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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

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

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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 2-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 ≥ 6 seconds; atrial fibrillation < 55 beats per minute (bpm), or > 200 bpm and duration > 30 seconds; persistent sinus bradycardia < 40 bpm while awake; and second- or third-degree atrioventricular block and ventricular tachycardia/fibrillation. We performed 12-lead electrocardiography (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 (<6 seconds) 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), and sinus tachycardia with a right bundle branch block configuration (n = 1).

Significance: 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.

KEYWORDS

cardiac arrhythmias, ECG, epilepsy, implantable loop recorders, sudden unexpected death in epilepsy

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1 | 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-electroencephalographic (EEG) recordings of SUDEP cases show periods of postictal apnea, bradycardia, and asystole prior to death.[5] Although ictal asystole is the most frequent arrhythmia, postictal rather than ictal asystole seems of greater importance to SUDEP.[6] Another concern is the threefold 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 2 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 seizure-related and non–seizure-related causes of asystole, including reflex syncope.

We aimed to determine the yield of long-term electrocardiographic (ECG) recordings in a large cohort of people with epilepsy. We assessed the 2-year prevalence of all clinically relevant arrhythmias and evaluated the potential of postictal arrhythmias as markers of SUDEP risk.

Key points

- No potentially lethal arrhythmias were found in a population with a high SUDEP risk profile
- Postictal asystole is associated with SUDEP; however, postictal arrhythmias are not useable as potential SUDEP biomarkers
- The absence of postictal arrhythmias does not support the use of loop recorders in people at high SUDEP risk

2 | MATERIALS AND 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.

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

Prior to implantation, a tilt table test was performed. Heart rate and blood pressure were measured noninvasively on a beat-to-beat basis (Nexfin, BMEYE; or Finometer, Finapres Medical Systems). After 10 minutes of supine rest, the subject was tilted upwards to 70° 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.[11] In case of syncope, the subject was tilted backward to terminate loss of consciousness. Positive tilt table tests were evaluated according to the classification of the Vasovagal Syncope International Study (VASIS)[12]: VASIS I, mixed type; VASIS IIa, cardioinhibition without asystole; VASIS IIb, cardioinhibition with asystole; and VASIS III, pure vasodepressor type.

2.1 | Definition of clinically relevant arrhythmias

Clinically relevant arrhythmias were defined as asystole of ≥6 seconds together with clinical symptoms of (near) syncope; asystole of ≥10 seconds regardless of clinical symptoms;[13,14] polymorphic sustained or nonsustained VT; nonsustained monomorphic VT of >180 beats per minute (bpm) and >2-second duration, or >175 bpm and >3-second duration, and sustained monomorphic VT; atrial fibrillation of >200 bpm and >30-second duration, or <55 bpm and clinical symptoms (near syncope or dyspnea); persistent sinus bradycardia of <40 bpm while awake; and asymptomatic second or third degree atrioventricular (AV) block of >4 seconds duration.

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Drug-refractory focal epilepsy[a]: failure of adequate trials of 2 AED schedules to achieve sustained seizure freedom[31]	Clinical suspicion of ictal asystole (e.g. focal seizures with sudden flacid falls)[15,17]
At least 1 focal seizure with impaired awareness or 1 tonic-clonic seizure per month	Loop recorder implantation (either current or in the past)
Aged 18-60 y	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[11] without proper cardiac evaluation to exclude these possibilities[b]: • Bifascicular block and other intraventricular conduction abnormalities • Asymptomatic inappropriate sinus bradycardia (<50 bpm) • Sinoatrial block or sinus pause ≥ 3 s in the absence of negative chronotropic medications • Nonsustained 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 antiarrhythmic/antiarrhythmogenic medication
	Current dissociative seizures
	People who live alone who are not able to recall seizures
	Pregnancy

Abbreviations: AED, antiepileptic drug; ECG, electrocardiographic; EEG, electroencephalographic; VT, ventricular tachycardia.
[a]Diagnosis based on history taking and eyewitness accounts and supported by at least one of the following: interictal EEG abnormalities, magnetic resonance imaging lesions known to cause epilepsy, home videos, and ictal EEG recordings.
[b]According to European Society of Cardiology guidelines on syncope.[11]

2.2 | Data collection

Devices continuously monitored heart rhythm. Automatic storage of ECG data took place in episodes of bradycardia (<40 bpm), asystole (>3 seconds), any tachycardia (>180 bpm) or atrial fibrillation, or when participants activated the device (eg, during or after a seizure). All arrhythmias that did not meet the above criteria of clinically relevant arrhythmias were classified as “non–clinically relevant arrhythmias.” The latter category also included short-lasting asystoles. When an individual activated the device, it stored the preceding 9 minutes and subsequent 1 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 per 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 (M.v.d.L.) 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 (A.J.A.) 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.

TABLE 2 Clinical characteristics

Characteristic	Value
Age, y	Mean = 43.1, SD = 12.1, range = 20-60
Gender, female, n (%)	26 (53)
Epilepsy etiology, n (%)	
Structural	25 (51)
Genetic	5 (10)
Infectious	4 (8)
Metabolic	1 (2)
Immune	1 (2)
Unknown	13 (27)
EEG localization, n (%)	
Temporal	25 (51)
Extratemporal	24 (49)
Age at onset, y	**Mean = 15.0, SD = 9.9, range = 1-34**
Seizure types, n (%)[a]	
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, n (%)	
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, n (%)	
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 AEDs, n (%)	
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, n (%)	7 (14)
Epilepsy surgery, n (%)	
Evaluation during the course of the trial	3 (6)
Rejected for epilepsy surgery	10 (20)
Having had epilepsy surgery	7 (14)

Abbreviations: AED, antiepileptic drug; EEG, electroencephalographic.
[a]Does not add up to 100%, as people can have multiple seizure types.

2.3 | Standard protocol approvals, registrations, and patient consents

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

3 | RESULTS

Fifty people were recruited. One person withdrew from the study 2 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 [n = 1], VASIS IIb [n = 1]); 13 vasodepressive (VASIS III).

A total of 1060 months were monitored, with median follow-up of 24 months (interquartile range = 21-27 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 (n = 6), wound infection (n = 3), contour of recorder too visible through the skin (n = 1), or vagal nerve stimulator insertion (n = 1).

A total of 16 474 seizures (median = 97, interquartile range = 52-321, range = 0-4344) were recorded in diaries (Table 3). ECG recordings were made of 4679 (median = 31, interquartile range = 11-74, 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.

We found no clinically relevant arrhythmias as predefined. 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

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

	Reported in seizure diaries	Recorded on implantable loop recorder
Tonic-clonic seizures, n (%)	350	77 (22)
Other seizures, n (%)	16 124	4602 (28.5)

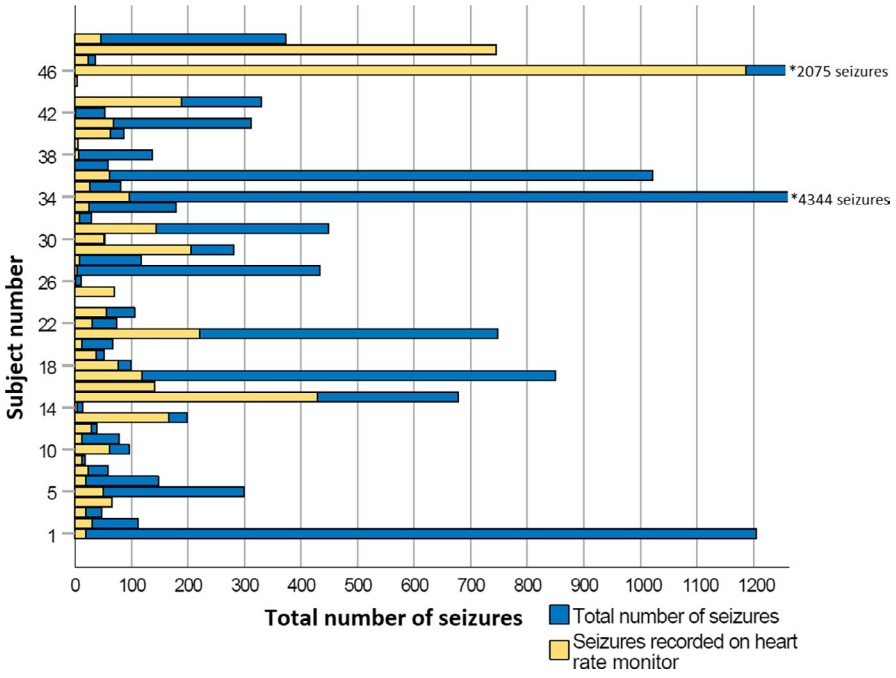

FIGURE 1 Total number of seizures per subject. Subject 9 was excluded from analysis due to newly diagnosed dissociative seizures. * number of seizures exceeds the value range of the x-axis

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) 13 periods of paroxysmal atrial fibrillation with a ventricular tracking frequency up to 140 bpm lasting maximum 2 minutes; and (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 of <50 bpm and 14 periods of asystole of 3 or 4 seconds were recorded over the course of 3 days; neither the subject nor relatives noticed symptoms or seizures in this period. The subject was monitored for an additional year. During the 3 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 4 minutes of bradycardia (median = 40 bpm) including three periods of asystole: one of 4 and two of 3 seconds (Figure 2). The tilt table test at baseline had provoked a mixed response including a cardioinhibitory component (Figure 2D,E). The event was diagnosed as a cardioinhibitory micturition syncope.

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

4 | 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 >16 000 seizures during long-term follow-up. We identified short-lasting periods of asystole in 3 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 nonfatal 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.

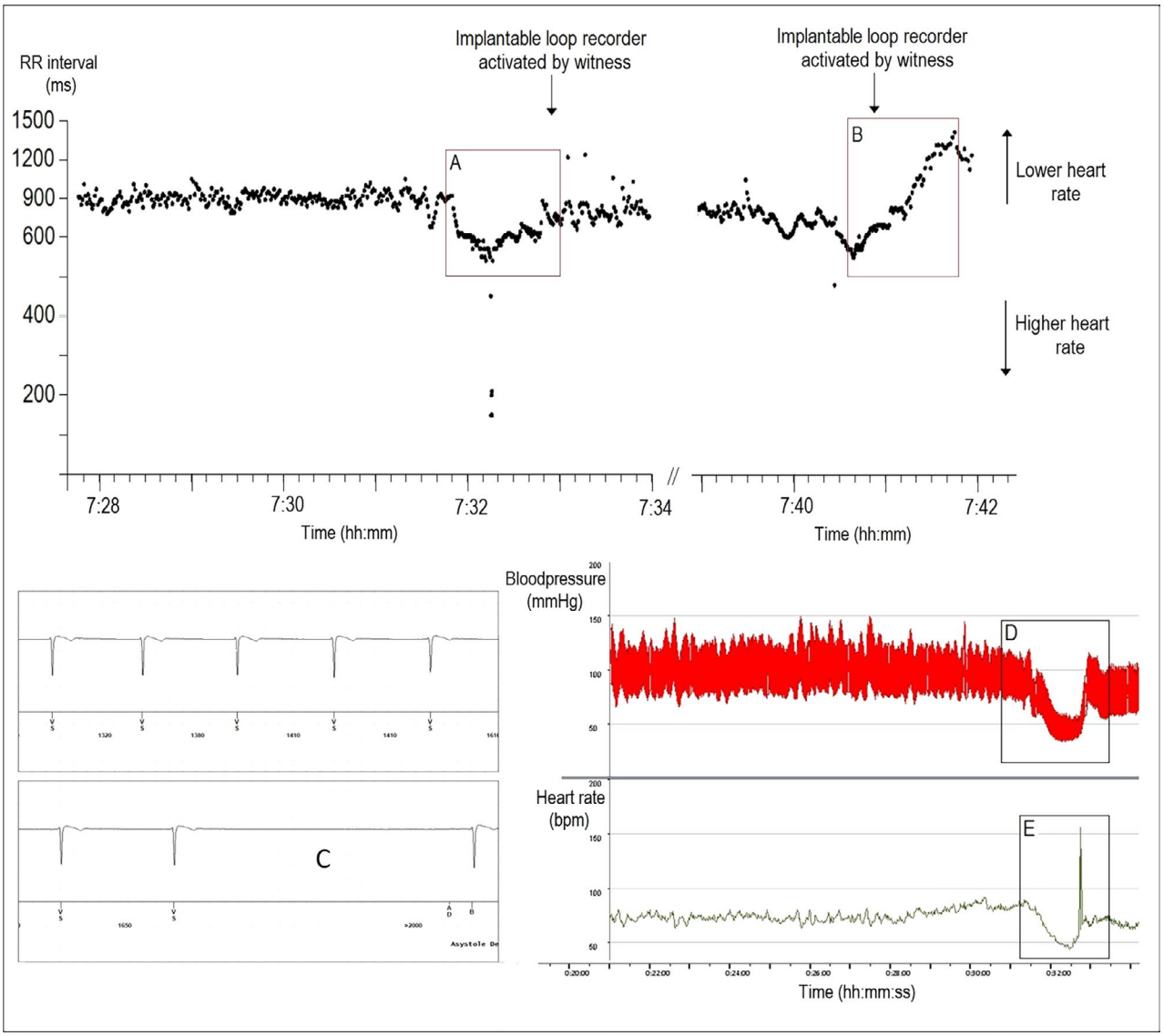

FIGURE 2 Subject 15 had a focal seizure with impaired awareness. (A) During the seizure, a sudden increase in heart rate is observed (as reflected by the decrease in the RR-interval). Shortly hereafter, the subject was pale and sweating profusely, fell suddenly and lost consciousness. (B) Electrocardiographic (ECG) recording initiated by his mother who witnessed the event shows a drop in heart rate. (C) Simultaneous automatic ECG recording demonstrated bradycardia leading to a 4-second asystole. (D & E) The tilt table test 1 year prior to the event showed vasovagal syncope with a cardioinhibitory component: a sudden drop in blood pressure (D) coinciding with a decrease in heart rate (E)

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[15]; loss of tone and falls during a typical focal seizure with impaired awareness provide an important diagnostic clue for ictal asystole.[16–18] 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] Although 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 4.8 seconds.[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 clinically relevant arrhythmias in a high-risk group. We were also able

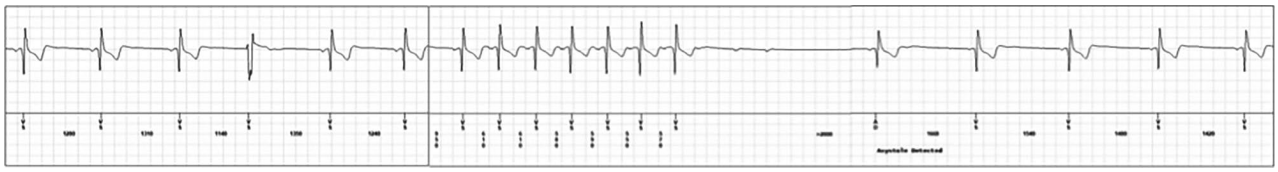

FIGURE 3 Non–seizure-related short-lasting paroxysmal atrial tachycardia followed by three blocked atrial beats, resulting in an asystole of 3.3 seconds

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 >4000 recorded seizures. Compared with the previous studies, we monitored three times as many patient-hours and recorded 10 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.[19,20] 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. We found an incidence of short-lasting (<6 seconds) periods of asystole of 2.91 per 1000 patient-months. Unfortunately, we could not compare these figures to reference data from the healthy population.

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.[21] We found that postictal arrhythmias, despite their specificity, are too rare to be used as a biomarker. Other, more sensitive biomarkers are thus needed. A prospective, multicenter epilepsy monitoring study demonstrated that postconvulsive central apnea (PCCA) is more prevalent than postictal asystole.[22,23] In 2 of 22 cases, PCCA coincided with asystole (near SUDEP); 1 case with PCCA and without concurring asystole died from probable SUDEP during long-term follow-up (incidence = 5.1 per 1000 person years).[23] Postictal generalized EEG suppression (PGES) is another potential biomarker that has been linked to SUDEP.[5,24,25] The clinical assessment may, however, be challenging, as the presence of PCCA or 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 video detection of respiratory arrest,[28] automated PGES detection,[29] or other closely related markers such as ictal increases of electrodermal activity[25] or interclonic intervals[30] 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. Ideally, these cohorts should also include those at high risk for other epilepsy types including genetic generalized epilepsies and developmental encephalopathies. 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.

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CONFLICT OF INTEREST

M.v.d.L., R.J.L., H.L.T., F.J.d.L., A.J.A., and H.P.S. report no disclosures. J.B.A. reports grants and personal fees from UCB, outside the submitted work. J.W.S. has received research funding from Eisai and UCB, and personal fees from Eisai, UCB, Bial, and Janssen, outside of the submitted work. R.D.T. receives research support from Medtronic and has received fees for lectures from Medtronic, which provided the implantable loop recorders used in this study. R.D.T. has received fees for lectures from UCB Pharma and GlaxoSmithKline, outside the submitted work. We confirm that we have read the Journal's position on issues involved

in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTION

All authors were involved in the conceptualization and design of the study. M.v.d.L., J.B.A., R.J.L., A.J.A., and H.P.S. did the data acquisition. M.v.d.L. and R.D.T. analyzed the data. M.v.d.L., J.B.A., J.W.S., and R.D.T. contributed to drafting the manuscript and the figures.

DATA AVAILABILITY STATEMENT

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

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