Uncovering the value of autonomic signs and seizure detection in epilepsy care

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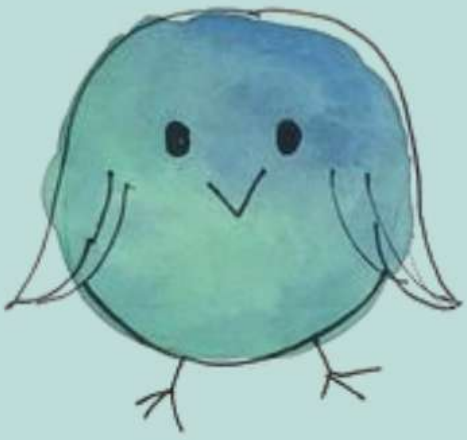

CHAPTER 11

GENERAL DISCUSSION

SUMMARY AND GENERAL DISCUSSION

We started our journey by exploring the value of various autonomic parameters for seizure detection. Following our review on hidden autonomic signs of epilepsy, we continued by studying the management of ictal asystole. We later focused on the home-based validation of a wearable autonomic and a remote non-autonomic seizure detection device in children with epilepsy and assessed the value of these devices for families and society. We extended our journey with qualitative user-evaluation studies aiming to explore needs of parents of children with epilepsy.

Uncovering autonomic signs in epilepsy

Autonomic manifestations in epilepsy can cause serious complications. Post-ictal arrhythmias are often associated with sudden unexpected death in epilepsy (SUDEP),[1, 2] and ictal asystole (IA) can cause dangerous, traumatic falls. Conversely, ictal autonomic phenomena may help in the development of interventions to prevent epilepsy complications.

In **Chapter 2** we explored the potential of changes in autonomic functions as a tool for timely seizure detection. We systematically reviewed the literature and evaluated the quality of studies using QUADAS-2[3] and recently reported quality standards on reporting seizure detection algorithms.[4] We found that the overall quality of studies on seizure detection using autonomic parameters was low. Heart rate (HR) and heart rate variability (HRV) were most frequently integrated into available detection algorithms. Overall, these algorithms yielded high sensitivity (mostly >80%)[5-18] and, especially for HRV, a short detection latency (varying from eight minutes prior to seizure onset to nineteen seconds after).[5-7, 9, 10, 13] False alarm rates (FARs), when mentioned, were high. These rates did not drop below one false alarm per three hours for an individual specific algorithm.[7] Generic algorithms resulted in up to five false alarms per hour.[13] We found evidence that the combination of multiple modalities may lower FAR. Another solution may be personalized tailoring of the detection algorithm to improve the FAR.[7, 8, 19] Long-term and real-time ambulatory validation studies are needed to obtain more reliable data, and to test the proposed strategies to optimize FAR.

In **Chapter 3** we discussed the complexity of IA management. IA is often misdiagnosed as a primary cardiac condition and treated with pacemaker implantation. While pacemaker therapy might help to prevent syncope in some

patients with IA, it will not prevent seizures. Pacemaker implantation should therefore only be considered in those in whom treatment failed to prevent seizures with syncope. The benefit of cardiac pacing may be limited when vasodepression dominates as the syncope triggering mechanism.[20-22] Cardioinhibition, vasodepression or a combination of both can cause syncope in IA.[23-26] In **Chapter 4** we examined a novel, indirect method of unravelling the dominant mechanism, considering the relative timing of IA onset and syncope onset. We retrospectively analysed video-electroencephalographic (EEG) recordings of 38 focal seizures in 29 individuals and found that in only two cases IA started too close to the onset of syncope (≤3 sec) to have been the primary cause. Awareness among physicians of the different pathophysiological mechanisms of syncope in IA might help to prevent unnecessary pacemaker implantation.

Validating the performance of seizure detection devices

The seizure detection device (SDD) market is booming, yet the level of performance evidence is low.[27] According to the standards for testing and clinical validation of seizure detection devices published in 2018,[4] only three available devices have been validated in phase 3 studies and two of them were also validated in a phase 4 study.[27] This shows that the majority of studies applied seizure detection algorithms that were trained and tested on the same dataset and also often lacked continuous real-time data, thus questioning the generalizability of the results.[4, 27] The two phase 4 studies demonstrated the feasibility and usability of wearables for the detection of convulsive seizures in the home environment, but included many people living in a residential care setting.[28, 29]

The PROMISE trial was the first prospective phase 4 multicentre implementation study in the home environment to combine long-term video-controlled performance data from NightWatch in a paediatric cohort with data from questionnaires on the effect of NightWatch on caregivers' stress, sleep, and quality of life (QoL). In **Chapter 5** we presented the results of the PROMISE trial. Based on 2310 recorded nights (28,173 hours), including 552 major seizures, NightWatch showed a median sensitivity of 100% (range 46 - 100%), with a median FAR of 0.04 (range 0.00 - 0.53) per participant per hour. Compared to previous results of NightWatch in adults, the sensitivity in this paediatric cohort was slightly higher and so was the frequency of false alarms.[29] One third of false alarms related to minor seizures, and the remainder to arousals or non-epileptic

rhythmic movements. Children present with different heart rate profiles than adults (i.e., higher resting values and greater HR variability)[30, 31] and with challenging behaviour and sleep-related rhythmic movements, particularly in those with developmental disorders.[32] Caregivers reported a positive effect on their experienced stress during NightWatch use, while their quality of sleep and QoL did not change significantly. A possible explanation for this minimal effect could be the duration of the intervention period, which might have been too short for parents to learn to trust the device and let go of their own alertness at night. Another explanation is that an SDD, at least in the short term, does not take away the overall burden of caring for a child with epilepsy and all its accompanying stressors.

The usability of two wearables has been shown in phase 4 studies,[28, 29] but not every person with epilepsy will tolerate a wearable device; some prefer remote solutions. We therefore retrospectively analysed the performance of a real-time video-based detection algorithm on 1661 recorded nights of 22 children (**Chapter 6**). The video algorithm had an overall sensitivity of 78% for the detection of convulsive seizures and 73% for the detection of hyperkinetic seizures. False alarms (n=87) occurred in only a minority of children (overall FAR 0.05/night) and were mainly behaviour related. Compared to the previous study in adults[33], we found a lower sensitivity for the detection of convulsive seizures as well as lower FARs. This was the first video-based seizure detection method that was tested on a large dataset (different from the training dataset) with continuous video recordings. Compared to other remote SDDs using bed sensors this method showed slightly lower sensitivity, but also lower FAR. It therefore provides an attractive alternative to wearable SDDs.[29]

The value of seizure detection devices for families and society

According to recent clinical practice guidelines, wearable devices are effective for accurate detection of convulsive seizures, but whether these detections result in meaningful outcomes remains unknown.[27] The value of SDDs can be measured on different levels; from clinical outcomes in the person with epilepsy, to the impact on a family, to even bigger effects from a societal perspective. All these contexts are important to establish the added value of SDDs.

In **Chapter 7** the first economic evaluation of an SDD from a societal perspective was described. Based on data from 41 children from the PROMISE study, we assessed the cost-utility and cost-effectiveness of NightWatch implementation. A decrease in mean costs of €775 during the two-month intervention period with NightWatch use was observed, compared to a two-month baseline period without any SDD. At a ceiling ratio of €50,000 per quality adjusted life year (QALY), NightWatch showed a 72% probability of being cost-effective. This effect was mainly due to changes in health care costs, including hospitalization, medication, and physiotherapy. Parental stress and QALYs did not, however, contribute to the cost-effectiveness, with similar scores between the baseline and intervention period. This may be explained by the short intervention period, as building trust in NightWatch might need more time. Alternatively, the NightWatch may already be manifesting its potential positive impact within this time frame, but the benefits may be outweighed by alarm fatigue thus resulting in unaltered levels of parental stress and QALYs.

In **Chapter 8** we explored the added value of seizure detection for parents caring for a child with epilepsy. In-depth interviews with 21 parents from the PROMISE study showed that the value of NightWatch was mainly influenced by the way parents handled the care of their child and experienced their burden of care. The detection performance of NightWatch seemed less important. Driven by the fear of child loss, parents developed a personal protective behaviour towards their child with epilepsy. This behaviour is also seen in parents of children with other chronic health conditions.[34-36] While it may be of help to feel in control of the situation and to decrease anxiety, this may also conversely increase the burden of care. Parental flexibility in the existing protective behaviour appeared to determine the extent to which NightWatch could support the family. In many families, NightWatch added value by providing an extra back-up and relieving the burden of seizure monitoring. NightWatch could not, however, take away the fear of child loss. Health care professionals and device companies should be aware of parental protective behaviour and the high parental burden of care. It is essential to appreciate differences in parental needs, and to keep an open mind for personalised adjustments to improve implementability.

User needs for seizure detection

During the development of SDDs crucial choices are made by device companies, often in collaboration with health care professionals. Their values,

however, may not be representative of all stakeholders. Successful SDD implementation requires a good fit with the end-user. It is therefore important to understand user preferences for SDDs.

In **Chapter 9**, we explored the deeper needs and wishes regarding SDDs of professional and informal caregivers of children with epilepsy, using a new qualitative research method in epilepsy: context mapping. Trust emerged as the most important theme; multiple elements were identified that could help caregivers gain trust in a device. The elements included integration of different modalities, ability to view all parameters overnight, personal adjustment of the algorithm, recommendation by a neurologist, and a set-up period. The most important elements were integrated into a discrete choice experiment (DCE) to quantify their relative strength influencing user preferences. **Chapter 10** shows the results from this online questionnaire, including the DCE, fully completed by 49 parents. All DCE attributes had a high impact on parental choices, in the following order of importance: “Introduction to use”, “personalisation”, “interaction”, “alert” and “interface”. Parents preferred to be alerted to both major and minor seizures, and to personalise the detection algorithm. This contrasts with results from previous studies in which preferences for limited and automated alerts and interactions with the device were expressed by users.[37] The online questionnaire also explored parental preferences regarding the trade-off between sensitivity and positive predictive value, while accounting for individual seizure frequency. Relatively more false alarms were favoured over missed seizures, particularly among those with a low seizure frequency. We identified considerable variation in SDD preferences between different user groups, both within our study and compared to other studies. For example, parents of children with a learning disability, compared to those without, were more likely to prefer consultation with a neurologist before SDD use, device interface options during an alarm, and the option to adjust the device’s algorithm by giving personal feedback. These findings underscore the heterogeneity among user groups and emphasises the importance of user-centred and tailored approaches of SDD development to meet the contrasting needs and to optimise implementation.

Future directions

Clinicians,[27] people with epilepsy and their caregivers[37-42] have expressed a need for reliable seizure detection at home. SDDs are being developed rapidly to meet this need, but device implementation does not always follow this pace.

The major delay in SDD implementation concerns the clinical validation process. This step is crucial in reliably estimating device performance and improving counselling, and reimbursement. Quality validations are, however, very time and cost consuming. There is a trend of SDDs becoming commercially available without any performance data published. The big advantage of this development is that these devices are instantly ready for use in practice. Yet, this overly ready availability may expose users to unknown risks without reimbursement of costs. The latter may create health care inequality if some people cannot buy a device. Another obstacle for successful SDD implementation is strict governmental regulations for medical devices. Recent adjustments in European Union legislations for medical devices (Medical Device Regulation; MDR) make it more difficult for devices to enter the market but are needed to guarantee quality.[43]

Decreasing seizure-related mortality is one of the main goals of SDDs.[27] Ideally, mortality may be chosen as a study endpoint, but this is not realistic. While SUDEP is the most common cause of epilepsy-related mortality,[44] it is still a relatively rare event with estimated incidence 1 in 1000 adults with epilepsy per year.[45-47] It is therefore impractical to use SUDEP as a primary study endpoint in the validation of SDDs. Instead, retrospective, long term cohort studies comparing SUDEP rates between SDD and non-SDD users could provide alternative evidence. These cohorts should, however, be large enough to account for the various factors affecting SUDEP risk.

Detecting different seizure types

Most available SDDs target potentially dangerous seizures only (focal to bilateral or generalized tonic-clonic seizures).[48] This thesis emphasises the need for devices that warn of all seizure types. Focal seizures without bilateral spread do not pose a SUDEP risk, but they do carry risks of other complications.[49] These risks include death by injury, drowning or traffic accidents, with important psychosocial consequences.[50] Focal seizures without bilateral spread are more difficult to detect, because they do not always show pronounced changes in autonomic function or motor signs.[51] Additionally their semiology is often less stereotyped and the variability between individuals may be high, which makes it hard for a generic device to detect them.[50, 52] The currently available evidence for the detection of seizure types other than convulsive seizures is derived exclusively from phase 2 validation studies.[4, 53] HRV algorithms seem to have the best performance (overall sensitivity 83%[54] and 91%[55]; FAR 0.11[55] and

0.22[54]/night), but only after a preselection of responders (i.e., >66% of seizures detected[55] or >50 bpm ictal HR increase[54]). A study on photoplethysmography (PPG) data from a wearable device, found significant changes during the ictal period of focal seizures.[56] A multimodal device combining electrodermal activity (EDA) and accelerometery was retrospectively tested on data from 22 individuals, which included six focal tonic-clonic seizures.[57] With optimal thresholds, the algorithm was able to detect half the focal seizures (sensitivity 50%).[57] Another study on bio-signals in focal seizures from twelve individuals confirmed the potential advantage of multimodal devices.[50] Common time-evolving patterns were recognised in HR, EDA and movement, especially in focal motor seizures with impaired awareness.[50] Prospective validation of these methods is needed to obtain reliable performance data for the detection of focal seizures.

Approaching big data

Commonly used bio-signals integrated in validated devices can also be used to monitor seizure severity.[27] Active monitoring of convulsive seizure frequency with markers of seizure severity can be used to further improve SUDEP prediction.[49] To expand the scope beyond convulsive seizures, new bio-signals and long-term ambulatory data is needed to recognise natural fluctuations and specific seizure-related patterns. Recently, the protocol was published for a long-term observational study on people with epilepsy using non-invasive SDDs at home (EEG@HOME study).[58] This study will collect EEG data from a portable EEG device twice a day, and continuous non-EEG bio-signals (HR, sleep quality index, steps) from a wrist-worn device (Fitbit Inc.). The person with epilepsy or the caregiver will register data related to seizure occurrence, medication taken, sleep quality, stress and mood using a smartphone application. This personal record represents the biggest challenge of collecting reliable long-term ambulatory recordings. Seizures are often underreported, which may result in unreliable seizure diaries.[59] Without an accurate reference standard, it is very difficult to identify the appropriate bio-signals and patterns in the data. Unfortunately, there is no simple solution to this problem. The optimal reference standard would consist of continuous video-EEG recordings. Scalp-EEG is very uncomfortable and obtrusive, and sufficient quality measurements require well-glued electrodes; this is impractical for ambulatory use. Smaller, less obtrusive EEG devices based on single-channel or multiple behind-the-ear channels are limited by their location, and have not yet provided high accuracy.[60, 61]

Intracranial EEG recording devices are highly accurate, though chronic implantation carries other disadvantages: cost and risk issues, and limitations in spatial sampling.[62] These devices may also detect subclinical seizure patterns, which may be valuable for seizure forecasting, but would not necessitate an alarm.[61, 63] To distinguish clinically relevant seizures from subclinical ones, EEG recordings are therefore often combined with video. Video monitoring is, however, limited to one place, unless multiple cameras or portable camera systems (e.g., drones) are used.

Another challenge is the interpretation of long-term SDD and reference data. Expert human analysis of this growing amount of data is very time consuming and will require automated approaches by artificial intelligence (AI) in the future.[64] As shown in chapter 2, machine learning (ML) techniques can help us to automate processes (e.g., algorithm feature selection) to improve SDD detection performances.[65, 66] ML algorithms have also shown good results for automated detection of ictal and interictal epileptiform discharges on scalp-EEG.[67] Recently, interest has grown in the application of deep learning (DL) in epilepsy care.[68] DL frameworks automatically and repeatedly optimise their parameters, so they presumably require less prior expert knowledge about the dataset for good performance.[68] Especially for large datasets, these methods can therefore have an advantage. Less control over the process is a huge disadvantage, and when bad quality data goes into the model, results will probably be of poor quality.

Seizure forecasting

Apart from seizure detection, ML and DL techniques can also be used for seizure forecasting. Seizure unpredictability is one of the major factors influencing the psychological burden of epilepsy and has great impact on QoL.[69] People with epilepsy and caregivers have emphasised the need for seizure forecasting to improve safety and independence.[70] A survey study using best-worst scaling on 346 people with epilepsy and 147 caregivers accentuated the importance of short forecasting range and notification of a high chance of a seizure.[70] As mentioned before, subclinical seizure patterns in the EEG signal can be used to forecast seizures.[63, 71] The Neurovista study was the first to collect long-term (six months - two years) intracranial EEG data from fifteen people with refractory epilepsy in an ambulatory setting.[71] The seizure-likelihood was predicted by pre-ictal electrical activity. Based on correlated clinical seizures in eleven subjects, the sensitivities to indicate ‘high seizure likelihood’

ranged from 65-100%. This dataset has been instrumental in unveiling circadian and multidien patterns in seizure occurrence and in improving forecasting algorithms.[72, 73] The methods described are, however, based on highly invasive devices and personalised algorithms, which makes them less generally applicable. Recently, seizure forecasting based on non-EEG wearables was examined, but these methods have not yet reached high accuracy.[74, 75] A feasibility study using wearable smartwatches found that circadian and multiday heart rate cycles showed the best predictive value for seizure forcasting.[76] Apart from bio-signal monitoring, SDDs and smartphones are able to detect more complex behavioural changes.[75] Activity and sleep patterns, and indicators of concentration and mood might provide an interesting tool for seizure forecasting in the future.

Personalized seizure detection

Multiple chapters of this thesis have discussed the potential advantages of tailored SDD approaches including personalised algorithms. The implementation of these strategies poses significant challenges. Manual adjustment by clinical experts is very time-consuming and can only be applied when a sufficient number of seizures is recorded. Real-time user feedback and automatic personalisation are more practical approaches.[7, 8] Personal feedback gives users control over their device and has the potential to optimise the device to the user's needs. Conversely, there is a high risk of incorrect feedback, especially in people with seizures with impaired awareness or post-ictal confusion. This might negatively influence device accuracy, and consequently may influence SDD certification and reimbursement. Automated personalisation methods using AI have more potential to become accurate. All performance claims, however, are based on the original, fixed algorithm, so they pose the same certification and reimbursement problems. A possible solution might be to develop a device with multiple certified and validated algorithms tailored to specific user groups and user needs. During ambulatory use, the device would recognise individual seizure characteristics and thus be able to select the best suitable algorithm in response to user feedback.

OVERALL CONCLUSIONS

In conclusion, while current wearable SDDs may accurately detect convulsive seizures, future long-term home-based trials are needed to improve performance for other seizure types, to offer tailored solutions for specific user groups and to explore their potential in monitoring individual treatments and seizure forecasting.

REFERENCES

1. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. J Neurol Neurosurg Psychiatry 2016;87:69-74.

2. 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;12:966-977.

3. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM, QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.

4. Beniczky S, Ryvlin P. Standards for testing and clinical validation of seizure detection devices. Epilepsia 2018;59(S1):9-13.

5. Jeppesen J, Beniczky S, Johansen P, Sidenius P, Fuglsang-Frederiksen A. Detection of epileptic seizures with a modified heart rate variability algorithm based on Lorenz plot. Seizure 2015;24:1-7.

6. De Cooman T, Varon C, Hunyadi B, Van Paesschen W, Lagae L, Van Huffel S. Online automated seizure detection in temporal lobe epilepsy patients using single-lead ECG. Int J Neural Syst 2017;27(7):1750022.

7. De Cooman T, Varon C, Van de Vel A, Jansen K, Ceulemans B, Lagae L, Van Huffel S. Adaptive nocturnal seizure detection using heart rate and low-complexity novelty detection. Seizure 2018;59:48-53.

8. De Cooman T, Kjaer TW, Van Huffel S, Sorensen HB. Adaptive heart rate-based epileptic seizure detection using realtime user feedback. Physiol Meas 2018;39:014005.

9. Fujiwara K, Miyajima M, Yamakawa T, Abe E, Suzuki Y, Sawada Y, Kano M, Maehara T, Ohta K, Sasai-Sakuma T, Sasano T, Matsuura M, Matsushimaet E. Epileptic seizure prediction based on multivariate statistical process control of heart rate variability features. IEEE Trans Biomed Eng 2016;63(6):1321-1332.

10. Jeppesen J, Beniczky S, Johansen P, Sidenius P, Fuglsang-Frederiksen A. Using Lorenz plot and cardiac sympathetic index of heart rate variability for detecting seizures for patients with epilepsy. IEEE Eng Med Biol Soc. 2014;4563-4566.

11. Moridani MK, Farhadi H. Heart rate variability as a biomarker for epilepsy seizure prediction. Bratisl Lek Listy. 2017;118(1):3-8.

12. Pavei J, Heinzen RG, Novakova B, Walz R, Serra AJ, Reuber M, Ponnusamy A, Marques JLB. Early seizure detection based on cardiac autonomic regulation dynamics. Front Physiol. 2017;8:1-12.

13. Qaraqe M, Ismail M, Serpedin E, Zulfi H. Epileptic seizure onset detection based on EEG and ECG data fusion. Epilepsy Behav. 2016;58:48-60.

14. Vandecasteele K, De Cooman T, Gu Y, Cleeren E, Claes K, Van Paesschen W, Van Huffel S, Hunyadi B. Automated epileptic seizure detection based on wearable ECG and PPG in a hospital environment. Sensors 2017;17(2338):1-12.

15. Boon P, Vonck K, van Rijckevorsel K, El Tahry R, Elger CE, Mullatti N et al. A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. Seizure 2015;32:52-61.

16. Van Elmpt WJC, Nijsen TME, Griep PAM, Arends JBAM. A model of heart rate changes to detect seizures in severe epilepsy. Seizure 2006;15:366-375.

17. Hampel KG, Vatter H, Elger CE, Surges R. Cardiac-based vagus nerve stimulation reduced seizure duration in a patient with refractory epilepsy. Seizure 2015;26:81-85.

18. Osorio I. Automated seizure detection using EKG. Int J Neural Syst. 2014;24(2):1450001.

19. Cogan D, Heydarzadeh M, Nourani M. Personalization of non EEG-based seizure detection systems. IEEE Eng Med Biol. 2016;Soc 6349-6352.

20. 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;27:930-6.

21. Moseley BD, Ghearing GR, Munger TM, Britton JW. The treatment of ictal asystole with cardiac pacing. Epilepsia 2011;52:e16-e19.

22. Mastrangelo V, Bisulli F, Muccioli L, Licchetta L, Menghi V, Alvisi L, Barletta G, Ribani MA, Cortelli P, Tinuper P. Ictal vasodepressive syncope in temporal lobe epilepsy. Clin Neurophysiol. 2020 Jan;131(1):155-157.

23. Nguyen-Michel VH, Adam C, Dinkelacker V, Pichit P, Boudali Y, Dupont S, Baulac M, Navarro V. Characterization of seizure-induced syncopes: EEG, ECG, and clinical features. Epilepsia 2014;55:146-155.

24. Tinuper P, Bisulli F, Cerullo A, Marini C, Pierangeli G, Cortelli P. Ictal bradycardia in partial epileptic seizures: Autonomic investigation in three cases and literature review. Brain 2001;124:2361-2371.

25. Saal DP, Thijs RD, van Zwet EW, Bootsma M, Brignole M, Benditt DG, van Dijk JG. Temporal Relationship of Asystole to Onset of Transient Loss of Consciousness in Tilt-Induced Reflex Syncope. JACC Clin Electrophysiol. 2017;3(13):1592-1598.

26. van Dijk JG, van Rossum IA, Thijs RD. Timing of Circulatory and Neurological Events in Syncope. Front. Cardiovasc. Med. 2020;7:36.

27. Beniczky S, Wiebe S, Jeppesen J, Tatum WO, Brazdil M, Wang Y, Herman ST, Ryvlin P. Automated seizure detection using wearable devices: A clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology. Clin Neurophysiol. 2021;132(5):1173-1184.

28. Meritam P, Ryvlin P, Beniczky S. User-based evaluation of applicability and usability of a wearable accelerometer device for detecting bilateral tonic-clonic seizures: A field study. Epilepsia 2018;59:48-52.

29. Arends J, Thijs RD, Gutter T, Ungureanu C, Cluitmans P, Van Dijk J et al. Multimodal nocturnal seizure detection in a residential care setting: A long-term prospective trial. Neurology 2018;91(21):e2010-e2019.

30. Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, 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;377:1011-8.

31. Schumann A, Bär KJ. Autonomic aging – A dataset to quantify changes of cardiovascular autonomic function during healthy aging. Sci Data 2022;9(1):95.

32. Prihodova I, Skibova J, Nevsimalova S. Sleep-related rhythmic movements and rhythmic movement disorder beyond early childhood. Sleep Medicine 2019;64:112-115.

33. Geertsema EE, Thijs RD, Gutter T, Vledder B, Arends JB, Leijten FSS, Visser GH, Kalitzin SN. Automated video-based detection of nocturnal convulsive seizures in a residential care setting. Epilepsia. 2018;59(Suppl 1):53-60.

34. Collins A, Hennessy-Anderson N, Hosking S, Hynson J, Remedios C, Thomas K. Lived experiences of parents caring for a child with a life-limiting condition in Australia: a qualitative study. Palliat Med 2016;30:950-959.

35. Verberne LM, Kars MC, Schouten-van Meeteren AYN, Bosman DK, Colenbrander DA, Grootenhuis MA, van Delden JJM. Aims and tasks in parental caregiving for children receiving palliative care at home: a qualitative study. Eur J Pediatr. 2017;176(3):343-354.

36. Woodgate RL, Edwards M, Ripat JD, Borton B, Rempel G. Intense parenting: a qualitative study detailing the experiences of parenting children with complex care needs. BMC Pediatr. 2015;15(1):197.

37. Bruno E, Viana PF, Sperling MR, Richardson MP. Seizure detection at home: Do devices on the market match the needs of people living with epilepsy and their caregivers? Epilepsia. 2020;61(S1):S11-S24.

38. Van de Vel A, Smets K, Wouters K, Ceulemans B. Automated non-EEG based seizure detection: Do users have a say? Epilepsy & Behavior 2016;62:121-128.

39. Bruno E, Simblett S, Lang A, Biondi A, Odoi C, Schulze-Bonhage A, Wykes T, Richardson MP, on behalf of the RADAR-CNS Consortium. Wearable technology in epilepsy: The views of patients, caregivers, and healthcare professionals. Epilepsy & Behavior 2018;85:141-149.

40. Hoppe C, Feldmann M, Blachut B et al. Novel techniques for automated seizure registration: Patients' wants and needs. Epilepsy & Behavior 2015;52:1-7.

41. Patel AD, Moss R, Rust SW et al. Patient-centered design criteria for wearable seizure detection devices. Epilepsy & Behavior 2016;64:116-121.

42. Tovar Quiroga DF, Britton JW, Wirrell EC. Patient and caregiver view on seizure detection devices: A survey study. Seizure 2016;64:179-181.

43. Website of the Dutch Government, Guide to medical devices: https://www.rijksoverheid.nl/onderwerpen/medische-hulpmiddelen/documenten/publicaties/2017/12/12/handreiking-medische-hulpmiddelen.

44. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality. Neurology 2016;86:779-786.

45. 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(17):1674-1680.

46. Keller AE, Ho J, Whitney R. Autopsy-reported cause of death in a population-based cohort of sudden unexpected death in epilepsy. Epilepsia 2021;62(2):472-480.

47. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study. Neurology 2017;89(2):170-177.

48. Beniczky S, Jeppesen J. Non-electroencephalography-based seizure detection. Curr Opin Neurol. 2019;32(2):198-204.

49. Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. Nat Rev Neurol. 2009 Sep;5(9):492-504.

50. Bruno E, Biondi A, Richardson MP, on behalf of the RADAR-CNS Consortium. Digital semiology and time-evolution pattern of bio-signals in focal onset motor seizures. Seizure: European Journal of Epilepsy 2021;87:114-120.

51. Ulate-Campos A, Coughlin F, Gaínza-Lein M, Sánchez Fernández I, Pearl PL, Loddenkemper T. Automated seizure detection systems and their effectiveness for each type of seizure. Seizure 2016 Aug;40:88-101.

52. Ryvlin P, Cammoun L, Hubbard I, Ravey F, Beniczky S, Atienza D. Noninvasive detection of focal seizures in ambulatory patients. Epilepsia 2020;61(S1):S47-S54.

53. Naganur V, Sivathamboo S, Chen Z, Kusmakar S, Antonic-Baker A, O'Brien TJ, Kwan P. Automated seizure detection with noninvasive wearable devices: A systematic review and meta-analysis. Epilepsia 2022;63(8):1930-1941.

54. Jeppesen J, Fuglsang-Frederiksen A, Johansen P, Christensen J, Wüstenhagen S, Tankisi H, Qerama E, Beniczky S. Seizure detection using heart rate variability: A prospective validation study. Epilepsia. 2020 Nov;61 Suppl 1:S41-S46.

55. Jeppesen J, Fuglsang-Frederiksen A, Johansen P, Christensen J, Wüstenhagen S, Tankisi H, et al. Seizure detection based on heart rate variability using a wearable electrocardiography device. Epilepsia 2019;60:2105-13.

56. El Atrache R, Tamilia E, Mohammadpour Touserkani F, Hammond S, Papadelis C, Kapur K, Jackson M, Bucciarelli B, Tsuboyama M, Sarkis RA, Loddenkemper T. Photoplethysmography: A measure for the function of the autonomic nervous system in focal impaired awareness seizures. Epilepsia 2020 Aug;61(8):1617-1626.

57. Onorati F, Regalia G, Caborni C, Migliorini M, Bender D, Poh MZ, et al. Multicenter clinical assessment of improved wearable multimodal convulsive seizure detectors. Epilepsia 2017;58(11):1870-9.

58. Biondi A, Laiou P, Bruno E, Viana PF, Schreuder M, Hart W, Nurse E, Pal DK, Richardson MP. Remote and Long-Term Self-Monitoring of Electroencephalographic and Noninvasive Measurable Variables at Home in Patients With Epilepsy (EEG@HOME): Protocol for an Observational Study. JMIR Res Protoc 2021;10(3):e25309.

59. Beniczky S, Arbune AA, Jeppesen J, Ryvlin P. Biomarkers of seizure severity derived from wearable devices. Epilepsia 2020;00:1-6.

60. Vandecasteele K, De Cooman T, Dan J, Cleeren E, Van Huffel S, Hunyadi B, Van Paesschen W. Visual seizure annotation and automated seizure detection using behind-the-ear electroencephalographic channels. Epilepsia 2020;61(4):766-775.

61. Frankel MA, Lehmkuhle MJ, Watson M, Fetrow K, Frey L, Drees C, Spitz MC. Electrographic seizure monitoring with a novel, wireless, single-channel EEG sensor. Clin Neurophysiol Pract. 2021;29(6):172-178.

62. Brinkmann BH, Karoly PJ, Nurse ES, Dumanis SB, Nasseri M, Viana PF, Schulze-Bonhage A, Freestone DR, Worrell G, Richardson MP, Cook MJ. Seizure Diaries and Forecasting With Wearables: Epilepsy Monitoring Outside the Clinic. Front Neurol. 2021 Jul 13;12:690404.

63. Karoly PJ, Ung H, Grayden DB, Kuhlmann L, Leyde K, Cook MJ, Freestone DR. The circadian profile of epilepsy improves seizure forecasting. Brain 2017;140:2169-2182.

64. Beniczky S, Karoly P, Nurse E, Ryvlin P, Cook M. Machine learning and wearable devices of the future. Epilepsia 2020;00:1-9.

65. Shoeibi A, Khodatars M, Ghassemi N, Jafari M, Moridian P, Alizadehsani R et al. Epileptic Seizures Detection Using Deep Learning Techniques: A Review. Int. J. Environ. Res. Public Health 2021;18:5780.

66. Tang J, El Atrache R, Yu S, Asif U, Jackson M, Roy S et al. Seizure detection using wearable sensors and machine learning: Setting a benchmark. Epilepsia 2021;62(8):1807-1819.

67. Baumgartner C, Koren JP. Seizure detection using scalp-EEG. Epilepsia. 2018;59:14-22.

68. Craik A, He Y, Contreras-Vidal JL. Deep learning for electroencephalogram (EEG) classification tasks: a review. J. Neural Eng. 2019;16:031001.

69. Jacoby A, Baker GA. Quality-of-life trajectories in epilepsy: a review of the literature. Epilepsy & Behavior 2008;12:557-71.

70. Janse SA, Dumanis SB, Huwig T, Hyman S, Fureman BE, Bridges JFP. Patient and caregiver preferences for the potential benefits and risks of a seizure forecasting device: A best–worst scaling. Epilepsy & Behavior 2019;96:183-191.

71. Cook MJ, O'Brien TJ, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. Lancet Neurol. 2013;12(6):563-71.

72. Karoly PJ, Cook MJ, Maturana M, Nurse ES, Payne D, Brinkmann BH, Grayden DB, Dumanis SB, Richardson MP, Worrell GA, Schulze-Bonhage A, Kuhlmann L, Freestone DR. Forecasting cycles of seizure likelihood. Epilepsia. 2020;00:1-11.

73. Karoly PJ, Ung H, Grayden DB, Kuhlmann L, Leyde K, Cook MJ, Freestone DR. The circadian profile of epilepsy improves seizure forecasting. Briain 2017;140:2169-2182.

74. Meisel C, El Atrache R, Jackson M, Schubach S, Ufongene C, Loddenkemper T. Machine learning from wristband sensor data for wearable, noninvasive seizure forecasting. Epilepsia 2020;61:2653-2666.

75. Brinkmann BH, Karoly PJ, Nurse ES, Dumanis SB, Nasseri M, Viana PF, Schulze-Bonhage A, Freestone DR, Worrell G, Richardson MP, Cook MJ. Seizure Diaries and Forecasting With Wearables: Epilepsy Monitoring Outside the Clinic. Front. Neurol. 2021;12:690404.

76. Stirling RE, Grayden DB, D'Souza W, Cook MJ, Nurse E, Freestone DR, Payne DE, Brinkmann BH, Pal Attia T, Viana PF, Richardson MP, Karoly PJ. Forecasting Seizure Likelihood With Wearable Technology. Front Neurol. 2021;12:704060.