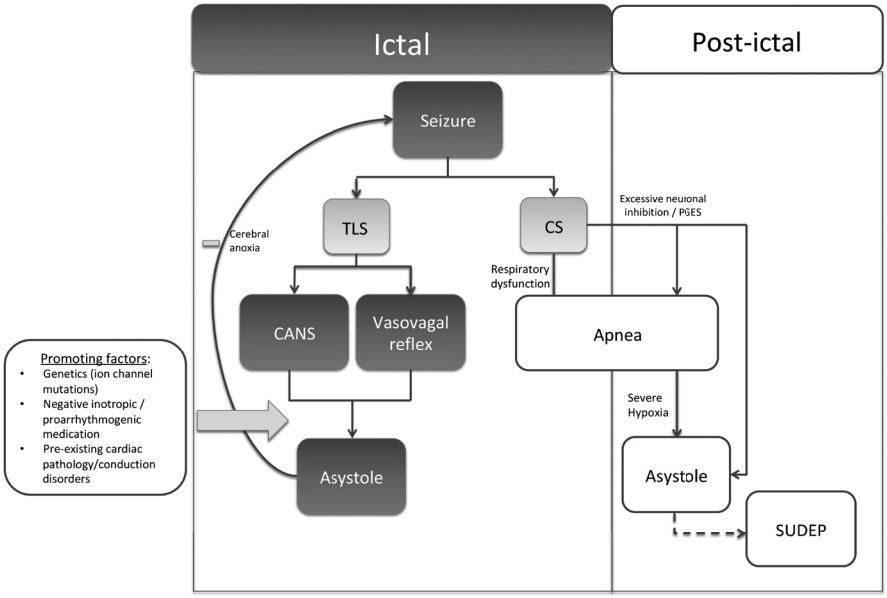


Figure 1. Schematic overview of the mechanisms for seizure-related asystole.

Ictal asystole is strongly associated with temporal lobe seizures. It could be a direct consequence of epileptic activity stimulating the central autonomic network or an indirect effect of the seizure (e.g. catecholamine release) evoking a vasovagal reflex. Ictal asystole is self-limiting, as cerebral anoxia caused by the asystole ceases the seizure. By contrast, postictal asystole is associated with convulsive seizures and could be fatal. Postictal asystole is often preceded by apnea and/or PGES. Prolonged apnea eventually causes arousal as well as bradycardia and asystole. Postictal coma may, however, block the arousal effect and thus the resumption of ventilation, explaining why postictal asystole may lead to SUDEP. SUDEP sudden unexpected death in epilepsy, TLS temporal lobe seizure, CS convulsive seizure, CANS central autonomic nervous system, PGES postictal generalized EEG suppression

Discussion

Seven distinct (post)ictal arrhythmia patterns were identified. Ictal asystole was the most frequently reported pattern. Ictal asystole, ictal bradycardia and ictal AV block predominantly occurred during focal dyscognitive seizures in people with temporal lobe epilepsy. No deaths were reported suggesting that ictal arrhythmias are self-limiting. By contrast, postictal arrhythmias including asystole, AV block and the less prevalent AF and VF usually occurred after a convulsive seizure and were frequently associated with (near-) SUDEP. The difference in timing, associated seizure types and mortality risk suggests that seizures may trigger cardiac arrhythmias in various ways. Postictal arrhythmias, rather than ictal arrhythmias, seem of greater importance to the pathophysiology of SUDEP. (Figure1)

Limitations

Publication biases are inevitable and may affect results. Reliable estimates of prevalence could only be made for ictal asystole, among those with refractory epilepsy, yielding an overall prevalence of 0.32%. Variable definitions were used (R-R interval of >3 seconds, >4 seconds, no definition at all) thus the prevalence number might be underestimated. For the other arrhythmias no estimations are available, but the few case reports and the lack of case series suggest that they are rare. Selection bias may also have been at play as evaluation for epilepsy surgery is the commonest indication for video-EEG registration, thus people with temporal lobe epilepsy may have been overrepresented. Only one case series reported on epilepsy types: almost twice as many people with temporal lobe epilepsy were monitored with vEEG compared to those with extra temporal lobe or generalized epilepsy.[6] This may have resulted in an overestimation of the association of temporal lobe epilepsy in those with ictal and postictal asystole.

Diagnostic validity is another potential limitation as we included cases of AF (n=11) and VF (n=1) without vEEG. In these cases we were unable to verify the seizure and to determine the exact time of onset of the arrhythmia. Therefore we reported those cases separately. Overall no major differences were seen between the two groups, particularly with respect to the relationship with seizure type and timing of the arrhythmia.

Muscle artifacts, particularly those during convulsive seizures, may have obscured the detection of ictal arrhythmias with a single lead ECG channel. This limitation may apply to all arrhythmias except for those causing (pre)syncope, as this will become apparent by a sudden diffuse slowing and flattening of the EEG.[12] Nevertheless, it should be noted that the prevalence of ictal arrhythmias without syncope might have been underestimated.

Many case reports did not report on cardiac history, use of cardiovascular drugs, withdrawal of antiepileptic drugs, baseline ECG or ECG pattern preceding the arrhythmia.

For example, two case series reported AV conduction time prior to asystole and found that 5 out 16 cases had complete AV block.[7, 13] As other case series did not provide these data, ictal AV block may be more or less common than our data suggest. We were also unable to assess the influence of cardiac history on ictal arrhythmias or the possible arrhythmogenic effects of medication. We would strongly recommend that future case series provide details on cardiac history, prior medication use, baseline ECG and ECG pattern to allow for such analyses.

Ictal asystole, bradycardia and AV-block

We found a point prevalence of people with ictal asystole of 0.32%. By contrast two small prospective studies (both n=19) with long-term implantable heart rhythm monitors up to two years, reported much higher prevalence of 5% and 21%.[14, 15] These contrasting figures suggest that ictal asystole does not occur during every seizure and may go unnoticed during short-term monitoring.

Ictal asystole, ictal bradycardia and ictal AV block coincided with a focal dyscognitive seizure and were predominantly seen in temporal lobe epilepsy. These three arrhythmias not only shared a similar clinical profile, but could also overlap. Both ictal bradycardia and ictal AV block may evolve into asystole.

It has been suggested that a seizure onset in the left hemisphere results in bradycardia and a right-sided onset in tachycardia.[2] We did not, however, find a consistent lateralization in the large group of ictal asystole and ictal bradycardia cases. In the small group of ictal AV block cases, there was tendency for a left-sided focus. We cannot exclude the possibility that seizure lateralization is relevant only for ictal AV block, as it is known that the left vagal nerve predominantly innervates the atrioventricular and the right vagal nerve the sino-atrial node. In view of the possible overlap between ictal asystole and ictal AV block,[7, 13] and the fact that most ictal asystole studies did not take this overlap into account, this would need larger studies for definite confirmation.

Ictal asystole could be a direct consequence of epileptic activity stimulating the central autonomic network.[2, 16] Focal stimulation of parts of the limbic system, such as the cingulate gyrus, amygdala, insular and orbitofrontal cortex, may provoke asystole.[17-19]

Ictal asystole may be promoted by use of drugs (e.g. effecting AV conduction or sinoatrial node activity) or genetic conditions affecting cardiac conduction (ion channel mutations). Prospective long term studies suggested that ictal asystole may be incidental (on average 1 out of 13 seizures within the same subject with ictal asystole).[14, 15] The variable expression between seizures could argue that ictal asystole is caused by an *indirect* effect of the seizure.

Ictal asystole may parallel centrally-mediated cardioinhibition seen in vasovagal syncope. As in emotionally-induced vasovagal syncope, seizure-induced fear and catecholamine release may coincide and culminate in cardioinhibition and vasodilatation.[20, 21]

Supporting this view, heart rate patterns preceding asystole were similar between subjects with ictal asystole and those with vasovagal syncope: heart rate increases markedly, followed by a progressive bradycardia, leading to asystole.[22] Vasovagal syncope is a self-limiting condition with an excellent long term prognosis.[23] Prolonged cerebral hypoperfusion is thought to shut down the initial central trigger, thereby explaining its benign course.[12] Following this analogy, cerebral anoxia-ischemia in ictal asystole could be a potential mechanism of seizure self-termination as well. Accordingly, total seizure duration was found to be shorter for seizures with ictal asystole compared to those without.[24]

The most extreme case of self-limiting ictal asystole we found lasted for 96 seconds.[25] In the single ictal asystole case with near SUDEP,[7] successful resuscitation was started after 44 seconds of cardiac arrest. Whether an asystolic event is labeled as near-SUDEP or as a self-limiting ictal asystole will thus critically depend on the action of the observing medical personnel: immediate resuscitation will increase the number of "near-SUDEP" cases. Therefore, as long as no fatal case has been reported, ictal asystole should not be considered a SUDEP pathomechanism.

Postictal asystole

We found postictal asystole is associated with convulsive, rather than focal dyscognitive temporal lobe seizures and is frequently associated with SUDEP. Most postictal asystoles were preceded by PGES and apnea. In the MORTEMUS study[26] vEEG recordings were used to estimate the presence of respiratory movements; all postictal asystoles were likely preceded by apnea.

Prolonged apnea activates the carotid chemoreceptors, causing arousal and eventually vagally mediated bradycardia or even cardiac arrest.[27] In the context of postictal coma, the arousal effect may be blocked and thus not result in resumption of normal ventilation, thus explaining why postictal asystole can be fatal. PGES has been linked to postictal coma.[28, 29] The exact mechanism underlying PGES and subsequent cardiorespiratory cessation remains unexplained, but may result from excessive brainstem inhibition.[26]

Postictal AF and VF

Postictal AF and VF were detected in the context of convulsive seizures and, in contrast to ictal asystole and ictal bradycardia, AF was usually present for several hours. Postictal VF is always classified as (near)SUDEP.

Convulsive seizures trigger the sympathetic nervous system as reflected by a peak in catecholamine and electrodermal activity.[30, 31] Increased sympathetic activity has also been implicated as a trigger for AF and VF.[32]

People with epilepsy were found to have a three-fold increased risk of VT/VF compared with the general population.[33] Most cases of VT/VF in epilepsy were, however, not seizure-related and were probably related to cardiovascular comorbidities. Nevertheless, in a subset of cases seizure-induced VF may have a played a role.[34]
As well as a rise in catecholamines[35] various other factors may contribute to postictal VF, including higher prevalence of ECG markers for sudden cardiac arrest;[36] peri-ictal QTc prolongation,[35, 37] ST-changes,[38] and increased troponin levels.[38, 39] Possibly all these factors converge over time, thus explaining the occurrence in the postictal phase.[40]

Clinical implications

In view of ictal asystole's self-limiting course, a reasonable approach is to optimize treatment with antiepileptic drugs, to consider epilepsy surgery and to withdraw negative inotropic or proarrhythmogenic drugs.[11] If this fails and there is documented recurrence of asystolic episodes, cardiac pacemaker implantation should be considered. Observational studies suggest that pacemakers can reduce falls and injuries due to seizure-induced syncope.[3, 11]

Postictal arrhythmias may be a marker of an increased SUDEP risk. No studies have yet addressed the management of these cases. In the absence of such evidence, we recommend optimization of seizure control and critical review of the clinical context (e.g. drug use, ECG markers) in order to identify other modifiable risk factors.

Supplementary data (are available online)

Appendix A: Search strategy
Appendix B: References per arrhythmia

References

1. Russell AE. CESSATION OF THE PULSE DURING THE ONSET OF EPILEPTIC FITS,: WITH REMARKS ON THE MECHANISM OF FITS. The Lancet 1906;**168**(4325):152-54 doi: http://dx.doi.org/10.1016/S0140-6736(01)30477-4%5B
2. Sevcencu C, Struijk JJ. Autonomic alterations and cardiac changes in epilepsy. Epilepsia 2010;**51**(5):725-37 doi: EPI2479 [pii];10.1111/j.1528-1167.2009.02479.x
3. Moseley BD, Ghearing GR, Munger TM, et al. The treatment of ictal asystole with cardiac pacing. Epilepsia 2011;**52**(4):e16-e19 doi: 10.1111/j.1528-1167.2010.02972.x
4. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011;377(9770):1011-8 doi: 10.1016/s0140-6736(10)62226-x
5. Britton JW, Ghearing GR, Benarroch EE, et al. The ictal bradycardia syndrome: localization and lateralization. Epilepsia 2006;**47**(4):737-44 doi: EPI509 [pii];10.1111/j.1528-1167.2006.00509.x
6. Schuele SU, Bermeo AC, Alexopoulos AV, et al. Video-electrographic and clinical features in patients with ictal asystole. Neurology 2007;**69**(5):434-41 doi: 69/5/434 [pii];10.1212/01.wnl.0000266595.77885.7f
7. Lanz M, Oehl B, Brandt A, et al. Seizure induced cardiac asystole in epilepsy patients undergoing long term video-EEG monitoring. Seizure 2011;**20**(2):167-72 doi: S1059-1311(10)00300-6 [pii];10.1016/j.seizure.2010.11.017
8. Rocamora R, Kurthen M, Lickfett L, et al. Cardiac asystole in epilepsy: clinical and neurophysiologic features. Epilepsia 2003;**44**(2):179-85 doi: epi15101
9. Scott CA, Fish DR. Cardiac asystole in partial seizures. Epileptic Disord 2000;**2**(2):89-92
10. Kerling F, Dutsch M, Linke R, et al. Relation between ictal asystole and cardiac sympathetic dysfunction shown by MIBG-SPECT. Acta Neurol Scand 2009;**120**(2):123-29 doi: ANE1135 [pii];10.1111/j.1600-0404.2008.01135.x
11. Strzelczyk A, Cenusa M, Bauer S, et al. Management and long-term outcome in patients presenting with ictal asystole or bradycardia. Epilepsia 2011;**52**(6):1160-67 doi: 10.1111/j.1528-1167.2010.02961.x
12. van Dijk JG, Wieling W. Pathophysiological basis of syncope and neurological conditions that mimic syncope. Progress in cardiovascular diseases 2013;**55**(4):345-56 doi: 10.1016/j.pcad.2012.10.016
13. Kouakam C, Daems C, Guedon-Moreau L, et al. Recurrent unexplained syncope may have a cerebral origin: report of 10 cases of arrhythmogenic epilepsy. Arch CardiovascDis 2009;**102**(5):397-407 doi: S1875-2136(09)00085-0 [pii];10.1016/j.acvd.2009.02.014
14. Nei M, Sperling MR, Mintzer S, et al. Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. Epilepsia 2012;**53**(8):e137-e40 doi: 10.1111/j.1528-1167.2012.03561.x

15. Rugg-Gunn FJ, Simister RJ, Squirrell M, et al. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. Lancet 2004;**364**(9452):2212-19 doi: S0140673604175946 [pii];10.1016/S0140-6736(04)17594-6
16. Leung H, Kwan P, Elger CE. Finding the missing link between ictal bradyarrhythmia, ictal asystole, and sudden unexpected death in epilepsy. Epilepsy Behav 2006;**9**(1):19-30 doi: S1525-5050(06)00203-4 [pii];10.1016/j.yebeh.2006.05.009
17. Pool JL, Ransohoff J. Autonomic effects on stimulating rostral portion of cingulate gyri in man. Journal of neurophysiology 1949;**12**(6):385-92
18. Oppenheimer SM, Gelb A, Girvin JP, et al. Cardiovascular effects of human insular cortex stimulation. Neurology 1992;**42**(9):1727-32
19. Altenmuller DM, Zehender M, Schulze-Bonhage A. High-grade atrioventricular block triggered by spontaneous and stimulation-induced epileptic activity in the left temporal lobe. Epilepsia 2004;**45**(12):1640-44 doi: EPI34403 [pii];10.1111/j.0013-9580.2004.34403.x
20. van Dijk JG, Thijs RD, van Zwet E, et al. The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes. Brain 2014;**137**(Pt 2):576-85 doi: 10.1093/brain/awt332
21. Goldstein DS, Holmes C, Frank SM, et al. Sympathoadrenal imbalance before neurocardiogenic syncope. Am J Cardiol 2003;**91**(1):53-8
22. Schuele SU, Bermeo AC, Locatelli E, et al. Ictal asystole: a benign condition? Epilepsia 2008;**49**(1):168-71 doi: EPI1330 [pii];10.1111/j.1528-1167.2007.01330.x
23. van Dijk JG, Thijs RD, Benditt DG, et al. A guide to disorders causing transient loss of consciousness: focus on syncope. Nature reviews Neurology 2009;**5**(8):438-48 doi: 10.1038/nrneurol.2009.99
24. Schuele SU, Bermeo AC, Alexopoulos AV, et al. Anoxia-ischemia: a mechanism of seizure termination in ictal asystole. Epilepsia 2010;**51**(1):170-73 doi: EPI2168 [pii];10.1111/j.1528-1167.2009.02168.x
25. Chaila E, Bhangu J, Tirupathi S, et al. Ictal bradycardia and asystole associated with intractable epilepsy: A case series. British Journal of Cardiology 2010;**17**(5):245-48
26. Ryvlin P. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurology 2013
27. Paton JF, Boscan P, Pickering AE, et al. The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. Brain research Brain research reviews 2005;**49**(3):555-65 doi: 10.1016/j.brainresrev.2005.02.005
28. Seyal M, Bateman LM, Li CS. Impact of periictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility. Epilepsia 2013;**54**(2):377-82 doi: 10.1111/j.1528-1167.2012.03691.x
29. Semmelroch M, Elwes RD, Lozsadi DA, et al. Retrospective audit of postictal generalized EEG suppression in telemetry. Epilepsia 2012;**53**(2):e21-4 doi: 10.1111/j.1528-1167.2011.03296.x
30. Simon RP, Aminoff MJ, Benowitz NL. Changes in plasma catecholamines after tonic-clonic seizures. Neurology 1984;**34**(2):255-7

31. Poh MZ, Loddenkemper T, Reinsberger C, et al. Autonomic changes with seizures correlate with postictal EEG suppression. Neurology 2012;**78**(23):1868-76 doi: 10.1212/WNL.0b013e318258f7f1
32. Volders PG. Novel insights into the role of the sympathetic nervous system in cardiac arrhythmogenesis. Heart Rhythm 2010;**7**(12):1900-6 doi: 10.1016/j.hrthm.2010.06.003
33. Bardai A, Lamberts RJ, Blom MT, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. PLoS One 2012;**7**(8):e42749 doi: 10.1371/journal.pone.0042749 [doi];PONE-D-11-21152
34. Lamberts RJB, M.T.; Wassenaar,M.; Bardai,A.; Leijten,F.S.S.; de Haan,G.J. Sudden cardiac arrest in people with epilepsy in the community: circumstances and risk factors. Neurology 2015 (accepted)
35. Lee S, Harris ND, Robinson RT, et al. Effects of adrenaline and potassium on QTc interval and QT dispersion in man. European journal of clinical investigation 2003;**33**(2):93-8
36. Lamberts RJ, Blom MT, Novy J, et al. Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. Journal of neurology, neurosurgery, and psychiatry 2014 doi: 10.1136/jnnp-2014-307772
37. Surges R, Adjei P, Kallis C, et al. Pathologic cardiac repolarization in pharmacoresistant epilepsy and its potential role in sudden unexpected death in epilepsy: a case-control study. Epilepsia 2010;**51**(2):233-42 doi: EPI2330 [pii];10.1111/j.1528-1167.2009.02330.x
38. Tigaran S, Molgaard H, McClelland R, et al. Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients. Neurology 2003;**60**(3):492-5
39. Schneider F, Kadel C, Pagitz M, et al. Takotsubo cardiomyopathy and elevated troponin levels following cerebral seizure. Int J Cardiol 2010;**145**(3):586-7 doi: 10.1016/j.ijcard.2010.05.072
40. Surges R, Thijs RD, Tan HL, et al. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. NatRev Neurol 2009;**5**(9):492-504 doi: nrneurol.2009.118 [pii];10.1038/nrneurol.2009.118

CHAPTER 4

The yield of long-term ECG recordings in refractory focal epilepsy

Marije van der Lende, MD[1,2] | Johan B Arends, MD, PhD[3,4] | Robert J Lamberts, MD, PhD[1] | Hanno L Tan, MD, PhD[5] | Frederik J de Lange, MD, PhD[5] | Josemir W Sander MD, PhD, FRCP[1,6] | Arnaud J Aerts MD, PhD[7] | Henk P Swart[8] MD | Roland D Thijs, MD, PhD[1,2,6]

[1] Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands
[2] Leiden University Medical Center (LUMC), Department of Neurology, Leiden, Netherlands
[3] Academic Center for Epileptology Kempenhaeghe, Heeze, Netherlands
[4] Technological University Eindhoven, Electronic Engineering Faculty, Signal Processing Group, Eindhoven, Netherlands
[5] Department of Cardiology, Heart Center, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands
[6] NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, and Chalfont Centre for Epilepsy, Chalfont St Peter, SL9 0RJ, UK
[7] Zuyderland Medical Center, Department of Cardiology, Heerlen, Netherlands
[8] Antonius Hospital Sneek, Department of Cardiology, Netherlands.

Submitted

Abstract

Objective To determine the incidence of clinically relevant arrhythmias in refractory focal epilepsy and to assess the potential of postictal arrhythmias as risk markers for Sudden Unexpected Death in Epilepsy (SUDEP).

Methods We recruited people with refractory focal epilepsy without signs of ictal asystole and who had at least one focal seizure per month, and implanted a loop recorder with two-year follow-up. The devices automatically record arrhythmias. Subjects and caregivers were instructed to make additional peri-ictal recordings. Clinically relevant arrhythmias were defined as: asystole ≥ 6s; atrial fibrillation <55bpm or >200bpm and >30s duration; persistent sinus bradycardia <40bpm while awake; second- or third-degree atrioventricular block and ventricular tachycardia/ fibrillation. We performed 12-lead ECG and tilt table testing to identify non-seizure-related causes of asystole.

Results We included 49 people and accumulated 1060 months of monitoring. A total of 16,474 seizures were reported of which 4679 were captured on ECG. No clinically relevant arrhythmias were identified. Three people had a total of 18 short-lasting (<6s) periods of asystole, resulting in an incidence of 2.91 events per 1000 patient-months. None of these coincided with a reported seizure; one was explained by micturition syncope. Other non-clinically relevant arrhythmias included: paroxysmal atrial fibrillation (n=2); supraventricular tachycardia (n=1); sinus tachycardia with a right bundle branch block configuration (n=1).

Conclusions We found no clinically relevant arrhythmias in people with refractory focal epilepsy during long-term follow-up. The absence of postictal arrhythmias does not support the use of loop recorders in people at high SUDEP risk.

Introduction

People with refractory epilepsy are at high risk of Sudden Unexpected Death in Epilepsy (SUDEP).[1, 2] The precise pathomechanism remains unknown and effective preventive strategies are lacking.[1, 3, 4] Sporadic video-EEG recordings of SUDEP cases show periods of postictal apnea, bradycardia and asystole prior to death.[5] While ictal asystole is the most frequent arrhythmia, postictal rather than ictal asystole seems of greater importance to SUDEP.[6] Another concern is the three-fold increased risk of ventricular tachycardia/fibrillation (VT/VF) in people with epilepsy in the community.[7] Cardiovascular disease, rather than epilepsy characteristics, is the main determinant of VT/VF in epilepsy, but VT/VF may partly overlap with SUDEP.[6, 8]

Cross-sectional studies of ictal EEG recordings suggested a prevalence of 0.32% of ictal asystole in refractory focal epilepsy.[6] Two small, long-term studies using implantable loop recorders for up to two years yielded different results: in one 5% of subjects had periods of asystole compared 21% in the other.[9, 10] These conflicting results may be explained by small sample sizes as well as differences in selection criteria. More importantly, no efforts were made to discriminate between ictal and postictal asystole and between seizure- and non-seizure-related causes of asystole, including reflex syncope.

We aimed to determine the yield of long-term ECG recordings in a large cohort of people with epilepsy. We assessed the two-year prevalence of all clinically relevant arrhythmias and evaluated the potential of postictal arrhythmias as markers of SUDEP risk.

Methods

Fifty people with refractory focal epilepsy were selected at two epilepsy referral centers. Selection criteria are listed in table 1. Prior to inclusion all eligible subjects had an ECG recorded and reviewed by an experienced cardiologist.

Prior to implantation a tilt table test was performed. Heart rate and blood pressure were measured non-invasively on a beat-to-beat basis (Nexfin, BMEYE, Amsterdam Netherlands; or Finometer, Finapres Medical Systems B.V., Enschede, Netherlands). After ten minutes supine rest, the subject was tilted upwards to 70 degrees head-up for 20 minutes. If negative, an additional 20 minutes was recorded in the tilted position after administration of 0.4 mg nitroglycerin sublingually.[14] In case of syncope, the subject was tilted backwards to terminate loss of consciousness. Positive tilt table tests were evaluated according to the classification of the vasovagal syncope international study (VASIS)[15]: VASIS I mixed type; VASIS IIa cardio-inhibition without asystole; VASIS IIb cardio-inhibition with asystole; VASIS III pure vasodepressor type.

Inclusion criteria	Exclusion criteria
Drug-refractory focal epilepsy#: failure of adequate trials of two AED schedules to achieve sustained seizure freedom[11]	Clinical suspicion of ictal asystole[12, 13]
At least one focal seizure with impaired awareness or one tonic clonic seizure per month	Loop recorder implantation (either current or in the past)
Aged 18 to 60 years	Clinically relevant known structural cardiac disease
Able to undergo the study procedure as judged by the treating neurologist.	Hereditary syndromes that increase the risk of cardiomyopathy
	12-lead ECG findings suggestive of arrhythmias without proper cardiac evaluation to exclude this possibility*: – bi-fascicular block and other intraventricular conduction abnormalities – asymptomatic inappropriate sinus bradycardia (<50 bpm) – sinoatrial block or sinus pause ≥3s in the absence of negative chronotropic medications – non-sustained VT – pre-excited QRS complexes – prolonged or short QT interval – Brugada pattern – pattern suggestive of arrhythmogenic right ventricular cardiomyopathy
	Pacemaker implantation
	Use of beta blockers or other anti-arrhythmic/anti-arrhythmogenic medication
	Current dissociative seizures
	People who live alone who are not able to recall seizures
	Pregnancy

Table 1. Inclusion and exclusion criteria

Diagnosis based on history taking, eyewitness accounts and supported by at least one of the following: interictal EEG abnormalities, MRI lesions known to cause epilepsy, home videos or ictal EEG recordings. *According to European Society of Cardiology guidelines on syncope.[14]

Implantable loop recorders (Reveal XT, Medtronic Inc., Minneapolis, MN, U.S.A.) were placed subcutaneously. To optimize detection of the ECG signal a standard protocol (mapping, factor check) was followed to define the optimal implantation site.

Definition of clinically relevant arrhythmias

Clinically relevant arrhythmias were defined as: asystole of ≥ 6s together with clinical symptoms of (near-) syncope; asystole of ≥10s regardless of clinical symptoms[16, 17]; polymorphic sustained or non-sustained ventricular tachycardia (VT); non-sustained monomorphic VT of >180 bpm and >2s duration, or >175 bpm and >3s duration, and sustained monomorphic VT; atrial fibrillation of >200 bpm and >30s duration, or <55 bpm and clinical symptoms (near-syncope or dyspnea); persistent sinus bradycardia of <40 bpm while awake; asymptomatic 2nd or 3rd degree atrioventricular (AV) block of >4s duration.

Data collection

Devices continuously monitored heart rhythm. Automatic storage of ECG-data took place in episodes of bradycardia (<40 bpm), asystole (>3 s), any tachycardia (>180 bpm) or atrial fibrillation or when participants activated the device (e.g. during or after a seizure). When an individual activated the device, it stored the preceding nine minutes and subsequent one minute of ECG recording. To record the entire seizure, participants and their caregivers were instructed to only activate the device after the seizure. ECG-data were uploaded at least once a month, as the device could only save up to two person activated episodes. Data were uploaded wirelessly to the central online study database. All incoming ECG recordings were reviewed by the study cardiologists within 24 hours.

All participants were asked to keep a seizure diary and to mark all seizures on the loop recorder. The research physician (MvdL) contacted participants monthly to update seizure diaries and check whether all the recorded data had been uploaded. For those who were unable to keep a detailed seizure diary, for example when they had multiple seizures each day, monthly estimates of the seizure frequencies per seizure type were recorded. When a person could not recall the semiological details of the reported seizures of the past month, seizures were classified as 'other seizure'. All participants were seen at the outpatient clinic by the research physician or cardiologist (AJA) at the end of the first year.

If arrhythmias occurred, the research physician contacted the subject within 24 hours and all circumstances surrounding the event were discussed. If clinically relevant arrhythmias occurred, subjects were referred to a predetermined regional cardiological center for additional investigations and treatment if needed.

Information on person-related (age, comorbidity, medication use) and epilepsy-related variables (epilepsy syndrome, localization, age of onset, epilepsy duration, seizure types, seizure frequency, presence of nocturnal seizures, use of antiepileptic drugs, history of epilepsy surgery) was collected from medical records.

Age (years)	Mean 43.1; SD 12.1 (range 20 - 60)
Gender	26 females (53%)
Epilepsy etiology:	
Structural	25 (51%)
Genetic	5 (10%)
Infectious	4 (8%)
Metabolic	1 (2%)
Immune	1 (2%)
Unknown	13 (27%)
EEG localization	
Temporal	25 (51%)
Extra-temporal	24 (49%)
Age of onset (years)	Mean 15.0; SD 9.9 (range 1 - 34)
Seizure types*:	
Tonic clonic seizures	27 (55%)
Focal seizures with impaired awareness	44 (90%)
Focal seizures without impaired awareness	11 (22%)
Tonic seizures	3 (6%)
Tonic clonic seizures per month	
No tonic clonic seizures	22 (45%)
<1 tonic clonic seizure	10 (20%)
1-2 tonic clonic seizures	16 (33%)
≥3 tonic clonic seizures	1 (2%)
Other focal seizures per month	
No other seizures	3 (6%)
<1 other seizure	3 (6%)
1-4 other seizures	17 (35%)
5-9 other seizures	9 (18%)
≥10 other seizures	17 (35%)
Number of anti-epileptic drugs (AED)	
none	1 (2%)
1 AED	13 (27%)
2 AEDs	20 (41%)
3 AEDs	13 (27%)
4 AEDs	1 (2%)
5 AEDs	1 (2%)
Vagal nerve stimulator	7 (14%)
Epilepsy surgery	
- Evaluation during the course of the trial	3 (6%)
-Rejected for epilepsy surgery	10 (20%)
- Having had epilepsy surgery	7 (14%)

Table 2. Clinical characteristics

*Does not add up to 100% as people can have multiple seizure types.

A total of 1060 months were monitored, with median follow-up of 24 months (range 0.5 – 40 months). Twelve subjects opted to keep the loop recorder after the study period of 2 years (median 30 months; range 26 – 40 months). Eleven people had their device removed prematurely (after 0.5 – 13 months, median 6 months) due to: belief that sufficient data were gathered (6); wound infection (3); contour of recorder too visible through the skin (1); vagal nerve stimulator insertion (1).

Standard protocol approvals, registrations, and patient consents

The protocol (clinicaltrial.gov identifier NCT01946776) was scrutinized and approved by the Medical Ethics Committee of the Zuyderland Hospital in Heerlen, Netherlands. Informed consent was obtained from all subjects.

Results

Fifty people were recruited. One person withdrew from the study two days before device implantation, thus leaving 49 people (see table 2) with an implantable loop recorder. One subject withdrew from tilt table testing after 10 minutes. Of the remaining 48 subjects, 23 had a positive tilt table test: 8 mixed type (VASIS I); 2 cardioinhibitory (VASIS IIa [1]; VASIS IIb [1]); 13 vasodepressive (VASIS III).

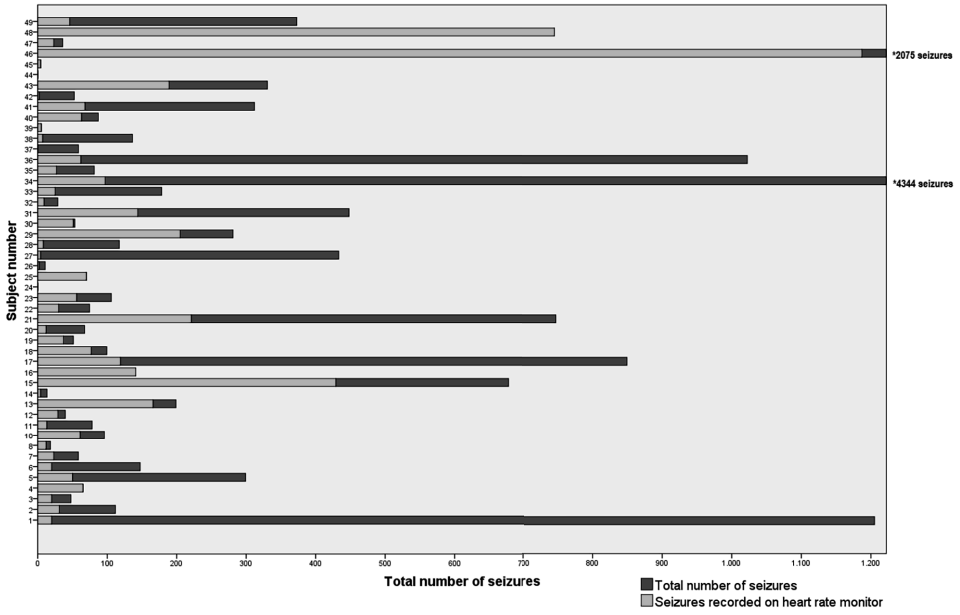


Figure 1. Total number of seizures per subject. Subject 9 was excluded from analysis due to newly diagnosed dissociative seizures.

A total of 16,474 seizures (median 97; range 0 - 4344) were recorded in diaries (table 3). ECG recordings were made of 4679 (median 31, range 0 – 1187) of these seizures (figure 1). One participant had a new diagnosis of dissociative seizures in addition to her definite epileptic seizures during the course of the trial. Her seizures were excluded from the total seizure counts to avoid misclassification.

	Reported in seizure diaries	Recorded on implantable loop recorder
Tonic clonic seizures (n)	350	77 (22%)
Other seizures (n)	16124	4602 (28.5%)

Table 3. Number of reported seizures and number of recorded seizures with implantable loop recorder.

We found no clinically relevant arrhythmias as pre-defined. Non-clinically relevant periods of asystoles were seen in three people, after 1032 months of follow-up (excluding months after detected asystole), resulting in an incidence of 2.91 per 1000 patient-months (95% confidence interval 0.74 – 7.91). All episodes of asystole were non-seizure-related.

Other cardiac arrhythmias not meeting our primary outcome measures occurred in four people: (1) 19 minutes of sustained supraventricular tachycardia up to 220 bpm, most likely atrial tachycardia, induced by extreme emotion; (2) sinus tachycardia lasting 30 seconds with coinciding right bundle branch block configuration; (3) thirteen periods of paroxysmal atrial fibrillation with a ventricular tracking frequency up to 140 bpm lasting maximum two minutes; (4) several periods of paroxysmal atrial fibrillation with a ventricular tracking frequency up to 146 bpm lasting up to 19 minutes. None of these arrhythmias was seizure-related. Those with atrial fibrillation were referred to a cardiologist and oral anticoagulant drugs were not recommended.

Subject 1 suffered from severe concussion due to a seizure-related fall. Six days later, while still reporting headache and nausea, short periods of bradycardia <50 bpm and fourteen periods of asystole of three or four seconds were recorded over the course of three days; neither the subject nor relatives noticed symptoms or seizures in this period. The subject was monitored for an additional year. During the three years of follow-up, no other arrhythmias were seen.

Subject 15 had a habitual seizure with impaired awareness in bed in the early morning. Following the seizure, he went to the toilet and started to sweat profusely, became pale and lost consciousness. According to his mother, this event did not resemble his habitual seizures. The loop recorder showed four minutes of bradycardia (median 40 bpm) including three periods of asystole: one of four and two of three seconds (figure 2). The tilt table test at baseline had provoked a mixed response including a cardioinhibitory component (figure 2-D and E). The event was diagnosed as a cardioinhibitory micturition syncope.

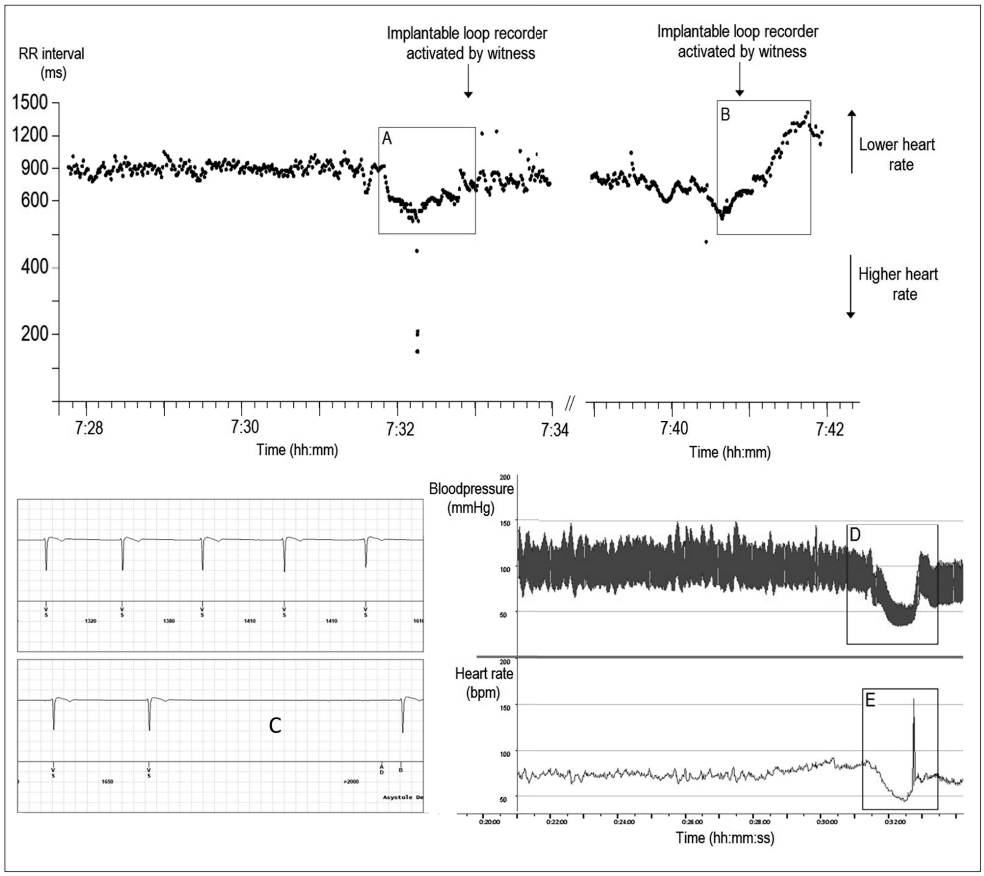


Figure 2.

Subject 15 had a focal seizure with impaired awareness. During the seizure a sudden increase in heart rate is observed (A). Shortly hereafter, the subject was pale and sweating profusely, fell suddenly and lost consciousness. ECG recording initiated by his mother who witnessed the event shows a drop in heart rate (B). Simultaneous automatic ECG recording demonstrated bradycardia leading to a 4s asystole (C). The tilt table test a year prior to the event showed vasovagal syncope with a cardioinhibitory component: a sudden drop in blood pressure (D) coinciding with decrease in heart rate (E).

Subject 39 had short-lasting paroxysmal atrial tachycardia followed by three blocked atrial beats, resulting in an asystole of 3.3 s (figure 3). The subject did not report a seizure or any cardiac symptoms. This was deemed as non-clinically relevant and no further tests were needed. The subject was monitored for 697 days and no other events occurred.

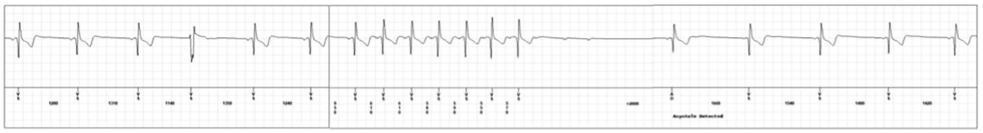


Figure 3.

Non-seizure-related short-lasting paroxysmal atrial tachycardia followed by three blocked atrial beats, resulting in an asystole of 3.3 s.

Discussion

We found no potentially lethal arrhythmias in a population with a high SUDEP risk profile with longstanding epilepsy and frequent convulsions. No postictal arrhythmias were identified that could serve as potential SUDEP biomarkers, despite recording over 16,000 seizures during long-term follow-up. We identified short-lasting periods of asystole in three subjects, but none was clinically relevant and none was seizure-related. Asystole was caused by vasovagal response in one, a diagnosis supported by the classical circumstances and the cardioinhibitory response at the tilt table test.

Video-EEG recordings of SUDEP cases indicate that postictal arrhythmias are highly specific markers of fatal seizures.[5] Cross-sectional studies showed that non-fatal postictal arrhythmias are rare,[6] yet long-term studies are lacking. The absence of postictal arrhythmias in our study despite the recording of thousands of seizures in a high-risk group, suggests that the demonstration of postictal arrhythmias is not sensitive enough to evaluate SUDEP risk.

Ictal asystole is the most common seizure-related cardiac arrhythmia, with a prevalence of 0.32% in people with refractory epilepsy who underwent video-EEG monitoring.[6] We did not identify any ictal asystole despite the high number of seizures. The most likely explanation is that we excluded those with a clinical suspicion of ictal asystole, suggesting that history taking is a powerful screening tool for ictal asystole. Accordingly, most periods of ictal asystole (80%) were found to be symptomatic:[13] loss of tone and falls during a typical focal seizure with impaired awareness provide an important diagnostic clue for ictal asystole.[12, 18, 19] The first of two previous studies reported that one fifth of people had a clinically relevant bradycardia or asystole with subsequent permanent pacemaker insertion.[9] While no special attention was given to exact timing of the arrhythmias, all events coincided with typical focal seizures and likely resemble ictal asystole. The second study reported only one person with short-lasting and non-seizure-related periods of asystole up to 4.8s.[10] Our study confirmed the findings of this study but is in contrast with the first. The major difference between our study and the study reporting a high

proportion of ictal asystole was that we excluded those using beta-blockers and those with clinical symptoms of ictal asystole. No episodes of VT/VF were recorded but this is likely to be explained by the exclusion of those with structural heart disease, the main cause of VT/VF in epilepsy.[8]

The size of our sample allowed us to exclude confidently clinically relevant arrhythmias in a high-risk group. We were also able to rule out more subtle arrhythmias on the implantable loop recorder, such as a second or third degree atrioventricular block without bradycardia, as we reviewed ECG tracings of more than 4000 recorded seizures. Compared to the previous studies, we monitored three times as many patient-hours and recorded ten times as many seizures. Other strengths of our work include the frequent contacts to optimize seizure diaries and to encourage the recording of as many seizures as possible, and tilt table testing at baseline allowing us to establish other non-seizure-related causes of asystole.

Our study also had some limitations. We relied on seizure diaries and did not have video-EEG data. As a consequence, seizures may have been underreported or misclassified.[20, 21] To avoid misclassification we labeled only those seizures with specific semiology as convulsions and we excluded the individual with newly diagnosed dissociative seizures from our analysis. The total number of convulsions may thus have been underestimated. Seizures surrounding arrhythmias, however, were always documented in detail, as subjects were immediately contacted after the occurrence of an arrhythmia. It is highly unlikely that we missed clinically relevant cardiac arrhythmias, as the device was programmed to record arrhythmias automatically.

The major challenge for SUDEP prevention is to obtain reliable individual risk prediction. We currently do not know whom to target and ultimately whom to treat with potential future preventative therapies.[22] We found that postictal arrhythmias, despite their specificity, are to rare to be used as a biomarker. Other, more sensitive biomarkers are thus needed. Prolonged central apnea is more prevalent than postictal asystole but rarely persists in the postictal period.[23] It is therefore questionable whether this marker could reliably predict SUDEP risk. Postictal generalized EEG suppression (PGES) is another potential biomarker that has been linked to SUDEP.[5, 24, 25] Its clinical assessment may, however, be challenging as the presence of PGES, similar to ictal asystole,[26] cannot be ruled out using a single ictal recording and would require recording of multiple seizures per subject.[27] Automated PGES detection[28] or other closely related markers such as ictal increases of electrodermal activity[25] or interclonic intervals[29] could provide alternatives for recordings in a home environment.

Due to the relatively low SUDEP incidence,[2] large cohorts are needed to demonstrate an association between any potential biomarker and SUDEP. Improved ability to process big data and to miniaturize sensors may permit long-term home-based monitoring and increase the identification of novel SUDEP biomarkers.

References

1. Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. Nature reviews Neurology 2009;5:492-504.
2. 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.
3. Massey CA, Sowers LP, Dlouhy BJ, Richerson GB. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. Nature reviews Neurology 2014;10:271-282.
4. Maguire MJ, Jackson CF, Marson AG, Nolan SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). The Cochrane database of systematic reviews 2016;7:CD011792.
5. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. The Lancet Neurology 2013;12:966-977.
6. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. Journal of neurology, neurosurgery, and psychiatry 2016;87:69-74.
7. Bardai A, Lamberts RJ, Blom MT, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. PloS one 2012;7:e42749.
8. Lamberts RJ, Blom MT, Wassenaar M, et al. Sudden cardiac arrest in people with epilepsy in the community: Circumstances and risk factors. Neurology 2015;85:212-218.
9. Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. Lancet (London, England) 2004;364:2212-2219.
10. Nei M, Sperling MR, Mintzer S, Ho RT. Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. Epilepsia 2012;53:e137-140.
11. Kwan P, Brodie MJ. Definition of refractory epilepsy: defining the indefinable? The Lancet Neurology 2010;9:27-29.
12. Schuele SU, Bermeo AC, Alexopoulos AV, et al. Video-electrographic and clinical features in patients with ictal asystole. Neurology 2007;69:434-441.
13. Nguyen-Michel VH, Adam C, Dinkelacker V, et al. Characterization of seizure-induced syncopes: EEG, ECG, and clinical features. Epilepsia 2014;55:146-155.
14. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). European heart journal 2009;30:2631-2671.
15. Brignole M, Menozzi C, Del Rosso A, et al. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. Vasovagal Syncope International Study. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2000;2:66-76.

16. Wieling W, Thijs RD, van Dijk N, Wilde AA, Benditt DG, van Dijk JG. Symptoms and signs of syncope: a review of the link between physiology and clinical clues. Brain : a journal of neurology 2009;132:2630-2642.
17. Brignole M, Moya A, de Lange FJ, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. European heart journal 2018;39:1883-1948.
18. Ghearing GR, Munger TM, Jaffe AS, Benarroch EE, Britton JW. Clinical cues for detecting ictal asystole. Clinical autonomic research : official journal of the Clinical Autonomic Research Society 2007;17:221-226.
19. Bermeo-Ovalle AC, Kennedy JD, Schuele SU. Cardiac and autonomic mechanisms contributing to SUDEP. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society 2015;32:21-29.
20. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Archives of neurology 2007;64:1595-1599.
21. Elger CE, Hoppe C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. The Lancet Neurology 2018;17:279-288.
22. Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: a realistic goal? Epilepsia 2013;54 Suppl 2:23-28.
23. Lacuey N, Zonjy B, Hampson JP, et al. The incidence and significance of periictal apnea in epileptic seizures. Epilepsia 2018.
24. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Annals of neurology 2010;68:787-796.
25. Poh MZ, Loddenkemper T, Reinsberger C, et al. Autonomic changes with seizures correlate with postictal EEG suppression. Neurology 2012;78:1868-1876.
26. Hampel KG, Thijs RD, Elger CE, Surges R. Recurrence risk of ictal asystole in epilepsy. Neurology 2017;89:785-791.
27. Lamberts RJ, Gaitatzis A, Sander JW, Elger CE, Surges R, Thijs RD. Postictal generalized EEG suppression: an inconsistent finding in people with multiple seizures. Neurology 2013;81:1252-1256.
28. Kalitzin SN, Bauer PR, Lamberts RJ, Velis DN, Thijs RD, Lopes Da Silva FH. Automated Video Detection of Epileptic Convulsion Slowing as a Precursor for Post-Seizure Neuronal Collapse. International journal of neural systems 2016;26:1650027.
29. Bauer PR, Thijs RD, Lamberts RJ, et al. Dynamics of convulsive seizure termination and postictal generalized EEG suppression. Brain : a journal of neurology 2017;140:655-668.

CHAPTER 5

5

Value of video monitoring for nocturnal seizure detection in a residential setting

M. van der Lende[1,2] | F.M.E. Cox[1] | G.H. Visser[1] | J.W. Sander[1,3] | R.D. Thijs[1,2,3]

[1] Stichting Epilepsie Instellingen Nederland (SEIN), Achterweg 5, 2103 SW, Heemstede, The Netherlands
[2] Department of Neurology, Leiden University Medical Center (LUMC), Leiden, The Netherlands
[3] NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical & Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, and Epilepsy Society, Chalfont St Peter

Epilepsia. 2016 Nov;57(11):1748-1753

Abstract

Objective Following a sudden death at a residential care unit, the Dutch Health and Care Inspectorate advised to intensify the use of video monitoring (VM) at the unit. We assessed whether VM resulted in increased identification of seizures requiring clinical intervention.

Methods The unit provides care for 340 individuals with refractory epilepsy and severe learning disabilities. Acoustic detection systems (ADS) cover all, 37 people also have a bed motion sensor (BMS) and 46 people with possible nocturnal seizures are now monitored by VM. During a six month period, in all cases of a suspected seizure we asked the caregivers to specify which device alerted them and to indicate whether this led to an intervention. Staff costs of VM were estimated using payroll information.

Results We identified 1208 seizures in 37 individuals; four had no nocturnal seizures; 393 (33%) seizures were only seen on video. In 169 of 1208 (14%) seizures an intervention was made and this included 39 of 393 (10%) seizures only seen on video.
When compared to seizures observed with an ADS or BMS, seizures only seen on video were more often tonic seizures (71% versus 22%, $p<0.001$) and occurred mostly in the beginning or at the end of the night (40% versus 26%, $p<0.001$). The extra staff costs of monitoring was 7,035 euro per seizure only seen on video and leading to an intervention.

Significance VM facilitates nocturnal surveillance, but the costs are high. This underscores the need for development of reliable seizure detection devices.

Introduction

Sudden unexpected death in epilepsy (SUDEP) happens mostly after unwitnessed, nocturnal convulsions [1-3]. Nocturnal supervision seems to be associated with a lower risk[4]. At a boarding school for pupils with epilepsy all SUDEPs occurred when students were unsupervised[5] suggesting that surveillance is protective for high-risk populations.

Various seizure detection systems have been promoted, including acoustic devices, mattress sensors, video detection systems and wearables recording electrodermal activity, heart rate, muscle activity or movement (accelerometry)[6-10]. It is, however, unclear which device can detect nocturnal seizures most accurately and whether this can reduce SUDEP risk[11; 12].

Following a SUDEP at our residential care facility, the Dutch Health and Care Inspectorate advised intensification of video monitoring (VM). It is likely that VM may facilitate seizure detection, but the clinical relevance is not established.

To quantify the benefits of additional nocturnal VM, we assessed whether nocturnal VM resulted in an increase in seizures requiring nursing intervention (e.g. emergency medication).

Methods

Study population

SEIN has a residential care facility housing 340 people with refractory epilepsy and severe learning disabilities. Residents are supported by care staff trained to recognize seizures and administrate rescue medication if required. All caregivers participate in mandatory recurrent epilepsy courses. Each resident has a seizure diary which is updated contemporaneously.

Various monitoring devices are used: all have an acoustic detection system (ADS) (DeHeerMedicom, Born, The Netherlands), and some have a bed motion sensor (BMS) (Epicare 3000, Danish Care Technology, Sorø, Denmark) or a video monitoring system (DeHeerMedicom, Born, The Netherlands). ADS and BMS detection thresholds are individually set.

There are six seizure monitoring units, each staffed with up to four caregivers. Each receives data from up to 80 people: up to 80 ADSs, up to 10 BMSs and up to 16 video feeds. One person monitors all systems in units with up to 12 video feeds. In units with

over 12 video feeds, two monitor the systems. Roles are rotated every 1.5 hours. Those not on monitoring duty perform physical checks. When a seizure is suspected, the resident is contacted through an intercom system. If there is no response, a caregiver will determine if assistance is required.

After the Inspectorate advice, new criteria for VM were formulated. It was recommended for all with (1) putative evidence of unwitnessed nocturnal convulsions such as incontinence or a tongue bite on awakening and (2) convulsions in the late evening or early morning as the ADS is less reliable then due to background noise of people getting ready for bed / getting out of bed. Up to 80 ADSs are monitored by one person and sounds made by a subject can drown out seizure-related noises of another. The number of video-monitored residents increased from 12 to 46, leading to an increment of night staff from 20 to 24 per shift.

All these 46 residents were asked to participate and informed consent was obtained from them or in some cases assent was obtained from legal guardians. Demographic data, medications, epilepsy syndrome, duration, seizure types, IQ and body mass index were extracted from the notes. Seizure frequencies were derived from the seizure diaries.

During a six-month period, caregivers recorded details of each nocturnal seizure in those video-monitored: time and type of seizure, detecting monitoring device, if the person was attended and if an intervention was required.

Caregivers used a similar seizure classification sheet to usual care including the following seizure types: convulsive, tonic, myoclonic, complex partial and unclassified. A nursing intervention was scored when the caregiver (1) repositioned the subject, (2) administered rescue medication, or (3) stimulated the vagal nerve stimulator. (see appendix A)

All data was collected into a database (SPSS for windows, version 22) and divided into two groups: seizures only seen on video and seizures detected by ADS or BMS, whether seen on video or not. These groups were then compared, looking for differences in seizure types, seizure timing and interventions performed. Actual staff costs were obtained from the appropriate department.

Validation of caregiver reports

If a seizure was suspected, staff pressed the record button thus saving ten minutes of video feed. A random sample of two seizures, per seizure type, per subject was selected of all seizures only seen on video to validate the caregivers' seizure classification. One neurologist from a panel (RDT, FC and GHV) blinded to the caregivers scores reviewed the videos. They recorded whether they agreed that the event was epileptic and classified the

seizure type. They used the same seizure nomenclature as the caregivers, but were asked to specify further the event type (e.g. hyperkinetic seizure). To score the certainty of the seizure classification and epileptic nature of the event a score from 1 (not certain at all) to 5 (very certain) was used (See appendix B). All videos for which there were doubts over the nature or classification (score 3 or lower) were reviewed by all three neurologists to establish a consensus agreement.

BMS and ADS event logs were automatically stored. BMS logs were used to check whether seizures reported as being only seen on video had no matching BMS record. For the ADS a random sample of three nights with nocturnal events per subject was selected and checked for event logs of seizures reported as picked up by the ADS.

Statistical analysis

Differences between seizures only seen on video versus all other seizures were estimated by fitting a multivariable logistic regression model. To account for the correlation between seizures in the same individual we used generalized estimating equations (GEE). All variables were entered as predictors using a backwards selection procedure ($p<0.05$) to determine which variables are independent determinants of seizures detected only with help of VM.

Results

Forty-one of 46 people monitored were included. Five declined participation. All had an ADS and fourteen a BMS. General characteristics are listed in table 1.

Reported events

During the six-month period caregivers reported 1260 events in 37 of the 41 participants. No seizures were identified in four. Fifty-two events were false positives as determined by the caregivers attending the individual.

An intervention occurred in 167 of 1208 seizures. Twelve of the 37 individuals with nocturnal seizures did not receive an intervention.

Age (years)		37 (SD 18.3)
Gender		24 male / 17 female
Epilepsy etiology:		
	Genetic	18 (44%)
	Structural metabolic	11 (27%)
	Unknown	12 (29%)
Seizure type:		
	Focal	29 (71%)
	Generalized	12 (29%)
Age of onset (years)		4.3 (SD 4.5)
Duration epilepsy (years)		33.1 (SD 17.7)
Seizure type (number of subjects):		
	Tonic seizures	20 (48.8%)
	Convulsive seizures	37 (90.2%)
	Complex partial seizures	22 (53.7%)
Daily seizure frequency		
	0 - 4 seizures / month	26 (63%)
	5 - 9 seizures / month	6 (15%)
	≥10 seizures / month	9 (22%)
Nocturnal seizure frequency		
	0 - 4 seizures / month	31 (76%)
	5 - 9 seizures / month	7 (17%)
	≥10 seizures / month	3 (7%)
Number of AEDs		
	none	2 (5%)
	1 AED	5 (12%)
	2 AEDs	11 (27%)
	3 AEDs	15 (37%)
	4 AEDs	8 (20%)
Vagal nerve stimulator		7 (17%)
IQ		
	≤20	9 (22%)
	21 - 40	6 (15%)
	41 - 60	10 24%)
	61 - 80	4 (10%)
	> 80	1 (2%)
	unknown	11 (27%)
Body Mass Index		24.2 (SD 5.8)

Table 1. Patient characteristics (N=41)

AED Anti-epileptic drug

Characteristics of seizures only seen on video

Caregivers reported that 393 (33%) seizures, in 29 of 37 people, were only seen on video. When compared to seizures observed with an ADS or BMS, seizures only seen on video occurred more often either at the beginning or end of the night (41% versus 26% of seizures, p<0.001) and were more often tonic seizures (71% versus 22% of seizures, p<0.001).

Convulsive seizures (CSs) and myoclonic seizures were also frequently observed with the ADS or BMS: 19 of 37 people had CSs seen only on video, but this was only 12% of all detected CSs (figure 1). Seven of these 19 people had a BMS and 19 of these 46 convulsive seizures (41%) occurred either in the early morning or late evening.

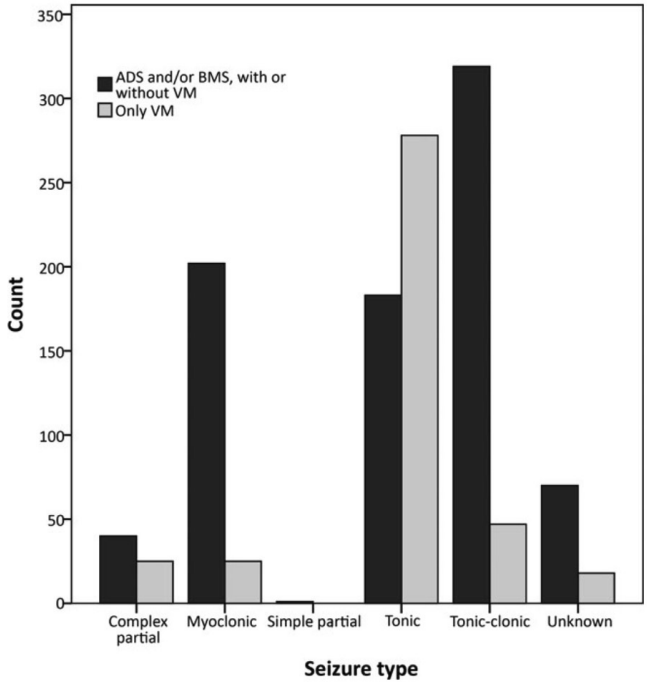


Figure 1. Seizures only seen on video, versus seizures observed using the ADS or BMS.

ADS acoustic detection system; *BMS* bed motion sensor

Of the 393 seizures only seen on video, 39 required an intervention (table 2) and 14 of 29 people with seizures only seen on video had an event requiring an intervention. When compared to seizures only seen on video, seizures identified on an ADS or BMS required more interventions (16% versus 10%, p=0.006).

	Seizures only seen on video (n = 393)	Seizures observed with ADS or BMS (n = 815)
All interventions	39 (9.9%)	128 (15.7%)
Repositioning the person	14 (3.6%)	58 (7.1%)
Activating VNS	6 (1.5%)	6 (0.7%)
Emergency medication	17 (4.3%)	59 (7.2%)
VNS activation and emergency medication	2 (0.5%)	5 (0.6%)

Table 2. Interventions

VM video monitoring, *VNS* vagal nerve stimulator

When fitting a multivariable logistic regression model using generalized estimating equations, only three variables (seizure time, seizure type and intervention) were significant independent predictors. (table 3)

	Only seen on VM (n = 393)	Seen on an ADS or BMS (n=815)	p-value	OR	95%CI OR
Seizure type:					
Tonic	278 (71%)	183 (22%)	0.010	2.34	1.23 – 4.46
Other	115 (29%)	632 (78%)			
Time of seizure:					
22.30–0.00 / 6.30–8.30 hours	160	214	<0.001	1.53	1.25 – 1.87
0.00–6.30 hours	233	601			
Intervention done:					
no	354	687	0.005	0.61	0.44 – 0.86
yes	39	128			

Table 3. Seizures only seen on VM versus all other seizures. P-value and odds ratios calculated using a multivariable model in generalized estimating equations.

VM videomonitoring; *ADS* acoustic detection system; *BMS* bed motion sensor; *OR* odds ratio

Validation of caregivers' reports

We randomly selected 89 videos of events only seen on video; 26 were excluded, as recording started too late in the course of the seizure to allow for a definite assumption. The remaining 63 were classified by the panel.

There was agreement on the epileptic nature of the event in 58 of 63 videos (92%). There were some differences in the caregivers' classification compared with those of the panel. Seizures classified as CSs by the caregivers were often categorized by the panel as focal hyperkinetic seizures.

BMS logs were reviewed for 161 seizures only seen on video as reported by the caregivers. In 134 (83%) it was confirmed that the BMS did not sound in the 15 minutes adjacent to the reported seizure onset.

If caregivers reported that the ADS alerted them, an event could be identified in the log in 76 of 82 (93%) seizures between 15 minutes prior to and after the reported seizure onset.

Cost-effectiveness

Due to the increase in people video-monitored, four extra staff were required per night, resulting in extra yearly personnel costs of €548,762 (€274,381/ 6 months). We identified 393 seizures which were only seen with VM: 274,381 / 393 = €698 per detected seizure. Thirty-nine seizures receiving an intervention were only seen on video: 274,381 / 39 seizures = €7,035 per seizure and 47 CSs were only seen on video: 274,381 / 47 = €5,838 per seizure.

Discussion

VM in conjunction with ADSs and BMSs facilitated nocturnal surveillance: 33% of all observed seizures were only seen on video. VM also helped detecting clinically relevant seizures: of all only seen on video, 10% required an intervention. Seizure timing (late night or early morning) and seizure type (tonic seizures) were significantly associated with seizures only seen on video. The added value of VM should, however, be weighed against extra costs.

We used the caregivers' reports as gold standard to determine which device alerted them to a seizure. This has implications as we cannot guarantee that all seizures were noticed. Those with subtle signs are likely missed but also those with obvious motor signs may have been ignored, as caregivers had to continuously pay attention to multiple video feeds and other detection devices. While we acknowledge that we may have underestimated the

number of seizures, we did not consider screening videos of reported seizure free periods, as we aimed to assess the added value of VM and not to quantify its (obvious) limitations. Such exercise would also require additional EEG monitoring. A study on a similar population reported that when using a combination of video-EEG and accelerometry, the number of detected seizures was seven-fold higher than seizures seen by nurses. [6].

Caregivers indicated which device captured a seizure. Multitasking may also have resulted in other alarms being ignored. We crosschecked caregivers' reports with ADS and BMS event logs and agreement was good: 93% for the ADS and 83% for the BMS. For the ADS, though, we could not ascertain whether seizures only seen on video were truly silent: the system records an event for any sound above the threshold. Other sounds in the peri-ictal period (e.g. door shutting) may also result in a data point. The same principle applies to BMSs: an alarm signal may also result from a subject repositioning after a seizure. No events were found in 83% of seizures without a staff record of a BMS alarm.

We also relied on caregivers' seizure classification. An expert panel, therefore, evaluated a random seizures subsection. We found a high agreement (92%) on the epileptic nature of an event between the panel and caregivers. Agreement on seizure type classification was, however, poor (38%), confirming previous report [13]. The caregivers' most frequent inaccuracy was classifying "hyperkinetic focal seizures" as CSs. Detection systems might have the same limitation as caregivers judgment: a BMS will not allow differentiation between frontal lobe seizures and CSs. In view of the classification errors we may have overestimated the number of CSs that were detected by video only.

The majority of seizures only seen on video were tonic seizures. BMSs are likely to miss seizures without excessive movement: a study on a BMS reported that it only identified three of eleven tonic seizures on an awake subject and none while asleep[14]. A high number of seizures only seen on video were either on late evening or early morning. ADSs are probably less reliable during periods of high background noise.

We found the greatest added value of VM to be for tonic seizures, but there is no evidence that these increase SUDEP risk. SUDEP was preceded by a CS in all monitored cases.[15] Case control studies show a high CS frequency to be a major SUDEP risk factor [4; 16-18]. Monitoring devices designed to detect nocturnal CSs may therefore decrease a person's SUDEP risk: people are less likely to die of SUDEP when they share a room or when there is a listening device[4]. An ADS is probably a sensitive way to detect CSs, as in 85% of CSs an ictal cry is heard [19].

Detecting a CS that could be followed by SUDEP is no guarantee for preventing SUDEP. There are several reports of observed SUDEP cases, where a witness could not prevent it [20]

and prompt resuscitation procedures failed [12]. We are aware of two (unpublished) cases of residents dying of SUDEP despite VM.

Clinical implications

VM appeared very costly: personnel outlays were estimated at €7,035 per seizure seen only on video and requiring an intervention. With SUDEP estimated to occur in 1 of every 2,000 – 5,000 CSs [21], it would costs millions to detect an additional seizure leading to SUDEP, without guarantee that this will be preventive. We believe that the limited added value of VM is outweighed by the high costs. VM might facilitate detection of CSs as well, but this seemed often related to ADS failure or BMS absence. We thus do not recommend widespread VM implementation. In view of high costs and questionable protective effects, it seems more reasonable to optimize ADS or to consider other seizure detection devices. Our study underscores the need for the development of less costly, reliable detection devices. As those with intellectual disabilities have a higher seizure burden and SUDEP risk, the search for protective measures is even more urgent in this population [18; 22-24].

References

1. Nashef L, Garner S, Sander JW, et al. Circumstances of death in sudden death in epilepsy: interviews of bereaved relatives. *J Neurol Neurosurg Psychiatry* 1998;64:349-352.
2. Nobili L, Proserpio P, Rubboli G, et al. Sudden unexpected death in epilepsy (SUDEP) and sleep. *Sleep Med Rev* 2011;15:237-246.
3. Lamberts RJ, Thijs RD, Laffan A, et al. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia* 2012;53:253-257.
4. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. *Neurology* 2005;64:1131-1133.
5. Nashef L, Fish DR, Garner S, et al. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. *Epilepsia* 1995;36:1187-1194.
6. Nijsen TM, Arends JB, Griep PA, et al. The potential value of three-dimensional accelerometry for detection of motor seizures in severe epilepsy. *Epilepsy Behav* 2005;7:74-84.
7. Kalitzin S, Petkov G, Velis D, et al. Automatic segmentation of episodes containing epileptic clonic seizures in video sequences. *IEEE Trans Biomed Eng* 2012;59:3379-3385.
8. Van de Vel A, Cuppens K, Bonroy B, et al. Non-EEG seizure-detection systems and potential SUDEP prevention: state of the art. *Seizure* 2013;22:345-355.
9. Ramgopal S, Thome-Souza S, Jackson M, et al. Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. *Epilepsy Behav* 2014;37:291-307.
10. van Andel J, Thijs RD, de Weerd A, et al. Non-EEG based ambulatory seizure detection designed for home use: What is available and how will it influence epilepsy care? *Epilepsy Behav* 2016;57:82-89.
11. Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: a realistic goal? *Epilepsia* 2013;54 Suppl 2:23-28.
12. Swinghamer J, Devinsky O, Friedman D. Can post-ictal intervention prevent sudden unexpected death in epilepsy? A report of two cases. *Epilepsy Behav* 2012;24:377-379.
13. Whitten E, Griffiths A. Implementing epilepsy guidelines within a learning disability service. *Seizure* 2007;16:471-478.
14. Poppel KV, Fulton SP, McGregor A, et al. Prospective Study of the Emfit Movement Monitor. *J Child Neurol* 2013;28:1434-1436.
15. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol* 2013;12:966-977.
16. Hesdorffer DC, Tomson T, Benn E, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. *Epilepsia* 2012;53:249-252.
17. Nilsson L, Farahmand BY, Persson PG, et al. Risk factors for sudden unexpected death in epilepsy: a case-control study. *Lancet* 1999;353:888-893.
18. Walczak TS, Leppik IE, D'Amelio M, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology* 2001;56:519-525.
19. Elzawahry H, Do CS, Lin K, et al. The diagnostic utility of the ictal cry. *Epilepsy Behav* 2010;18:306-307.

20. Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. *J Neurol Neurosurg Psychiatry* 2000;68:211-213.
21. Shorvon SD. Handbook of Epilepsy Treatment. John Wiley & Sons, 2010; 2010.
22. Kiani R, Tyrer F, Jesu A, et al. Mortality from sudden unexpected death in epilepsy (SUDEP) in a cohort of adults with intellectual disability. *J Intellect Disabil Res* 2014;58:508-520.
23. Young C, Shankar R, Palmer J, et al. Does intellectual disability increase sudden unexpected death in epilepsy (SUDEP) risk? *Seizure* 2015;25:112-116.
24. Devinsky O, Asato M, Camfield P, et al. Delivery of epilepsy care to adults with intellectual and developmental disabilities. *Neurology* 2015;85:1512-1521

CHAPTER 6

6

Nocturnal supervision and SUDEP risk at different epilepsy care settings

M. van der Lende, MD[1,2] | D.C. Hesdorffer, PhD[3] | J.W. Sander MD, PhD, FRCP[1,4] | R.D. Thijs MD, PhD[1,2,4]

[1] Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands
[2] Leiden University Medical Center (LUMC), Leiden, Netherlands
[3] GH Sergievsky Center and Department of Epidemiology, Columbia University, New York, New York, U.S.A.
[4] NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, and Chalfont Centre for Epilepsy, Chalfont St Peter, SL9 0RJ, UK

Neurology. 2018 Oct 16;91(16):e1508-e1518.

Abstract

Objective To estimate SUDEP incidence in people with intellectual disabilities in residential care settings and ascertain effects of nocturnal seizures and nocturnal supervision on SUDEP risk.

Methods We conducted a nested case-control study reviewing records of all people who died at two residential care settings over 25-years. Four controls per case were selected from the same population, matched on age (+/- 5 years) and residential unit. Nocturnal supervision was graded in three categories: (1) no supervision; (2) a listening device or a roommate or physical checks at least every 15 minutes; (3) two of the following: a listening device, roommate, additional device (bed motion sensor/video monitoring) or physical checks every 15 minutes. Outcome measures were compared using Mann Whitney U tests and Fischer's exact tests.

Results We identified 60 SUDEP cases and 198 matched controls. People who died of SUDEP were more likely to have nocturnal convulsive seizures in general (77% of cases vs. 33% of controls, $p<0.001$) and a higher frequency of nocturnal convulsive seizures. Total SUDEP incidence was 3,53/1000 patient/years (95% CI 2.73 – 4.53). Incidence differed among centers: 2.21/1000 patient/years (95% CI 1.49 – 3,27) vs. 6.12/1000 patient/years (95% CI 4.40 – 8.52). There was no significant difference in nocturnal supervision among cases and controls but there was a difference among centers: the center with a lowest grade of supervision had the highest SUDEP incidence.

Conclusions Having nocturnal seizures, in particular convulsions may increase SUDEP risk. Different levels of nocturnal supervision may account for some of the difference in incidence.

Introduction

Sudden unexpected death in epilepsy (SUDEP) is one of the most frequent causes of death in people with epilepsy, particularly chronic epilepsy. It may account for up to a fifth of all cases of premature mortality amongst people with epilepsy.[1] The pathological mechanisms are unclear but multiple SUDEP risk factors have been identified. Having frequent convulsive seizures is the greatest risk factor.[2, 3] Circadian factors seem important, with higher risk for those with nocturnal sleep-related convulsive seizures,[4] but this still needs confirmation.

SUDEP is mostly a sleep-related and unwitnessed event.[4-6] Conversely, nocturnal supervision seems to lower SUDEP risk.[7] This poses a problem for residential care facilities housing people with refractory epilepsy and intellectual disabilities.[8] SUDEP incidence is substantial (3.6 – 3.8 per 1000 person years)[9, 10] but recommendations for nocturnal supervision are lacking.[11] It is also well recognized that nocturnal seizures may go unnoticed. A recent survey indicated that one third of nocturnal seizures in a residential population were missed despite the use of an acoustic detection system.[12]

This raises the question whether enhancing nocturnal supervision may lower SUDEP risk. We aimed to estimate SUDEP incidence in residential care settings and to determine the effects of nocturnal seizures and nocturnal supervision on the risk of SUDEP.

Methods

Selection of cases and controls

We selected all cases of SUDEP in two epilepsy residential care facilities: Stichting Epilepsie Instellingen Nederland (SEIN) and Chalfont Centre for Epilepsy (CCE) which provide residential care facilities for people with complex needs. People are assigned to a specific residential unit depending on epilepsy severity, behavioral problems and co-morbidities. For SEIN we reviewed all people who died while in residential care from 1987 to 2012. For the CCE we reviewed all deaths from 1989 to 2014. Deaths at the CCE between 1989 and 2009 were previously reported.[13]

All cases of definite and probable SUDEP were selected. Deaths of those aged over 60 years were excluded, due to higher risk of competing causes of death. Four controls per case were matched on age (+/-5 years) and residential unit. The date of death of the case was used as an index date for matching and extraction of individual attributes of the controls.

Identification of probable SUDEP cases

All sudden deaths were reviewed by MvdL and classified as non-SUDEP deaths or as possible, probable and definite SUDEP according to the Unified SUDEP definitions.[14] As an additional criterion to portray the diagnosis of "probable SUDEP", we developed a point score based on established SUDEP circumstances. Factors increasing SUDEP probability included age under forty years,[15] signs of a recent seizure,[16-18] and an unwitnessed and sleep-related death.[4-6] Circumstances making SUDEP less likely included: having a fever or illness at time of death, a history of heart disease or being seizure-free for over a year[19] (Table 1). These criteria were weighted on effect and points were assigned to all cases. The cut-off score for the differentiation of probable SUDEP vs. probable non-SUDEP sudden death was determined by applying the point scores to the SUDEP and non-SUDEP cases with a postmortem examination.

Items suggestive for SUDEP	Yes	No	Unknown	Items not suggestive for SUDEP	Yes	No	Unknown
Under forty years of age	+3	-3	0	Fever	-2	+2	0
Signs of seizure	+3	-3	0	Illness, no fever	-1	+1	0
Nocturnal event	+1	-1	0	History of cardiac arrhythmia	-1	+1	0
Unwitnessed	+1	-1	0	History of ischaemic heart disease / heart failure	-2	+2	0
				Seizure-free	-2	+2	0

Table 1. Classification system for sudden unexpected deaths.

All cases with a score ≥ 1 were labelled as "probable SUDEP".
Sudden deaths with a score ≥ 1 were presumed to be probable SUDEP and those with a score < 1 were categorized as non-SUDEP sudden deaths. An expert panel (RDT and JWS) discussed cases if the initial clinical assessment (MvdL) was not consistent with the test score, or if > 3 variables were unknown.

Degree of nocturnal supervision

Until the late nineties, both care facilities had twin rooms and small dormitories (up to four people per room) but from 2000 onwards all residents moved to single room accommodations. In 1999, SEIN deployed a central nocturnal acoustic detection system covering all residents. Bed motion sensors were added in 2008 and video monitoring in 2010 for those in whom there was a suspicion of unwitnessed nocturnal events. The number of staff allocated to ensure proper monitoring of seizure detection systems increased to one carer per fourteen residents. Individuals were physically checked at least once or twice a night and additional checks are carried out on a need basis.

No central nocturnal seizure detection system was used at the CCE, although individual devices such as listening devices and so called 'exit alarms' (sensors which alert when someone leaves their bed) were used in some. Over the years, the number of carers increased from one per twelve to one per six residents. The institutional protocol recommends that all residents were physically checked once every 15 or 30 minutes.

We graded the intensity of nocturnal supervision for all cases and controls (table 2). The grading entails various factors including the presence and type of seizure detection devices, the presence of a roommate (who may alert the nursing staff in case of a seizure) and the frequency of physical checks. A survey of video EEG recorded SUDEP cases indicated that terminal apnea occurred within 11 minutes postictally.[17] We therefore only assigned a higher grade of nocturnal supervision to those with physical checks, occurring once every 15 minutes.

Grade 1	• No central acoustic or listening device AND sleeping alone AND physical checks > 15 minutes apart
Grade 2	• Central acoustic or listening device • Having a roommate • Having a physical check at least every 15 minutes
Grade 3	• Central acoustic or listening device AND dormitory • Central acoustic or listening device AND additional device (e.g. bed motion sensor / video monitoring) • Central acoustic or listening device AND Having a physical check at least every 15 minutes

Table 2. Grades of nocturnal supervision

Individual characteristics

For all SUDEP cases and controls, medical records were abstracted for the following variables: age, sex, age of onset of epilepsy, seizure types, seizure frequency, epilepsy classification, number of antiepileptic drugs, use of benzodiazepines, IQ, type of nocturnal supervision, number of residents per carer at night.

The nocturnal and diurnal seizure frequency were estimated for the year prior to death of the case, as an average per month, specified by seizure type (convulsions or other seizure type(s)).

Analysis

The incidence of (probable) SUDEP was estimated by dividing the number of SUDEP cases by the total number of person years per center. A nested case-control study compared SUDEP cases to controls. Mann Whitney U tests and Fischer's exact tests were used to analyze differences in SUDEP risk factors between cases and controls. Grade of supervision

was corrected for epilepsy severity (number of nocturnal convulsive seizures) by fitting a multivariable logistic regression model.

Standard Protocol Approvals, Registrations, and Consents
The study was approved by the Leiden University Medical Center Ethics Committee with a waiver of informed consent. It was also registered as a service evaluation in the UK.

Data availability
Anonymized data will be shared by request from any qualified investigator.

Results

Altogether, we identified 60 SUDEP cases: 25 at center 1 (8 SUDEP and 17 probable SUDEP) and 35 in center 2 (22 SUDEP and 13 probable SUDEP cases). All definite SUDEP and probable SUDEP cases scored >1 on the SUDEP probability score. Two cases could not be assessed with the SUDEP score due to missing values but were classified as probable SUDEP by the expert panel.

Total duration of follow-up was 17016.5 patient years, resulting in a total SUDEP incidence of 3.53 per 1000 patient/years (95% CI 2.73 – 4.53). At center 1, over 26 years we accumulated 11302 patient/years resulting in a SUDEP incidence of 2.21/1000 patient/years (95% CI 1.49 – 3.27). In center 2, a total 5714.5 patient years was accumulated leading to an incidence of 6.12/1000 patient/years (95% CI 4.40 – 8.52).

Cases more often had convulsive seizures ($p = 0.019$) and had a higher IQ compared to controls ($p = 0.005$) (table 3). Compared to controls, SUDEP cases more often had nocturnal convulsive seizures ($p < 0.001$). Cases also had a higher frequency of convulsive seizures ($p = 0.001$) and nocturnal convulsive seizures in particular ($p < 0.001$) (Table 4; Figure 1). There was no significant difference in the grade of supervision; also after correction for epilepsy severity (number of nocturnal convulsive seizures (logistic regression nocturnal supervision grade 1: OR 0.73; 95% confidence interval 0.15 – 3.46; $p = 0.693$; grade 2 OR 0.37; 95% confidence interval 0.08 – 1.83; $p = 0.225$)

	Cases (n=60)		Controls (n=198)		Fischer's exact test p-value
Age (years)	39.3 SD 12,94	N=60	40.0 SD 13,45	N=198	0.666*
Sex	70% male	N=60	67% male	N=198	0.753
Epilepsy etiology:		N=58		N=177	0.179
Genetic	12	21%	21	12%	
Structural metabolic	25	43%	95	54%	
Unknown	21	36%	61	35%	
Seizure type:		N=60		N=182	0.436
Focal	47	78%	152	84%	
Generalized	13	22%	30	17%	
Age of onset (years)	7.6 SD 9,63	N = 54	6,0 SD 6.23	N=122	0.946*
Duration epilepsy (years)	32.7 SD 14,3	N = 54	36.3 SD 12,75	N=122	0.126*
Seizures:					
Convulsive seizures	58/59	98%	160/182	88%	0.019
Focal seizures with impaired awareness	42/56	75%	135/174	78%	0.717
Focal aware seizures	2/55	4%	13/150	9%	0.363
Tonic seizures	15/56	27%	54/163	33%	0.409
Myoclonic seizures	10/56	18%	32/163	82%	0.846
Absence seizures	16/55	29%	47/167	28%	1.000
Atonic seizures	10/56	18%	17/159	11%	0.167
Number of AEDs		N=54		N=179	0.097
None	2	4%	0	0%	
1 AED	7	13%	21	12%	
2 AEDs	22	41%	71	40%	
3 AEDs	19	35%	70	39%	
≥4 AEDs	4	8%	17	10%	
Use of benzodiazepines		N=53		N=178	0.079
Yes	15	28%	75	42%	
No	38	72%	103	58%	
IQ		N=43		N=138	0.005
<20	1	2%	0	0%	
20 – 35	5	12%	10	7%	
35 – 49	3	7%	28	20%	
50 – 69	15	35%	55	40%	
70 – 79	4	9%	25	18%	
80 – 89	7	16%	14	10%	
≥90	8	19%	6	4%	

Table 3. Characteristics of SUDEP cases versus controls.

AED= anti-epileptic drug * Mann-Whitney U test

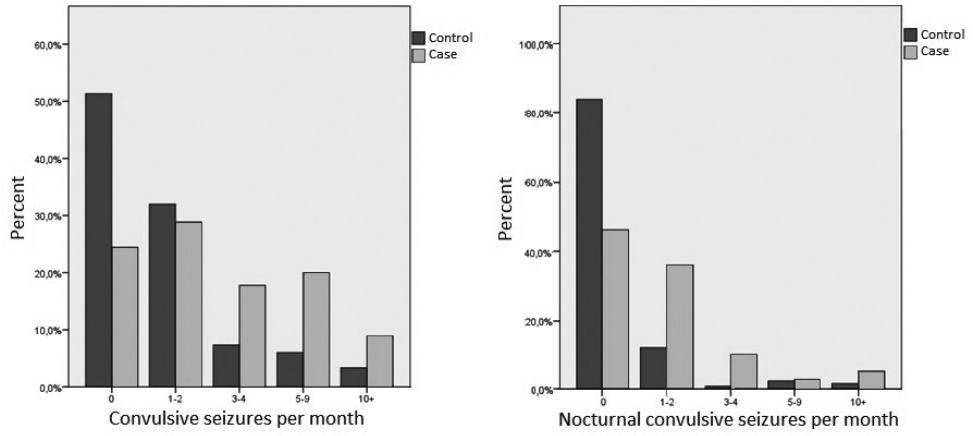


Figure 1.Number of all convulsive seizures and nocturnal convulsive seizures in cases versus controls.

		Cases (n)	Controls (n)	Fischer's exact test p-value
Having convulsive seizures		58/59 (98%)	160/182 (88%)	0.019
Having nocturnal convulsive seizures		34/44 (77%)	47/146 (32%)	< 0.001
Convulsive seizure frequency (n)				0.001
	0	11/45 (24%)	77/150 (51%)	
	1-2	13/45 (29%)	48/150 (32%)	
	3-4	8/45 (18%)	11/150 (7%)	
	5-9	9/45 (20%)	9/150 (6%)	
	10+	4/45 (9%)	5/150 (3%)	
Nocturnal convulsive seizure frequency (n)				< 0.001
	0	18/39 (46%)	117/140 (84%)	
	1-2	14/39 (36%)	17/140 (12%)	
	3-4	4/39 (10%)	1/140 (1%)	
	5-9	1/39 (3%)	3/140 (2%)	
	10+	2/39 (5%)	2/140 (1%)	
Grade of supervision				0.208
	1	28/48 (58%)	84/163 (52%)	
	2	16/48 (33%)	73/163 (45%)	
	3	4/48 (8%)	6/163 (4%)	

Table 4. SUDEP risk factors and grade of supervision of cases and controls.

When comparing cases of center 1 and center 2, no significant differences were seen for the presence of convulsive seizures, presence of nocturnal convulsive seizures, frequency of convulsive seizures and frequency of nocturnal convulsive seizures. Cases from center 1 had a significantly higher grade of nocturnal supervision compared to cases from center 2 ($p < 0.001$) (Table 5). The same applied to the controls from center 1 versus center 2 ($p < 0.001$) (Table 5 and Figure 2). Patient characteristics for cases and controls per center are listed in table 6.

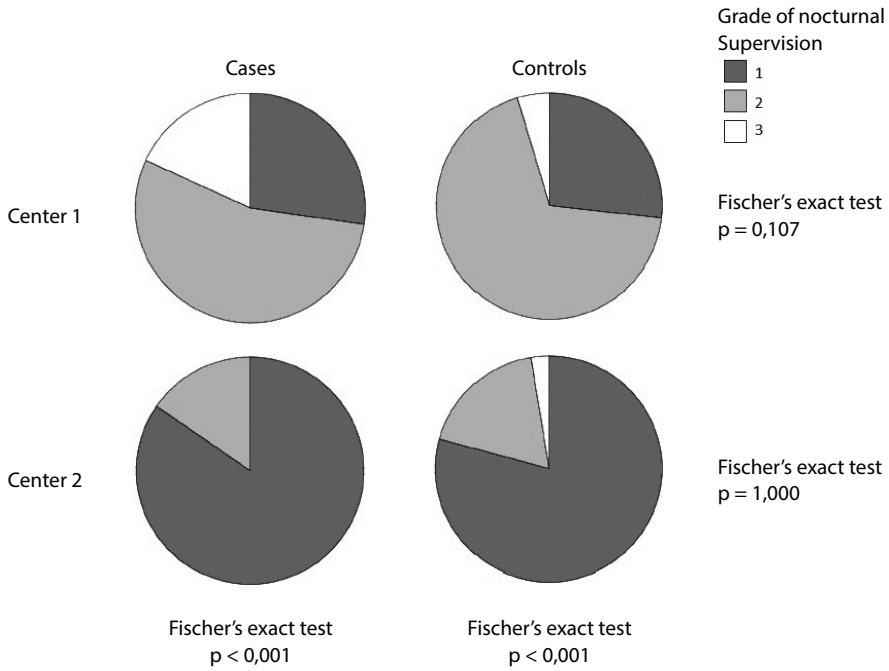


Figure 2. Comparisons of nocturnal supervision grade among centers 1 and 2 for cases and controls in percentages.

	Cases center 1	Cases center 2	Fischer's exact test p-value	Controls centre 1	Controls centre 2	Fischer's exact test p-value
Having convulsive seizures	23/24 (96%)	35/35 (100%)	0.407	69/81 (85%)	91/101 (90%)	0.364
Having nocturnal convulsive seizures	14/17 (82%)	20/27 (74%)	0.716	24/65 (37%)	23/81 (28%)	0.290
Frequency of convulsive seizures			0.557			0.090
0	4/19 (21%)	7/26 (27%)		39/69 (57%)	38/81 (47%)	
1-2	4/19 (21%)	9/26 (35%)		16/69 (23%)	32/81 (40%)	
3-4	5/19 (26%)	3/26 (12%)		7/69 (10%)	4/81 (5%)	
5-9	5/19 (26%)	4/26 (15%)		3/69 (4%)	6/81 (7%)	
10+	1/19 (5%)	3/26 (12%)		4/69 (6%)	1/81 (1%)	
Nocturnal convulsive seizure frequency			0.594			0.833
0	5/14 (36%)	13/25 (52%)		51/63 (81%)	66/77 (86%)	
1-2	5/14 (36%)	9/25 (36%)		9/63 (14%)	8/77 (10%)	
3-4	2/14 (14%)	2/25 (8%)		0/63 (0%)	1/77 (1%)	
5-9	1/14 (7%)	0/25 (0%)		2/63 (3%)	1/77 (1%)	
10+	1/14 (7%)	1/25 (4%)		1/63 (2%)	1/77 (1%)	
Grade of supervision			< 0.001			< 0.001
1	6/22 (27%)	22/26 (85%)		23/86 (27%)	61/77 (79%)	
2	12/22 (55%)	4/26 15%)		59/86 (69%)	14/77 (18%)	
3	4/22 (18%)	0/26 (0%)		4/86 (5%)	2/77 (3%)	
Witnessed death			0.218			
Witnessed	4/21 (19%)	5/23 (22%)				
Seen minutes after death	2/21 (10%)	7/23 (30%)				
Unwitnessed	15/21 (71%)	11/23 (48%)				
Resuscitated	6/21 (29%) (4 witnessed SUDEP, 2 seen minutes after death)	9/20 (45%) (4 witnessed SUDEP, 5 seen minutes after death)	0.424			

Table 5. SUDEP risk factors and grade of nocturnal supervision: center 1 cases versus center 2 cases and center 1 controls versus center 2 controls

	Cases center 1 (n=25)		Cases center2 (n=35)		Cases total (n=60)		Controls center 1 (n=92)		Controls center 2 (n=106)		Controls total (n=198)	
Age (years)	**33.9 SD 14.4**		**43.1 SD 10.4**		**39.3 SD 12.94**		**34.4 SD 14.1**		**44.5 SD 11.1**		40.0 SD 13.45	
Sex	68% male		71% male		70% male		64% male		69% male		67% male	
Epilepsy etiology:	N=23		N=35		N=58		N=87		N=90			
Genetic	6	26%	6	17%	12	21%	9	10%	12	13%	21	12%
Structural metabolic	9	39%	16	46%	25	43%	42	48%	53	59%	95	54%
Unknown	8	35%	13	37%	21	36%	36	41%	25	28%	61	35%
Seizure type:	N=25		N=35				N=86		N=96			
Focal	18	72%	29	83%	47	78%	67	78%	85	89%	152	84%
Generalized	7	28%	6	17%	13	22%	19	22%	11	12%	30	17%
Age of onset (years)	8.9 SD 10.5	N=20	6.9 SD 9.2	N=34	7.6 SD 9.63	N = 54	6.1 SD 4.4	N=29	6.0 SD 6.7	n=93	6.0 SD 6.23	N=122
Duration epilepsy (years)	25.8 SD 14.5	N=20	36.8 SD 12.6	N=34	32.7 SD 14.3		30.0 SD 14.7	N=29	38.3 SD 11.5	n=93	36.3 SD 12.75	N=122
Seizures:												
Convulsive seizures	23/24	96%	35/35	100%	58/59	98%	69/81	85%	91/101	90%	160/182	88%
Focal seizures with impaired awareness	16/22	73%	26/34	76%	42/56	75%	54/73	74%	81/101	80%	135/174	78%
Focal aware seizures	1/21	5%	1/34	3%	2/55	4%	3/50	6%	10/100	10%	13/150	9%
Tonic seizures	12/22	55%	3/34	9%	15/56	27%	44/62	71%	10/101	10%	54/163	33%
Myoclonic seizures	6/22	27%	4/34	12%	10/56	18%	19/62	31%	13/101	13%	32/163	82%
Absence seizures	9/21	43%	7/34	21%	16/55	29%	37/66	56%	10/101	10%	47/167	28%
Atonic seizures	5/22	23%	5/34	15%	10/56	18%	11/58	19%	6/101	6%	17/159	11%
Number of AEDs	N=23		N=31		N=54		N=84		N=95		N=179	
none	1	4%	1	3%	2	4%	0	0%	0	0%	0	0%
1 AED	3	13%	4	13%	7	13%	12	14%	9	10%	21	12%
2 AEDs	10	44%	12	39%	22	41%	29	35%	42	44%	71	40%
3 AEDs	6	26%	13	42%	19	35%	31	37%	39	41%	70	39%
4 AEDs	2	9%	1	3%	3	6%	12	14%	5	5%	17	10%
5 AEDs	1	4%	0	0%	1	2%	0	0%	0	0%	0	0%

Use of benzodiazepines	N=22		N=31		N=53		N=83		N=95		N=178	
Yes	5	23%	10	32%	15	28%	36	43%	39	41%	75	42%
No	17	77%	21	68%	38	72%	47	57%	56	59%	103	58%
IQ	N=21		N=22		N=43		N=80		N=58		N=138	
<20	1	5%	0	0%	1	2%	0	0%	0	0%	0	0%
20 – 35	3	14%	2	9%	5	12%	10	13%	0	0%	10	7%
35 - 49	3	14%	0	0%	3	7%	23	29%	5	9%	28	20%
50 - 69	4	19%	11	50%	15	35%	27	34%	28	48%	55	40%
70 - 79	1	5%	3	14%	4	9%	9	11%	16	28%	25	18%
80 - 89	2	10%	5	23%	7	16%	6	8%	8	14%	14	10%
≥90	7	33%	1	5%	8	19%	5	6%	1	2%	6	4%

Table 6. Patient characteristics for cases and controls per center.

AED anti-epileptic drug

Discussion

We found that the presence and frequency of nocturnal seizures increased SUDEP risk in two residential populations of people with refractory epilepsy and intellectual disabilities. SUDEP incidence differed significantly among sites. This difference could not be explained by markers of epilepsy severity. Instead differences in institutional policies on nocturnal supervision seemed the most plausible explanation with more SUDEP victims in the center with less supervision.

There was a difference in supervision among the sites but nocturnal supervision was similar for cases and controls within each site. This is likely explained by the fact that cases were matched to controls from the same site. Most supervision systems were implemented per residential unit. Cases and controls were from the same unit resulting in no significant differences between cases and controls within a center. There were clear differences in institutional policies and reimbursement systems among the sites resulting in different resources. Accordingly, the level of supervision was also different when comparing controls from the sites, thus explaining why no differences were found between cases and controls at the same site.

To explain difference in SUDEP incidence among sites, we compared known SUDEP risk factors such as the presence and frequency of diurnal and nocturnal convulsive seizures among cases and found no difference. The only difference we identified was the grade of nocturnal supervision and this seems to be the only likely explanation for the differing SUDEP incidence among sites.

Our work has several limitations. We lacked autopsies in some cases. To avoid misclassification of probable SUDEP and avoid diagnostic bias, we restricted our analysis to those aged < 60 years and developed a SUDEP point score based on clinical criteria of the postmortem cases. Due to the retrospective design, there were missing values precluding a matched analysis. For most people, extensive seizure charts were available for the extraction of seizure frequency. Still, we had to rely on carer's reports for nocturnal seizure frequency. Lack of supervision may have led to an underestimation of nocturnal seizure frequency,[12, 20] affecting our results. Convulsive seizures, the most relevant seizure type for SUDEP risk, are less likely to be missed than other seizure types.[12, 20] Even if these seizures missed, they can still be reported as there are often signs such as tongue bite. We compared all major SUDEP risk factors among centers, however, additional factors such as different policies and different medication regimes should also be considered. Different antiepileptic regimes might have led to different seizure frequencies. The seizure frequencies, however, were similar among centers, suggesting that this was not a major factor.

Our data on SUDEP incidence in this population with epilepsy and complex needs is comparable to previous reports on similar but smaller populations.[9, 10] Our number of person-years followed is over five times more than previous reports and this enabled us to compare confidently incidence numbers in the two sites. Our data confirmed well-established SUDEP risk factors such as convulsive seizures and a high frequency of these seizures in general.[2, 3, 21] We also confirmed that the presence and high frequency of nocturnal convulsive seizures to be independent SUDEP risk factors.[4]

The strong association between SUDEP and sleep is explained by the interaction with two environmental factors: prone position and the absence of a witness. Most SUDEP cases are found in the prone position,[6, 17, 22] which is remarkable as people seldom are prone following non-fatal convulsive seizures.[23, 24] When an individual is in the prone position after a seizure, respiratory dysfunction may lead to apnea and asystole, which should normally evoke an arousal response.[25] Postictal coma might, however, prevent arousal and thus the resumption of ventilation, consequently leading to SUDEP.[26] Nursing interventions such as repositioning and oxygen administration have been reported to significantly shorten the duration of respiratory dysfunction after a convulsive seizure.[27, 28] Further study of the mechanisms involving nursing interventions (other than CPR) may help prevent postictal coma or even SUDEP.[29]

Our study as well as two previous reports suggest that nocturnal supervision is protective for SUDEP. A case control study showed SUDEP cases less often had a roommate or a listening device compared to the controls.[7] In a cohort study of children with severe epilepsy and intellectual disabilities, all 14 SUDEP deaths occurred while the young students were not under the supervision of the boarding school once they had left the school or were on leave.[30]

While we provide some support for the protective effect of nocturnal supervision, specific recommendations to reduce SUDEP risk require further research.[31, 32] Many seizure detection systems are available,[33, 34] but what system works best for individuals in different populations is yet unknown. The variation in nocturnal supervision among the sites in our study was predominantly explained by the implementation of an acoustic detection system in one center. Acoustic detection systems are often useful, as in 85% of tonic clonic seizures an ictal cry is heard[35] and at least half of major seizures are captured with a listening device.[36] In case these measures failed, additional individually tailored devices such as a bed motion sensor and video monitoring were deployed in center 1. This only concerned a small subgroup with nocturnal supervision grade 3 and is thus unlikely to be a major determinant for the differences in SUDEP incidence. We have previously shown that residential care center video monitoring facilitated the detection of 10% of all seizures requiring an intervention.[12] Video monitoring, however, has large implications for

privacy and is costly. This study underlines the importance of nocturnal supervision and reliable seizure detection systems for different populations.

References

1. Walczak TS, Leppik IE, D'Amelio M, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 2001;56:519-525.
2. Hesdorffer DC, Tomson T, Benn E, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia 2012;53:249-252.
3. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52:1150-1159.
4. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. Epilepsia 2012;53:253-257.
5. Nashef L, Garner S, Sander JW, Fish DR, Shorvon SD. Circumstances of death in sudden death in epilepsy: interviews of bereaved relatives. Journal of neurology, neurosurgery, and psychiatry 1998;64:349-352.
6. Ali A, Wu S, Issa NP, et al. Association of sleep with sudden unexpected death in epilepsy. Epilepsy & behavior : E&B 2017;76:1-6.
7. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005;64:1131-1133.
8. Devinsky O, Asato M, Camfield P, et al. Delivery of epilepsy care to adults with intellectual and developmental disabilities. Neurology 2015;85:1512-1521.
9. Klenerman P, Sander JW, Shorvon SD. Mortality in patients with epilepsy: a study of patients in long term residential care. Journal of neurology, neurosurgery, and psychiatry 1993;56:149-152.
10. McKee JR, Bodfish JW. Sudden unexpected death in epilepsy in adults with mental retardation. American journal of mental retardation : AJMR 2000;105:229-235.
11. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. The Lancet Neurology 2016;15:1075-1088.
12. van der Lende M, Cox FM, Visser GH, Sander JW, Thijs RD. Value of video monitoring for nocturnal seizure detection in a residential setting. Epilepsia 2016;57:1748-1753.
13. Novy J, Belluzzo M, Caboclo LO, et al. The lifelong course of chronic epilepsy: the Chalfont experience. Brain : a journal of neurology 2013;136:3187-3199.
14. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;53:227-233.
15. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia 2014;55:1479-1485.
16. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. Lancet (London, England) 1999;353:888-893.
17. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. The Lancet Neurology 2013;12:966-977.

18. Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. Journal of neurology, neurosurgery, and psychiatry 2000;68:211-213.
19. Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: a search for risk factors. Epilepsy & behavior : E&B 2007;10:138-141.
20. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Archives of neurology 2007;64:1595-1599.
21. 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.
22. Liebenthal JA, Wu S, Rose S, Ebersole JS, Tao JX. Association of prone position with sudden unexpected death in epilepsy. Neurology 2015;84:703-709.
23. Wang S, Graf S, Xu J, et al. The incidence of peri-ictal prone position in patients with generalized convulsive seizures. Epilepsy & behavior : E&B 2016;61:158-161.
24. Shmuely S, Surges R, Sander JW, Thijs RD. Prone sleeping and SUDEP risk: The dynamics of body positions in nonfatal convulsive seizures. Epilepsy & behavior : E&B 2016;62:176-179.
25. Paton JF, Boscan P, Pickering AE, Nalivaiko E. The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. Brain research Brain research reviews 2005;49:555-565.
26. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. Journal of neurology, neurosurgery, and psychiatry 2016;87:69-74.
27. Seyal M, Bateman LM, Li CS. Impact of periictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility. Epilepsia 2013;54:377-382.
28. Wu S, Issa NP, Rose SL, Ali A, Tao JX. Impact of periictal nurse interventions on postictal generalized EEG suppression in generalized convulsive seizures. Epilepsy & behavior : E&B 2016;58:22-25.
29. Rugg-Gunn F, Duncan J, Hjalgrim H, Seyal M, Bateman L. From unwitnessed fatality to witnessed rescue: Nonpharmacologic interventions in sudden unexpected death in epilepsy. Epilepsia 2016;57 Suppl 1:26-34.
30. Nashef L, Fish DR, Garner S, Sander JW, Shorvon SD. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. Epilepsia 1995;36:1187-1194.
31. Maguire MJ, Jackson CF, Marson AG, Nolan SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). The Cochrane database of systematic reviews 2016;7:CD011792.
32. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: A call for action. Neurology 2016;86:779-786.
33. van Andel J, Thijs RD, de Weerd A, Arends J, Leijten F. Non-EEG based ambulatory seizure detection designed for home use: What is available and how will it influence epilepsy care? Epilepsy & behavior : E&B 2016;57:82-89.

34. Van de Vel A, Cuppens K, Bonroy B, et al. Non-EEG seizure detection systems and potential SUDEP prevention: State of the art: Review and update. Seizure 2016;41:141-153.
35. Elzawahry H, Do CS, Lin K, Benbadis SR. The diagnostic utility of the ictal cry. Epilepsy & behavior : E&B 2010;18:306-307.
36. Arends JB, van Dorp J, van Hoek D, et al. Diagnostic accuracy of audio-based seizure detection in patients with severe epilepsy and an intellectual disability. Epilepsy & behavior : E&B 2016;62:180-185.

CHAPTER 7

Summary and general discussion

Sudden Unexpected Death in Epilepsy (SUDEP) is the most common cause of direct epilepsy-related premature mortality. Multiple risk factors have been identified: people with refractory epilepsy and frequent convulsions are at highest risk.[1, 2] Individual risk prediction is not yet possible and effective preventative measures are missing. The lack of SUDEP biomarkers is a critical barrier. SUDEP pathophysiology is poorly understood. Video-EEG recordings of SUDEP cases show a similar pattern in all cases including postictal generalized EEG suppression (PGES), apnea and asystole.[3] Little is known, however, about the frequency and timing in which asystole occurs in people with a high SUDEP risk. The first part of this thesis focusses on the cardiovascular comorbidities in epilepsy. Emphasis is laid on cardiac arrhythmias to understand its role in SUDEP pathophysiology and to assess the potential of heart rhythm as a SUDEP biomarker.

In **chapter two** the clinical presentation and the possible mechanisms for shared pathophysiology between epilepsy and cardiovascular conditions is explored. Epidemiological studies have consistently shown that people with epilepsy have a higher prevalence of structural cardiac disease and a poorer cardiovascular risk profile compared to those without epilepsy.[4-7] Several mechanisms explain why these conditions tend to co-exist: shared cardiovascular risk factors, genetics and etiological factors may account for the relationship between epilepsy and structural cardiac disease. Certain anti-epileptic drugs may negatively affect cardiovascular risk profile, while seizures may (rarely) evoke ictal bradyarrhythmias, transient myocardial ischaemia or Takotsubo syndrome.

In **chapter three** the results of a systematic literature review on the full spectrum of clinically relevant cardiac arrhythmias during or after epileptic seizures are reported. Seven distinct (post)ictal arrhythmia patterns were identified. Ictal asystole was the most frequently arrhythmia, with a prevalence of 0,318% in people with refractory focal epilepsy admitted for video-EEG recordings. Ictal asystole, ictal bradycardia and ictal AV block predominantly occurred during focal seizures in people with temporal lobe epilepsy. No deaths were reported. We hypothesized ictal asystole could be a direct consequence of epileptic activity stimulating the central autonomic network or an indirect effect of the seizure (eg, catecholamine release) evoking a vasovagal reflex. Either way, ictal asystole is self-limiting, as cerebral anoxia caused by the asystole terminates the seizure and also the mechanism causing the asystole.

In contrast, postictal arrhythmias including asystole, AV block and the less prevalent atrial fibrillation and ventricular fibrillation usually occurred after a convulsive seizure and were frequently associated with near-SUDEP. Postictal asystole was often preceded by apnea and/or PGES. Prolonged apnea eventually causes arousal, as well as bradycardia and asystole.[8] Postictal coma may, however, block the arousal effect and thus the resumption of ventilation, explaining why postictal asystole may lead to SUDEP. Postictal arrhythmias,

rather than ictal arrhythmias, seem of greater importance to the pathophysiology of SUDEP and could potentially serve as a SUDEP biomarkers.

While we have shown that ictal and postictal arrhythmias are rare in retrospective studies, the frequency and timing of arrhythmias in prospective studies remains unknown. Two prospective studies (n=19) with two year follow-up using implantable loop recorders showed conflicting results: 21% vs 4% had asystole.[9, 10]

The objective of **chapter four** was to study the yield of long-term ECG recordings in a large cohort of people with refractory focal epilepsy. We implanted loop recorders in 49 people and monitored their heart rhythm for a total of 1060 months. Seizure diaries showed 16.474 reported seizures. ECG recordings were made of 4679 of 16.474 seizures. We found no potentially lethal arrhythmias in this population with a high SUDEP risk profile with longstanding refractory epilepsy and frequent convulsions. In particular no postictal arrhythmias were identified, that could serve as potential SUDEP biomarkers, despite recording over 16.000 seizures during long term follow up. Non-clinically relevant asystoles (<4s) were found in three subjects, all not directly seizure-related. Asystole was caused by vasovagal syncope in one, a diagnosis supported by the classical circumstances and the cardioinhibitory response at the tilt table test. The absence of clinically relevant asystole in our study, in contrast to a previous study,[9] is most likely explained by the fact that we excluded those with a clinical suspicion of ictal asystole, suggesting that history taking a powerful screening tool for ictal asystole. Therefore, there is no added value for long-term follow up with implantable loop recorders in people with high SUDEP risk.

The second part of this thesis addresses the effect of nocturnal supervision on SUDEP risk. Circadian factors seem important, with higher risk for those with nocturnal sleep-related convulsive seizures, but this still needs confirmation.[11] The same is true for the preventive effects of supervision: nocturnal supervision seems to lower SUDEP risk.[12] This poses a problem for residential care facilities housing people with refractory epilepsy and intellectual disabilities. SUDEP incidence for these populations is substantial (3,6 – 3,8 per 1000 person years), but recommendations for nocturnal supervision are lacking.

Following a SUDEP case at Stichting Epilepsie Instellingen Nederland (SEIN), the Dutch Health and Care Inspectorate advised intensification of video monitoring. It is likely that video monitoring may facilitate seizure detection, but the clinical relevance is questionable.

In **chapter five** we assess whether nocturnal video monitoring resulted in an increase in seizures requiring nursing intervention (e.g., emergency medication) to quantify the benefits of additional nocturnal video monitoring.

We found video monitoring in conjunction with acoustic detection devices and bed motion sensors facilitated nocturnal surveillance: 33% of all observed seizures were seen only on video. Video monitoring also helped detecting clinically relevant seizures: of all seen only on video, 10% required an intervention. We found the greatest added value of video monitoring, however, to be for tonic seizures and not for convulsive seizures. Seizures late at night or early in the morning were also more often seen only on video, most likely due to background noise drowning out sounds of seizures, making acoustic detection systems less reliable.

Although video monitoring has added value, it should be weighed against extra costs: personnel outlays were estimated at 7,035 euro per seizure seen only on video and leading to an intervention. With SUDEP estimated to occur in one of every 2,000–5,000 convulsions,[13] it would cost millions to detect an additional seizure leading to SUDEP, without guarantee that this will be preventive.[14, 15] Therefore the limited added value of video monitoring is outweighed by the high costs. The few convulsive seizures only detected using video monitoring, often seemed related to failure of the acoustic detection system, or absence of a bed motion sensor. In view of high costs and questionable protective effects, it seems more reasonable to optimize acoustic detection systems or to consider other seizure detection devices.

Because people with intellectual disabilities have a higher seizure burden and SUDEP risk, the search for protective measures is even more urgent in this population. Few small studies are available on SUDEP incidence in this population.[16, 17] Nocturnal supervision is suggested to lowered SUDEP risk, but evidence is scarce.

In **chapter six** the results of a SUDEP case-control study are presented. The aim of this study was to estimate SUDEP incidence in residential care facilities and to determine the effects of nocturnal seizures and nocturnal supervision on the risk of SUDEP. We selected all SUDEP cases over a 25-year period in two epilepsy residential care facilities, housing people with refractory epilepsy and intellectual disabilities. As an additional criterion to portray the diagnosis of 'probable SUDEP', we developed a point score based on established SUDEP circumstances. Four controls per case were matched on age (+/-five years) and residential unit.

We identified 60 SUDEP cases (30 definite and 30 probable SUDEP cases) and 198 matched controls. The presence and frequency of nocturnal seizures increased SUDEP risk: People who died of SUDEP were more likely to have nocturnal convulsive seizures (77% of cases vs. 33% of controls, $p<0.001$) and a higher frequency of nocturnal convulsive seizures. Total SUDEP incidence was 3,53/1000 patient/years. SUDEP incidence differed significantly between sites: 2,21/1000 patient/years vs. 6,12/1000 patient/years. The

center with a lowest grade of supervision had the highest SUDEP incidence. To explain difference in SUDEP incidence between sites, we compared all established SUDEP risk factors between the cases and found no difference. The only difference we identified was the grade of nocturnal supervision and this seems to be the only likely explanation for the differing SUDEP incidence between the sites. This underscores the need for reliable seizure detection systems. The variation in nocturnal supervision between the sites in this study was predominantly explained by the implementation of an acoustic detection system in one site. It is unclear, however, which device can detect nocturnal seizures most accurately and whether this detection can reduce SUDEP risk.

Future perspectives

The ultimate goal of SUDEP research is to prevent SUDEP. Only two measures are available to reduce SUDEP risk: optimizing medical treatment to reduce the risk of convulsive seizures and increasing nocturnal supervision.[18, 19] Wearable and remote seizure detection devices may help to improve nocturnal supervision. Current devices reliably detect convulsive seizures, but false alarm rates are often high.[20, 21] A multimodal approach and algorithms that can be tailored to an individual's seizures, seem to be best equipped to meet the complex requirements of seizure detection.[21] Most seizure detection devices have been tested exclusively on small populations in an epilepsy monitoring unit. Future research should focus on implementing multimodal devices in large populations, in ambulatory settings.

To develop specific preventative measures, we need to know whom to target and to understand SUDEP pathophysiology. Video-EEG recordings of SUDEP cases show similar patterns: a tonic clonic seizure, followed by postictal generalized EEG suppression (PGES), transient apnea, bradycardia and asystole, resulting into terminal asystole.[3] It has been hypothesized that a release of endogenous opioids and adenosine within the brain associated with seizure termination, explains these postictal changes.[18] Mouse models of genes associated with SUDEP have shown mutations in Kv1.1 potassium and Scn1a sodium ion channels cause brainstem-spreading depolarization.[22] This resulted in PGES, apnea and asystole, similar to events in video-EEG recordings of human SUDEP cases.[3] As monitored human SUDEP is very rare, animal studies are highly valuable and provided us with important insight in SUDEP pathophysiology.

To know whom to target with preventative interventions, individual SUDEP risk profiles are needed. Currently generic SUDEP risk factors have been identified, but these cannot estimate an individual's SUDEP risk.[2] This is already a major problem in SUDEP communication. Neurologists rarely discuss SUDEP with all their patients, not wanting

to cause anxiety and stress when risk is likely low and preventative interventions are lacking.[23] The majority of people with epilepsy, however, do wish to be informed about SUDEP risks.[24] Individual risk profiles could help to provide more specific information to those for whom it is most important.

There are multiple ways to achieve individual risk prediction. Promising work has been done in the field of genetics. The search for variants in genes related to epilepsy, cardiac arrhythmia, and respiratory function, using whole exome or genome sequencing of SUDEP cases, has resulted into the identification of multiple genes possibly associated with SUDEP.[25, 26] No single gene was identified in all SUDEP cases thus suggesting a complex multifactorial interaction. More prospective research on genetic profiles of people with epilepsy using large cohorts might reveal more precise genetic profiles of those with highest SUDEP risk.

SUDEP biomarkers are another important factor in the quest for individual SUDEP risk prediction. The search for SUDEP biomarkers should start with parameters we already know to be affiliated with SUDEP: PGES, apnea and asystole. We have studied the potential of postictal asystole as a SUDEP biomarker and concluded asystole is to rare to be an efficient biomarker. Another component of heart rate, heart rate variability, can be derived from ECG or heart rate measurements. A recent case report showed marked changes in heart rate variability, indicating parasympathetic hyperactivity, prior to SUDEP. No differences in interictal heart rate variability were found between SUDEP cases and controls.[27] Potential differences in ictal heart rate variability, however, have yet to be studied.
Prolonged central apnea (≥60 s) is associated with severe hypoxemia and may be a potential SUDEP biomarker. It, however, rarely persists in the postictal period[28] and therefore it is questionable whether this marker could reliably predict SUDEP risk.
A more interesting potential SUDEP biomarker is PGES. PGES could be attractive as it is seen in all monitored SUDEP cases. PGES turned out to be more frequent among SUDEP cases than in controls in one study[29] while another study failed to confirm this association.[30] This discrepancy may be explained by sampling error, as a clinical assessment of the presence (and frequency) of PGES will critically depend on the number of recorded seizures.[31] Automated PGES detection[32] or other closely related markers like ictal increases of electrodermal activity[33, 34] or interclonic intervals[35] could provide alternatives for recordings in a home environment.

For all potential biomarkers, very large cohorts with long term follow up need to be studied, due to the rarity of SUDEP. Improved ability to process big data and to miniaturize sensors may permit long term home-based monitoring and fuel the identification of novel SUDEP biomarkers. This approach would also allow to explore the relevance of

other patterns explaining sudden death in epilepsy including non-seizure SUDEP and the overlap between SUDEP and sudden cardiac arrest.[36]

Gathering of big data in SUDEP research is being hampered by imprecise reporting of the cause of death and lack of postmortem examinations. SUDEP awareness among health care professionals should be raised and death registration could be improved by instating an ICD code for SUDEP.

If postmortem examination has not been done, a case can still be classified as 'probable SUDEP'. There are no internationally validated criteria, however, for probable SUDEP. In chapter five we developed and used our own criteria, yet it would be of great importance to prospectively validate these criteria in large population-based cohorts.

In conclusion, the key way to prevent SUDEP is to reduce the number of convulsive seizures, increase awareness and to implement multimodal seizure detection. For the long term a prevention trial could be feasible if high risk groups can be targeted. Important information on potential biomarkers could be gathered using seizure detection devices. Due to the rarity of SUDEP, large cohorts with long follow up are most essential to study preventative interventions and unravel the pathophysiology.

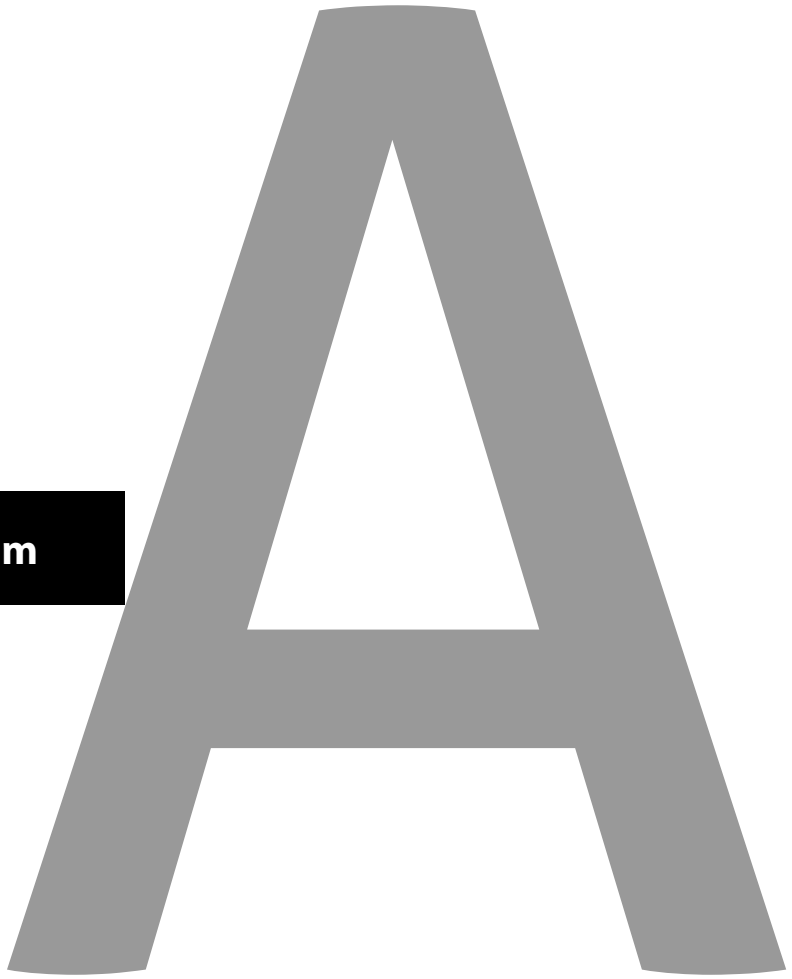
References

1. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52:1150-1159.
2. 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.
3. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. The Lancet Neurology 2013;12:966-977.
4. Tellez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. Epilepsy research 2005;65:101-115.
5. Elliott JO, Lu B, Shneker B, Charyton C, Layne Moore J. Comorbidity, health screening, and quality of life among persons with a history of epilepsy. Epilepsy & behavior : E&B 2009;14:125-129.
6. Comorbidity in adults with epilepsy--United States, 2010. MMWR Morbidity and mortality weekly report 2013;62:849-853.
7. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. The Lancet Neurology 2016;15:106-115.
8. Paton JF, Boscan P, Pickering AE, Nalivaiko E. The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. Brain research Brain research reviews 2005;49:555-565.
9. Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. Lancet (London, England) 2004;364:2212-2219.
10. Nei M, Sperling MR, Mintzer S, Ho RT. Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. Epilepsia 2012;53:e137-140.
11. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. Epilepsia 2012;53:253-257.
12. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005;64:1131-1133.
13. Shorvon SD. Handbook of epilepsy treatment. Chichester: John Wiley & Sons 2010.
14. Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. Journal of neurology, neurosurgery, and psychiatry 2000;68:211-213.
15. Swinghamer J, Devinsky O, Friedman D. Can post-ictal intervention prevent sudden unexpected death in epilepsy? A report of two cases. Epilepsy & behavior : E&B 2012;24:377-379.
16. Klenerman P, Sander JW, Shorvon SD. Mortality in patients with epilepsy: a study of patients in long term residential care. Journal of neurology, neurosurgery, and psychiatry 1993;56:149-152.

17. McKee JR, Bodfish JW. Sudden unexpected death in epilepsy in adults with mental retardation. American journal of mental retardation : AJMR 2000;105:229-235.
18. Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: a realistic goal? Epilepsia 2013;54 Suppl 2:23-28.
19. Maguire MJ, Jackson CF, Marson AG, Nolan SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). The Cochrane database of systematic reviews 2016;7:CD011792.
20. van Andel J, Thijs RD, de Weerd A, Arends J, Leijten F. Non-EEG based ambulatory seizure detection designed for home use: What is available and how will it influence epilepsy care? Epilepsy & behavior : E&B 2016;57:82-89.
21. Van de Vel A, Cuppens K, Bonroy B, et al. Non-EEG seizure detection systems and potential SUDEP prevention: State of the art: Review and update. Seizure 2016;41:141-153.
22. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. Science translational medicine 2015;7:282ra246.
23. Friedman D, Donner EJ, Stephens D, Wright C, Devinsky O. Sudden unexpected death in epilepsy: knowledge and experience among U.S. and Canadian neurologists. Epilepsy & behavior : E&B 2014;35:13-18.
24. Xu Z, Ayyappan S, Seneviratne U. Sudden unexpected death in epilepsy (SUDEP): what do patients think? Epilepsy & behavior : E&B 2015;42:29-34.
25. Leu C, Balestrini S, Maher B, et al. Genome-wide Polygenic Burden of Rare Deleterious Variants in Sudden Unexpected Death in Epilepsy. EBioMedicine 2015;2:1063-1070.
26. Bagnall RD, Crompton DE, Petrovski S, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. Annals of neurology 2016;79:522-534.
27. Surges R, Henneberger C, Adjei P, Scott CA, Sander JW, Walker MC. Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy? Epilepsy research 2009;87:277-280.
28. Lacuey N, Zonjy B, Hampson JP , et al. The incidence and significance of perictal apnea in epileptic seizures. Epilepsia 2018; 59(3):573-582
29. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Annals of neurology 2010;68:787-796.
30. Surges R, Strzelczyk A, Scott CA, Walker MC, Sander JW. Postictal generalized electroencephalographic suppression is associated with generalized seizures. Epilepsy & behavior : E&B 2011;21:271-274.
31. Lamberts RJ, Gaitatzis A, Sander JW, Elger CE, Surges R, Thijs RD. Postictal generalized EEG suppression: an inconsistent finding in people with multiple seizures. Neurology 2013;81:1252-1256.
32. Theeranaew W, McDonald J, Zonjy B, et al. Automated Detection of Postictal Generalized EEG Suppression. IEEE transactions on bio-medical engineering 2018;65:371-377.

33. Poh MZ, Loddenkemper T, Reinsberger C, et al. Autonomic changes with seizures correlate with postictal EEG suppression. Neurology 2012;78:1868-1876.
34. Picard RW, Migliorini M, Caborni C, et al. Wrist sensor reveals sympathetic hyperactivity and hypoventilation before probable SUDEP. Neurology 2017;89:633-635.
35. Bauer PR, Thijs RD, Lamberts RJ, et al. Dynamics of convulsive seizure termination and postictal generalized EEG suppression. Brain : a journal of neurology 2017;140:655-668.
36. Bardai A, Lamberts RJ, Blom MT, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. PloS one 2012;7:e42749.

Addendum



Nederlandstalige samenvatting
en discussie

List of publications

Dankwoord

Curriculum vitae

Nederlandstalige samenvatting en discussie

Sudden Unexpected Death in Epilepsy (SUDEP) is de meest voorkomende oorzaak van direct aan epilepsie gerelateerde mortaliteit. Verschillende risico factoren zijn reeds vastgesteld: mensen met refractaire epilepsie en frequente tonisch clonische aanvallen lopen het hoogste risico.[1, 2] Individuele risico voorspelling is nog niet mogelijk en er zijn geen maatregelen om SUDEP te voorkomen. Het gebrek aan SUDEP biomarkers is een groot probleem. De pathofysiologie van SUDEP is nog niet opgehelderd. VideoEEG opnames van mensen die aan SUDEP overlijden tonen in alle gevallen een vergelijkbaar patroon: postictale gegeneraliseerde EEG suppressie (PGES), apneu en asystolie.[3] Hoe vaak en wanneer asystolieën voorkomen bij mensen met een hoog SUDEP risico is niet bekend. Het eerste gedeelte van dit proefschrift gaat over de cardiovasculaire comorbiditeiten bij epilepsie. Hierbij wordt dieper ingegaan op hartritmestoornissen om de rol van hartritmestoornissen binnen de SUDEP-pathofysiologie beter te begrijpen en om de potentie van hartritme als SUDEP biomarker te onderzoeken.

In **hoofdstuk twee** worden de klinische presentatie en mogelijke mechanismen voor een gedeelde pathofysiologie van epilepsie en cardiovasculaire aandoeningen besproken. Epidemiologische onderzoeken hebben meerdere malen aangetoond dat mensen met epilepsie een hogere prevalentie van structurele hartziekten hebben en een slechter cardiovasculair risicopatroon vergeleken met mensen zonder epilepsie.[4-7] Verschillende mechanismen zijn beschreven waarom deze aandoeningen samen voorkomen: gedeelde cardiovasculaire risicofactoren, genetica en etiologische factoren zouden de relatie tussen epilepsie en structurele hartziekten kunnen verklaren. Enkele anti-epileptica kunnen het cardiovasculaire risicoprofiel negatief beïnvloeden en epileptische aanvallen kunnen (zeer zeldzaam) ictale hartritmestoornissen, passagere ischemie van het myocard of het syndroom van Takotsubo uitlokken.

Hoofdstuk drie beschrijft de resultaten van een systematische review over het volledige spectrum van klinisch relevante hartritmestoornissen tijdens of na epileptische aanvallen. Zeven verschillende (post)ictale ritmestoornissen werden geïdentificeerd. Ictale asystolie was de meest voorkomende hartritmestoornis, met een prevalentie van 0,318% voor mensen met refractaire epilepsie die waren opgenomen voor een videoEEG. Ictale asystolie, ictale bradycardie en ictaal AV-blok kwamen voornamelijk voor tijdens focale aanvallen bij mensen met temporale epilepsie. Er werden geen overlijdens gerapporteerd. Onze hypothese is dat ictale asystolieën een directe consequentie kunnen zijn van epileptische activiteit dat het centrale autonome zenuwstelsel stimuleert of een indirect effect van de aanval (bijvoorbeeld een piek van catecholaminen) wat een vasovagale reflex uitlokt. In beide gevallen is ictale asystolie self-limiting, omdat de cerebrale anoxie veroorzaakt door

de asystolie ook de aanval beëindigd en daarmee het onderliggende mechanisme wat de asystolie veroorzaakte.

In tegenstelling tot ictale hartritmestoornissen, kwamen postictale hartritmestoornissen zoals postictale asystolieën, AV-blok en artrium- en ventrikelfibrilleren (zeldzaam), altijd voor na tonisch clonische aanvallen en werden ze vaak geassocieerd met near-SUDEP.

Postictale asystolieën werden vaak voorafgegaan door apneu en/of PGES. Langdurige apneus veroorzaken uiteindelijk arousal, naast bradycardie en asystolie.[8] Dit arousal effect kan echter geblokkeerd worden door het postictale coma, waardoor de ademhaling niet meer op gang komt, wat verklaard waarom postictale asystolie tot SUDEP kan leiden. Postictale hartritmestoornisen, in tegenstelling tot ictale hartritmestoornissen, lijken dan ook belangrijker in de pathofysiologie van SUDEP en zouden als potentiele SUDEP biomarkers gebruikt kunnen worden.

Hoewel we hebben aangetoond dat ictale en postictale hartritmestoornissen zeldzaam zijn in retrospectieve onderzoeken, is de frequentie en timing van hartritmestoornissen bij mensen met epilepsie in prospectieve onderzoeken onbekend. Twee prospectieve onderzoeken (n=19) met twee jaar follow up en gebruik makend van implanteerbare hartritmemonitoren lieten tegenstrijdige resultaten zien: 21% versus 4% van de patiënten had een asystolie.[9, 10]

Het doel van **hoofdstuk vier** was om de opbrengst van lange termijn ECG opnames in een groot cohort van mensen met refractaire focale epilepsie te onderzoeken. We hebben bij 49 mensen implanteerbare hartritmemonitoren geplaatst en hebben hun hartritme in totaal 1060 maanden gemonitord.

Er werden in totaal 16.474 aanvallen in de aanvalsdagboeken geregistreerd. Van 4679 van deze 16.474 aanvallen zijn ECG opnames gemaakt. We hebben geen potentieel fatale hartritmestoornissen gevonden in onze populatie met een hoog SUDEP-risico en lang bestaande refractaire epilepsie met een hoge aanvalsfrequentie. Er werden met name geen postictale hartritmestoornissen gevonden die als potentiële SUDEP biomarkers zouden kunnen dienen, ondanks de meer dan 16.000 epileptische aanvallen gedurende de lange termijn follow up.

Bij drie personen werden klinisch niet relevante asystolieën (<4sec) gevonden, waarvan geen een gerelateerd aan een epileptische aanval. Bij een persoon werd de asystolie veroorzaakt door vasovagale syncope, een diagnose die werd ondersteund door de typische omstandigheden en een cardioinhibitoire reactie tijdens de kanteltafeltest. Het gebrek aan klinisch relevante asystolieën in ons onderzoek, in tegenstelling tot een eerder

onderzoek,[9] wordt meest waarschijnlijk verklaard door het feit dat wij mensen met een klinische verdenking op ictale asystolieën geëxcludeerd hebben bij aanvang van het onderzoek. Dit suggereert dat anamnese een belangrijk screeningsmiddel is voor ictale asystolieën en er dus geen toegevoegde waarde is voor lange termijn follow up met implanteerbare hartritmemonitoren bij mensen met een hoog SUDEP-risico.

Het tweede gedeelte van dit proefschrift gaat over het effect van nachtelijk toezicht op het SUDEP-risico. Circadiaanse factoren lijken belangrijk, met een hoger risico voor mensen met nachtelijke, slaap gerelateerde, tonisch clonische aanvallen, maar dit moet nog worden bevestigd.[11] Hetzelfde geldt voor het preventieve effect van toezicht: nachtelijk toezicht lijkt het SUDEP-risico te verlagen.[12] Dit creëert een probleem voor woonzorg instellingen die huisvesting bieden aan mensen met refractaire epilepsie en een verstandelijke beperking. De SUDEP-incidentie in deze populaties is substantieel (3,6 – 3,8 per 1000 persoonsjaren), maar er zijn geen aanbevelingen over nachtelijk toezicht beschikbaar.

Na een SUDEP overlijden in een woongebouw bij Stichting Epilepsie Instellingen Nederland (SEIN), adviseerde de inspectie voor de Gezondheidszorg dat de nachtelijke videomonitoring geïntensiveerd moest worden. Hoewel het waarschijnlijk is dat videomonitoring de detectie van aanvallen gemakkelijker zal maken, is de klinische relevantie niet aangetoond.

In **hoofdstuk vijf** beoordelen we of nachtelijke videomonitoring resulteert in een toename van gedetecteerde aanvallen waarbij een interventie noodzakelijk was (bijvoorbeeld toedienen van medicatie) om de voordelen van (het toevoegen van) nachtelijke videomonitoring te kunnen kwantificeren.

We hebben aangetoond dat videomonitoring naast akoestische uitluistersystemen en matrassensoren nachtelijk toezicht faciliteerde: 33% van alle geobserveerde aanvallen werden alleen op video gezien. Videomonitoring hielp ook bij het detecteren van klinisch relevante aanvallen: van alle aanvallen alleen op video gezien was bij 10% een interventie nodig. De toegevoegde waarde van videomonitoring was echter het grootste voor tonische aanvallen en niet voor tonisch clonische aanvallen. Daarnaast werden aanvallen laat op de avond en vroeg in de ochtend ook vaker alleen op video gezien, meest waarschijnlijk door achtergrond geluid wat de akoestische uitluistersystemen op deze tijdstippen minder betrouwbaar maakte.

Hoewel videomonitoring dus toegevoegde waarde heeft, moet dit worden afgewogen tegen de extra kosten: de extra personeelskosten werden geschat op 7035 euro per aanval alleen op video gezien waarbij geïntervenieerd werd. Aangezien SUDEP wordt geschat

voor te komen bij 1 op 2000-5000 tonisch clonische aanvallen,[13] zou het miljoenen kosten om een extra aanval te detecteren die tot SUDEP zou leiden, zonder garantie dat SUDEP daar ook mee voorkomen zou kunnen worden.[14, 15] Daarom lijkt de beperkte toegevoegde waarde van videomonitoring niet op te wegen tegen de hoge kosten. Bij de enkele tonisch clonische aanvallen alleen met videomonitoring gedetecteerd, was vaak sprake van een probleem met het akoestische systeem of afwezigheid van een matrassensor. Gezien de hoge kosten en het dubieuze beschermende effect van videomonitoring lijkt het redelijker om de akoestische uitluistersystemen te optimaliseren of om andere aanvalsdetectiesystemen te overwegen.

Omdat mensen met een verstandelijke beperking een hogere aanvalsfrequentie en een hoger SUDEP-risico hebben, is de zoektocht naar beschermende maatregelen tegen SUDEP extra belangrijk voor deze populatie. Slechts enkele kleine onderzoeken vermelden de SUDEP-incidentie voor deze populatie.[16, 17] Nachtelijk toezicht lijkt het SUDEP-risico te verlagen, maar dit is nog niet goed bewezen.

In **hoofdstuk zes** worden de resultaten van een SUDEP case control onderzoek beschreven. Het doel van dit onderzoek was het bepalen van de SUDEP-incidentie in woonzorg instellingen voor mensen met epilepsie en het bestuderen van het effect van nachtelijk toezicht op het SUDEP-risico. We hebben alle SUDEP-cases van de afgelopen 25 jaar geselecteerd in twee woonzorgcentra voor mensen met refractaire epilepsie en een verstandelijke beperking. Als extra criterium om de diagnose "probable SUDEP" vast te kunnen stellen, hebben we een puntenscore ontwikkeld gebaseerd op bekende SUDEP-omstandigheden. Per case werden vier controles gematcht op leeftijd (+/- vijf jaar) en woongebouw.
We hebben 60 SUDEP-cases geïdentificeerd (30 definite en 30 probable SUDEP-cases) en 198 gematchte controles. De aanwezigheid en frequentie van nachtelijke tonisch clonische aanvallen verhoogde het SUDEP-risico: Mensen die aan SUDEP overleden hadden vaker überhaupt nachtelijke tonisch clonische aanvallen (77% van de cases versus 33% van de controles, $p<0.001$) en een hogere frequentie van nachtelijke tonisch clonische aanvallen. De totale SUDEP-incidentie was 3,53/1000 patiënten/jaar. De SUDEP-incidentie verschilde significant tussen de twee centra: 2,21/1000 patiënten/jaar versus 6,12/1000 patiënten/jaar. Het centrum met de minste mate van nachtelijk toezicht had de hoogste SUDEP-incidentie. Om het verschil in SUDEP-incidentie te verklaren hebben we alle bekende SUDEP-risicofactoren vergeleken tussen de cases en de controles en hebben we geen verschil gevonden. Het enige verschil was de mate van nachtelijk toezicht en dit lijkt de enige plausibele verklaring voor het verschil in SUDEP-incidentie tussen de centra. Dit onderstreept de noodzaak voor betrouwbare aanvalsdetectiesystemen. Het verschil in nachtelijk toezicht tussen de centra in dit onderzoek werd vooral verklaard door de invoering van een akoestisch uitluistersysteem in een centrum. Het is echter nog

onduidelijk welk systeem nachtelijke aanvallen het best kan detecteren en in hoeverre dit dan het SUDEP-risico verlaagd.

Toekomstperspectieven

Het ultieme doel van SUDEP-onderzoek is het voorkómen van SUDEP. Op dit moment zijn slechts twee maatregelen beschikbaar om het SUDEP-risico te verlagen: het optimaliseren van de medicamenteuze behandeling om het risico van tonisch clonische aanvallen te verlagen en het toevoegen van nachtelijk toezicht.[18, 19] Draagbare- en aanvalsdetectiesystemen op afstand kunnen helpen om nachtelijk toezicht te verbeteren. De huidige systemen kunnen tonisch clonische aanvallen goed detecteren, maar geven vaak veel valse alarmen.[20, 21] Een multimodale aanpak en algoritmes die aangepast kunnen worden aan de aanvallen van een individu, lijken het meest geschikt om aan de complexe voorwaarden van aanvalsdetectie te kunnen voldoen.[21] De meeste aanvalsdetectie systemen zijn slechts op kleine populaties op een epilepsie monitoring unit getest. Toekomstig onderzoek zal zich moeten richten op de implementatie van multimodale systemen in grote populaties in een ambulante omgeving.

Om specifieke preventieve maatregelen te kunnen ontwikkelen, moeten we weten wat de doelgroep is en de SUDEP-pathofysiologie begrijpen. Video-EEG opnames van SUDEP cases laten vergelijkbare patronen zien: een tonisch clonische aanval, gevolgd door postictale gegeneraliseerde EEG suppressie (PGES), voorbijgaande apneus, bradycardieën en asystolieën uiteindelijk resulterend in terminale asystolie.[3] Er is een hypothese dat deze posticale veranderingen verklaard worden door het vrijkomen van endogene opioïden en adenosine in de hersenen, geassocieerd met het einde van een epileptische aanval.[18] Muismodellen met genen geassocieerd met SUDEP hebben laten zien dat mutaties in Kv1.1 kalium en Scn1a natrium ion kanalen een depolarisatie golf in de hersenstam kunnen veroorzaken.[22] Dit resulteerde in PGES, apneu en asystolie, vergelijkbaar met de gebeurtenissen in videoEEG opnames van menselijke SUDEP cases.[3] Aangezien gemonitorde gevallen van SUDEP bij mensen erg zeldzaam zijn, zijn dieronderzoeken zeer waardevol en bieden ons belangrijke inzichten in de SUDEP pathofysiologie.

Om te weten op welke mensen we ons moeten richten met preventieve interventies, hebben we individuele SUDEP-risicoprofielen nodig. Op het moment zijn algemene SUDEP-risicofactoren geïdentificeerd, maar deze kunnen niet gebruikt worden om het SUDEP-risico van een individu te bepalen.[2] Dit geeft al een groot probleem in de communicatie over SUDEP. Neurologen bespreken SUDEP zelden met al hun patiënten, om geen angst en stress te veroorzaken wanneer het risico waarschijnlijk zeer laag is en er geen interventies voor handen zijn.[23] De meeste mensen met epilepsie willen echter

wel over het risico op SUDEP geïnformeerd worden.[24] Individuele risicoprofielen zouden kunnen helpen om gerichte informatie te geven aan diegene voor wie dit het meest belangrijk is.

Er zijn verschillende manieren om individuele risicoprofielen te ontwikkelen. Veelbelovend onderzoek wordt reeds gedaan in de genetica. De zoektocht naar varianten in genen gerelateerd aan epilepsie, hartritmestoornissen en respiratoire functies, gebruik makend van whole exome of genoom sequencing van SUDEP-cases, heeft geresulteerd in de identificatie van verschillende genen mogelijk geassocieerd met SUDEP.[25, 26] Er is geen specifiek gen gevonden in alle SUDEP-cases, wat suggereert dat er sprake is van een complexe multifactoriële interactie. Toekomstig prospectief onderzoek naar genetische profielen van mensen met epilepsie, gebruikmakend van grote cohorten, zou een exacter genetisch profiel voor mensen met het hoogste SUDEP-risico kunnen opleveren.

SUDEP-biomarkers zijn een andere belangrijke factor in de zoektocht naar individuele SUDEP-risicoprofielen. De zoektocht naar SUDEP-biomarkers zou moeten beginnen met parameters waarvan we al weten dat ze met SUDEP geassocieerd zijn: PGES, apneu en asystolie. Wij hebben de potentie van postictale asystolie als SUDEP-biomarker bestudeerd en hebben geconcludeerd dat asystolie te zeldzaam is om een goede biomarker te zijn. Een andere component van het hartritme, hartritme variabiliteit, kan van een ECG worden afgeleid. Een recent case report toonde veranderingen in de hartritme variabiliteit, wat wijst op parasympatische hyperactiviteit, voor een overlijden aan SUDEP. Er werd geen verschil in interictale hartritme variabiliteit gevonden tussen SUDEP-cases en controles.[27] Potentiele verschillen in ictale hartritme variabiliteit, zijn echter nog niet onderzocht.

Langdurige centrale apneu (≥60 s) is geassocieerd met ernstige hypoxemie en zou een potentiele SUDEP-biomarker kunnen zijn. Zo'n apneu houdt echter zelden aan in de postictale periode[28] en daarom is het onwaarschijnlijk dat deze marker betrouwbaar het SUDEP-risico zou kunnen voorspellen.

PGES is een interessantere potentiele SUDEP biomarker. PGES zou aantrekkelijk kunnen zijn, omdat het bij alle gemonitorde SUDEP-cases gezien is. PGES bleek ook meer frequent bij SUDEP cases dan bij controles in een onderzoek,[29] terwijl dit in een ander onderzoek niet aangetoond werd.[30] Dit verschil zou verklaard kunnen worden als een steekproeffout, aangezien de klinische beoordeling van de aanwezigheid (en frequentie) van PGES af zal hangen van het aantal opgenomen aanvallen.[31] Automatische PGES detectie[32] of registratie van andere sterk gerelateerde markers zoals ictale toename van electrodermale activiteit[33,34] of interclonische intervallen[35] zouden goede alternatieven kunnen zijn voor thuisregistraties.

Voor alle potentiele biomarkers geldt dat er hele grote cohorten met lange follow-up bestudeerd moeten worden, in verband met de zeldzaamheid van SUDEP. Het verbeterde vermogen om grote data sets te verwerken en meetapparatuur te verkleinen zorgt dat thuismonitoring gedurende lange termijnen mogelijk wordt. Dit zal het identificeren van nieuwe SUDEP biomarkers vergemakkelijken. Middels deze aanpak kunnen we ook de relevantie van andere patronen die plotse dood kunnen verklaren gaan bestuderen bij mensen met epilepsie, inclusief non-seizure SUDEP en de overlap tussen SUDEP en plotse hartdood.[36]

Het verzamelen van big data voor SUDEP-onderzoek wordt belemmerd door weinig nauwkeurige rapportages van doodsoorzaken en gebrek aan obducties. Zorgprofessionals zouden beter op de hoogte moeten zijn van het bestaan van SUDEP en de registratie van SUDEP als doodoorzaak zou verbeterd kunnen worden door het aanmaken van een ICD-code voor SUDEP. Wanneer obductie niet is verricht, zou een SUDEP-case alsnog kunnen worden geclassificeerd als 'probable SUDEP'. Er zijn echter nog geen internationaal gevalideerde criteria voor 'probable SUDEP'. In hoofdstuk vijf hebben we onze eigen criteria ontwikkeld en gebruikt, het zou echter zeer waardevol zijn om deze prospectief in grote cohorten te valideren.

Concluderend zijn de belangrijkste manieren om het SUDEP-risico te verlagen het aantal tonisch clonische aanvallen te verlagen, de kennis van zorgprofessionals over SUDEP te verhogen en multimodale aanvalsdetectie systemen te implementeren. Voor de lange termijn zou een preventie onderzoek mogelijk zijn, mits we ons kunnen richten op groepen met hoog SUDEP-risico. Belangrijke informatie over potentiele biomarkers zou verzameld kunnen worden door gebruik te maken van aanvalsdetectiesystemen. Vanwege de zeldzaamheid van SUDEP is onderzoek in grote cohorten met een lange follow up essentieel om preventieve interventies te onderzoeken en de pathofysiologie te ontrafelen.

Referenties

1. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52:1150-1159.
2. 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.
3. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. The Lancet Neurology 2013;12:966-977.
4. Tellez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. Epilepsy research 2005;65:101-115.
5. Elliott JO, Lu B, Shneker B, Charyton C, Layne Moore J. Comorbidity, health screening, and quality of life among persons with a history of epilepsy. Epilepsy & behavior : E&B 2009;14:125-129.
6. Comorbidity in adults with epilepsy--United States, 2010. MMWR Morbidity and mortality weekly report 2013;62:849-853.
7. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. The Lancet Neurology 2016;15:106-115.
8. Paton JF, Boscan P, Pickering AE, Nalivaiko E. The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. Brain research Brain research reviews 2005;49:555-565.
9. Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. Lancet (London, England) 2004;364:2212-2219.
10. Nei M, Sperling MR, Mintzer S, Ho RT. Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. Epilepsia 2012;53:e137-140.
11. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. Epilepsia 2012;53:253-257.
12. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005;64:1131-1133.
13. Shorvon SD. Handbook of epilepsy treatment. Chichester: John Wiley & Sons 2010.
14. Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. Journal of neurology, neurosurgery, and psychiatry 2000;68:211-213.
15. Swinghamer J, Devinsky O, Friedman D. Can post-ictal intervention prevent sudden unexpected death in epilepsy? A report of two cases. Epilepsy & behavior : E&B 2012;24:377-379.
16. Klenerman P, Sander JW, Shorvon SD. Mortality in patients with epilepsy: a study of patients in long term residential care. Journal of neurology, neurosurgery, and psychiatry 1993;56:149-152.

17. McKee JR, Bodfish JW. Sudden unexpected death in epilepsy in adults with mental retardation. American journal of mental retardation : AJMR 2000;105:229-235.
18. Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: a realistic goal? Epilepsia 2013;54 Suppl 2:23-28.
19. Maguire MJ, Jackson CF, Marson AG, Nolan SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). The Cochrane database of systematic reviews 2016;7:CD011792.
20. van Andel J, Thijs RD, de Weerd A, Arends J, Leijten F. Non-EEG based ambulatory seizure detection designed for home use: What is available and how will it influence epilepsy care? Epilepsy & behavior : E&B 2016;57:82-89.
21. Van de Vel A, Cuppens K, Bonroy B, et al. Non-EEG seizure detection systems and potential SUDEP prevention: State of the art: Review and update. Seizure 2016;41:141-153.
22. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. Science translational medicine 2015;7:282ra246.
23. Friedman D, Donner EJ, Stephens D, Wright C, Devinsky O. Sudden unexpected death in epilepsy: knowledge and experience among U.S. and Canadian neurologists. Epilepsy & behavior : E&B 2014;35:13-18.
24. Xu Z, Ayyappan S, Seneviratne U. Sudden unexpected death in epilepsy (SUDEP): what do patients think? Epilepsy & behavior : E&B 2015;42:29-34.
25. Leu C, Balestrini S, Maher B, et al. Genome-wide Polygenic Burden of Rare Deleterious Variants in Sudden Unexpected Death in Epilepsy. EBioMedicine 2015;2:1063-1070.
26. Bagnall RD, Crompton DE, Petrovski S, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. Annals of neurology 2016;79:522-534.
27. Surges R, Henneberger C, Adjei P, Scott CA, Sander JW, Walker MC. Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy? Epilepsy research 2009;87:277-280.
28. Lacuey N, Zonjy B, Hampson JP , et al. The incidence and significance of perictal apnea in epileptic seizures. Epilepsia 2018; 59(3):573-582
29. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Annals of neurology 2010;68:787-796.
30. Surges R, Strzelczyk A, Scott CA, Walker MC, Sander JW. Postictal generalized electroencephalographic suppression is associated with generalized seizures. Epilepsy & behavior : E&B 2011;21:271-274.
31. Lamberts RJ, Gaitatzis A, Sander JW, Elger CE, Surges R, Thijs RD. Postictal generalized EEG suppression: an inconsistent finding in people with multiple seizures. Neurology 2013;81:1252-1256.
32. Theeranaew W, McDonald J, Zonjy B, et al. Automated Detection of Postictal Generalized EEG Suppression. IEEE transactions on bio-medical engineering 2018;65:371-377.

33. Poh MZ, Loddenkemper T, Reinsberger C, et al. Autonomic changes with seizures correlate with postictal EEG suppression. Neurology 2012;78:1868-1876.
34. Picard RW, Migliorini M, Caborni C, et al. Wrist sensor reveals sympathetic hyperactivity and hypoventilation before probable SUDEP. Neurology 2017;89:633-635.
35. Bauer PR, Thijs RD, Lamberts RJ, et al. Dynamics of convulsive seizure termination and postictal generalized EEG suppression. Brain : a journal of neurology 2017;140:655-668.
36. Bardai A, Lamberts RJ, Blom MT, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. PloS one 2012;7:e42749.

List of publications

van der Lende M, Surges R, Sander JW, Thijs RD; *Cardiac arrhythmias during or after epileptic seizures*; J Neurol Neurosurg Psychiatry. 2016 Jan;87(1):69-74. doi: 10.1136/jnnp-2015-310559.

van der Lende M, Shmuely S, Thijs RD. *Comment on falling status epilepticus mortality rates in England and Wales: 2001-2013*. Epilepsia. 2016 Oct;57(10):1731-1732.

van der Lende M, Cox FME, Visser GH, Sander JW, Thijs RD; *Value of video monitoring for nocturnal seizure detection in a residential setting*; Epilepsia. 2016 Nov;57(11):1748-1753.

Shmuely S, **van der Lende M**, Lamberts RJ, Sander JW, Thijs RD; *The heart of epilepsy: current views and future concepts*; Seizure. 2017 Jan;44:176-183.

de Meel RHP, Lipka AF, **van der Lende M**, van Zwet EW, Tannemaat MR, Verschuuren JJGM; *Activity limitations in myasthenia gravis and relation to clinical variables*; Muscle Nerve. 2017 Jul;56(1):64-70.

van der Lende M, Schmuely S, Aronica EMA, Thijs RD, *Sudden Unexpected Death in Epilepsy*; Tijdschr Neurol Neurochir, jaargang 118; nummer 4; december 2017

van der Lende M, Hesdorffer DC, Sander JW, Thijs RD; *Nocturnal supervision and SUDEP risk at different epilepsy care settings;* Neurology. 2018 Oct 16;91(16):e1508-e1518.

van der Lende M, Arends JB, Lamberts RJ, Tan HL, de Lange FJ, Sander JW, Aerts AJ, Swart HP, Thijs RD; *The yield of long term ECG recordings in refractory focal epilepsy;* Epilepsia. 2019

Dankwoord

Mijn grootste dank gaat uit naar alle mensen die mee hebben gedaan aan de onderzoeken. In het bijzonder heel veel dank aan alle mensen die mee hebben gedaan aan het CARELINK onderzoek, ik realiseer me heel goed dat we heel veel van jullie vroegen. Dank voor jullie onvermoeibare inzet. Ik hoop dat er in de toekomst een manier gevonden wordt om SUDEP te voorkomen.

Graag zou ik mijn promotor Gert van Dijk en mijn copromotor Roland Thijs willen bedanken. Gert, bedankt voor de begeleiding, de nuttige discussies en voor het altijd zien van een nieuwe invalshoek. Roland, zonder jou was dit proefschrift er niet gekomen. Hartelijk dank voor je aanstekelijke enthousiasme, goede feedback, realistische onderzoeksplannen en steun; met name tijdens de laatste maanden waarin ik veel moest schrijven, je hebt me daar echt doorheen gesleept.

Veel dank gaat ook uit naar mijn collega's uit het LUMC. Maar vooral dank aan mijn SEIN collega's. Allereerst mijn onderzoekscollega's collega's van de 'zolder': Trusjen, Sharon, Rob, Evelien, Merel, Marc, Yfke, Anouk, Robert en Matteo. Dank voor de wetenschappelijke discussies, hulp met de statistiek, maar vooral voor alle gezelligheid tijdens de barbecues, congressen en koffiepauzes. Jullie hebben mijn promotieonderzoek tot een onvergetelijke, leuke tijd gemaakt. Dank aan alle andere SEIN collega's voor de leerzame tijd. Met speciale dank aan alle collega's van de nachtzorg voor het opname en registreren van alle nachtelijke aanvallen voor een van de onderzoeken.

Also a big thanks to my colleagues of Chalfont Centre for Epilepsy for helping me find all the information I needed and of course for the 'high tea Fridays'.

Ten slotte dank aan mijn familie en vrienden. In het bijzonder veel dank aan mijn ouders: aan mijn vader, die altijd het volste vertrouwen in mij heeft, ook wanneer ik dat zelf niet heb. En aan mijn moeder die me altijd heeft gesteund, wat ik ook wilde doen. Dankzij jullie heb ik zover kunnen komen. Aan Sander dank voor alle liefde, steun en geduld. Zonder jou was dit proefschrift er nu nog niet geweest.

Curriculum vitae

Marije van der Lende is geboren op 1 februari 1987 in Delft, Nederland. In 2005 behaalde zij haar gymnasium diploma aan het Christelijk Lyceum Delft, waarna zij begon aan haar studie Geneeskunde in het Leids Universitair Medisch Centrum (LUMC). In 2006 behaalde zijn haar propdeuse. Na de reguliere coschappen heeft ze een verlengde wetenschapstage gevolgd bij professor Verschuuren in het LUMC over het syndroom van Lambert Eaton. Hierna heeft ze een semi-arts stage interne geneeskunde gevolgd in het HAGA ziekenhuis gevolgd door een keuze co-schap neurologie in het Alrijne ziekenhuis in Leiderdorp. In november 2011 behaalde zij haar artsexamen, waarna zij in 2012 begon in het Alrijne ziekenhuis te Leiderdorp als arts-assistant neurologie. In 2013 is zij begonnen bij Stichting Epilepsie Instellingen Nederland (SEIN) aan haar promotietraject over Sudden Unexpected Death in Epilepsie (SUDEP). Tijdens haar promotietraject heeft ze enkele maanden onderzoek gedaan bij Chalfont Centre for Epilepsy te Chalfont St Peter, Engeland, onder begeleiding van professor Sander. Tijdens haar promotietraject heeft ze in 2017 nog negen maanden als arts-assistant neurologie in het Reinier de Graaf ziekenhuis in Delft gewerkt. In april 2018 is zij begonnen aan de opleiding tot neuroloog in het LUMC.