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(article begins on next page)

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Review

Non-EEG seizure-detection systems and potential SUDEP prevention: State of the art

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ABSTRACT

Purpose: There is a need for a seizure-detection system that can be used long-term and in home situations for early intervention and prevention of seizure related side effects including SUDEP (sudden unexpected death in epileptic patients). The gold standard for monitoring epileptic seizures involves video/EEG (electro-encephalography), which is uncomfortable for the patient, as EEG electrodes are attached to the scalp. EEG analysis is also labour-intensive and has yet to be automated and adapted for real-time monitoring. It is therefore usually performed in a hospital setting, for a few days at the most. The goal of this article is to provide an overview of body signals that can be measured, along with corresponding methods, state-of-art research, and commercially available systems, as well as to stress the importance of a good detection system.
Method: Narrative literature review.
Results: A range of body signals can be monitored for the purpose of seizure detection. It is particularly interesting to include monitoring of autonomic dysfunction, as this may be an important patho-physiological mechanism of SUDEP, and of movement, as many seizures have a motor component.
Conclusion: The most effective seizure detection systems are multimodal. Such systems should also be comfortable and low-power. The body signals and modalities on which a system is based should take account of the user's seizure types and personal preferences.
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1. Introduction

Epilepsy is the most common serious neurological condition, affecting almost 60 million people (close to 1% of the world population) and 2.5 million new cases each year. Its prevalence has a bimodal distribution with peaks in infancy and older age (65+). For 25–30% of all patients, no combination of standard therapy (medication or surgery) can control their seizures. These patients are said to suffer from refractory or intractable epilepsy.[1–5]

Compared to a normal population, the mortality risk for patients with epilepsy is elevated by a factor of two to three, with a mean annual mortality rate of 1%. Epilepsy-related deaths can be divided into four categories. First, deaths resulting from the underlying cause of epilepsy, neurological or anatomical (e.g. brain tumour). Second, deaths caused directly by epilepsy itself (status epilepticus or SE, drowning, burning, traffic and other traumatic accidents) or its treatment. Third, deaths due to co-morbidities, including depression leading to suicide, co-existent neurologic compromise, and respiratory tract infection or pneumonia after repetitive aspiration during seizures. Fourth, deaths of unknown cause, called sudden unexpected death in epilepsy (SUDEP).[6–8]

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure (with onset within the preceding hour) and excluding documented SE (seizure duration ≥30 min or

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seizures without recovery in between), in which postmortem examination does not reveal a cause of death.[9]

Three of these most common causes of death could possibly be prevented through seizure detection. SE contributes to up to 16% of deaths, traumatic accidents comprise up to 30% and SUDEP accounts for up to 38%.[1,10]

Of the limited number (7–38%) of witnessed incidents of SUDEP, 33–100% were preceded by seizures (in most cases, convulsive). In the unwitnessed incidents of SUDEP, it is not always clear whether a seizure took place, although almost 90% involve evidence of tongue biting, incontinence or disrupted environment, strongly suggesting a recent convulsive seizure (but not excluding other explanations).[11–13]

This article is based on our own work, the difficulties that have been encountered by other research teams in the field and the many requests from parents and patients for a robust seizure-detection system, and inspired by our observation that information on this topic is difficult to obtain. Even though non-EEG (electro-encephalography) systems have appeared on the market recently, experience with these systems is still limited.[4,14–18] The goal of this article is to provide healthcare professionals, engineers, as well as interested patients with an overview of body signals that can be measured, along with the corresponding methods of measurement, state-of-art research and available systems. The article also stresses the importance of a good system for early intervention, reassurance of patient and environment, and prevention of SUDEP.

2. SUDEP

2.1. Risk factors and triggers

It has been suggested that SUDEP is caused by the co-existence of several predisposing (inter-ictal) and triggering (peri-ictal) factors. The former are known as risk factors and the latter as patho-physiological mechanisms or direct causes. Knowledge of the different risk factors could provide clues to possible patho-physiological mechanisms. Likewise, understanding the mechanisms may lead to the identification of previously unrecognised risk factors that could possibly be amenable to correction, thus preventing SUDEP.[8,19]

Cardiac, respiratory and other autonomic dysfunctions have been thoroughly investigated and proposed as patho-physiological mechanisms for SUDEP. These dysfunctions result in decreased cerebral oxygen supply and electro-cerebral shutdown. In other words, inhibition of brain activity can be both a cause (seizure) and a response.[20]

Risk factors that have been consistently identified include epilepsy onset at young age, long duration of epilepsy, generalised tonic–clonic seizures (GTCS), partial seizures (symptomatic epilepsy) and polytherapy.[21] Furthermore, many risk factors constitute a risk due to their negative effects on the patho-physiological mechanisms. For example, young people are known to have a higher baseline vagal tone.[22] In many cases, GTCS present with tachycardia and tachypnoea.[23,24] Partial seizures influence the cardiopulmonary instability: ictal asystole and apnoea or hypoventilation can occur in temporal lobe seizures, while ictal tachycardia and irregular breathing often occur in hypermotor frontal lobe seizures.[25–27] Polytherapy can lead to cardiac and respiratory dysfunction.[28] In other words, it is particularly interesting to include methods for monitoring cardiac, respiratory and other autonomic body signals in detection systems.

2.2. Prevention

Because we are far from having a perfect method for predicting seizures, let alone SUDEP, supervision is one of the key measures in addition to control over risk factors. In one large case–control study, supervision was associated with a substantial decrease in the risk for SUDEP.[11] Supervision might thus prevent SUDEP both by detecting seizures and by monitoring SUDEP risk factors or patho-physiological mechanisms, depending upon the methods used (Section 4).

Possible actions by the caregiver after an alert include enabling a proper position (from prone or supine to recovery); stimulating the patient by rolling over or similar means (passive muscle movement); cardio-pulmonary resuscitation and defibrillation; administrating medication or oxygen; clearing the airway; protecting against injuries; and seeking help if needed. Supervision also allows the caregiver to reassure and calm down the patient, to maintain a vigil in the post-ictal phase and to clean the bed in case of vomiting or incontinence.

3. Seizure detection

3.1. Seizure detection in general

The gold standard for monitoring epileptic seizures involves video/EEG (electro-encephalography), which is uncomfortable for the patient, as EEG electrodes are attached to the scalp. EEG analysis is also labour-intensive and has yet to be automated or adapted for real-time monitoring. It is therefore usually performed in a hospital setting, for a few days at the most, and it is generally used to confirm the diagnosis of epilepsy instead of for objectively quantifying seizure frequency or warning for potential SUDEP.

The interest in ambulant systems originates from the need to monitor patients over extensive periods (weeks to months) and in the natural home and outdoor environment (domiciliary and residential settings).[29] Long-term home monitoring might also reduce costs by eliminating the need for hospital admission and clinical observation.

Detecting seizures makes it possible to alert the caregiver, who can take action, as described in Section 2.2. Generating an objective log of the number, order, duration, affected body part and type of seizures can inform the neurologist and help to optimise treatment. Objective seizure logs could significantly enhance the somewhat unreliable patient-diary technique, which is subjective and can be influenced by peri-ictally affected consciousness or memory. One limitation of non-EEG seizure detection is that it cannot provide retroactive verification (by video/EEG) for events that are logged as seizures.[30]

It should be made possible to adjust seizure alerts according to the user's personal preferences. Some parents might want to be informed of every seizure, in order to reassure their child, while institutions might request this information in order to comply with insurance requirements. Other parents might not want to wake the patient unnecessarily, and also hospital caregivers might prefer to be informed only in the event of life-threatening seizures that could signal near-SUDEP events and require immediate action. In other words, an ideal system should be customised to seizure type, as well as to seizure severity and quality of life.

Another factor to consider is which events need detection. One common difficulty involves distinguishing epileptic seizures from non-epileptic events (e.g. syncope, hypoglycaemic seizures in diabetes, psychogenic non-epileptic seizures or pseudo-seizures), life-threatening events (e.g. suffocation) and sleep-related disorders (e.g. restless-leg syndrome, periodic limb movement disorder, somnambulism, pavor nocturnus). However the relative need for differential diagnosis is unclear. Because non-epileptic events might also need care, similar safety protocols should be administered.[31] Furthermore, many patients have overlapping disorders. For example, a third of all patients with nocturnal frontal lobe seizures (NFLS) have a history of somnambulism, pavor

nocturnus, rhythmic movement disorder and enuresis.[32] On the other hand, detecting 'normal' sleep-related movement or vocalisations (e.g. nocturnal leg cramps, hypnic jerks, somniloquy) might be redundant.

Monitoring during the day and when the patient is awake is useful primarily for (young) adults. It is important when the patient is alone, and allows for emergency care in case of drowning, burning, traffic and other traumatic accidents. One advantage of daytime monitoring is that false alarms are less problematic and can be turned off by the patient. On the other hand, detection during sleep might be easier, as patients remain at the same location within the detection range, since there is less noise from voluntary movements and because convulsions occur in a relatively controlled, reproducible manner. It is also more important because of the reduction or lack of supervision, as subjective elements that precede seizures (auras that allow patients to foresee them) are unavailable and since some types (particularly frontal lobe seizures)[33] occur more often at night.

3.2. Intracerebral seizure detection

The main reasons why many studies focus on the early detection or prediction of seizures using EEG (cortical or intracranial) are obviously that epilepsy is a neurological disease and that the ultimate purpose should be to prevent damage to the brain by preventing seizures.

Electrographic seizures can already start before and propagate to the clinically observable seizure, thus allowing the prediction and possible prevention of clinical seizures or SUDEP (Fig. 1). Automated EEG analysis could also allow predicting/detecting seizures that remain sub-clinical or those for which clinical expression is very subtle (e.g. absence seizures).

In addition to the risks of implanting intracranial systems and the discomfort of head-attached devices, they raise a number of other questions as well.

Does EEG detect all seizures? Some nocturnal seizures produce subtle or no ictal EEG patterns during scalp recording, or their EEG patterns may be obscured by excessive muscle artefacts. In fact, certain forms of epilepsy (in which seizures occur almost exclusively at night, including NFLS, where ictal EEG findings are visible in only half of all cases)[34] were not definitively recognised as epileptic until the past 20–25 years.

Should EEG recordings be combined with physiological sources as a standard form, given that the difficulty of detecting seizures is exacerbated by contamination of EEG recordings with environmental and biological artefacts?[35]

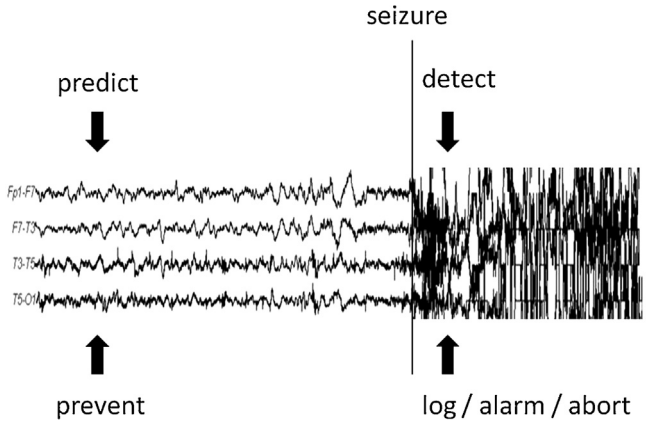

Fig. 1. EEG sample of a seizure. Prediction can lead to prevention and early detection to abortion of seizures.

Could a seizure indeed be aborted through stimulation after the onset of electrographic seizure activity, or has the brain already passed the 'point of no return', to a state that will inevitably progress into a clinical seizure manifestation?[36] In other words, how important is the latency period between the onset and detection of electrographic seizures for allowing alarming and action?

Do sub-clinical events require action at all? Who would benefit from preventive measures? Which actions should be taken and when, both for preventing seizures and for preventing SUDEP?

3.3. Extracerebral or non-EEG seizure detection

Most engineers and neuroscientists focus on the link between brain and epilepsy and not on the link between brain and body. Extracerebral body signals are under cortical control and altered by seizures as well, thus providing indirect but valuable information about the state of the brain.[30]

Given that no ideal intracerebral devices are yet available (automated detection and predictability of seizures have been studied since the 1970s)[36] and considering the many advances of non-EEG seizure detection described below, it is surprising that such devices are not mentioned more often in strategies for epilepsy and preventing SUDEP.

First, regardless of their value, scientific advances may not translate into improved care unless the devices are broadly accessible. Extracerebral (or, more specifically, non-EEG devices) are more widely applicable than intracranial devices are, as they are not invasive and can, if contactless, even be non-obtrusive.[30] In other medical conditions, many devices for physiological signs (e.g. for sleep disorders) and movement detection (e.g. for Parkinson and fall detection) are already on the market, thus allowing the transfer of knowledge. Non-EEG body signals might be less complex.[30] They might therefore allow smaller and less expensive devices that use less power for automated analysis. Finally, non-EEG devices could immediately be tested on human subjects.

Similar to coupling intracerebral detection to a preventive or aborting action (Fig. 1), extracerebral or, more specifically, non-EEG devices could include responsive stimulation of heart, respiration or muscles (including diaphragmatic pacing), administration of medication or oxygen or (less obviously) the inflation of an 'airbag' to prevent injury. The latter has been tested in the context of hip protection in order to prevent fall-related injuries in the elderly.[37] So strategies for epilepsy and preventing SUDEP should not focus solely on 'cure' (if preventing or aborting seizures can be considered a cure) but also on 'care' (disease control) as part of the overall treatment plan.

4. Detection systems

4.1. Slow progression

Despite the plea for additional research focusing on non-EEG detection devices for epileptic seizures, the field is moving slowly, and there is no clear overview of the devices that are on the market. The obtrusiveness and excessive false alarms associated with these devices often make patients reluctant to use them. Moreover, many commercial systems detect primarily intense, long and repetitive movements in general, and there is apparently no scientific proof or information from clinical trials to provide users with reliable information on their efficacy.

Perhaps the greatest difficulty to overcome, and one reason why companies might be reluctant to invest, involves the necessity of customising the devices to the patient's seizures (supervised learning or patient-specific training) and the user's personal preferences (Section 3.1).

4.2. Research focus

Seizures may result (ictally, post-ictally or peri-ictally) in a sudden alteration of sensation, motor activity or behaviour, psyche (consciousness, responsiveness, post-ictal dysnomia), vocalisations or autonomic signs.

A significant number of seizures is characterised by motor symptoms,[38] and partial seizures often show motor phenomena in the early stages.[30,39] Autonomic changes might even occur pre-ictally,[26] and ictal cardio-respiratory events appear to play a crucial role in the context of SUDEP (before or without seizure occurrence). For these reasons, non-EEG detection focuses on one or a combination of these signals.

The following sections provide an overview of various detection methods. Detection by metabolic (including hormonal) or tissue stress biomarkers is not listed, as such devices are usually invasive. It also provides a description of human studies (published recently or in the past) involving non-EEG seizure-detection methods. The discussed studies include development of a detection device, as well as seizure algorithms and their results (Table 1).

4.3. Detecting cardiovascular changes

4.3.1. Electrocardiography (ECG)

Persistent heart rate (HR) elevations after exercise, decreased heart rate variability (HRV, changes in the heart's beat-to-beat interval reflecting autonomic nervous system activation) and cardiac repolarisation abnormalities are established predictors of sudden cardiac death in other medical conditions or in healthy populations.[24]

One-lead ECG recording allows detecting HR, HRV and ECG morphology. As mentioned in Section 2.1, seizure-related HR changes commonly occur, and they are more pronounced with generalised tonic–clonic (GTCS), hypermotor frontal lobe and temporal lobe (TLS) seizures. Such events subsequently increase the risk of SUDEP. Ponnusamy and colleagues observed HRV differences (high sympathetic and low vagal tone) in TLS, as compared to psychogenic non-epileptic seizures.[40] An example of a change in ECG morphology is the QT interval shortening in GTCS, found by Surges and colleagues.[24]

Challenges include the use of continuous ECG for distinguishing arousal from sleep, standing from reclining and exercises (e.g. climbing stairs) from seizures. The combination with a chest accelerometer (ACM, Section 4.6.3) to determine position might already be a first step towards a possible solution.

A team from the Netherlands and Belgium and the partnership between **Holst Centre/imec and Hobo Heeze BV** are working to develop a system that is attached to the chest and arm, which uses ECG for seizure detection. Published results and more information are mentioned in Tables 1 and 2.[4,41] Table 2 further mentions that the commercially available bed-mounted seizure-detection system Emfit (Finnish company **Emfit Ltd**) can detect the heartbeat by monitoring movement. This information was taken from its website, no publication could be found. In addition, the AspireSR system (US company **Cyberonics, Inc.**) uses ECG-based seizure detection and is currently undergoing a clinical trial.

4.3.2. Blood pressure

Blood pressure measurements can be performed by finger plethysmography (or peripheral arterial tonometry, used for recognising arousals), which is included in pulse oximeters (Section 4.4). This technique investigates changes in autonomic activity, and it can detect irregular heartbeat, pulse wave amplitude and pulse transit time. The latter is inversely correlated with blood pressure.[42]

4.4. Detecting respiration changes

Respiration is frequently altered during seizures, and monitoring is also important in preventing SUDEP, not only for monitoring breathing and apnoea, but for detecting sighs, yawns and arousal. Low arousability is a possible sign of near-SUDEP, and two important mechanisms involved in auto-resuscitation are arousal and gasping.[43,44] Numerous methods exist for monitoring respiration, including the sensing of airflow temperature, pressure or velocity; chest movement or volume changes; transcutaneous blood-oxygen concentration or partial pressure; respiratory gases oxygen or carbon dioxide concentration; and transcutaneous audio or vibration signals resulting from breathing turbulence in the larynx.

A thermocouple or thermistor placed below the nose senses airflow temperature, a mask covering the nose and mouth senses airflow pressure and a pneumotachography mask senses airflow pressure or velocity. Although these devices are in common use, they are associated with several disadvantages, including their discomfort and influence on breathing.[45]

Sensing chest and abdominal wall movement in order to measure respiratory rate/depth/effort is often performed by measuring volume differences between the upper and lower chest using two straps (respiratory inductance plethysmography, or RIP),[45] two electrodes (impedance pneumography)[23] or magnetometers,[45] although it can also be performed using a single EMG (electromyography, on diaphragm or intercostals muscles) or ACM sensor (on chest or bed), and through remote measurement using video or microwaves (Section 4.6). One disadvantage is that respiratory movements can continue when there is already apnoea. As mentioned in Table 2, the commercially available bed-mounted seizure-detection systems Ep-It P139 (UK company **Alert-It**) and Emfit (**Emfit Ltd**) can detect respiration changes by monitoring movement. This information was again taken from their websites, no publications could be found.

A pulse oximeter is a clamp attached to ear lobe or fingertip (which could be integrated into a ring). For babies, it can be integrated into a foot strap or body sticker. It consists of a saturometer (which uses infrared waves to sense blood-oxygen concentration) and a plethysmograph (which measures changes in volume within an organ, resulting from fluctuations in the amount of blood, as described in Section 4.3.2, or of air, as described in reference to RIP). Oximetry is important, as it can identify rises in blood pressure due to airway blockage (e.g. because of prone position), despite continuing respiratory movements. The complex interaction between brain, heart and respiration makes data on oxygenation crucial in addition to information on respiration and ECG.[20,44]

Electrodes that sense the transcutaneous partial pressure of oxygen can detect respiration abnormalities faster and with fewer false positives than saturometers produce. Poets and colleagues have searched for possible mechanisms of Sudden Infant Death Syndrome by measuring different respiration parameters. In this study, electrodes were combined with pulse oximetry and chest-movement detection, with the following findings: decreased pressure without decreased saturation indicates changes in skin perfusion, but not arterial hypoxaemia; decreases in both pressure and saturation accompanied by tachycardia and slower, irregular or absent respiration indicates an epileptic seizure; and decreases in both pressure and saturation, preceded by increased amplitude and irregular breathing movement (often combined with tachycardia and massive body movements) indicates suffocation.[44]

Oxygraphy and capnography monitor the concentration (using infrared waves, as in pulse oximetry) or partial pressure (using electrodes, as above) of oxygen and carbon dioxide in respiratory gases.[46]

Table 1
Human studies involving non-EEG seizure detection methods, including development of a device, as well as algorithms and their results. Below the bold line: articles on seizure alarm systems that are commercially available or under clinical trial investigation, further discussed in Table 2. 2r = secondarily generalised, A = automotor seizure, ACM = accelerometer, C = clonic seizure, CPS = complex partial seizure, ECG = electrocardiography, EDA = electrodermal activity, EEG = electro-encephalography, EMG = electromyography, FDR = false detection rate, FLS = frontal lobe seizures, (G)TC(S) = (generalised) tonic–clonic seizure, gyro = gyroscope, h = hours, H = hyperkinetic/hypermotor seizure, HR = heart rate, IR = infrared wave, M = myoclonic seizure, magneto = magnetometer, μS = microsiemens, NPV = negative predictive value, PPV = positive predictive value, s = seconds, SIDS = sudden infant death syndrome, SPS = simple partial (motor) seizure, T = tonic seizure, TLS = temporal lobe seizure, V = versive seizure, w/ = with.

Article	Team location	Detection method(s)	Test subjects	Seizures	Real time (alarm)	Contact (-less)	Results
Becq et al.[38]	France	ACM + magneto	2 patients	46	Yes	Attached to torso/wrist	Sensitivity 90%, FDR per night 0.7
Conradsen et al.[60]	Denmark	ACM + gyro + EMG (integrated magneto not used)	10 healthy adults, 1 adult patient	Simulated M/V/TC, 1 real TC	No	Sensor suit + electrodes attached to belly/limbs	For different combinations of methods: see article, best results when combining all three: sensitivity 100%, FDR per hour 0, mean latency 0.75 s
Cuppens et al.[54]	Belgium	Video	3 paediatric patients	14 M	No	Contactless	Sensitivity > 75%, PPV > 85%
Dalton et al.[2]	US/Ireland	ACM	5 adult patients	21 M, C	No	Attached to limbs	Sensitivity 91%, specificity 84%, 50 false positives (during day)
de Bruijne et al.[67]	Netherlands	Audio	17 patients	95	No	Contactless	Sound observed in 61/95 seizures, 78 real and 175 simulated sounds studied, average sensitivity 95–98%, specificity 72–97%, PPV 2–40% depending on sound type
Jallon[61]	France	ACM	2 patients	46	Yes	Attached to torso/wrist	Sensitivity 88–89%, false alarms 25–45%
Karayiannis et al.[55]	US	Video	54 infant patients	M/C	No	Contactless	Sensitivity and specificity > 90%
Nijssen et al.[62]	Netherlands	ACM	36 patients (18 with seizures)	27 T	No	Attached to arm	Sensitivity 80% (5 missed e.g. because movement was blocked), PPV 35% (42% of the false alarms being M or C)
Nijssen et al.[63]	Netherlands	ACM	15 patients for training, 21 for testing	29 M for training, 35 for testing	No	Attached to arms	Sensitivity 80%, PPV 16% (148 false positives during 3.6 h, amongst which also C and T)
Poh et al.[49]	US	EDA + ACM	80 paediatric patients (7 with seizures)	16 GTCS	No	Wristband with electrodes	Sensitivity 94% (15/16), FDR per 24 h 0.74 (130 false alarms, mainly during day)
Rémi et al.[50]	Germany/ Portugal	Video	17 patients	10 H (FLS) + 10 A (TLS)	No	Attached IR reflectors	Sensibility for H 80.8%
Schulc et al.[64]	Austria	ACM	20 adult patients (3 w/seizures)	4 GTCS	Yes	Attached to arm	Sensitivity 100%, specificity ≥88%, PPV ≥75%
Van de Vel et al.[65]	Belgium	ACM	7 paediatric patients	51 H of which 2 per patient used	No	Attached to limbs	Sensitivity 95.71%, PPV 57.84%
Beniczky et al.[14]	Denmark	ACM	73 paediatric and adult patients (20 w/seizures)	39 GTCS	Yes	Bracelet	Sensitivity 89.7% (35/39), mean latency 55 s, FDR per day 0.2 (40, all during day-time tasks)
Carlson et al.[15]	US	Audio	64 paediatric and adult patients	8 TC	Yes	Between bed and matrass	Sensitivity 63% (5 detected), specificity 90%, NPV 99%, PPV 3.3% (269 false positives during 1528 h)
Conradsen et al.[58]	Denmark	EMG	5 patients (2 with seizures)	7 GTCS	Yes	Electrodes attached to leg	Mean sensitivity 57% (4/7), latency 25 s, FDR per hour 0.003 (1 false positive)
Fulton et al.[16]	US	Audio (and body pressure)	27 paediatric patients (15 w/seizures)	9 TC + 8 2r TC + 10 CPS + 2 SPS + 40 M, T, M + T = 69	Yes	Between bed and matrass	MP5: detection rate 4.3% (1/23: a TC), ST-2: 2.2% (1/46: a CPS)
Kramer et al.[17]	Israel	ACM	31 patients (15 with seizures)	22 T, C, TC	Yes	Watch-like	Sensitivity 91% (20 detected), 8 false positives in 1692 h (FDR per 24 h 0.11, all during day), median latency 17 s
Lockman et al.[18]	US	ACM	40 adult patients (6 with seizures)	8 TC	Yes	Watch	7/8 (87.5%) detected of which 2 during day (1 possibly missed because of uncharged battery or Bluetooth failure), PPV > 50% (204 false positives during day when alarm can be turned off, 1 at night), latency to onset C phase 4–15 s
Massé et al.[4] and van Elmpt et al.[41]	Netherlands/ Belgium	ECG (integrated ACM not used)	17 patients (10 with seizures)	104 (mostly T and M but also absence and TC)	Yes (but not yet in article)	Necklace or attached to arm + electrodes on chest	HR changes in 50/104 (48%) of 8 patients, algorithm tested on 3 patients with > 10 seizures with HR changes: sensitivity > 90%, PPV > 50%

Finally, a miniature device attached to the skin of the suprasternal notch on the neck can measure airflow by detecting sound created by turbulence occurring in the human respiratory system. Table 2 mentions such a device manufactured by the UK company **Ervitech**. Although it is assumed to detect apnoea during seizures, the only article published to date does not focus on epilepsy.[47]

4.5. Detecting other autonomic changes: electrodermal activity (EDA)

Autonomic changes can affect the skin in three different ways. Skin perfusion, manifested by flushing, can be measured with electrodes (Section 4.4). For goose bumps/piloerection, forms of detection other than by video or self-reporting have not been described.[48] EDA, defined as skin resistance or conductance, is measured by ohm-metres or galvanometers respectively and shows as sweating/sudomotor signs.

GTCS show an increase in autonomic discharges, particularly sympathetic. While changes in blood pressure, HR(V), respiration and other autonomic signs are controlled by both the parasympaticus and the orthosympaticus, sweat glands are surrounded by sympathetic fibres. Modulation in EDA thus reflects purely sympathetic activity and could be used for GTCS detection. One US team has published a report on a wrist-attached device that combines EDA and ACM in order to detect seizures. The results are mentioned in Table 1.[49]

4.6. Detecting motor seizures

Movement can be detected by various methods that can serve different purposes. Movement energy can be monitored by video or by ACM, gyroscopes (gyro), magnetometers (magneto) or EMG attached to the limbs. It can warn of possible trauma by hitting an object. Attached to the trunk, ACM, gyro or magneto devices can provide information on the position of the patient, thereby providing warning when seizures occur in the prone position (risk of suffocation). In combination with a humidity metre, they could provide an alert when there is risk of inhaling vomit or other fluids in the supine position. Video or ACM devices attached to the trunk can also detect falling or loss of balance during a seizure. Finally, movement duration could warn of evolvement to status epilepticus.

4.6.1. Video

Video detection is part of the gold standard for seizure detection, and it is the only means of performing retroactive visual evaluation of detected events. It is contactless, unless infrared wave reflectors are affixed to motion-relevant locations on the patient's body (e.g. joints or extremities).[50] Video might even be used to detect HR(V) and respiration rate (Sections 4.3.1 and 4.4).[51,52]

One disadvantage of video detection involves the difficulty of detecting movement under blankets (although shapes on the blanket help) or the need to sleep without a blanket when using coloured pyjamas.[53] Further, recording all aspects of a movement requires the patient to be constantly within the scope of one or more cameras (this is less problematic at night).

A thermal or thermographic camera detecting infrared waves from body (movement) through blankets and clothing could also be used. Such cameras are also assumed able to detect respiration. Disadvantages involve the current reliability of such cameras (e.g. the resolution is considerably inferior to that of optical cameras), and their cost.

Teams from Belgium, Germany/Portugal and the US are independently focusing on seizure detection using automated video analysis. Results from these studies can be found in Table 1.[50,54,55]

4.6.2. Electromagnetic waves

Using the Doppler effect, microwaves and radio waves have been tested for detecting movement, as well as heart rate and respiration (Sections 4.3.1 and 4.4).[56,57] Such techniques offer the advantage of allowing contactless recording through blankets and clothing.

Disadvantages of electromagnetic devices involve their current reliability and the constant electromagnetic radiation exposure. Radiation damage depends upon the wave type (some have ionising, electrical or biological/heating effects on the human body), intensity, cumulative exposure and exposure duration.

4.6.3. Accelerometer (ACM), gyroscope (gyro), magnetometer (magneto) and electromyography (EMG)

ACM devices measure translational acceleration. They have a low cost and with their low energy consumption, they enable ambulatory monitoring with a small device. They can be used for detecting *clonic seizures*.[18] Gyro sensors measure angular/rotational acceleration and are useful for detecting *versive seizures*. Magneto sensors can determine position and orientation changes of limbs or body and are interesting for detecting *tonic seizures*, because of the 'positioning' that takes place in these seizures. They are thus also useful for detecting tonic–clonic seizures because of their capacity to detect the tonic phase early.[38] Because they record muscle signals, EMG devices are well suited for detecting *tonic seizures* and the early phase of tonic–clonic seizures.[58]

Attached to the patient, these sensors have the advantage of being linked directly to movement (including motor seizures) and of being able to distinguish between the movements of individual limbs. Attached to the bed or mattress, however, they are more comfortable for the patient and possibly less susceptible to dislocation over time.

Several teams from Austria, Belgium, Denmark, France, Israel, the Netherlands, the US and US/Ireland are performing research on movement detection using any or a combination of the methods mentioned above. The results of their research are mentioned in Table 1.[2,14,17,18,59–65] Finally, many commercially available systems use these or other unspecified movement-detection methods. See Table 2 and Section 5 for more information.

4.7. Detecting non-motor seizures

4.7.1. Audio

Noises that occur during seizures include stereotypical screams, singing or humming, autonomic laughing or weeping, bronchial secretions, lip smacking and bed noises when moving. In addition, some audio devices can even detect respiration (Section 4.4).

The advantages of audio devices include their low cost, comfort (contactless) and practical use. They are often based on baby-phone systems and, to date, they are the most commonly used system for paediatric patients.

One disadvantage of audio devices involves their generally poor performance and detection of many false positives. One major challenge to this technique involves the development of algorithms that can suppress background noises originating from the environment, as well as from the patient (e.g. speech or snoring). In some cases, however, snoring can be a seizure manifestation. For example tonic–clonic seizures are often followed by loud and typically stertorous breathing.[66]

Various audio systems produced by the UK company **Medpage** have undergone testing by US research teams. Results and more information can be found in Tables 1 and 2.[15,16] Table 1 also shows research results regarding audio-based seizure detection conducted by a team from the Netherlands.[67] Table 2 further lists Ep-It (**Alert-It**), a system that combines audio with other detection methods, but of which no publications could be found.

Table 2
Non-EEG based alarm systems that are commercially available or under clinical trial investigation and that are specifically aimed at epilepsy and epileptic seizures. Information given as available in article or on website. ACM = accelerometer, C = clonic seizures, ECG = electrocardiography, EMG = electromyography, EOG = electro-oculography, H = hypermotor seizures, Hz = hertz, M = myoclonic seizures, npf = no publication found with our search strategy, PPG = photo plethysmography, S = spasms, s = seconds, T = tonic seizures, TC = tonic–clonic seizures, VNS = vagus nerve stimulation.

Company	Device name	Detection method	Contact(less)	Seizures/events	Article	Status	Website
Alert-It (UK)	Ep-It Companion Monitor (S1029)	Unspecified movement sensor, audio, moisture sensor, body pressure	Under mattress (mat) and on mattress or under pillow sheet	TC and S, urination and vomiting, prolonged bed vacancy	npf	On market	http://www.alert-it.co.uk
	Ep-It Guardian Monitor (P139)	Unspecified movement sensor that can also detect respiration, audio, moisture sensor, body pressure	Under mattress (mat) and on mattress or under pillow sheet	TC, S and complex seizures, abnormal breathing, urination and vomiting, prolonged bed vacancy, allows monitoring of up to 32 patients	npf	On market	
BioLert (Israel)	EpiLert	ACM for movement	Watch-like	TC, T, C	Kramer et al.[17]	FDA/CE approval expected	http://www.biolertsys.com
Cyberonics, Inc. (US)	AspireSR	ECG	Implanted (linked to VNS therapy so closed-loop)	Cardiac events during (unspecified) seizures	npf	Clinical trial recruiting	http://clinicaltrials.gov/ct2/show/NCT01325623
Danish Care (Denmark)	Epi-Care Free	ACM for movement	Bracelet	TC in adults and teenagers	Beniczky et al.[14]	On market	http://danishcare.dk/dk
	Epi-Care 3000	ACM for movement	Affixed to mattress	Convulsions such as TC, S mainly in small children	npf	On market	
D.C.T. Associates Pty Ltd (Australia)	Vigil-Aide	Unspecified vibration detection	Affixed to bed or worn in pouch/belt during day	Convulsions	npf	On market	http://www.dctassociates.com.au/convul.htm
Emfit Ltd (Finland)	Emfit Seizure Monitor	ACM for movement and respiration (even heart beating according website), body pressure	Under mattress mat	Convulsions such as TC and S, micro-movements caused by breathing and heart beating, prolonged bed vacancy	npf	On market	http://www.emfit.com
Ep Detect (UK)	EpDetect	Unspecified movement sensor	Application for mobile phone	Seizures with 2–5 Hz movements that persist 10 s	npf	To be downloaded (free of charge)	http://www.epdetect.com
Epicall Ltd (Israel)	Epicall	EOG, PPG	Sticker placed on side of face	Eye movements, heart rate and pulse as pre- or early (unspecified) seizure markers	npf	Clinical trial not yet recruiting	http://clinicaltrials.gov/show/NCT01436695
Ervitech (UK)	–	Audio for respiration	Placed in neck	Apnea during (unspecified) seizures	Corbishley and Rodríguez-Villegas[47] (not on seizures yet)	Clinical trial	http://www.theengineer.co.uk/advanced-acoustic-monitor-detects-breathing-difficulties/1004884.article
Holst Centre/imec, Hobo Heeze BV (Netherlands)	–	ECG	Armband with chest electrodes	Major epileptic seizures such as TC, T, C, H	Massé et al.[4] and van Elmpt et al.[41]	Patent taken, clinical trial ongoing	http://www.holstcentre.com http://www.hoboheeze.nl
IctalCare A/S (Denmark)	IctalCare 365	EMG	ePatch attached to upper arm or leg	TC	Conradsen et al.[58]	Launch expected beginning 2013	http://www.ictalcare.dk
Medpage (UK)	MP5	Audio for movement (bed noises) and vocalizations	Under mattress	TC in patients weighing ≥12.7 kg	Carlson et al.[15] and Fulton et al.[16]	On market	http://www.medpage-ltd.com
	MP2	Unspecified movement sensor	Under mattress	TC in patients weighing ≥12.7 kg	npf	On market	
	ST-2	Unspecified movement sensor (audio?) and body pressure	Under mattress mat	TC and prolonged bed vacancy in patients weighing ≥12.7 kg	Fulton et al.[16]	On market	
Sensorium (UK)	Sensalert (102/EP200)	Unspecified movement sensor and optional moisture sensor	Under mattress	TC, optional enuresis	npf	On market	http://www.sensorium.co.uk
Smart Monitor Corp. (US)	SmartWatch	ACM for movement	Watch	Convulsive seizures mainly TC, C	Lockman et al.[18]	FDA/CE approval expected, clinical tri-al ongoing	http://www.smart-monitor.com
Vahlkamp (Netherlands)	Epi-Watcher	Unspecified movement sensor	Under mattress mat	TC	npf	On market	http://www.vahlkamp.nl

4.7.2. Electro-oculography (EOG)

Both eyelid and ocular movements can be detected by EOG, which is capable of differentiating epileptic seizures from syncope, psychogenic or other non-epileptic seizures.[68] Table 2 mentions the Epicall system (Israeli company **Epicall Ltd**), which uses a sticker placed on the side of the face to measure eye movements, heart rate and pulse as pre-seizure or early seizure markers. A clinical trial is expected.

4.7.3. Temperature

It remains to be investigated whether temperature measurement can detect seizures. Although it would be an appropriate method for detecting febrile seizures, the exact relationship of these seizures to epilepsy is not known. Temperature changes can be measured by thermometers that exist in the form of adhesive stickers, and by thermal cameras that additionally could detect movement (Section 4.6.1).

4.8. Additional detection

4.8.1. Body pressure

Pressure mats can be used to detect bed vacancy (falling or somnambulism), although they are not designed specifically as a method for detecting seizures. These mats should be combined with other detection modalities, as is the case with some commercially available seizure-detection devices, including Ep-It (**Alert-It**), Emfit (**Emfit Ltd**) and ST-2 (**Medpage**) (Table 2).

4.8.2. Moisture

In addition to the measurement of sweating (Section 4.5), humidity metres can detect some ictal symptoms, including salivation, vomiting and incontinence. One disadvantage is that such manifestations are not related exclusively to seizures. Some commercial seizure-detection systems, however, including Sensalert (UK company **Sensorium**) and Ep-It (**Alert-It**), make use of a sheet with sensor wires sewn into silver in order to combine moisture sensing with other detection methods.

5. Commercial systems

Devices for monitoring heart rate, oxygen saturation, respiration and body movements are commonly used in fields other than epilepsy, although their reliability for detecting seizures or identifying high-risk patients has yet to be proven. Further studies could determine whether these measures could play a role preventing SUDEP.[69]

In this section (and in Table 2), the focus is on systems that are commercially available or under clinical trial investigation and that are specifically aimed at epilepsy and seizures. As mentioned in Section 4, published studies are rare, and additional investigation is needed in order to provide neurologists and patients with an objective overview of advantages, disadvantages and efficacy of these systems.

Devices that have been described in literature (last seven listed in Table 1) include the under-mattress MP5 and ST-2 by **Medpage** (UK),[15,16] an electrocardiography armband with chest electrodes by **Holst Centre/imec and Hobo Heeze B.V.** (Netherlands),[4,41] the electromyography-based ePatch IctalCare 365 by **IctalCare A/S** (Denmark),[58] the Epi-Care Free bracelet by **Danish Care** (Denmark),[14] SmartWatch by **Smart Monitor Corporation** (US)[18] and the watch-like EpiLert by **BioLert** (Israel).[17] All but the Medpage devices can be used during the day/outside of bed, and they have shown good results for tonic–clonic seizures. Latency from clinical seizure onset to detection has been mentioned for the latter three. The majority of seizures was detected relatively late, as the devices are based on accelerometry, thus mainly identifying the clonic phase.

Another mobile device is the belt-worn or pouch-worn Vigil-Aide by **D.C.T. Associates Pty Ltd** (Australia), which has a maximal range of 150 metres (as compared to 20 metres for the Epi-Care Free). Visibility (or non-visibility) is important to consider for devices that are worn during the daytime.

Sensors attached under the mattress or bed are the most widespread, although they often lack specificity[59]: They are not mobile and are therefore used primarily for detecting nocturnal seizures. They include MP2 by **Medpage** (UK), Epi-Care 3000 by **Danish Care** (Denmark), Emfit Seizure Monitor by **Emfit Ltd** (Finland), Sensalert (102 and EP200) by **Sensorium** (UK), Epi-Watcher by **Vahlkamp** (Netherlands) and Ep-It (S1029 and P139) by **Alert-It** (UK).

Information on the following devices is available online, although they are not yet commercially available: the combined electro-oculography and photo plethysmography device Epicall by **Epicall Ltd** (Israel), an audio sensor for respiration monitoring by **Ervitech** (UK) and a device with cardiac-based seizure detection and responsive vagal-nerve stimulation therapy by **Cyberonics, Inc.** (US).

Finally, the EpDetect software programme by **Ep Detect** (UK) can be downloaded onto a mobile phone. It monitors the movements of the wearer and alerts the caregiver of the patient's status in case of tonic–clonic seizures.

Some devices have additional valuable features: cancelling alerts that are set off inadvertently (SmartWatch, EpDetect); adjusting patient-specific parameters, including threshold for seizure intensity (MP5, SmartWatch), seizure duration (SmartWatch), user weight (Sensalert), mattress type (MP5, Sensalert) and seizure nature (Sensalert); warning with a pre-alarm buzz (Sensalert); setting the alarm delay at different interval times (Vigil-Aide, Emfit Seizure Monitor); or alerting the caregiver of the patient's position through an incorporated GPS (EpDetect, EpiLert, IctalCare 365, SmartWatch).

6. Multimodal systems

Epileptic seizures have a stereotypical nature, however, seizure manifestations vary by patient and a given patient may have different seizure types. Detection devices may therefore be developed based on a template using the composite features of the various non-EEG body signals, which may serve as the signature of a particular seizure type in an individual patient. The template-matching method may be applied within a larger population for various seizure types, and it may even detect different patterns for true and pseudo-seizures.[2]

The advantages and disadvantages associated with each method (Section 4) can determine which methods should be combined and which body signals should be measured in order to develop an efficient device. It is particularly interesting to include monitoring cardiac, respiratory or other autonomic dysfunction as these are possible patho-physiological mechanisms of SUDEP. Monitoring movement is important as well, as many seizures have a motor component.

We nevertheless believe that there is a trade-off between the number of sensors and the patient's comfort, unless non-contacting sensors are used. Moreover, even though non-EEG body-signal monitoring and automated analysis might be less complex than are those used in EEG devices, and as a consequence use less power, it is obvious that power consumption increases when more sensors are used, thus resulting in larger and more expensive devices.

Some published studies, including those reported by the teams in Denmark[58,60] and France,[38,59,61] have already combined

several methods for movement detection, and some commercial devices even combine methods for detecting multiple body signals.

Table 3 provides a summary of the seizure manifestations and corresponding detection methods that have been discussed and proposes possible combinations.

7. Discussion

The number of refractory patients, the mortality rate of epilepsy and the many requests from patients and caregivers indicate that there is a medical need as well as societal pressure for an optimal seizure-detection system, as well as a clearer overview of commercial devices that can be used for long-term and home monitoring. In addition, those with a diagnosis that has yet to be confirmed could use such devices before seeing a neurologist. Detection systems are also useful if only to offer reassurance to patient and environment.

Finally, detection systems (and the logging of information) are important in the context of SUDEP. First, these systems have been identified as one of the key measures for preventing SUDEP, although their protective effects require further investigation. Detection is especially important for patients who are refractory to treatment or those who experience only a few but dangerous seizures. Second, detection systems can enhance the understanding and definition of SUDEP-related risk factors and pathophysiological mechanisms. They are objective and can provide information on whether SUDEP or near-SUDEP events were preceded by seizures. Third, when there is additional clarity concerning risk factors and mechanisms, devices (together with genetic and lifestyle information) could contribute by allowing patient screening, creating risk profiles and identifying high-risk patients.

The efficacy and reliability of many commercial non-EEG devices has yet to be demonstrated, and research tends to focus more on EEG than it does on non-EEG signals. Nevertheless, non-EEG signals provide valuable indirect information about the state of the brain, in many cases, they are more directly related to seizure symptoms. Non-EEG devices are more widely applicable than EEG devices are, as they are not invasive and less obtrusive. Long-term home monitoring reduces costs by eliminating the necessity of hospital admission and clinical observation. Non-EEG detection methods allow direct testing on humans. Finally, automated detection algorithms might be less complex than are those used in EEG devices. This should make it possible to generate an optimal multimodal device sooner than intracerebral detection and prediction systems.

Due to the large variety in seizures and movement patterns, the differences between adult, paediatric and neonatal patients, and the difficult distinction between epileptic and non-epileptic manifestations, it will probably never be possible to produce a truly universal system. Should it prove necessary to differentiate between various seizure types, particular emphasis should be placed on nocturnal frontal lobe (e.g. hypermotor) and tonic–clonic seizures. Both are risk factors for SUDEP, hypermotor seizures are often refractory and accompanied by a high level of morbidity (injuries), and tonic–clonic seizures can lead to status epilepticus. In addition to seizure type, detection systems should also consider the seizure severity and the patient's quality of life. It should be possible to customise devices to the user's needs and personal preferences (e.g. such that they would not wake the patient and environment for situations that are not life-threatening, unless requested). This raises issues regarding the need to distinguish between detecting seizures and detecting danger.

Table 3
Non-EEG seizure manifestations and corresponding detection methods. ACM = accelerometer, BP = blood pressure, ECG = electrocardiography, EMG = electromyography, EOG = electro-oculography, gyro = gyroscope, HR(V) = heart rate (variability), magneto = magnetometer, pO_2/CO_2 = partial pressure oxygen/carbon dioxide, RIP = Respiratory Inductance Plethysmography.

	Audio	Video	Electromagnetic waves	ACM/gyro/magneto	Electrodes	Plethysmograph (volume)	Pressure	Temperature
Motor								
Body	X (bed noise)	X (optical camera)	X (e.g. radio waves)	X (bed or body)	X (EMG)		X (pressure mat for bed vacancy)	X (thermal camera)
Eye (lid)		X (optical camera)			X (EOG/EMG)			
Autonomic								
HR (V)/pulse/BP			X (micro waves)		X (ECG)	X (oximetre)		
Respiration	X (neck)	X (optical or thermal camera)	X (micro waves chest or infrared waves of oximeter/capnograph)	X (ACM/magneto chest)	X (EMG/impedance pneumograph chest, electrodes for pO_2/CO_2)	X (RIP chest)	X (pneumotachograph airflow)	X (thermo-couple airflow/thermal camera)
Sweating					X (ohm-/galvanometer)			
Vomiting/salivation/coughing	X (baby phone)				X (humidity metre)			
Incontinence								
Vocalizations	X (baby phone)				X (humidity metre)			
Fever	X (thermal camera)							X (sticker)

8. Conclusion

There is an obvious need for a seizure-detection system that can be used for long periods and in the home situation in order to facilitate early intervention for and prevention of seizure-related side effects, including SUDEP. Considerable research has focused on intracerebral detection and action. Most extracerebral, non-EEG devices are developed using only one modality for monitoring one physiological signal.

We propose the need to develop multimodal non-EEG based systems, and we believe that the primary focus should lie on modalities that can monitor cardiac, respiratory or other autonomic signals, as they are possible patho-physiological mechanisms of SUDEP. The devices should also detect movement, as many seizures have motor manifestations.

Conflict of interest statement

None of the authors has any conflict of interest to disclose. 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.

Search strategy

PubMed: different combinations epilepsy + seizure + detection + system + device + alarm + alert, SUDEP reviews and meta-analyses since 2002; Patents: http://worldwide.espacenet.com; Clinical trials: http://clinicaltrials.gov.

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