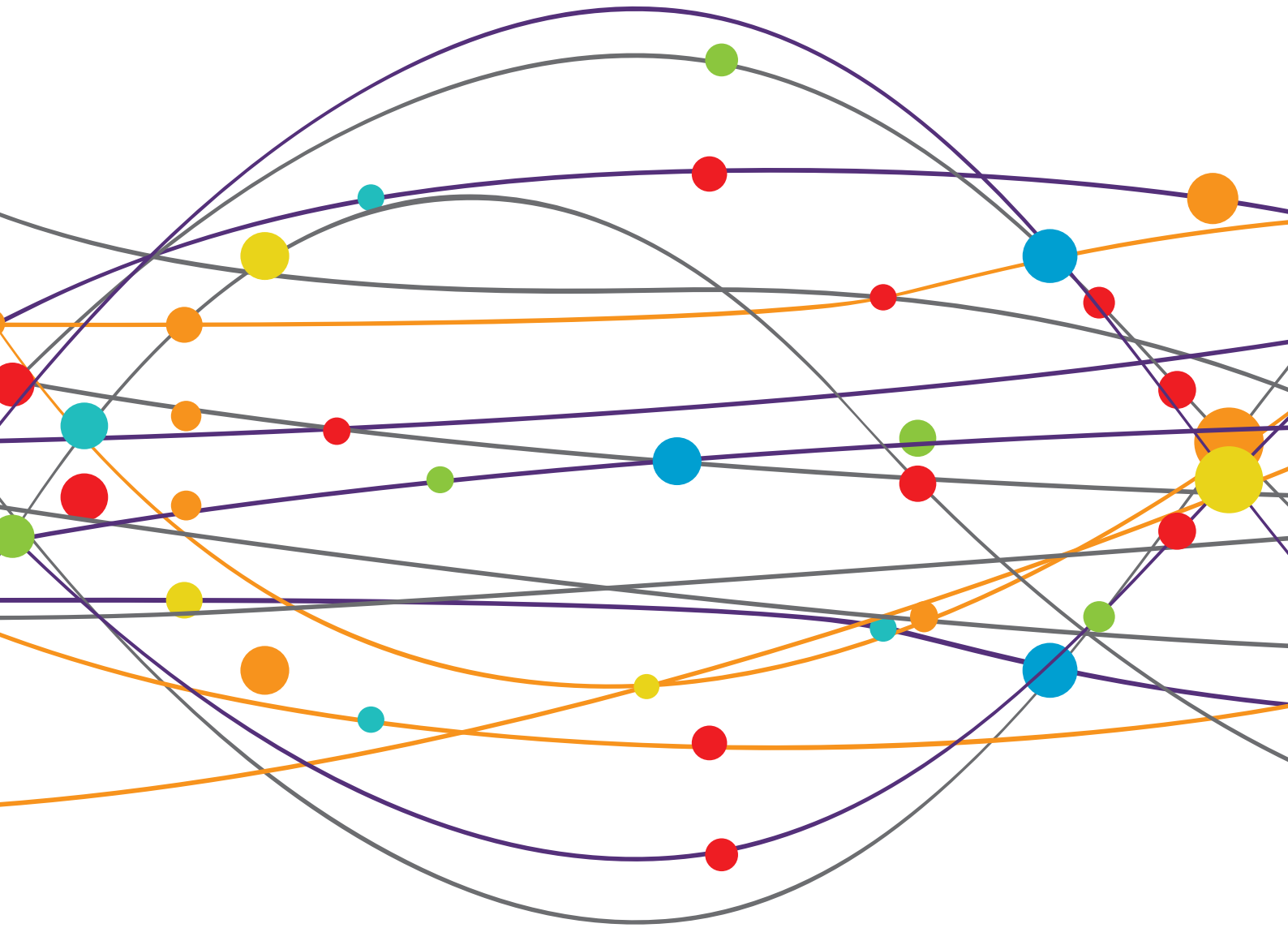
EPILEPSY MORTALITY: LEADING CAUSES OF DEATH, CO-MORBIDITIES, CARDIOVASCULAR RISK AND PREVENTION

EDITED BY: Christopher Michael DeGiorgio, Rohit Shankar and Brian Darryl Moseley

PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88974-461-9
DOI 10.3389/978-2-88974-461-9

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

EPILEPSY MORTALITY: LEADING CAUSES OF DEATH, CO-MORBIDITIES, CARDIOVASCULAR RISK AND PREVENTION

Topic Editors:
Christopher Michael DeGiorgio, University of California, Los Angeles, United States
Rohit Shankar, University of Plymouth, United Kingdom
Brian Darryl Moseley, University of Cincinnati, United States

We would like to acknowledge that Dr. Luke Allen , University College London, has acted as a coordinator and has contributed to the preparation of the proposal for this Research Topic.

Citation: DeGiorgio, C. M., Shankar, R., Moseley, B. D., eds. (2022). Epilepsy Mortality: Leading Causes of Death, Co-morbidities, Cardiovascular Risk and Prevention. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88974-461-9

Table of Contents

frontiers in Neurology

PERSPECTIVE
published: 08 September 2020
doi: 10.3389/fneur.2020.00925

Are Variants Causing Cardiac Arrhythmia Risk Factors in Sudden Unexpected Death in Epilepsy?

*Lauren E. Bleakley[1], Ming S. Soh[1], Richard D. Bagnall[2,3], Lynette G. Sadleir[4], Samuel Gooley[5], Christopher Semsarian[2,3], Ingrid E. Scheffer[1,5,6], Samuel F. Berkovic[5] and Christopher A. Reid[1]**

[1] Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia, [2] Agnes Ginges Centre for Molecular Cardiology Centenary Institute, The University of Sydney, Sydney, NSW, Australia, [3] Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia, [4] Department of Paediatrics and Child Health, University of Otago, Wellington, New Zealand, [5] Department of Medicine, Epilepsy Research Centre, Austin Health, University of Melbourne, Heidelberg, VIC, Australia, [6] Department of Paediatrics, Royal Children's Hospital, University of Melbourne, Melbourne, VIC, Australia

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of premature mortality in individuals with epilepsy. Acute and adaptive changes in heart rhythm in epilepsy implicate cardiac dysfunction as a potential pathogenic mechanism in SUDEP. Furthermore, variants in genes associated with Long QT syndrome (LQTS) have been identified in patients with SUDEP. LQTS is a cardiac arrhythmia condition that causes sudden cardiac death with strong similarities to SUDEP. Here, we discuss the possibility of an additive risk of death due to the functional consequences of a pathogenic variant in an LQTS gene interacting with seizure-mediated changes in cardiac function. Extending this general concept, we propose a hypothesis that common variants in LQTS genes, which cause a subtle impact on channel function and would not normally be considered risk factors for cardiac disease, may increase the risk of sudden death when combined with epilepsy. A greater understanding of the interaction between epilepsy, cardiac arrhythmia, and SUDEP will inform our understanding of SUDEP risk and subsequent potential prophylactic treatment.

Keywords: sudden unexpected death in epilepsy, epilepsy, cardiac arrhythmia, genetics, ion channels, common variants

OPEN ACCESS

Edited by:
Brian Darryl Moseley, University of Cincinnati, United States

Reviewed by:
Torbjörn Tomson, Karolinska Institutet (KI), Sweden
Vincenzo Belcastro, Ospedale Sant Anna, ASST Lariana, Italy

****Correspondence:***
Christopher A. Reid
careid@unimelb.edu.au

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *28 May 2020*
Accepted: *17 July 2020*
Published: *08 September 2020*

Citation:
Bleakley LE, Soh MS, Bagnall RD, Sadleir LG, Gooley S, Semsarian C, Scheffer IE, Berkovic SF and Reid CA (2020) Are Variants Causing Cardiac Arrhythmia Risk Factors in Sudden Unexpected Death in Epilepsy? Front. Neurol. 11:925. doi: 10.3389/fneur.2020.00925

INTRODUCTION

People with epilepsy have a two- to threefold increased risk of premature mortality, with sudden unexpected death in epilepsy (SUDEP) the most common epilepsy-related cause (1–5). 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 and excluding documented status epilepticus, in which postmortem examination does not reveal a cause of death" (6). The incidence of SUDEP varies widely depending upon the subpopulation of interest, from 0.2 per 1,000 persons per year in children, and 1.2 per 1,000 persons per year in adults (7), to 2.46 or higher per 1,000 persons per year in people with refractory epilepsy (8, 9),

and up to 10 per 1,000 persons per year in candidates for epilepsy surgery (10). In addition, certain severe epilepsy syndromes, such as the Developmental and Epileptic Encephalopathies (DEEs), place individuals at a greater risk of sudden death (11). A well-established example of this is Dravet syndrome, an intractable infantile-onset DEE mainly caused by pathogenic variants in *SCN1A* (12, 13). Dravet syndrome has a mortality rate of 16 per 1,000 persons per year, which translates to a 17% mortality risk in the first two decades of life with 59% of these deaths due to SUDEP (14). As expected, many rare variants in other genes that are closely associated with DEE have been identified in studies exploring the genetic architecture of SUDEP (11, 15).

Risk factors have been identified for SUDEP, with the most important being that the individual experiences tonic–clonic seizures, especially if they occur with high frequency (11, 16, 17). Other risk factors include epilepsy duration, age of onset of epilepsy, frequent changes in antiseizure medication doses, and, in some studies, antiepileptic drug polytherapy (3, 11, 16, 18). However, SUDEP can also occur in individuals with mild types of epilepsy (19, 20), as well as those with well-controlled epilepsy (3, 20), suggesting that other risk factors exist.

The pathophysiological mechanism(s) responsible for SUDEP remain largely unclear, despite considerable interest and research endeavor. A prevailing hypothesis is that SUDEP occurs following centrally mediated autonomic failure, which is most likely triggered by a tonic–clonic seizure (21). This hypothesis is strongly supported by a seminal paper, which reported findings from a systematic retrospective survey of SUDEP deaths that occurred in epilepsy video-electroencephalogram (video-EEG) monitoring units. This study found that SUDEP followed a consistent pattern whereby individuals had a tonic–clonic seizure (most were focal to bilateral tonic–clonic, and some were generalized tonic–clonic), followed by a period of rapid breathing, and then cardiorespiratory dysfunction leading to terminal apnea and asystole (22). Of particular note is the finding that terminal apnea always preceded terminal asystole (22). However, while these results are compelling, they are unlikely to be telling the whole story. The patient population in this study was small and involved individuals who were undergoing long-term monitoring, implying refractory epilepsy—a selected subset of patients who we know are at greater risk of SUDEP. Such a subset does not provide a representative sample of all individuals with SUDEP, raising the possibility that other pathological mechanisms can also cause SUDEP. One such mechanism, which has been widely studied, is the presence of abnormal cardiac rhythms (4, 15).

There are several lines of evidence supporting a role for cardiac arrhythmia in SUDEP. First, there are clear similarities between SUDEP and sudden cardiac death: in both cases, death is unexpected, and no cause of death is identified after comprehensive postmortem (23). Second, both human and animal studies show that seizure-mediated changes in cardiac electrophysiology occur, including seizure-driven cortical autonomic dysfunction and altered cardiac ion channel expression (24). Finally, recent genetic studies have found variants in genes associated with cardiac arrhythmia syndromes in some individuals with SUDEP (15, 25–28). Here, we propose that there may be an interaction between seizure activity and increased risk of sudden death in epilepsy patients who harbor variants (including common variants) in arrhythmogenic genes (**Figure 1**).

ARRHYTHMOGENIC GENES IN SUDEP

A number of studies have explored the genetic architecture of SUDEP (25, 26, 29, 30). These studies have identified variation in several genes known to cause cardiac arrhythmia syndromes—in particular, long QT syndrome (LQTS)—and sudden death. LQTS is a cardiac arrhythmia syndrome resulting from delayed myocardial repolarization that manifests as a prolonged QT interval on the electrocardiogram (ECG) (31). This increases the risk of "torsades de pointes," a distinctive form of ventricular tachycardia (32, 33) that can trigger sudden cardiac death in otherwise healthy individuals with structurally normal hearts (31). About 75% of familial LQTS is accounted for by three major genes, *KCNQ1*, *KCNH2*, and *SCN5A* (31). Variants in these three genes (25–28), and in several other cardiac and LQTS genes (25, 34), have been identified in SUDEP cases (**Table 1**).

It is important to highlight that the presence alone of a rare variant in a case of SUDEP does not confirm its pathogenicity or contribution to SUDEP risk. Furthermore, in cases of sudden death, where seizures have been diagnosed, but where pathogenic variants in cardiac genes are present, other potential explanations—such as misdiagnosis of convulsive syncope due to a cardiac cause, a common occurrence in individuals with LQTS—must be ruled out. This does not always occur (35, 36). A recent systematic review has highlighted the issues in diagnosis of SUDEP and the challenges in inferring causation in cases with variants in cardiac genes (37). That being said, current genetic findings that associate variants in cardiac arrhythmia genes with SUDEP do allow for some discussion and hypothesis generation about pathogenic mechanisms.

POTENTIAL IMPACT OF SEIZURES IN PATIENTS HARBORING PATHOGENIC VARIANTS IN ARRHYTHMOGENIC GENES

The LQTS pathogenic variants in *KCNH2*, p.Arg744*, and p.Gly924Ala, have each been identified in a SUDEP patient (25). It is intuitive to think that an individual with epilepsy who also harbors a pathogenic cardiac genetic variant will be at higher risk of sudden unexpected death. The finding of validated LQTS variants in SUDEP provides indirect evidence supporting this premise (**Table 1**). It is also well-recognized that numerous acute postictal arrhythmia patterns occur in epilepsy patients, presumably through significant changes in autonomic function (38). It is possible that these rhythm changes could interact with the physiological consequences of harboring arrhythmogenic variants to increase the risk of sudden death (**Figure 1**). Data

Abbreviations: DEE, developmental and epileptic encephalopathy; ECG, electrocardiogram; EEG, electroencephalogram; LQTS, long QT syndrome; SUDEP, sudden unexpected death in epilepsy.

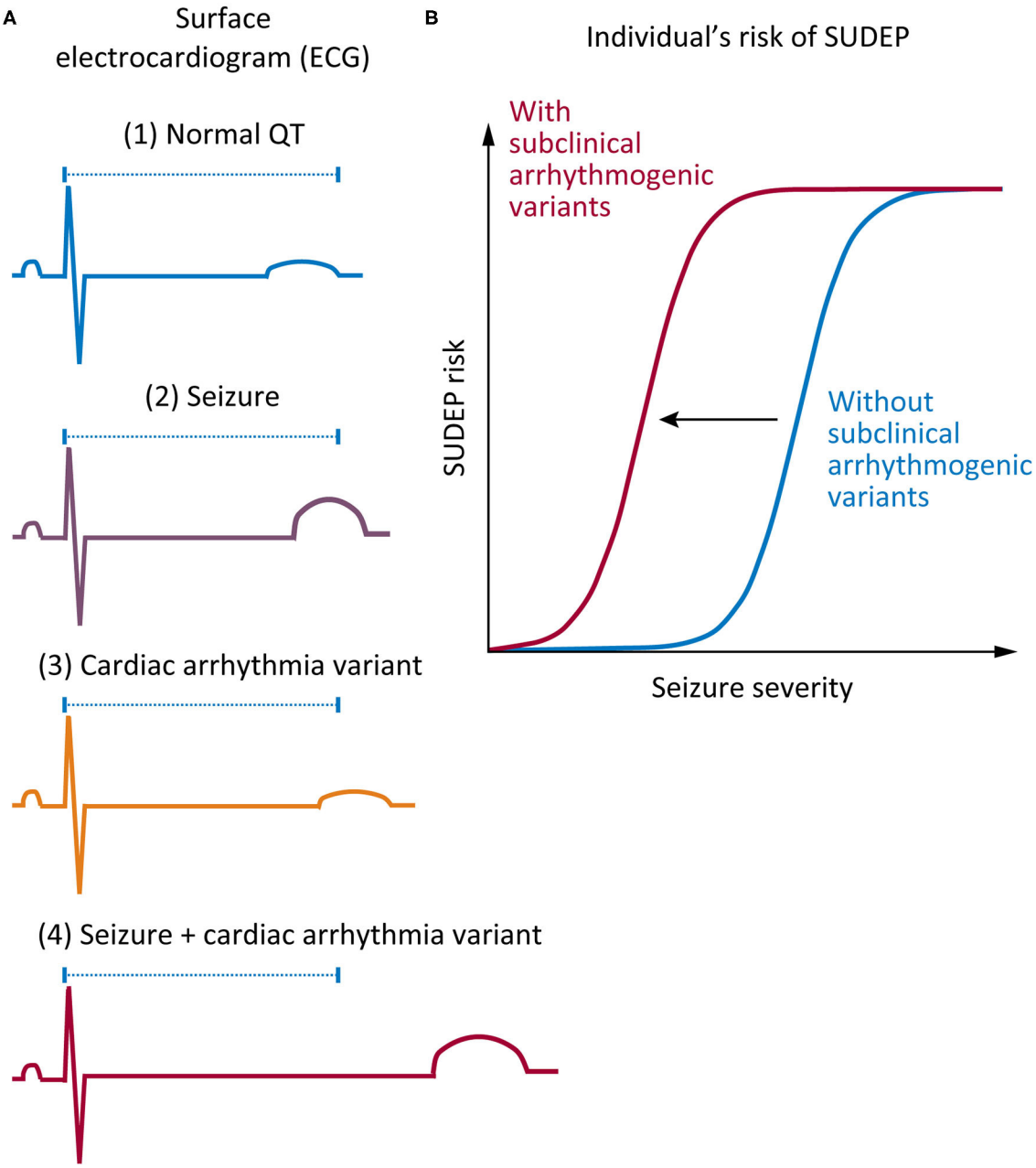


FIGURE 1 | Proposed mechanism on how genetic variants associated with cardiac arrhythmia may increase risk of sudden unexpected death in epilepsy (SUDEP). **(A)** Comparison of surface electrocardiogram (ECG) in various conditions. (1) A normal QT interval in a healthy individual without epilepsy or cardiac arrhythmia (blue). (2) A small shift in the QT interval might occur in a patient with epilepsy during a seizure (purple). (3) A "subclinical" individual carrying a functional variant in a cardiac arrhythmia gene, which only subtly shifts the QT interval (orange). (4) A combination of a "subclinical" variant and a seizure event results in a nonlinear increase in the QT interval, thus increasing the risk of sudden death (red). **(B)** The increased risk of sudden death that is conferred by harboring a "subclinical" functional variant in a cardiac gene presents itself in the acute context of a seizure, which causes disruption of normal cardiac function. Such cardiac disruption is more likely with longer seizures, seizures with more intense autonomic discharges, and perhaps more violent seizures with more systemic metabolic changes, all effects encapsulated by the term "seizure severity." This risk is present on every occasion when an affected individual has a seizure.

from the Kcnq1 p.Thr311Ile mouse model of LQTS provides more direct evidence that an interaction between acute seizures and elongation of the QT interval may occur. This mouse has a prolonged QT interval and frequent seizures relative to controls (39, 40), and interestingly, over half of ECG-detected cardiac abnormalities are associated with epileptiform discharges on the EEG (40). Furthermore, we know that in many epilepsy patient populations and animal models of epilepsy, basal ECG properties

TABLE 1 | Nonsynonymous variants in cardiac arrhythmia genes that have been identified in sudden unexpected death in epilepsy (SUDEP).

Gene	Variant	gnomAD allele count	Sorting intolerant from tolerant (SIFT)	PolyPhen-2	References
AKAP9	Ile1749Thr	195	Deleterious	Probably damaging	(25)
	Arg2607Gly	0	Deleterious	Probably damaging	(25)
ANK2	Ala1027Asp	0	Deleterious	Probably damaging	(25)
	Ser2440Asn	0	Deleterious	Probably damaging	(25)
	Ile3903Asn	1	Deleterious	Probably damaging	(25)
HCN1	Gly46Val	0	Deleterious	Benign	(34)
HCN2	Phe738Cys	0	Tolerated	Probably damaging	(34)
	Pro802Ser	10	Tolerated low confidence	Benign	(34)
HCN3	Lys69Arg	3,014	Tolerated	Benign	(34)
	Pro630Leu	6,780	Deleterious low confidence	Benign	(34)
HCN4	Gly36Glu	7,166	Deleterious low confidence	Benign	(34)
	Val759Ile	870	Tolerated	Benign	(34)
	Gly973Arg	19	Tolerated low confidence	Possibly damaging	(34)
	Arg1044Trp	4	Deleterious low confidence	Probably damaging	(34)
	Glu1193Gln	205	Tolerated low confidence	Probably damaging	(25)
KCNH2	Ile82Thr	0	Deleterious	Benign	(28)
	Arg176Trp	44	Deleterious	Possibly damaging	(26)
	Arg744*	0			(25)
	Gly749Ala	0	Deleterious	Possibly damaging	(25)
	Gly924Ala	8	Tolerated	Possibly damaging	(25)
	Arg1047Leu	3,117	Tolerated	Possibly damaging	(26)
KCNQ1	Tyr662*	12			(25)
RYR2	Cys1489Arg	40	Tolerated	Benign	(25)
SCN5A	Val223Gly	0	Deleterious	Probably damaging	(25)
	Ile397Val	1	Deleterious	Probably damaging	(25)
	Arg523Cys	2	Deleterious	Benign	(27)
	His558Arg	62,556	Tolerated	Benign	(26)
	Ala572Asp	1,451	Tolerated	Benign	(26)
	Pro1090Leu	458	Tolerated	Benign	(26)
	Pro2006Ala	252	Tolerated low confidence	Benign	(26)

**indicates a nonsense mutation resulting in a premature stop codon.*

are changed (24). In patients who also harbor underlying variants in arrhythmogenic genes, these long-term changes in heart rhythm may increase the risk of sudden death. It will be challenging to rigorously test whether seizures increase the risk of sudden death in patients harboring pathogenic LQTS variants. Designs could include cross-sectional analyses of families with LQTS and determining if the death rate is higher in those with known coexistent epilepsy or longitudinal follow-up of subjects with epilepsy stratified into those with and without known LQTS variants.

CAN "SUBCLINICAL" VARIANTS IN ARRHYTHMOGENIC GENES CONTRIBUTE TO SUDEP RISK?

Consider a potentially more broadly applicable situation, where a patient with epilepsy harbors a common variant in a gene associated with cardiac arrhythmia, but the variant is not normally associated with clinical events. Such a "subclinical" variant alters cardiac function but to a degree that is below the threshold to cause clinically recognized LQTS; thus, it would not normally be considered a risk factor for cardiac disease. Could patients such as this be at an increased risk of death during or immediately following seizures (**Figure 1**)? We propose that small shifts in the QT interval, which are present in seizures and independently in people harboring common variants in arrhythmogenic genes that cause minor changes in channel function, will only increase the risk of sudden death slightly. However, when combined, seizures and a common variant in an arrhythmogenic gene may interact to significantly increase SUDEP risk.

There is a precedent for this idea in a recently published study that investigated the relationship between *KCNQ1* common variants and sudden death during illegal drug use. The missense variant KCNQ1 p.Gly643Ser (found 1,433 times in the gnomAD database) was more common in patients who died of drug-related causes than in the general population (41). Interestingly, this common variant has been found to cause a mild loss-of-function of the $K_v7.1$ voltage-gated potassium channel when studied in a heterologous expression assay (42, 43). This finding

provides evidence that a common variant, which is unlikely to be pathogenic in isolation, could potentially increase the risk of death under certain circumstances.

Numerous common variants in LQTS genes have been identified in SUDEP patients (25–28) (**Table 1**). This is exemplified by variation in *KCNH2*, a cardiac gene that encodes the α subunit of the voltage-gated potassium channel $K_v11.1$ (44). The common KCNH2 p.Arg1047Leu variant (found >3,000 times in gnomAD) has been observed in four patients that have suffered SUDEP (26). Functional testing of this variant suggests that it causes mild loss of channel function (45). It is well-established that loss-of-function *KCNH2* variants cause LQTS type 2, which does predispose individuals to greater risk of sudden death (31, 44, 46, 47). As such, although the KCNH2 p.Arg1047Leu variant is not disease causing in its own right, the mild loss-of-function that it causes positions it as a potential risk factor for SUDEP. Owing to the prevalence of this variant in the population, very large sample sizes would be needed to show a statistical association with SUDEP, with a similar issue arising with all common variants in LQTS genes that are identified in patients.

CONCLUSION AND POTENTIAL CLINICAL IMPLICATIONS

For patients with epilepsy and their families, SUDEP is a frightening possibility, made even more so by its unpredictability. SUDEP is undoubtedly a highly heterogeneous condition, and a given individual's risk is likely to be determined by a complex interaction of many contributing factors. These include both genetic and environmental risk factors for mechanisms as diverse as seizures, cardiac arrhythmias, respiratory dysfunction, and autonomic dysfunction (15). Reducing seizure frequency and severity is important in reducing SUDEP risk. However, in such a multifactorial condition, the potential risk conferred by other mechanisms—such as cardiac arrhythmias—also warrants consideration. Variants in diverse cardiac arrhythmia genes have been found in SUDEP patients (25–29, 34), but we clearly need a much better understanding of the impact of these variants in the context of an individual with epilepsy.

Although it seems obvious, an increased risk of death associated with an epilepsy patient having a validated LQTS variant has not been shown. It is also not known whether SUDEP risk increases in cases of epilepsy when a patient harbors one or more variants of unknown significance in cardiac arrhythmia genes, such as in the case of the patients with the KCNH2 p.Arg1047Leu common variant outlined above. We propose that genetic studies in SUDEP should be extended to include the characterization of common variants in cardiac arrhythmia genes. Additionally, functional studies are required to identify if these variants cause subclinical biophysical changes, which could exacerbate the risk of sudden death during a seizure. Currently, the prevalence of rare variants with functional impact is unknown. Without such information, and indeed until such time as the genetic architecture of SUDEP overall is understood, we are unable to predict the relative contribution of genetic cardiac dysfunction to SUDEP incidence and risk.

Identifying and confirming genetic risk factors that predispose patients with epilepsy to cardiac arrhythmia would have therapeutic implications. Patients identified to be at risk of cardiac arrhythmia could be advised to avoid medications that interact with cardiac ion channels; commence prophylactic treatment with beta blockers, which are used effectively in LQTS to reduce the risk of life-threatening arrhythmias (48); or even consider the implantation of an internal defibrillator or pacemaker to reduce risk of sudden death (49), although evidence for the benefit of such an approach is currently limited (50). Concurrent EEG and ECG monitoring may also be warranted to gain greater insight into the interactions between seizures and cardiac rhythm.

In summary, here we highlight that variants in cardiac genes, both those known to be pathogenic and also those that are currently thought of as "subclinical," are potential contributors to SUDEP risk. However, there is currently a lack of direct evidence for cardiac variants increasing the risk of SUDEP, demonstrating a need for further research. Given the sample-size challenges of clinical research in this area, we suggest that exploring this hypothesis in experimental animals is a useful next step.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

LB, MS, RB, LS, CS, IS, SB, and CR developed the concept. LB and CR wrote the manuscript. MS generated the figure. All authors contributed to revising and editing the manuscript and approved the submitted version.

FUNDING

This work was supported by the National Health and Medical Research Council (NHMRC) Program Grant (10915693) to SB, IS, and CR; by Cure Kids New Zealand to LS; and by an anonymous philanthropic gift for SUDEP research to SB and IS. CR would like to acknowledge the CURE foundation for support. CS was the recipient of an NHMRC Practitioner Fellowship (#1154992). IS holds an NHMRC Practitioner Fellowship and an Investigator Fellowship. LB acknowledges the support of an Australian Government Research Training Program Scholarship. The Florey Institute of Neuroscience and Mental Health were supported by the Victorian State Government infrastructure funds.

ACKNOWLEDGMENTS

We thank Marie Phillips for carefully reading and providing feedback on this manuscript.

REFERENCES

1. Sander JW, Bell GS. Reducing mortality: an important aim of epilepsy management. *J Neurol Neurosurg Psychiatry.* (2004) 75:349–51. doi: 10.1136/jnnp.2003.029223
2. Bell GS, Sander JW. The epidemiology of epilepsy: the size of the problem. *Seizure.* (2001) 10:306–14; quiz 15–6. doi: 10.1053/seiz.2001.0584
3. Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: a search for risk factors. *Epilepsy Behav.* (2007) 10:138–41. doi: 10.1016/j.yebeh.2006.11.010
4. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol.* (2008) 7:1021–31. doi: 10.1016/S1474-4422(08)70202-3
5. Thurman DJ, Logroscino G, Beghi E, Hauser WA, Hesdorffer DC, Newton CR, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia.* (2017) 58:17–26. doi: 10.1111/epi.13604
6. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia.* (2012) 53:227–33. doi: 10.1111/j.1528-1167.2011.03358.x
7. Harden C, Tomson T, Gloss D, Buchhalter J, Cross H, Donner E, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the guideline development, dissemination, and implementation subcommittee of the american academy of neurology and the american epilepsy society. *Neurology.* (2017) 88:1674–80. doi: 10.1212/WNL.0000000000003685
8. DeGiorgio CM. Editorial: sudden death in epilepsy: basic and translational research. *Front Neurol.* (2018) 9:484. doi: 10.3389/fneur.2018.00484
9. Mohanraj R, Norrie J, Stephen LJ, Kelly K, Hitiris N, Brodie MJ. Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study. *Lancet Neurol.* (2006) 5:481–7. doi: 10.1016/S1474-4422(06)70448-3
10. Téllez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. *Epilepsy Res.* (2005) 65:101–15. doi: 10.1016/j.eplepsyres.2005.05.004
11. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. *Lancet Neurol.* (2016) 15:1075–88. doi: 10.1016/S1474-4422(16)30158-2
12. De Jonghe P. Molecular genetics of Dravet syndrome. *Dev Med Child Neurol.* (2011) 53 (Suppl. 2):7–10. doi: 10.1111/j.1469-8749.2011.03965.x
13. Richards KL, Milligan CJ, Richardson RJ, Jancovski N, Grunnet M, Jacobson LH, et al. Selective NaV1.1 activation rescues Dravet syndrome mice from seizures and premature death. *Proc Natl Acad Sci USA.* (2018) 115:E8077–E85. doi: 10.1073/pnas.1804764115
14. Cooper MS, McIntosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome. *Epilepsy Res.* (2016) 128:43–7. doi: 10.1016/j.eplepsyres.2016.10.006
15. Bagnall RD, Crompton DE, Semsarian C. Genetic basis of sudden unexpected death in epilepsy. *Front Neurol.* (2017) 8:348. doi: 10.3389/fneur.2017.00348
16. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. *Epilepsia.* (2011) 52:1150–9. doi: 10.1111/j.1528-1167.2010.02952.x
17. DeGiorgio CM, Markovic D, Mazumder R, Moseley BD. Ranking the leading risk factors for sudden unexpected death in epilepsy. *Front Neurol.* (2017) 8:473. doi: 10.3389/fneur.2017.00473
18. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case control study. *Lancet.* (1999) 353:888–93. doi: 10.1016/S0140-6736(98)05114-9
19. Hirsch LJ. Is sudden unexpected death in epilepsy due to postictal brain shutdown? *Ann Neurol.* (2010) 68:773–5. doi: 10.1002/ana.22242
20. Verducci C, Hussain F, Donner E, Moseley BD, Buchhalter J, Hesdorffer D, et al. SUDEP in the North American SUDEP Registry: the full spectrum of epilepsies. *Neurology.* (2019) 93:e227–e36. doi: 10.1212/WNL.0000000000007778
21. Ryvlin P, Cascino GD. Sudden unexpected death in epilepsy patients is often misdiagnosed as sudden cardiac death. *Neurology.* (2017) 89:878–9. doi: 10.1212/WNL.0000000000004301
22. 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) 12:966–77. doi: 10.1016/S1474-4422(13)70214-X
23. Bagnall RD, Weintraub RG, Ingles J, Duflou J, Yeates L, Lam L, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med.* (2016) 374:2441–52. doi: 10.1056/NEJMoa1510687
24. Ravindran K, Powell KL, Todaro M, O'Brien TJ. The pathophysiology of cardiac dysfunction in epilepsy. *Epilepsy Res.* (2016) 127:19–29. doi: 10.1016/j.eplepsyres.2016.08.007
25. Bagnall RD, Crompton DE, Petrovski S, Lam L, Cutmore C, Garry SI, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. *Ann Neurol.* (2016) 79:522–34. doi: 10.1002/ana.24596
26. Tu E, Bagnall RD, Duflou J, Semsarian C. Post-mortem review and genetic analysis of sudden unexpected death in epilepsy (SUDEP) cases. *Brain Pathol.* (2011) 21:201–8. doi: 10.1111/j.1750-3639.2010.00438.x
27. Aurlien D, Leren TP, Tauboll E, Gjerstad L. New SCN5A mutation in a SUDEP victim with idiopathic epilepsy. *Seizure.* (2009) 18:158–60. doi: 10.1016/j.seizure.2008.07.008
28. Partemi S, Cestele S, Pezzella M, Campuzano O, Paravidino R, Pascali VL, et al. Loss-of-function KCNH2 mutation in a family with long QT syndrome, epilepsy, and sudden death. *Epilepsia.* (2013) 54:e112–6. doi: 10.1111/epi.12259
29. Friedman D, Kannan K, Faustin A, Shroff S, Thomas C, Heguy A, et al. Cardiac arrhythmia and neuroexcitability gene variants in resected brain tissue from patients with sudden unexpected death in epilepsy (SUDEP). *NPJ Genom Med.* (2018) 3:9. doi: 10.1038/s41525-018-0048-5
30. Partemi S, Vidal MC, Striano P, Campuzano O, Allegue C, Pezzella M, et al. Genetic and forensic implications in epilepsy and cardiac arrhythmias: a case series. *Int J Legal Med.* (2015) 129:495–504. doi: 10.1007/s00414-014-1063-4
31. Tester DJ, Ackerman MJ. Genetics of Long QT Syndrome. *Methodist Debakey Cardiovasc J.* (2014) 10:29–33. doi: 10.14797/mdcj-10-1-29
32. Banai S, Tzivoni D. Drug therapy for torsade de pointes. *J Cardiovasc Electrophysiol.* (1993) 4:206–10. doi: 10.1111/j.1540-8167.1993.tb01224.x
33. Schwartz PJ, Crotti L, Insolia R. Long QT syndrome: from genetics to management. *Circ Arrhythm Electrophysiol.* (2012) 5:868–77. doi: 10.1161/CIRCEP.111.962019
34. Tu E, Waterhouse L, Duflou J, Bagnall RD, Semsarian C. Genetic analysis of hyperpolarization-activated cyclic nucleotide-gated cation channels in sudden unexpected death in epilepsy cases. *Brain Pathol.* (2011) 21:692–8. doi: 10.1111/j.1750-3639.2011.00500.x
35. Hunt DPJ, Tang K. Long QT syndrome presenting as epileptic seizures in an adult. *Emerg Med J.* (2005) 22:600–1. doi: 10.1136/emj.2003.007997
36. MacCormick JM, McAlister H, Crawford J, French JK, Crozier I, Shelling AN, et al. Misdiagnosis of long QT syndrome as epilepsy at first presentation. *Ann Emerg Med.* (2009) 54:26–32. doi: 10.1016/j.annemergmed.2009.01.031
37. Chahal CAA, Salloum MN, Alahdab F, Gottwald JA, Tester DJ, Anwer LA, et al. Systematic review of the genetics of sudden unexpected death in epilepsy: potential overlap with sudden cardiac death and arrhythmia-related genes. *J Am Heart Assoc.* (2020) 9:e012264. doi: 10.1161/JAHA.119.012264
38. 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. doi: 10.1016/j.autneu.2015.07.066
39. Casimiro MC, Knollmann BC, Yamoah EN, Nie L, Vary JC Jr, Sirenko SG, et al. Targeted point mutagenesis of mouse Kcnq1: phenotypic analysis of mice with point mutations that cause Romano-Ward syndrome in humans. *Genomics.* (2004) 84:555–64. doi: 10.1016/j.ygeno.2004.06.007
40. Goldman AM, Glasscock E, Yoo J, Chen TT, Klassen TL, Noebels JL. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. *Sci Transl Med.* (2009) 1:2ra6. doi: 10.1126/scitranslmed.3000289
41. Nagasawa S, Saitoh H, Kasahara S, Chiba F, Torimitsu S, Abe H, et al. Relationship between KCNQ1 (LQT1) and KCNH2 (LQT2) gene mutations and sudden death during illegal drug use. *Sci Rep.* (2018) 8:8443. doi: 10.1038/s41598-018-26723-8
42. Kubota T, Horie M, Takano M, Yoshida H, Takenaka K, Watanabe E, et al. Evidence for a single nucleotide polymorphism in

the *KCNQ1* potassium channel that underlies susceptibility to life-threatening arrhythmias. *J Cardiovasc Electrophysiol.* (2001) 12:1223–9. doi: 10.1046/j.1540-8167.2001.01223.x
43. Villa C, Combi R. Potassium channels and human epileptic phenotypes: an updated overview. *Front Cell Neurosci.* (2016) 10:81. doi: 10.3389/fncel.2016.00081
44. Smith JL, Anderson CL, Burgess DE, Elayi CS, January CT, Delisle BP. Molecular pathogenesis of long QT syndrome type 2. *J Arrhythm.* (2016) 32:373–80. doi: 10.1016/j.joa.2015.11.009
45. Chevalier P, Bellocq C, Millat G, Piqueras E, Potet F, Schott JJ, et al. Torsades de pointes complicating atrioventricular block: evidence for a genetic predisposition. *Heart Rhythm.* (2007) 4:170–4. doi: 10.1016/j.hrthm.2006.10.004
46. Liu L, Tian J, Lu C, Chen X, Fu Y, Xu B, et al. Electrophysiological characteristics of the LQT2 syndrome mutation KCNH2-G572S and regulation by accessory protein KCNE2. *Front Physiol.* (2016) 7:650. doi: 10.3389/fphys.2016.00650
47. Murphy C, Gill J. Long-QT syndrome in a family with a *KCNH2* mutation. *Heart Metab.* (2008) 41:30–3.
48. Ackerman MJ, Priori SG, Dubin AM, Kowey P, Linker NJ, Slotwiner D, et al. Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: are all beta-blockers equivalent? *Heart Rhythm.* (2017) 14:e41–e4. doi: 10.1016/j.hrthm.2016.09.012
49. Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. *Lancet.* (2004) 364:2212–9. doi: 10.1016/S0140-6736(04)17594-6
50. Dlouhy BJ, Gehlbach BK, Richerson GB. Sudden unexpected death in epilepsy: basic mechanisms and clinical implications for prevention. *J Neurol Neurosurg Psychiatry.* (2016) 87:402–13. doi: 10.1136/jnnp-2013-307442

Conflict of Interest: LS was a consultant for the Epilepsy Consortium, has received travel grants from Sequirus and Nutricia, and has received research funding from Zynerba, the Health Research Council of New Zealand and Cure Kids New Zealand. IS has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin and Eisai; has served as an investigator for Zogenix, Zynerba, Ultragenyx, GW Pharma, UCB, Eisai, Anavex Life Sciences, Ovid Therapeutics, Epigenyx, Encoded Therapeutics and Marinus; and has consulted for Zynerba Pharmaceuticals, Atheneum Partners, Ovid Therapeutics, Epilepsy Consortium and UCB. SB declares unrestricted educational grants from UCB Pharma, SciGen and Eisai and consultancy fees from Praxis Precision Medicines.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 18 December 2020
doi: 10.3389/fneur.2020.618841

Severity of Peri-ictal Respiratory Dysfunction With Epilepsy Duration and Patient Age at Epilepsy Onset

Kiran Kanth†, *Katherine Park*† *and Masud Seyal**†

Department of Neurology, University of California, Davis, Sacramento, CA, United States

Respiratory dysfunction preceding death is fundamental in sudden unexpected death in epilepsy (SUDEP) pathophysiology. Hypoxia occurs with one-third of seizures. In temporal lobe epilepsy, there is volume loss in brainstem regions involved in autonomic control and increasing neuropathological changes with duration of epilepsy suggesting increasingly impaired regulation of ventilation. In animal models, recurrent hypoxic episodes induce long-term facilitation (LTF) of ventilatory function, however, LTF is less robust in older animals. LTF of ventilation may, to some degree, ameliorate the deleterious effects of progressive brainstem atrophy. We investigated the possibility that the duration of epilepsy, or age at epilepsy onset, may impact the severity of seizure-associated respiratory dysfunction. Patients with focal epilepsy undergoing video-EEG telemetry in the epilepsy monitoring unit (EMU) were studied. We found a significant relationship between age at epilepsy onset and duration of peri-ictal oxygen desaturation for focal seizures not progressing to bilateral tonic-clonic seizures, with longer duration of peri-ictal oxygen desaturation in patients with epilepsy onset at an older age but no significant relationships between duration of epilepsy or age at EMU admission and ventilatory dysfunction. Our findings suggest an intriguing possibility that LTF of ventilation may be protective when epilepsy starts at a younger age.

Keywords: SUDEP, seizure, epilepsy duration, respiration, apnea

OPEN ACCESS

Edited by:
Brian Darryl Moseley,
University of Cincinnati, United States

Reviewed by:
Stephan Schuele,
Northwestern University, United States
Rainer Surges,
University Hospital Bonn, Germany

****Correspondence:***
Masud Seyal
mseyal@ucdavis.edu

†ORCID:
Kiran Kanth
orcid.org/0000-0002-4722-5843
Katherine Park
orcid.org/0000-0002-4115-8061
Masud Seyal
orcid.org/0000-0002-7060-3654

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *18 October 2020*
Accepted: *01 December 2020*
Published: *18 December 2020*

Citation:
Kanth K, Park K and Seyal M (2020) Severity of Peri-ictal Respiratory Dysfunction With Epilepsy Duration and Patient Age at Epilepsy Onset. Front. Neurol. 11:618841. doi: 10.3389/fneur.2020.618841

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is a common cause of epilepsy related mortality (1–5). Respiratory dysfunction preceding death is implicated as fundamental in SUDEP pathophysiology (6). Ictal apnea, hypoxemia and hypercapnia frequently occur in the ictal and postictal period (7, 8). It has not been established whether the duration of epilepsy or age at epilepsy onset might influence the severity of seizure-related apnea or hypoxia. Imaging studies, in patients who subsequently die of SUDEP, show alterations in brain regions essential for cardiorespiratory recovery and respiratory patterning (9) that may negatively influence the severity of peri-ictal respiratory dysfunction. Physiological studies in animals indicate that recurrent hypoxic episodes result in long-term facilitation (LTF) of respiratory function (10, 11). The degree of LTF with recurrent hypoxia is reduced in older animals (10, 11). In patients with epilepsy and recurrent ictal hypoxic episodes, LTF may provide protection by reducing the severity of respiratory dysfunction with uncontrolled seizures.

We investigated ictal-related respiratory dysfunction in patients admitted to the epilepsy monitoring unit (EMU). The aim of this study was to investigate whether the duration of epilepsy, age at epilepsy onset or age on admission to the EMU were associated with the severity of ictal-associated respiratory dysfunction.

MATERIALS AND METHODS

Patients with pharmacoresistant focal epilepsy undergoing scalp electroencephalography (EEG) monitoring in the EMU were studied. Details of video-EEG and respiratory function monitoring in the EMU have been described previously (7). Focal seizures without progression to bilateral tonic-clonic seizures as well as focal seizures that progressed to bilateral tonic-clonic seizures (FBTCS) were analyzed. We considered that there may be a floor/ceiling effect on the depth and duration of peri-ictal oxygen desaturation with FBTCS. Such effects might mask any age-related changes, and therefore, we performed an analysis of focal seizures that did not progress to bilateral tonic-clonic seizures.

Patients in this EMU have synchronized recordings of nasal airflow, abdominal excursions, and digital pulse oximetry during video-EEG telemetry monitoring. Patients were selected for analysis if a usable nasal airflow signal, respiration-related abdominal excursion signal, or digital pulse oximetry, was available during recorded seizures. Apnea was defined as cessation of either the nasal airflow or respiratory abdominal excursion signal for 5 s or longer during a recorded seizure. The end of apnea was defined by the onset of regular respirations and cessation of apneic events of 5 s or longer. Oxygen desaturation nadir and duration of oxygen desaturation <90%, as determined by pulse oximetry, were evaluated. In patients where more than one seizure was recorded, the mean apnea duration, mean oxygen desaturation nadir, and the mean desaturation duration was determined for that individual and those values used for subsequent analysis. Age at epilepsy onset, duration of epilepsy, and age at EMU admission were recorded in years. Seizure duration for all seizures and seizures without progression to bilateral tonic-clonic seizures was recorded. The retrospective study was approved by the University of California, Davis Institutional Review Board. Statistical analysis was performed using Sigmaplot. Linear regression analysis was used to determine whether there was a relationship between age at epilepsy onset, duration of epilepsy, or age at EMU admission and the various measures of peri-ictal respiratory dysfunction. Statistical significance was defined as a $p < 0.05$. For significant associations determined on simple linear regressions analysis, a Pearson Product Moment Correlation was performed. To account for multiple comparisons, a multivariable linear regression analysis was performed for possible predictors of respiratory dysfunction that included associations with significance levels of $p \leq 0.2$ on simple linear regression. A Fisher Exact Test was performed to compare the proportion of temporal and extratemporal seizures in childhood (<21 years) vs. adult onset epilepsy.

TABLE 1 | Clinical characteristics.

Patient gender	37 female 36 male
Seizure frequency at EMU evaluation (seizures/month)	Mean 17.2 Median 7.5 Range 0.33–180
Number of antiseizure medications	Mean 1.9 Median 2 Range 0–3
Focal seizure classification	**Number of patients**
Focal aware seizures	43
Focal unaware seizures	177
Lobar location of epilepsy	**Number of patients**
Temporal	54
Frontal	8
Parietal	1
Occipital	2
Multifocal	2
Undetermined	6
Etiology of epilepsy	**Number of patients**
Mesial Temporal Sclerosis	21
Focal Cortical Dysplasia	3
Neuronal Migration Disorder	2
Neoplasm	7
Traumatic Brain Injury	5
Vascular Malformation	2
Infection	1
Other Structural	4
Unknown	28
Seizure Onset lateralization	**Number of Seizures**
Bilateral	21
Left	196
Right	204
Unknown	75

TABLE 2 | Summary data including all focal and FBTC seizures.

	Mean	Median	Range
Age at epilepsy onset (Years)	14.2	12	0–61
Age at EMU admission (Years)	35.9	34	16–66
Duration of epilepsy at EMU admission (Years)	22.3	18	1–52
Mean desaturation duration (Seconds)	74.6	62	7–347
Mean oxygen desaturation nadir (%)	84.8	87	58–99
Mean apnea duration (Seconds)	50.4	40	10–180
Mean seizure duration (focal seizures only) (Seconds)	89.6	72	7.4–360
Mean seizure duration (all seizures) (Seconds)	97.7	80	8.1–376

RESULTS

Data from 73 patients (37 female) were analyzed. Relevant clinical information is shown in **Table 1**. Data on patient age, age at epilepsy onset, and epilepsy duration and relevant analyses of peri-ictal respiratory dysfunction are shown in **Table 2**.

There was a significant relationship ($p = 0.012$) between age at epilepsy onset and duration of peri-ictal oxygen desaturation for focal seizures that did not progress to bilateral tonic-clonic seizures (BTCS) (**Figure 1**) with greater duration of peri-ictal oxygen desaturation in patients with older age at epilepsy onset (Simple regression analysis: Mean O_2 desaturation duration (seconds) = 28.91 + (1.632 * Age (years) at epilepsy onset). Pearson correlation coefficient 0.399, $p = 0.012$. On multiple linear regression analysis for age at epilepsy onset, duration of epilepsy and age at EMU admission, only the age at epilepsy onset was significantly associated with oxygen desaturation duration ($p = 0.045$).

Seizure duration, for all seizures or focal only seizures, was not associated ($p > 0.1$) with duration of epilepsy, age on EMU admission or age at epilepsy onset. There were no significant relationships ($p = >0.1$) between duration of epilepsy or age at EMU admission and the various measures of peri-ictal dysfunction (oxygen desaturation nadir, duration of desaturation below 90% and apnea duration for focal seizures with or without progression to BTCS. Oxygen desaturation nadir was significantly associated with the duration of oxygen desaturation ($p < 0.001$). Reported seizure frequency at EMU admission was not associated with the duration of postictal oxygen desaturation. There was no significant difference ($p = 0.095$) in the proportion of temporal vs. extratemporal seizures comparing childhood onset epilepsy (<21 years) vs. patients where seizures started in adulthood (≥21 years).

Oxygen desaturation nadir data were available for 71 patients, apnea duration data were available for 30 patients, and data for duration of oxygen desaturation below 90% were available for 57 patients.

DISCUSSION

We have shown that there is a significant relationship between the age at epilepsy onset and the duration of peri-ictal oxygen desaturation. An older age at epilepsy onset is related to a more prolonged period of seizure-related oxygen desaturation. Our data suggest that the age of the patient at epilepsy onset is unrelated to the initial severity of peri-ictal oxygen desaturation as indicated by the oxygen desaturation nadir. There is, however, significantly delayed recovery of respiratory function in patients with older age at epilepsy onset. The duration of epilepsy was not related to the severity of respiratory dysfunction.

Our findings cannot be accounted for by the possibility that seizure durations are longer when seizures start at an older age. We had previously shown that the duration of individual seizures was directly associated with the degree and duration of peri-ictal oxygen desaturation (7, 8). In the present study we find that seizure duration is not related to the age at epilepsy onset or duration of epilepsy. These findings make it unlikely that the longer duration of postictal respiratory dysfunction, at an older age of epilepsy, onset is a consequence of longer seizure duration.

MRI studies in patients with temporal lobe epilepsy demonstrate volume loss in the brainstem regions considered important in autonomic control (12, 13). These alterations are more pronounced in patients dying of SUDEP (12, 13). It has been hypothesized that recurrent seizure-related hypoxic events

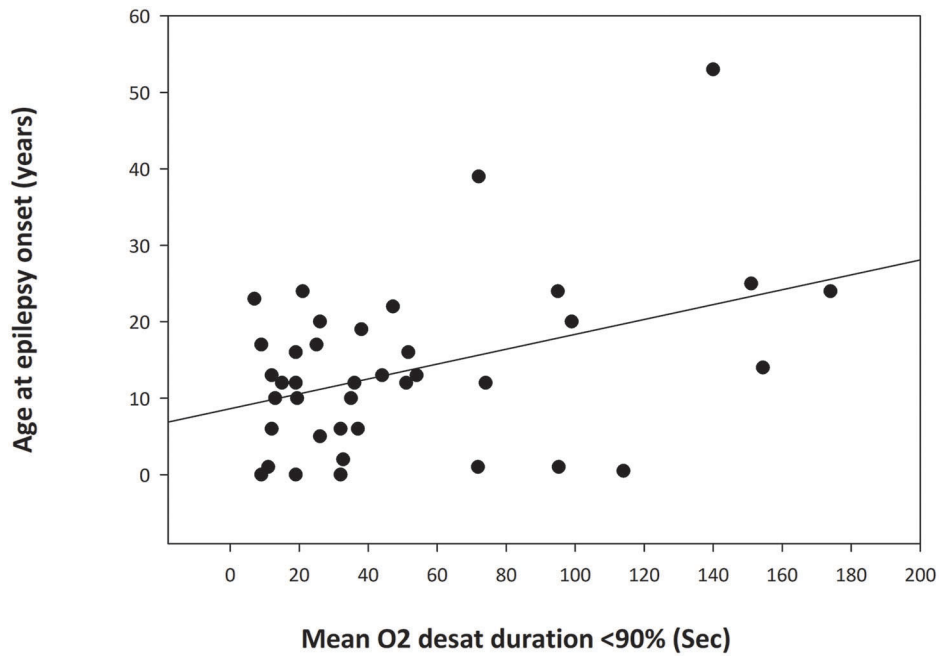


FIGURE 1 | Simple Linear Regression analysis graph demonstrating relationship between the age at epilepsy onset and duration of oxygen desaturation of <90% in focal seizures without secondary generalization ($p = 0.012$). The abscissa indicates the mean duration of postictal oxygen desaturation below 90% in seconds. The ordinate is the patient age at onset of epilepsy in years. The filled circles are data points for each patient. The solid line through the data points is the regression line.

may cause increasing damage to these brainstem regions (12, 13). Immunohistochemical studies of the ventrolateral medulla demonstrate reductions in neuromodulatory neuropeptides and monoaminergic systems in patients dying of SUDEP relative to control (14), and there was an association of neuropathological alterations with duration of seizures (14). As such, one may expect to find increasing seizure-related respiratory dysfunction with longer duration of uncontrolled epilepsy, however, this was not observed in the present study.

Hypoxic episodes with oxygen desaturation to <90% occur in about one-third of focal onset seizures (7). There is convincing evidence for persistent long-term facilitation (LTF) of respiratory activity following recurrent hypoxic episodes (10, 15–19). It is conceivable that LTF of respiratory function with uncontrolled seizures and hypoxic events may, to some degree, counteract the potentially deleterious effects of seizure-related brainstem atrophy and reductions in neuromodulatory neuropeptides considered important in respiratory control. These brainstem LTF changes may account for the fact that no significant peri-ictal respiratory disturbance with duration of epilepsy was detected in our group of patients. In animal models, exposure to intermittent hypoxia results in augmentation of respiratory activity that can persist for, at least, many hours after hypoxic episodes are ended (10). LTF has been demonstrated for phrenic nerve activity in rodents under anesthesia and LTF of ventilation occurs in awake animals (15, 16). LTF can be induced by hypoxic episode durations similar to those that occur in obstructive sleep apnea (17, 18). LTF appears dependent on changes in mitochondrial ultrastructure and increased cytochrome oxidase activity in the pre-Bötzinger nucleus, a structure in the ventrolateral medulla essential for the generation of respiratory rhythms (19). The mitochondrial alterations suggest that the effects of hypoxia are robust and persistent.

In the absence of recurrent hypoxic events, however, any post-ictal LTF of respiratory function would be expected to diminish with time following a seizure-related hypoxic event with an unknown decay rate. LTF, if present, may have a greater effect on respiratory function in patients with frequent seizures than in those with rare events.

Limitations of this retrospective study include the lack of a reliable estimate of seizure frequency since epilepsy onset and, perhaps more importantly, the frequency of seizure-related hypoxic events prior to EMU admission. These are potentially important factors that could, by cumulative damage to respiratory networks, progressively influence the severity of respiratory dysfunction over extended periods of time. Investigation of these issues in future prospective studies is warranted.

Of particular interest to the findings of our study is the observation that, in animal models, old age results in loss of LTF, whereas younger age is associated with greater LTF (11). Recent population-based cohort studies indicate that SUDEP incidence is similar in all age groups including patients < 16 years old and those older than 50 years (4). The weighting of factors contributing to BTCS and SUDEP may vary across the age spectrum. More profound respiratory dysfunction in the peri-ictal period contributing to SUDEP may be of greater concern when epilepsy starts at an older age. However, while intriguing, the relevance of our findings with regards to SUDEP pathophysiology remains speculative.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of California, Davis. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KK jointly conceived the study, contributed to design of study, writing of manuscript, and manuscript revisions. KP contributed to writing of manuscript and manuscript revisions. MS conceived the study, wrote the initial draft, performed data analysis, and contributed to manuscript revisions. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Department of Neurology, University of California, Davis.

REFERENCES

1. Einarsdottir AB, Sveinsson O, Olafsson E. Sudden unexpected death in epilepsy. A nationwide population-based study. *Epilepsia.* (2019) 60:2174–81. doi: 10.1111/epi.16349
2. Keller AE, Whitney R, Li SA, Pollanen MS, Donner EJ. Incidence of sudden unexpected death in epilepsy in children is similar to adults. *Neurology.* (2018) 91:e107–11. doi: 10.1212/WNL.0000000000005762
3. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology and the American epilepsy society. *Neurology.* (2017) 88:1674–80. doi: 10.1212/WNL.0000000000003685
4. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: a nationwide population-based cohort study. *Neurology.* (2017) 89:170–7. doi: 10.1212/WNL.0000000000004094
5. Thurman DJ, Logroscino G, Beghi E, Hauser WA, Hesdorffer DC, Newton CR, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the mortality task force of the international league against epilepsy. *Epilepsia.* (2017) 58:17–26. doi: 10.1111/epi.13604
6. 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) 12:966–77. doi: 10.1016/S1474-4422(13)70214-X
7. Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain.* (2008) 131(Pt. 12):3239–45. doi: 10.1093/brain/awn277
8. Seyal M, Bateman LM, Albertson TE, Lin TC, Li CS. Respiratory changes with seizures in localization-related epilepsy: analysis of periictal hypercapnia and airflow patterns. *Epilepsia.* (2010) 51:1359–64. doi: 10.1111/j.1528-1167.2009.02518.x
9. Allen LA, Vos SB, Kumar R, Ogren JA, Harper RK, Winston GP, et al. Cerebellar, limbic, and midbrain volume alterations in sudden unexpected death in epilepsy. *Epilepsia.* (2019) 60:718–29. doi: 10.1111/epi.14689
10. McGuire M, Zhang Y, White DP, Ling L. Phrenic long-term facilitation requires NMDA receptors in the phrenic motonucleus in rats. *J Physiol.* (2005) 567(Pt. 2):599–611. doi: 10.1113/jphysiol.2005.087650
11. Zabka AG, Behan M, Mitchell GS. Long term facilitation of respiratory motor output decreases with age in male rats. *J Physiol.* (2001) 531(Pt. 2):509–14. doi: 10.1111/j.1469-7793.2001.0509i.x
12. Mueller SG, Bateman LM, Laxer KD. Evidence for brainstem network disruption in temporal lobe epilepsy and sudden unexplained death in epilepsy. *Neuroimage Clin.* (2014) 5:208–16. doi: 10.1016/j.nicl.2014.06.010
13. Mueller SG, Nei M, Bateman LM, Knowlton R, Laxer KD, Friedman D, et al. Brainstem network disruption: a pathway to sudden unexplained death in epilepsy? *Hum Brain Mapp.* (2018) 39:4820–30. doi: 10.1002/hbm.24325
14. Patodia S, Somani A, O'Hare M, Venkateswaran R, Liu J, Michalak Z, et al. The ventrolateral medulla and medullary raphe in sudden unexpected death in epilepsy. *Brain.* (2018) 141:1719–33. doi: 10.1093/brain/awy078
15. Cao KY, Zwillich CW, Berthon-Jones M, Sullivan CE. Increased normoxic ventilation induced by repetitive hypoxia in conscious dogs. *J Appl Physiol.* (1992) 73:2083–8. doi: 10.1152/jappl.1992.73.5.2083
16. Turner DL, Mitchell GS. Long-term facilitation of ventilation following repeated hypoxic episodes in awake goats. *J Physiol.* (1997) 499(Pt. 2):543–50. doi: 10.1113/jphysiol.1997.sp021947
17. Peng YJ, Overholt JL, Kline D, Kumar GK, Prabhakar NR. Induction of sensory long-term facilitation in the carotid body by intermittent hypoxia: implications for recurrent apneas. *Proc Natl Acad Sci USA.* (2003) 100:10073–8. doi: 10.1073/pnas.1734109100
18. Peng YJ, Prabhakar NR. Reactive oxygen species in the plasticity of respiratory behavior elicited by chronic intermittent hypoxia. *J Appl Physiol.* (2003) 94:2342–9. doi: 10.1152/japplphysiol.00613.2002
19. Kang JJ, Guo B, Liang WH, Lam CS, Wu SX, Huang XF, et al. Daily acute intermittent hypoxia induced dynamic changes in dendritic mitochondrial ultrastructure and cytochrome oxidase activity in the pre-Botzinger complex of rats. *Exp Neurol.* (2019) 313:124–34. doi: 10.1016/j.expneurol.2018.12.008

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 21 January 2021
doi: 10.3389/fneur.2020.623139

Alcohol-Specific Mortality in People With Epilepsy: Cohort Studies in Two Independent Population-Based Datasets

Hayley C. Gorton[1], Roger T. Webb[2,3], Rosa Parisi[4], Matthew J. Carr[2,5], Marcos DelPozo-Banos[6], Kieran J. Moriarty[7], W. Owen Pickrell[8,9], Ann John[6] and Darren M. Ashcroft[2,5]*

[1] School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom, [2] NIHR Greater Manchester Patient Safety Translational Research Centre, Manchester Academic Health Sciences Centre (MAHSC), University of Manchester, Manchester, United Kingdom, [3] Division of Psychology & Mental Health, Centre for Mental Health and Safety, Manchester Academic Health Sciences Centre (MAHSC), Faculty of Biology, Medicine and Health, School of Health Sciences, University of Manchester, Manchester, United Kingdom, [4] Division of Informatics, Imaging & Data Sciences, Manchester Academic Health Sciences Centre (MAHSC), Faculty of Biology, Medicine and Health, School of Health Sciences, University of Manchester, Manchester, United Kingdom, [5] Centre for Pharmacoepidemiology and Drug Safety, Manchester Academic Health Sciences Centre (MAHSC), Faculty of Biology, Medicine and Health, School of Health Sciences, University of Manchester, Manchester, United Kingdom, [6] Farr Institute, Swansea University Medical School, Swansea, United Kingdom, [7] Bolton NHS Foundation Trust, Bolton, United Kingdom, [8] Neurology and Molecular Neuroscience Research Group, Swansea University Medical School, Swansea University, Swansea, United Kingdom, [9] Neurology Department, Morriston Hospital, Swansea Bay University Health Board, Swansea, United Kingdom

OPEN ACCESS

Edited by:
Rohit Shankar, Cornwall Partnership NHS Foundation Trust, United Kingdom

Reviewed by:
Brendan Mclean, Royal Cornwall Hospital Trust, United Kingdom
Adrian Pace, University of Malta, Malta

***Correspondence:**
Hayley C. Gorton
H.C.Gorton@hud.ac.uk

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *29 October 2020*
Accepted: *14 December 2020*
Published: *21 January 2021*

Citation:
Gorton HC, Webb RT, Parisi R, Carr MJ, DelPozo-Banos M, Moriarty KJ, Pickrell WO, John A and Ashcroft DM (2021) Alcohol-Specific Mortality in People With Epilepsy: Cohort Studies in Two Independent Population-Based Datasets. Front. Neurol. 11:623139. doi: 10.3389/fneur.2020.623139

Objectives: The risk of dying by alcohol-specific causes in people with epilepsy has seldom been reported from population-based studies. We aimed to estimate the relative risk of alcohol-specific mortality in people with epilepsy, and the extent to which problematic alcohol use was previously identified in the patients' medical records.

Method: We delineated cohort studies in two population-based datasets, the Clinical Practice Research Datalink (CPRD GOLD) in England (January 01, 2001–December 31, 2014) and the Secure Anonymised Information Linkage (SAIL) Databank in Wales (January 01, 2001–December 31, 2014), linked to hospitalization and mortality records. People with epilepsy were matched to up to 20 persons without epilepsy on gender, age (±2 years) and registered general practice. We identified alcohol-specific death from Office for National Statistics (ONS) records using specified ICD-10 codes. We further identified prescriptions, interventions and hospitalisations related to alcohol use.

Results: In the CPRD GOLD, we identified 9,871 individuals in the incident epilepsy cohort and 185,800 in the comparison cohort and, in the SAIL Databank, these numbers were 5,569 and 110,021, respectively. We identified a five-fold increased risk of alcohol-specific mortality in people with epilepsy vs. those without the condition in our pooled estimate across the two datasets (deprivation-adjusted HR 4.85, 95%CI 3.46–6.79).

Conclusions: People with epilepsy are at increased risk of dying by an alcohol-specific cause than those without the disorder. It is plausible that serious alcohol misuse could either contribute to the development of epilepsy or it could commence subsequent to epilepsy being diagnosed. Regardless of the direction of the association, it is important

that the risk of dying as a consequence of alcohol misuse is accurately quantified in people affected by epilepsy. Systematically-applied, sensitive assessment of alcohol consumption by healthcare professionals, at opportunistic, clinical contacts, with rapid access to quality treatment services, should be mandatory and play a key role in reduction of health harms and mortality.

Keywords: epilepsy, alcohol, alcohol-specific, cohort, observational

INTRODUCTION

People with epilepsy are known to die prematurely compared to the rest of the general population (1, 2). However, the need for improved identification of specific causes of death, and associated risks of these deaths in people with epilepsy has been recognized. Devinsky et al. suggest that the contribution of alcohol to death in people with epilepsy may be underestimated (2). Recently, we reported that people with epilepsy were three-times more likely to die from unnatural causes than those without (3). Whilst we did not study alcohol-specific mortality, we noted the greater frequency of alcohol misuse in people with epilepsy (6.0%) vs. the comparison cohort (1.4%). This warranted further investigation.

Death due to alcohol-dependence syndrome in people with epilepsy was associated with a standardized mortality rate of 3.9 (95% CI 1.8–7.4) in a prevalent epilepsy cohort identified from attendees at an Austrian epilepsy hospital clinic (4). In 2016, of the 137,000 epilepsy deaths and 14.7 million epilepsy Disability-adjusted life years (DALYs) in the United Kingdom, an estimated 17,000 epilepsy deaths and 1.5 million epilepsy DALYs were attributed to alcohol, representing 12.7% of all deaths and 10.2% of all DALYs due to epilepsy (5). Alcohol-related death is a wide definition that may include end-organ disease attributed to alcohol (6). To our knowledge, the only published study that specifically examines alcohol-related death in people with epilepsy is a Finnish register-based cohort in which people with epilepsy were compared to a population-based reference cohort. A three-fold elevation in risk of death due to alcohol-related diseases and accidental poisoning by alcohol was observed (HR 3.38, 95%CI 2.76–4.16) (7). These deaths were identified by certain codes from the *International Classification of Diseases and Related Health Problems, ninth and tenth editions (ICD-9, ICD-10).* The specific ICD-10 codes used have some parallels with, but are not identical to those which the Office for National Statistics (ONS) in the UK identified as alcohol-related deaths in the UK until 2016 in official death statistics (6). In 2017, the ONS replaced the definition for alcohol-related death with one for alcohol-specific death, in response to an expert consultation. To our knowledge, this is the first study to utilize this new categorization to examine the risk of alcohol-specific death in people with epilepsy.

The aims of this study were therefore to (i) estimate the incidence and relative risk of alcohol-specific death in people with epilepsy vs. persons without the condition; and (ii) estimate the extent of alcohol-related consultation, treatment or referral in relation to epilepsy status and alcohol-related death.

MATERIALS AND METHODS

Data Source

We examined the Clinical Practice Research Datalink (CPRD GOLD), an electronic healthcare dataset which comprises general practice data from 7% of the UK population (8). It includes demographic, diagnostic, prescription, referral and test data from individuals in registered practices; and is considered to be broadly representative of the UK population as a whole in terms of its age, gender and ethnicity distributions. We defined our study populations from a subset of practices that were linked to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) data; all of which were in England and represented ∼58% of all practices in the CPRD. The HES provides hospital discharge dates and diagnoses whilst ONS provides date and causes of death (8). We extracted the incident epilepsy and matched cohorts from the July 2015 release of the CPRD which included 7,378,852 patients from 387 practices in England with routine data linkage implemented. We also estimated the incidence rates and relative risks of alcohol-specific death in the Secure Anonymised Information Linkage (SAIL) Databank, which enabled meta-analysis of relative risk estimates across two independent datasets. The SAIL Databank is comprised of 13 health and social care datasets. These include the general practice dataset (GPD) which contains similar data to the CPRD and includes 76% of all general practices in Wales (practice $n = 360$, patients $n = 4{,}052{,}388$) (9). ONS death data is detailed within the Annual District Death Extract (ADDE) and hospital discharge dates and diagnoses are included in the Patient Episode Database for Wales (PEDW) (10). As the CPRD cohort only included practices in England, there was no overlap with those individuals in the SAIL Databank. Approvals to conduct these studies in the CPRD and the SAIL Databank were granted by the Independent Scientific Advisory Committee (ISAC) of the Medicine and Healthcare Regulatory Agency (MHRA) (protocol 15_046RA2R) and the Information Governance Review Panel (approval 0728), respectively.

Delineation of the Matched-Cohort

Epilepsy diagnoses were identified from the general practice data in the CPRD and the SAIL Databank using Read codes, version 2 (11). Separately in each dataset, we identified people as having incident epilepsy if they had the first evidence of a code for epilepsy diagnosis and an associated prescription for an antiepileptic drug (AED) in the month before or 6 months after the diagnosis. The requirement for both an epilepsy diagnosis and AED treatment is suggested to increase the reliability of

TABLE 1 | Reproduced from Office for National Statistics.

ICD-10 Code	Condition
E24.4	Alcohol-induced pseudo-Cushing's syndrome
F10	Mental and behavioral disorders due to use of alcohol
G31.2	Degeneration of nervous system due to alcohol
G62.1	Alcoholic polyneuropathy
G72.1	Alcoholic myopath
I42.6	Alcoholic cardiomyopathy
K29.2	Alcoholic gastritis
K70	Alcoholic liver disease
K85.2	Alcohol-induced acute pancreatitis
K86.0	Alcohol induced chronic pancreatitis
Q86.0	Fetal alcohol syndrome (dysmorphic)
R78.0	Excess alcohol blood levels
X45	Accidental poisoning by and exposure to alcohol
X65	Intentional self-poisoning by and exposure to alcohol
Y15	Poisoning by and exposure to alcohol, undetermined intent

Alcohol-specific deaths in the UK: registered in 2016. Newport: Office for National Statistics; 2016.

the ascertainment of epilepsy in observational studies, by the International League Against Epilepsy (ILAE) (12) and is a definition we have previously applied in epidemiological studies of epilepsy (13). The use of primary care records in the SAIL Databank to identify people with epilepsy has been validated (14). The codes used to identify epilepsy diagnoses and AEDs, and an explanation of the verification process, are available on www.clinicalcodes.org (15). A minimum age of 18 years on study entry was imposed to align with the minimum legal age of alcohol purchase in the UK. Individuals were also required to have at least 1 year of prior registration in the practice, during which time they could not have had a diagnosis of epilepsy. This increased our confidence that we had delineated an incident epilepsy cohort. We defined the study period as January 1, 2001–March 31, 2014 in the CPRD and January 1, 2001–December 31, 2014 in the SAIL Databank, to correspond with linkage availability.

We matched each individual with epilepsy to up to 20 individuals without an epilepsy diagnosis on year of birth (±2 years), gender and general practice. Individuals were eligible for inclusion in the comparison cohort if they had at least 1 year of prior registration in the general practice and were alive on the index epilepsy date of the matched individual with epilepsy, and follow-up began on this date. Individuals were followed until the earliest date of: death, patient left practice, end of data collection in the practice, or the final observation date for the study cohort.

Identification of Alcohol-Specific Mortality

We used the ONS definition of alcohol-specific mortality, which was introduced in 2017 to replace the previous definition of alcohol-related mortality, following a UK government consultation with leading experts in the field (6). It includes underlying cause of death codes assigned from the ICD-10 (**Table 1**).

Statistical Analysis

We used descriptive statistics to report baseline characteristics of age, gender and area-level deprivation. We estimated alcohol-specific mortality rate per 10,000 person-years and the risk of alcohol-specific mortality as a hazard ratio (HR), using stratified Cox-proportional hazards models to account for the matched cohort design. We report estimates separately based on the CPRD and the SAIL Databank data, and meta-analyzed estimates using the DerSimonian-Laird Random Effects model (16). To better understand whether alcohol consumption had been acknowledged in primary or secondary care records prior to death in those who died by alcohol-specific causes, we estimated the proportion of individuals who were: (i) coded as a heavy drinker; (ii) received a prescription for acamprosate, disulfiram, nalmefene or naltrexone for alcohol dependence; (iii) referred for psychological support for alcohol use and (iv) hospital admission for alcohol-related causes; in relation to their epilepsy status. We used codes and algorithms that were previously published to define these variables (17), and they are available on www.clinicalcodes.org.uk (15). Alcohol consumption was defined in relation to the national guidance on intake, which was in place during the study's observation period (18).

RESULTS

Baseline Characteristics

We matched 9,871 people with incident epilepsy with 185,800 individuals in the comparison cohort in the CPRD (**Table 2**). The median age on entry was 57 (IQR 39–73) in the epilepsy cohort and 58 (IQR 40–74) in the comparison cohort and 51% of both cohorts were male. The epilepsy cohort was followed-up for a median of 3.2 years (1.2–6.6) whilst the comparison cohort was followed-up for a median of 4.3 years (1.9–7.7). 9.7% of people in the epilepsy cohort and 6.4% in the comparison cohort were categorized as being a "heavy drinker." Death due to any cause was a more common reason for end of follow-up in the epilepsy cohort (23.1%) than in the comparison cohort (11%). The distribution of covariates was similar in the analysis conducted in the SAIL Databank, which included 5,569 people with incident epilepsy and 110,021 people in the comparison cohort (**Table 2**).

Risk of Alcohol-Specific Mortality in People With Epilepsy

There were 29 alcohol-specific deaths in the incident epilepsy cohort and 106 in the comparison cohort in the CPRD, and the corresponding numbers were 18 and 96 in the SAIL Databank, respectively. The deprivation-adjusted hazard ratios for alcohol-specific mortality in people with epilepsy vs. those without were 5.47 (95%CI 3.52–8.48) in the CPRD and 4.08 (95%CI 2.42–6.90) in the SAIL Databank, and the pooled estimate was 4.85 (95%CI 3.46–6.79) (**Table 3**).

TABLE 2 | Baseline characteristics of epilepsy and comparison cohorts in the CPRD and SAIL databank.

Baseline characteristic	CPRD		SAIL	
	Epilepsy cohort (n = 9,871)	Comparison cohort (n = 185,800)	Epilepsy cohort (n = 5,569)	Comparison cohort (n = 110,021)
Male	5,062 (51·3%)	95,647 (51.5%)	2,874 (51.6%)	56,729 (51.6%)
Median age on entry (IQR)	57 (39–73)	58 (40–74)	54 (37–70)	54 (37–70)
Level of deprivation[a]				
1 (least deprived)	1,908 (19.3%)	40,105 (21.5%)	905 (16.3%)	21,022 (19.1%)
2	2,190 (22.2%)	43,077 (23.2%)	928 (16.7%)	20,186 (18.4%)
3	1,870 (18.9%)	37,066 (20.0%)	1,248 (22.4%)	24,158 (22.0%)
4	1,959 (19.9%)	35,257 (19.0%)	1,204 (21.6%)	22,714 (20.7%)
5 (most deprived)	1,937 (19.6%)	30,111 (16.2%)	1,280 (23.0%)	21,776 (19.8%)
missing	7 (0.1%)	184 (0.1%)	<5 (0.1%)	165 (0.2%)
Follow up				
Median follow-up time (years)	3.2 (1.2–6.6)	4.3 (1.9–7.7)	4.7 (IQR 1.8–8.6)	5.9 (IQR 2.6–9.7)
Alcohol consumption[b,c]				
Non-drinker	1,774 (18.0%)	26,360 (14.2%)		
Former drinker	315 (3.2%)	2,772 (1.5%)		
Occasional drinker	1,248 (12.6%)	24,087 (13.0%)		
Moderate drinker	3,359 (34.0%)	74,782 (40.3%)		
Heavy drinker	958 (9.7%)	11,881 (6.4%)		
Missing	2,217 (22.5%)	45,968 (24.6%)		

Data on alcohol consumption could only be calculated in the CPRD. [a]Based-on quintiles of multiple deprivation where 1 is the most deprived and 5 is the least deprived. [b]Alcohol consumption status estimated at index date based on algorithm by Parisi et al. (17). [c]P < 0.001. The black shaded portion represents that the descriptive analysis was not conducted in the SAIL Databank.

TABLE 3 | Incidence and relative-risk of Alcohol-specific death in people with incident epilepsy vs. comparison cohort.

Alcohol-related death	Number	Rate/10,000PY (95%CI)	Number	Rate/10,000 PY (95%CI)	HR (95% CI)	Deprivation-adjusted HR (95%CI)
CPRD	Epilepsy cohort (n = 9,871; PY = 41,253)		Comparison cohort (n = 185,800; PY = 916,572)			
	29	7.0 (4.7–10.1)	106	1.2 (0.9–1.4)	6.09 (3.96–9.37)	5.47 (3.52–8.48)
SAIL	Epilepsy cohort (n = 5,569; PY = 30,011)		Comparison cohort (n = 110,021; PY = 685,575)			
	18	6.0 (3.6–9.5)	96	1.4 (1.1–1.7)	4.40 (2.62–7.37)	4.08 (2.42–6.90)
	Meta-analyzed hazard ratios				5.33 (3.83–7.42)	4.85 (3.46–6.79)

Alcohol Consumption and Alcohol-Related Diagnoses, Treatment, Psychological Support and Hospitalization

Amongst those in the CPRD who died due to alcohol specific causes, compared to the matched cohort, a greater proportion of people with epilepsy had medication prescribed for alcohol dependence (24.1 vs. 9.3%; $p = 0.03$). There were proportionally more people in the epilepsy cohort than the comparison cohort who were referred for psychological support for alcohol use, but this was not statistically significant (20.7 vs. 11.3%; $P = 0.19$). There was no statistically significant difference between coding as a "heavy drinker" at any time prior to death in the epilepsy and comparison cohorts in the CPRD (79.3 vs. 67.0%; $p = 0.2$). A similar proportion of each group had ever been hospitalized for reasons related to alcohol use (84.9 vs. 86.2%). A greater proportion of the epilepsy cohort than the comparison cohort had a history of alcohol misuse, as determined by any of these indicators, prior to index date (i.e., prior to epilepsy diagnosis), but this difference was not statistically significant (79.3 vs. 72.6%; $p = 0.47$).

DISCUSSION

Elevated Risk of Alcohol-Specific Death

We have shown across two, large population-based cohort studies that people with epilepsy are approximately five times more likely to die from alcohol-specific causes than persons without the condition (deprivation-adjusted meta-analyzed HR: 4.85,

95%CI 3.46–6.79). Of those people who died from alcohol-specific causes, the majority had a hospital admission that was attributed to alcoholism (epilepsy cohort: 86.2%; comparison cohort: 84.9%). Many were coded as being a heavy drinker in primary care records, but fewer were prescribed medication for alcohol or received psychological support. Still, alcohol misuse had not been coded in primary care records prior to death in 20 to 28% of people. For those individuals whose alcohol misuse has been identified in primary care or due to previous hospitalization, thought should be given as to how to maximize these contact opportunities to try to prevent the sequel of events that culminate in hospitalization and premature death.

Our estimate of relative risk of dying by an alcohol-specific cause in people with epilepsy is of a greater magnitude than that predicted by Nevalainen et al. (HR 4.85, 95%CI 3.46–6.79 compared to 3.44, 95%CI 3.11–3.71) from Finnish mortality records. That study's somewhat lower estimate could be a reflection in differences in habits in population drinking habits or access to healthcare in Finland, England and Wales. Estimates of per capita alcohol consumption in 2016 were higher in the UK (11.4 L/capita) than Finland (10.7 L/capita) (19). It may also be a function of study design. We used a more recent time period than the 2008 study-end in the Finnish study. We both used ICD-10 codes to define the outcome, but the Finnish study reported alcohol-related deaths whereas we report alcohol-specific deaths. In some aspects we were broader; for example inclusion of intentional poisoning with alcohol, whereas the Finnish investigators included only accidental poisoning (7). In other aspects, the previous study employed broader codes, for example, "Special epilepsy syndromes" of which alcohol is one potential cause. In a systematic review of systematic reviews, alcohol involvement was identified as a high risk cause of alcohol-related mortality (20).

Other studies have reported the proportion or likelihood of alcohol involvement in death among persons with epilepsy. The National Drug-Related Deaths Index of Ireland is a surveillance system that records all causes of death in people who are dependent on alcohol or drugs, or die due to poisoning (21). Two percent of individuals in this register were known to have epilepsy and 81% of these had a history of alcohol dependence prior to death. In a nested case-control study conducted in the General Practice Research Database (the predecessor to the CPRD), Risdale et al. (22) identified that amongst people with epilepsy, those who died during follow-up were more likely to have a record of alcohol misuse (OR 2.96, 95%CI 2.25–3.89) than those who did not die. Our study design does not permit us to compare to these estimates. It does, however highlight that alcohol misuse have been identified as a major contributor to premature death in people with epilepsy. We have not found any literature that maps primary care recording of alcohol misuse prior to alcohol-specific death in people with epilepsy.

In the UK General Practice Survey, there was a three-fold increased risk of death (HR 2.9, 95%CI 1.5–5.7) if alcohol was a cause of epilepsy compared to if it was not (23). In a meta-analysis of studies, a relative risk of 2.19 (95%CI 1.83–2.63) was estimated for epilepsy or unprovoked seizures in relation to alcohol consumption, and a dose-dependent relationship was evident (24). Consuming 12, 48, 72, and 96 g/day of alcohol was associated with relative risk increases, vs. non-drinkers, of 1.2 (95%CI; 1.1–1.2), 1.8 (95% CI 1.6–2.1), 2.4 (2.0, 3.0) and 3.3 (95%CI 2.5–4.3), respectively (25). One confounder in studies has been the difficulty in distinguishing between alcohol-withdrawal and non-withdrawal seizures.

A two-fold increased risk in Sudden Unexpected Death in Epilepsy (SUDEP) has been associated with alcohol dependence (26). This is not recorded in the datasets we used. Our findings must be interpreted with the important caveat that pre-existing alcohol dependence may have caused seizures or epilepsy in some cases. Alcohol has been suggested to be responsible for 1/20–1/5 of Disability-adjusted Life Years in people with epilepsy (27). The great majority of individuals in the epilepsy cohort (∼80%) had codes for non-specific epilepsy. It was therefore not possible to determine whether seizures were classified as alcohol-induced. Our use of the incident epilepsy cohort somewhat overcomes this limitation by allowing us to identify the first epilepsy diagnosis and therefore understand whether any history of alcohol misuse or dependence was identified before or after this diagnosis. However, it is possible that alcohol dependence occurs some time before diagnosis, treatment or psychological intervention was recorded in the general practice data.

Strengths and Limitations

To our knowledge, this is the first study to estimate the relative risk of death specific to alcohol misuse in those with epilepsy across two large population-based databases and to pool the estimates to optimize statistical precision. We have applied the most up-to-date definition of alcohol-specific death that is now being used in routine mortality registration in England & Wales (6). This will enable any recommendations that we make to be implemented and measured against this standard definition in future years. We report for the first time estimates for primary care identification of alcohol misuse or dependence prior to alcohol-specific death in a matched epilepsy and comparison cohort.

We could not stratify by type of epilepsy or seizure frequency due to limitations in recording, nor could we report relative risk for each individual alcohol-specific cause. This is due to the low numbers of death at this more granular analytical level, which could not be reported without compromising anonymity, and that would produce imprecise relative risk estimates. The availability of self-reported alcohol consumption data in the CPRD is likely to be incomplete, and may not be entirely accurate, influenced by the individual's willingness to accurately report alcohol use and opportunity to record this information, such as during primary care consultations. Given that alcohol misuse and dependence can induce seizures, whether the primary cause of epilepsy or not, it might be expected that people with epilepsy would have their alcohol status recorded more so than those people in our comparison cohort. This could artificially widen the gap in reporting. There should be no differential misclassification between the groups for prescription or psychological referral recording.

Implications for Clinicians

Regardless of the direction of the association between epilepsy and alcohol misuse, clinicians should be mindful of the large elevation in risk of alcohol-specific death among people with epilepsy. Any progress toward stopping drinking alcohol can have a beneficial effect on survival of people with alcohol-related cirrhosis (28). Given the magnitude of the risk elevation observed, it is important that clinicians who are treating people with epilepsy are aware of alcohol misuse. This might enable targeted intervention and person-centered holistic care, both of which have been recommended to enhance the care for people with alcohol-related diseases (29). Indeed, exploration of alcohol use in people with epilepsy is recommended through use of the "SUDEP and seizure safety" checklist in the UK (30). Additional, candid discussions about level of alcohol use at the point of epilepsy diagnosis and at regular reviews could be warranted. It should be noted that, in the same study cohort, the incidence of alcohol-specific death is lower than we previously observed for other potentially preventable causes of mortality, such as accident and suicide (3). However, the considerable morbidity related to alcohol-induced seizures in epilepsy, whether this was the initial cause or not, supports the need to discuss the impact of alcohol misuse among epilepsy. Indeed, the observed difference in rate might reflect the immediacy that may be related to accident or suicide, whereas many of the alcohol-specific causes are a culmination over time.

The historical, global stigmatization of people with epilepsy (31) or alcohol problems, of particular concern when the two co-exist, can lead to denied or delayed acceptance, presentation, detection, treatment and health risks, including death, from the two conditions. The commonality of concurrent mental illness in people with epilepsy and the independent increased risk of accident (32), suicide (33), and alcohol use related to mental illness should not be ignored. Upstream identification, treatment and management of mental illness in people with epilepsy has the potential to mitigate preventable causes of death, a priority described in the 2016 Call to Action on this issue (2).

CONCLUSION

We have observed a five-fold elevated risk of alcohol-specific deaths in people with epilepsy compared to those without. Many but not all of those who died had a hospitalization or primary care event signifying excessive alcohol use. Hence, in people with epilepsy, systematically-applied, sensitive assessment of alcohol consumption (34) by healthcare professionals, at opportunistic, clinical contacts, with rapid access to quality treatment services, should be mandatory and play a key role in reduction of health harms and mortality.

DATA AVAILABILITY STATEMENT

The data analyzed in this study are subject to the following licenses/restrictions: The clinical codes used in this study are published on Clinicalcodes.org. Electronic health records are, by definition, considered "sensitive" data in the UK by the Data Protection Act and cannot be shared *via* public deposition because of information governance restriction in place to protect patient confidentiality. Access to data are available only once approval has been obtained through the individual constituent entities controlling access to the data. The primary care data can be requested *via* application to the Clinical Practice Research Datalink (www.cprd.com) or the SAIL Databank (https://www.saildatabank.com/application-process). Requests to access these datasets should be directed to enquiries@cprd.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ISAC of the CPRD, MHRA, and IGRP of the SAIL Databank. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HCG, RTW, and DMA contributed to the conceptualization of the study. HCG, RTW, DMA, AJ, MD-B, and MJC designed the study. HCG, MJC, and MD-B extracted data. HCG conducted the statistical analysis. HCG, DMA, RTW, MJC, MD-B, AJ, and KJM contributed to interpretation of results. RP developed the algorithm to quantify alcohol consumption. HCG drafted the initial manuscript. KJM contributed to the section on alcohol screening, misuse, and treatment services. RTW, DMA, RP, MJC, KJM, WOP, AJ, and MD-B amended and revised the manuscript. All authors approved the submitted version.

FUNDING

This work was funded by the National Institute for Health Research (NIHR) Greater Manchester Patient Safety Translational Research Centre. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care (Grant number: PSTRC-2016-003).

ACKNOWLEDGMENTS

This study is partly based on data from the Clinical Practice Research Datalink obtained under license from the MHRA. The data are provided by patients and collected by the NHS as part of their care and support. This study also used anonymized data held in the SAIL system, which is part of the national e-health records infrastructure for Wales. The Office for National Statistics (ONS) is the provider of the ONS mortality data. HES and ONS data is subject to Crown copyright (2015) protection, re-used with the permission of The Health & Social Care Information Center, all rights reserved. The interpretation and conclusions contained in this study are those of the authors alone, and not necessarily those of the SAIL, UK Medicines and Healthcare Products Regulatory Agency (MHRA), the National Institute for Health Research (NIHR), National Health Service

(NHS), or the Department of Health. We acknowledge the contributing patients and practices to the CPRD GOLD and SAIL Databank who have allowed their data to be used for research purposes.

REFERENCES

1. Thurman DJ, Logroscino G, Beghi E, Hauser A, Hesdorffer DC, Newton CR, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia.* (2017) 58:17–26. doi: 10.1111/epi.13604
2. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality. A call for action. *Neurol.* (2016) 86:779–86. doi: 10.1212/WNL.0000000000002253
3. Gorton HC, Webb RT, Carr MJ, DelPozo-Banos M, John A, Ashcroft DM. Risk of unnatural mortality in people with epilepsy. *JAMA Neurology.* (2018) 75:929–38. doi: 10.1001/jamaneurol.2018.0333
4. Granbichler CA, Oberaigner W, Kuchukhidze G, Bauer G, Ndayisaba J-P, Seppi K, et al. Cause-specific mortality in adult epilepsy patients from Tyrol, Austria: hospital-based study. *J Neurol.* (2015) 262:126–33. doi: 10.1007/s00415-014-7536-z
5. World Health Organization (2018). Available online at: https://www.who.int/publications/i/item/9789241565639 (accessed September 12, 2020).
6. Office for National Statistics (2017). Available online at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/theimpactofusingthenewdefinitionofalcoholspecificdeaths/2017-10-27 (accessed September 12, 2020).
7. Nevalainen O, Raitanen J, Ansakorpi H, Artama M, Isojarvi J, Auvinen A. Long-term mortality risk by cause of death in newly diagnosed patients with epilepsy in Finland: a nationwide register-based study. *Eur J Epidemiol.* (2013) 28:981–90. doi: 10.1007/s10654-013-9848-1
8. Herrett EG, ABhaskaran M, Forbes K, Mathur H, van Staa R, Smeeth TL. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol.* (2015) 44:1740. doi: 10.1093/ije/dyv098
9. SAIL Databank (2020). Available online at: https://saildatabank.com (accessed August 10, 2020).
10. John AD, Kosnes M, Gunnell L, Scourfield D, Ford J, Lloyd DV. Suicide Information Database-Cymru: a protocol for a population-based, routinely collected data linkage study to explore risks and patterns of healthcare contact prior to suicide to identify opportunities for intervention. *BMJ Open.* (2014) 4:e006780. doi: 10.1136/bmjopen-2014-006780
11. Chisholm J. The read clinical classification. *BMJ.* (1990) 300:1092. doi: 10.1136/bmj.300.6732.1092
12. Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, et al. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia.* (2011) 52(Suppl 7):2–26. doi: 10.1111/j.1528-1167.2011.03121.x
13. Gorton HC, Webb RT, Pickrell WO, Carr MJ, Ashcroft DM. Risk factors for self-harm in people with epilepsy. *J Neurol.* (2018) 265:3009–16. doi: 10.1007/s00415-018-9094-2
14. Fonferko-Shadrach B, Lacey AS, White CP, Powell HR, Sawhney IM, Lyons RA, et al. Validating epilepsy diagnoses in routinely collected data. *Seizure.* (2017) 52:195–8. doi: 10.1016/j.seizure.2017.10.008
15. Springate DA, Kontopantelis E, Ashcroft DM, Olier I, Parisi R, Chamapiwa E. et al. ClinicalCodes: an online repository to improve the validity and reproducibility of research using electronic medical records. *PLoS One.* (2014) 9:e99825. doi: 10.1371/journal.pone.0099825
16. Higgins JP, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: The Cochrane Collaboration (2011).
17. Parisi R, Webb RT, Carr MJ, Moriarty KJ, Kleyn E, Griffiths CE, et al. Alcohol-related mortality in patients with psoriasis. A population-based cohort study. *JAMA Dermatol.* (2017) 153:1256–62. doi: 10.1001/jamadermatol.2017.3225
18. Department of Health. *Sensible Drinking The Report of an Inter-Departmental Working Group*. London: Department of Health (1995).
19. Ritchie H, Roser M. Available online at: https://ourworldindata.org/alcohol-consumption (2018). (accessed August 10, 2020).
20. Mbizvo GK, Bennett K, Simpson CR, Duncan SE, Chin RFM. Epilepsy-related and other causes of mortality in people with epilepsy: A systematic review of systematic reviews. *Epilepsy Res.* (2019) 157:106192. doi: 10.1016/j.eplepsyres.2019.106192
21. Lynn E, Lyons S, Langan Y, Craig S, Doherty C. The role of alcohol dependency in deaths among people with epilepsy recorded by the National Drug-Related Deaths Index (NDRDI) in Ireland, 2004–2013. *Seizure.* (2017) 45:52–5. doi: 10.1016/j.seizure.2016.11.014
22. Risdale L, Charlton J, Ashworth M, Richardson MP, Gulliford MC. Epilepsy mortality and risk factors for death in epilepsy: a population-based study. *Br J Gen Pract.* (2011) 61:e271–78. doi: 10.3399/bjgp11X572463
23. Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander WAS, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. *Ann Neurol.* (2001) 49:336–44. doi: 10.1002/ana.70
24. Samokhvalov AV, Irving H, Mohapatra S, Rehm J. Alcohol consumption, unprovoked seizures, and epilepsy: a systematic review and meta-analysis. *Epilepsia.* (2010) 51:1177–84. doi: 10.1111/j.1528-1167.2009.02426.x
25. Public Health England (2018). Available online at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/733108/alcohol_public_health_burden_evidence_review_update_2018.pdf (accessed December 4, 2020).
26. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP. *Neurology.* (2020) 94:e419–29. doi: 10.1212/wnl.0000000000008741
27. Beghi E, Giussani G, Nichols E, Abd-Allah F, Abdela J, A. Abdelalim, et al. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:357–75. doi: 10.1016/S1474-4422(18)30454-X
28. Verrill C, Markham H, Templeton A, Carr NJ, Sheron N. Alcohol-related cirrhosis-early abstinence is a key factor in prognosis, even in the most severe cases. *Addiction.* (2009) 104:768–74. doi: 10.1111/j.1360-0443.2009.02521.x
29. Moriarty KJ. Alcohol care teams: where are we now? *Frontline Gastroenterol.* (2020) 11:293–302. doi: 10.1136/flgastro-2019-101241
30. Shankar R, Newman C, McLean B, Anderson T, Obe JH. Can technology help reduce risk of harm in patients with epilepsy? *Br J Gen Pract.* (2015) 65:448–9. doi: 10.3399/bjgp15X686413
31. de Boer, H.M. Epilepsy stigma: Moving from a global problem to global solutions. *Seizure.* (2010) 19:630–6. doi: 10.1016/j.seizure.2010.10.017
32. Crump C, Sundquist K, Winkleby MA, Sundquist J. Mental disorders and risk of accidental death. *BJ Psych.* (2013) 203:297–302. doi: 10.1192/bjp.bp.112.123992
33. Singhal A, Ross J, Seminog O, Hawton K, Goldacre MJ. Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage. *J R Soc Med.* (2014) 107:194–204. doi: 10.1177/0141076814522033
34. Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction.* (1993) 88:791–804.

Conflict of Interest: HCG is a member of Epilepsy Action Health & Clinical Advisory Panel. This is a voluntary position.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 25 January 2021
doi: 10.3389/fneur.2020.618859

Proposed Mechanism-Based Risk Stratification and Algorithm to Prevent Sudden Death in Epilepsy

Michael Lucchesi[1], *Joshua B. Silverman*[2], *Krishnamurthi Sundaram*[3], *Richard Kollmar*[3,4] *and Mark Stewart*[5,6]*

[1] Department of Emergency Medicine, State University of New York Health Sciences University, Brooklyn, NY, United States,
[2] Department of Otolaryngology, North Shore Long Island Jewish Medical Center, New Hyde Park, NY, United States,
[3] Department of Otolaryngology, State University of New York Health Sciences University, Brooklyn, NY, United States,
[4] Department of Cell Biology, State University of New York Health Sciences University, Brooklyn, NY, United States,
[5] Department of Neurology, State University of New York Health Sciences University, Brooklyn, NY, United States,
[6] Department of Physiology & Pharmacology, State University of New York Health Sciences University, Brooklyn, NY, United States

OPEN ACCESS

Edited by:
Brian Darryl Moseley,
University of Cincinnati, United States

Reviewed by:
Daniel Friedman,
NYU Grossman School of Medicine, United States
Theoden I. Netoff,
University of Minnesota Twin Cities, United States

***Correspondence:**
Mark Stewart
mark.stewart@downstate.edu

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: 18 October 2020
Accepted: 30 December 2020
Published: 25 January 2021

Citation:
Lucchesi M, Silverman JB, Sundaram K, Kollmar R and Stewart M (2021) Proposed Mechanism-Based Risk Stratification and Algorithm to Prevent Sudden Death in Epilepsy. Front. Neurol. 11:618859. doi: 10.3389/fneur.2020.618859

Sudden Unexpected Death in Epilepsy (SUDEP) is the leading cause of death in young adults with uncontrolled seizures. First aid guidance to prevent SUDEP, though, has not been previously published because the rarity of monitored cases has made the underlying mechanism difficult to define. This starkly contrasts with the first aid guidelines for sudden cardiac arrest that have been developed based on retrospective studies and expert consensus and the discussion of resuscitation challenges in various American Heart Association certificate courses. However, an increasing amount of evidence from documented SUDEP cases and near misses and from animal models points to a consistent sequence of events that starts with sudden airway occlusion and suggests a mechanistic basis for enhancing seizure first aid. In monitored cases, this sudden airway occlusion associated with seizure activity can be accurately inferred from inductance plethysmography or (depending on recording bandwidth) from electromyographic (EMG) bursts that are associated with inspiratory attempts appearing on the electroencephalogram (EEG) or the electrocardiogram (ECG). In an emergency setting or outside a hospital, seizure first aid can be improved by (1) keeping a lookout for sudden changes in airway status during a seizure, (2) distinguishing thoracic and abdominal movements during attempts to inspire from effective breathing, (3) applying a simple maneuver, the laryngospasm notch maneuver, that may help with airway management when aggressive airway management is unavailable, (4) providing oxygen early as a preventative step to reduce the risk of death, and (5) performing cardiopulmonary resuscitation before the limited post-ictal window of opportunity closes. We propose that these additions to first aid protocols can limit progression of any potential SUDEP case and prevent death. Risk stratification can be improved by recognition of airway occlusion, attendant hypoxia, and need for resuscitation.

Keywords: apnea, laryngospasm, SUDEP, airway obstruction, respiratory arrest

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is a major cause of death among children and adults with epilepsy, particularly individuals whose seizures are poorly controlled [e.g., (1, 2)]. The prevalence of epilepsy in the US population is ∼1% and between 2 and 17% of deaths in these patients are labeled SUDEP [e.g., (3)], the single most common cause of death among persons with epilepsy (4, 5). Mortality rates in adults with epilepsy are 2–3 times greater than their non-epileptic counterparts (6, 7). Fortunately, the incidence of sudden death in epilepsy is low (8–11), but it is the rarity of the condition that contributes to its unexpected presentation and paucity of detailed physiological data. Given the elusive mechanism of death and a diffuse risk profile that includes: (1) highest SUDEP risk when seizure control is poor, (2) unpredictable, often nocturnal timing of life-threatening or fatal events, and (3) an apparent absence of significant pre-existing cardiovascular pathology, SUDEP prevention has centered on prevention of seizures [e.g., (12)].

The Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) identified a consistent sequence of events in epilepsy patients beginning with a generalized tonic clonic seizure and ending in death (10). Curated cases with detailed records from multiple epilepsy centers were used to demonstrate a sequence of events from the end of the seizure consisting of "terminal" apnea, bradycardia, and asystole. Other work in rats and mice showed that seizure-associated laryngospasm could cause obstructive apnea that may persist to the point of respiratory arrest (13–15). The linkage between preclinical and clinical data was formed by EMG evidence of inspiratory attempts and specific changes in cardiac rhythm (14, 16, 17) [see also Supplemental Data in Ryvlin et al. (10)].

The goal of this review is to make first-responders look out for abrupt changes in airway status during a seizure and to offer preventative as well as interventional steps against the life-threatening consequences of obstructive apnea. First, we want to emphasize that a dangerous mechanism for the airway status to abruptly change from open to closed is internal, i.e., laryngospasm, making airway obstruction unexpected and thus potentially catching responders off guard. Second, we want to highlight the value of oxygen as a step that, when available early, protects against the consequences of obstructive apnea without actually influencing whether obstructive apnea occurs or not. Finally, we hope to raise awareness of the ictal and postictal sequence of events and time points for intervention in relation to the underlying mechanism so that efficacy of intervention steps can be optimized.

BASIC FIRST AID

Seizure first aid generally takes a "wait for the seizure to end" approach, emphasizing "care and comfort" first aid while remaining vigilant for uncommon severe features that would warrant a call for emergency help (18–21). According to one of the most detailed sets of guidelines (21), "During a convulsive or tonic-clonic seizure, it may look like the person has stopped breathing. As this part of a seizure ends, the muscles will relax and breathing will resume normally. Rescue breathing or CPR is generally not needed during these seizure-induced changes in a person's breathing."

All seizure first aid protocols emphasize the importance of checking the airway and airway protection is emphasized in the "turn the person onto their side" guidance (https://www.epilepsy.com/learn/seizure-first-aid-and-safety/first-aid-seizures-stay-safe-side). First aid flowcharts for emergency departments are clear that cardiorespiratory compromise warrants oxygen as part of an active treatment (e.g., https://www.rch.org.au/clinicalguide/guideline_index/Afebrile_seizures/).

Critically, Ryvlin et al. (10) report on the successful resuscitation of potential SUDEP cases with cardiopulmonary resuscitation (CPR) applied within a narrow timeframe around the end of the seizure and terminal apnea. In the Ryvlin et al. dataset, 7/7 patients receiving CPR within 3 min of respiratory arrest (i.e., after "terminal apnea" occurred) were successfully resuscitated and 11/11 patients in whom CPR was initiated only after 10 min following respiratory arrest all died (10). It is the particular, narrow timeframe for CPR, and the reasons CPR may be necessary, that deserve discussion.

PATHOPHYSIOLOGY AND RISK STRATIFICATION

Seizure-associated changes in cardiac rate and rhythm and respiratory rate and rhythm indicate seizure spread to medullary sympathetic premotor and parasympathetic motor neurons [e.g., (22, 23)] and adjacent respiratory brainstem regions [e.g., (24–27)]. Multiple pathways exist for the spread of seizure activity from subiculum to paraventricular nucleus (PVN) of the hypothalamus (28) and then from PVN to medullary regions [e.g., (29)], where seizure activity can access medullary autonomic nuclei, respiratory centers, and laryngeal motor neurons.

Respiratory derangements during seizures can be serious [reviewed in (2, 24, 30)]. Reports of ictal tachypnea, bradypnea, and apnea [e.g., (10, 13, 31–38)] all point to an impact of seizure activity on respiratory rhythm generation and thereby a role in oxygen desaturation during seizures (32, 36).

The significance of seizure-associated hypoxemia as a contributor to death has been shown in a number of animal models, including rats (13, 23, 39), mice (25, 40–42), cats (43, 44), and sheep (45, 46). In rats, seizure-associated obstructive apneic episodes were demonstrated with nerve recordings and laryngoscopy to be due to seizure spread to the recurrent laryngeal nerve (the principal motor nerve of the larynx), which caused severe laryngospasm and complete airway closure (13). Significant ST segment elevation indicative of hypoxia was also present in ECG recordings. Seizure-associated central apneic episodes, even when tens of seconds in duration, however, were associated with an open airway as observed with continuous laryngoscopy, modest decreases in heart rate, and no evidence of hypoxia in ECG records (13, 27). Importantly, Rheims et al. (47) used data from the REPO$_2$MSE study to evaluate the

occurrence and degree of post-ictal hypoxemia and found that early administration of oxygen was associated with an early recovery of oxygen saturation and less frequent post-ictal EEG suppression. While they leave the issue of central vs. obstructive apnea as "an open question," they do demonstrate value for early oxygen with completely independent metrics.

An important step in defining the mechanism of SUDEP came from differentiation of first-order, seizure-induced pathophysiological events from second-order consequences of these first-order derangements (17). This review develops the arguments in favor of obstructive apnea and discusses potential alternative mechanisms for SUDEP in greater detail. Obstructive apnea, which occurs in a subset of seizures that include seizure-induced laryngospasm, was identified as the major cause of desaturation and death, but neither obstructive apnea nor laryngospasm has been specifically addressed in first aid guidance.

Laryngospasm has been suspected during seizures in patients or observed postictally, based on findings of stridor and a narrowed airway when attempting to place an endotracheal tube (48) or intensive inspiratory effort (16, 49), but ictal laryngospasm is difficult to directly assess in patients or animals [see e.g., (50–52)]. Pulmonary edema, a common finding at autopsy in SUDEP cases, is also indirect evidence of laryngospasm (53–55). Once obstructed, attempts to inspire against the closed glottis contribute to a rapid desaturation (13, 56). The hypoxemia and decreased cardiac output cause the seizure to abort, but the laryngospasm can persist to the point of respiratory arrest (defined as a cessation of attempts to inspire), followed ultimately by cardiac arrest (13, 14). Based on the clinical and animal data, respiratory arrest occurs very close in time to the end of seizure activity or the end of a motor convulsion [reviewed in (17)]. This work included a demonstration that early oxygen could significantly delay the time to respiratory arrest, even when available for a relatively short period of time before the onset of obstructive apnea (56). In mouse studies, early oxygen guaranteed survival in animals that had an extremely high probability of mortality (40, 41).

In persons who are monitored, seizure-associated airway occlusion can be accurately inferred from inductance plethysmography or (depending on recording bandwidth) electromyographic (EMG) bursts associated with inspiratory attempts appearing on the electroencephalogram (EEG) or the electrocardiogram (ECG). Evidence of significant hypoxia can appear as ST changes in the ECG or as EEG evidence of hypoxic seizure termination (decreasing amplitude with increasing frequency). With such data, individuals can be placed in a high-risk stratum that can be divided into three substrata when a seizure occurs with (1) evidence of airway occlusion only, (2) evidence of airway occlusion and significant hypoxia, or (3) requiring resuscitation.

For clarification, some additional discussion of central vs. obstructive apnea and the issue of stertor as a source of EMG is warranted. Concepts such as post-convulsive central apnea (PCCA) (57) have been put forth with mechanistic implications in SUDEP. For example, a paper by Vilella et al. (58) offered PCCA as a clinical biomarker for SUDEP. Their conclusions derive from a study of 148 seizures in 87 patients, none of whom died while being monitored, and only 21 seizures included airflow monitoring to distinguish central from obstructive apnea (59). Two patients were labeled as near misses (neither of which had airflow data) and a third patient died nearly 2 years after being recorded for the dataset. Twenty other patients displayed PCCA with no SUDEP concerns accounting for the lack of a statistical association of PCCA with SUDEP. This paper attempts to dismiss both laryngospasm and EMG signals associated with respiratory effort, in spite of the fact that the study data come from as early as 2011 when laryngospasm and obstructive apnea were not on most clinicians' radar.

With regard to the EMG signal associated with respiratory effort, Vilella et al. (58) imply that stertorous breathing is the explanation for respiration-related EMG signals appearing on EEG or ECG channels. Data on stertor in temporal relation to the EMG signals are not available and their own figures show the EMG signal in association with larger excursions on the inductance plethysmograms. As we reviewed in Stewart et al. (17), such respiratory effort-associated EMG signals were seen in (1) the MORTEMUS results (where stertorous breathing was either missed or not detected) (10), (2) in multiple animal experiments where the airway is known to be completely closed so that vocalizations are impossible [e.g., (14)], (3) in a published case of laryngospasm (16) where "inspiratory effort became increasingly prominent, accompanied by prominent tracheal movements and inspiratory stridor, also evidenced by increasing EMG artifact in EEG and EKG channels" (no mention of stertor), (4) in obstructive sleep apnea where there is no mention of stertor (60), and even (5) in breath holding divers where no sounds are reported (61). Vilella et al. conclude "breathing related rhythmic muscle artifact is more indicative of breathing effort than obstructed breathing and thus may not be a particularly useful biomarker for SUDEP," but this is exactly the point—such effort would occur during obstructive and not central apnea. In our opinion, the arguments supporting obstructive apnea as the link between seizure activity and events leading to SUDEP are strong enough to warrant the first aid recommendations presented here.

AIRWAY MANAGEMENT

Most healthcare facilities have emergency airway protocols and even difficult airway rapid response teams (62–64) to deal with non-routine airway management. Emergency airway management, from repositioning, to relieving an obstruction, to bag-valve mask ventilation (BVM), rapid sequence intubation (RSI), and if necessary, establishing a surgical airway are all part of the armamentarium of clinicians skilled in airway management [e.g., (65, 66)]. Sedative hypnotics and paralytics can often aid in positive pressure mask ventilation. Depending on the situation, these agents are often used in the controlled environment of rapid sequence intubation [e.g., (66, 67)]. The absence of intravenous access and the immediate unavailability of these medications compound the challenges of dealing with a difficult airway (68, 69). Reestablishing ventilation and the

success of a return of spontaneous ventilation depends critically on the time spent without oxygen as cardiac failure, and long-term neurologic deficits can result as possible consequences even after resuscitation. Aggressive airway management is key, and anticipation of airway difficulty can save critical minutes.

The vast majority of SUDEP cases occur outside a hospital where airway management is even more challenging. One option, not intended to substitute for the steps in an emergency airway protocol, but rather as a tool in the absence of hospital resources, is the laryngospasm notch maneuver (70). Often used by anesthesiologists to relieve laryngospasm after extubation and emergency medicine physicians, the laryngospasm notch maneuver consists of applying strong pressure behind the angles of the jaw in a supine individual together with a forward jaw thrust (71). It is described by some as universally successful in breaking laryngospasm. As reported by Larson, the middle finger of each hand is placed in the notch below the pinna of the ear between the mandible and the mastoid process of the temporal bone. Very firm pressure toward the base of the skull combined with forward pressure on the jaw (the jaw thrust) combine to abolish laryngospasm (70). The maneuver, in addition to shifting epiglottic structures for a better airway (71), is a painful stimulus that may relax the vocal folds (70). The laryngospasm notch maneuver requires no equipment, may break the laryngospasm early, and is simple to learn and apply (e.g., https://www.youtube.com/watch?v=eIdWRYOQenQ).

PROPOSED RESUSCITATION GUIDANCE

Based on the recent recognition of obstructive apnea as the proximal cause of death during seizures, we propose three additions to the standard first aid algorithm for seizures. In contrast to the age-old emergency response teaching for patients having a generalized tonic clonic seizure—allow the seizure to terminate on its own prior to any airway-related interventions—we posit that the life-threatening consequences of obstructive apnea warrant immediate preventative and interventional measures during and after a seizure. At the same time, none of the proposed additions require manipulating the oral cavity of a patient having a generalized seizure, in keeping with the traditional rationale to protect both patient and responder from injury (18–21).

The three proposed additions are illustrated in **Figure 1**, together with potential outcomes following a generalized seizure with mechanistic landmarks of obstructive apnea (OA), respiratory arrest (RA), respiratory failure (RF), and cardiac arrest (CA) (adapted from (17):

(1) Early oxygen protects against prolonged obstructive apnea and limits desaturation. In a rat model, access to an atmosphere enriched with oxygen approximately doubled the time between the onset of obstructive apnea and respiratory arrest (56). By delaying the time to respiratory arrest, oxygen exposure prior to the onset of obstructive apnea dramatically increases the probability that the seizure ends spontaneously and safely. As desaturation is a major factor in all SUDEP mechanisms (17), the prophylactic benefit of oxygen is compelling. A number of epilepsy monitoring units apply oxygen routinely at the first signs of a seizure.

(2) Aggressive airway management may become suddenly and unexpectedly necessary during or after a seizure. The emergency first aid protocols for airway management are excellent, but we believe that emergency medical personnel and care givers must be made more aware that airway status can rapidly change without evidence of positional issues or obvious aspiration danger. Obstructive apnea due to laryngospasm will be accompanied by vigorous attempts to inspire, which can look like clonic movements or successful breaths, but the force of laryngospasm will diminish as the seizure abates and will eventually permit lung inflation by resuscitative effort. The time at which evidence indicates laryngospasm abates is between the point at which the seizure ends and the point of respiratory arrest. Lung inflation may not be efficacious until the laryngospasm has fully abated closer to the point of respiratory arrest. We are not suggesting that large numbers of seizure patients will need intubation. We are emphasizing that (a) an understanding of what to expect will inform decisions about intubation and, more importantly, that (b) the laryngospasm will abate or can be broken with the laryngospasm notch maneuver to permit ventilation in cases where obstructive apnea is suspected.

(3) CPR alone, in or out of the hospital, can be sufficient. As discussed above, CPR was effective in all cases reported in the MORTEMUS study when applied within 3 min of respiratory arrest (10). Such resuscitation would only be possible if the airway had spontaneously opened, reinforcing the point that the airway will open when the seizure ends and the stimulus for laryngospasm ends. Chest compressions are important because, as described earlier, cardiac contractility near the time of respiratory arrest is severely impaired. CPR should be continued until the individual demonstrates a return of spontaneous circulation, and ventilation assistance should continue until the individual is clearly breathing on their own.

LIMITATIONS

A number of critical research questions remain, including how to help individuals at risk for SUDEP and their caregivers anticipate life-threatening events, and approaches to resuscitation that can be utilized anywhere. A greater understanding of the mechanisms by which seizures cause laryngospasm sufficient to completely obstruct the airway will also enable potential preventative strategies. One could argue, however, each two points: (1) that the vast majority of SUDEP cases are unwitnessed, and thus no first aid can be attempted, and (2) that the vast majority of witnessed seizures, whether they occur in the hospital or out of the hospital, are not fatal and thus do not require a change in first aid recommendations. Neither of these arguments, in our opinion, are arguments against simple, safe recommendations (including increasing awareness) that can prevent death in the

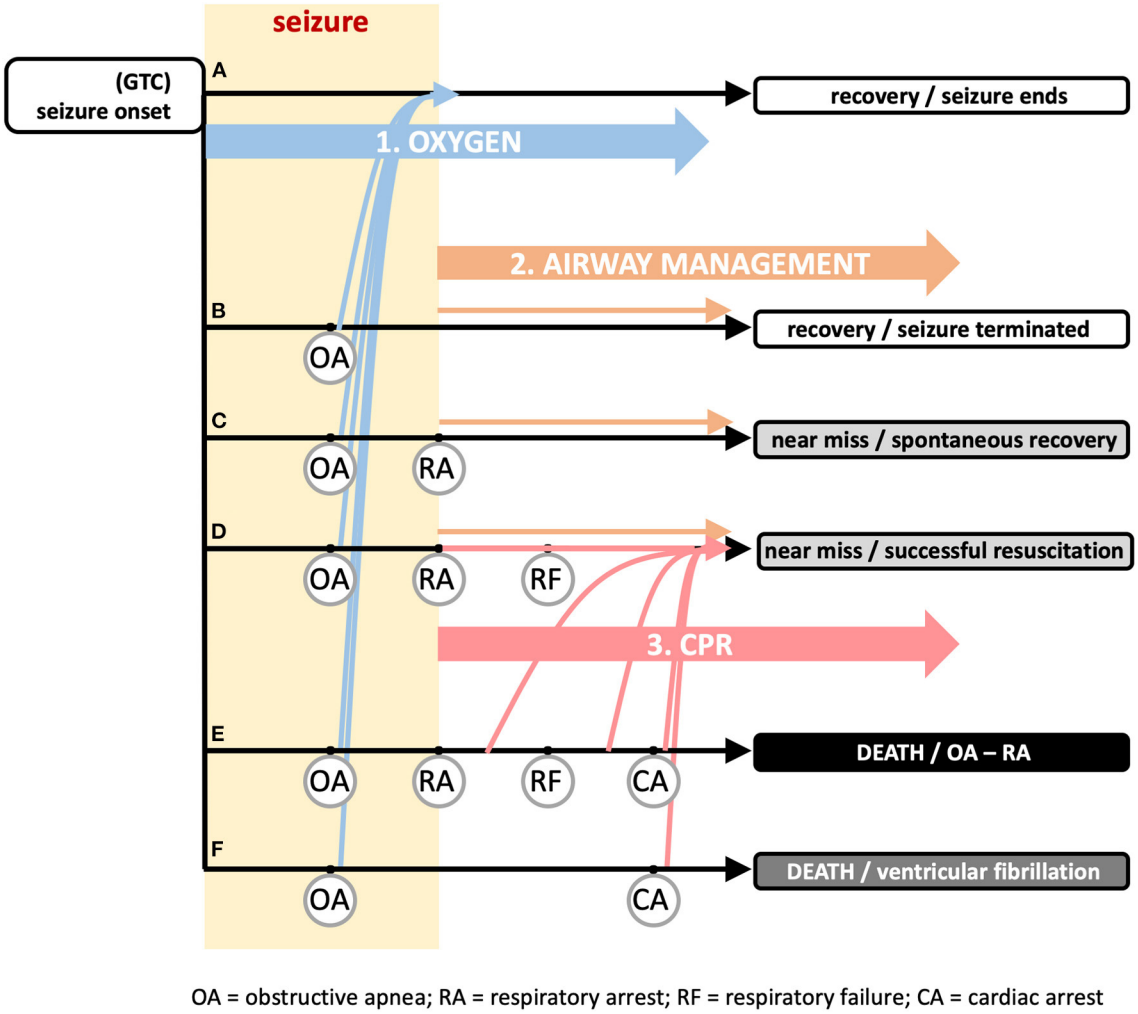


FIGURE 1 | Recommended additional first aid guidance and timing to reduce sudden death risk associated with seizure activity. The vast majority of seizures end spontaneously (track a) with a rapid return of autonomic, cardiac, and respiratory function to baseline levels. The general first aid guidance of "(1) STAY with the person and start timing the seizure, (2) keep the person SAFE, and (3) turn the person onto their SIDE if they are not awake and aware" (https://www.epilepsy.com/learn/seizure-first-aid-and-safety/first-aid-seizures-stay-safe-side) is sufficient for these cases. Onset of generalized tonic clonic (GTC) seizure (left) can be followed by a succession of physiological "landmarks" illustrated in tracks b–f that are defined by the set of landmarks included in the track. The onset of obstructive apnea (OA) can occur suddenly and unexpectedly due to laryngospasm and is shown occurring on all (tracks b–f). OA can persist until the point of respiratory arrest (RA), defined as the time at which attempts to inspire stop. RA is shown in (tracks c–e). If the seizure does not end on its own, hypoxemia from OA can cause the seizure to terminate (yellow rectangle denotes duration of seizure, ending by either mechanism). The hypoxemia developed from OA can be severe enough that the point of respiratory failure (RF) is reached. Within the period between RA and RF, a spontaneous return of respiration is possible if an airway becomes available; after the point of RF, the spontaneous return of respiration is not possible, even if an airway becomes available; resuscitation by a care giver is essential. Continued hypoxemia will lead to cardiac arrest (CA) and death (track e). In track f, the global hypoxemia triggers ventricular fibrillation and death by cardiac arrest. Early oxygen (intervention 1; blue arrows), i.e., applied during the period between seizure onset and the onset of OA, will not prevent OA, but will shift all tracks b–f to track a where the seizure ends on its own and the OA abates as the seizure abates. This is illustrated by the blue arrows from tracks b–f jumping to track a without eliminating OA. Airway management (intervention 2; orange arrows) will ensure one of the recovery or near miss outcomes (tracks b–d), depending upon when the airway opens on its own or if the airway is actively manipulated. CPR (intervention 3; red arrows) is useful even without active airway management, but depends on an airway (spontaneously open or managed). As documented in the literature, this can be applied within several minutes after RA to successfully resuscitate an individual. In track f, the airway is important, but not the critical issue for resuscitation. Ventricular fibrillation will rapidly terminate the seizure and thus release the airway, but necessitates defibrillation for resuscitation. Each intervention has its own separate impact or can be combined. Adapted from Stewart et al. (17).

small number of cases whose lives depend on modified first aid when it is available.

At this point in time, the best prevention is adequate seizure control (11), but we believe early oxygen can help reduce a number of other potential consequences. For example, seizure-associated ventricular fibrillation (VF), which is a less common cause of SUDEP, can be triggered by global cardiac hypoxia (17, 72, 73). Additionally, it has long been thought that in patients with epilepsy, sudden cardiac arrest usually occurs in relationship to an acute seizure (9, 74, 75). Although epilepsy is a risk factor for sudden cardiac arrest (76–78), Stecker et al. (77) found that the majority of patients with epilepsy who

sustained a sudden cardiac arrest, did not have a seizure just prior to their arrest. In the Oregon Sudden Unexpected Death Study, only about 1/3 of patients with history of epilepsy and a witnessed arrest had evidence of seizure activity before the arrest (11/32) (77). The epilepsy patient population also had >4-fold poorer rate of survival to hospital discharge after attempted resuscitation (77). Hypoxia from laryngospasm for example, can both precipitate ventricular fibrillation and negatively impact outcomes even after resuscitation.

CONCLUSIONS

We believe that research on SUDEP has converged to permit an understanding of why early intervention with CPR has been successful in epilepsy patients and that vigilance with regard to assessing airflow and inspiratory effort can save lives, in spite of the sudden, unexpected occurrence of life-threatening airway obstruction.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by NIH/NINDS (NS104796) and philanthropic contributions.

REFERENCES

1. Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: a review of incidence and risk factors. *Epilepsia.* (2005) 46(Suppl 11):54–61. doi: 10.1111/j.1528-1167.2005.00411.x
2. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. *Lancet Neurol.* (2016) 15:1075–88. doi: 10.1016/S1474-4422(16)30158-2
3. Nei M, Hays R. Sudden unexpected death in epilepsy. *Curr Neurol Neurosci Rep.* (2010) 10:319–26. doi: 10.1007/s11910-010-0116-4
4. Wannamaker BB. Autonomic nervous system and epilepsy. *Epilepsia.* (1985) 26(Suppl 1):S31–39. doi: 10.1111/j.1528-1157.1985.tb05722.x
5. Lathers CM, Schraeder PL, Boggs JG. Chapter 1183: Sudden unexplained death and autonomic dysfunction. In: eds J. Engel and T.A. Pedley, editors. *Epilepsy: A Comprehensive Textbook.* Philadelphia: Lippincott-Raven (1998), p. 1943–55.
6. Langan Y. Sudden unexpected death in epilepsy (SUDEP): risk factors and case control studies. *Seizure.* (2000) 9:179–83. doi: 10.1053/seiz.2000.0388
7. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. *Epilepsia.* (2014) 55:1479–85. doi: 10.1111/epi.12666
8. Annegers JF, Coan SP. SUDEP: overview of definitions and review of incidence data. *Seizure.* (1999) 8:347–52. doi: 10.1053/seiz.1999.0306
9. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol.* (2008) 7:1021–31. doi: 10.1016/S1474-4422(08)70202-3
10. 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) 12:966–77. doi: 10.1016/S1474-4422(13)70214-X
11. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology.* (2017) 88:1674–80. doi: 10.1212/WNL.0000000000003685
12. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: a call for action. *Neurology.* (2016) 86:779–86. doi: 10.1212/WNL.0000000000002253
13. Nakase K, Kollmar R, Lazar J, Arjomandi H, Sundaram K, Silverman J, et al. Laryngospasm, central and obstructive apnea during seizures: defining pathophysiology for sudden death in a rat model. *Epilepsy Res.* (2016) 128:126–39. doi: 10.1016/j.eplepsyres.2016.08.004
14. Stewart M, Kollmar R, Nakase K, Silverman J, Sundaram K, Orman R, et al. Obstructive apnea due to laryngospasm links ictal to postictal events in SUDEP cases and offers practical biomarkers for review of past cases and prevention of new ones. *Epilepsia.* (2017) 58:e87–e90. doi: 10.1111/epi.13765
15. Irizarry R, Sukato D, Kollmar R, Schild S, Silverman JB, Sundaram K, et al. Seizures induce obstructive apnea in DBA/2J audiogenic seizure-prone mice: lifesaving impact of tracheal implants. *Epilepsia.* (2020) 61:e13–e16. doi: 10.1111/epi.16431
16. Lacuey N, Vilella L, Hampson JP, Sahadevan J, Lhatoo SD. Ictal laryngospasm monitored by video-EEG and polygraphy: a potential SUDEP mechanism. *Epileptic Disord.* (2018) 20:146–50. doi: 10.1684/epd.2018.0964
17. Stewart M, Silverman JB, Sundaram K, Kollmar R. Causes and effects contributing to sudden death in epilepsy and the rationale for prevention and intervention. *Front Neurol.* (2020) 11:765. doi: 10.3389/fneur.2020.00765
18. American_Heart_Association. *Web-Based Integrated 2010 and 2015 American Heart Association and American Red Cross Guidelines for First Aid*. Part 15: First Aid. 6.5 Seizures. Available online at: https://eccguidelines.heart.org/circulation/aha-red-cross-first-aid-guidelines/part-15-first-aid (accessed January 7, 2021).
19. Epilepsy_Society. First *Aid for All Seizures*. Buckinghamshire: The National Society for Epilepsy. Available online at: https://www.epilepsysociety.org.uk/seizure-first-aid; https://www.epilepsysociety.org.uk/seizure-first-aid (accessed January 7, 2021).
20. Centers_for_Disease_Control_and_Prevention. *Epilepsy. Seizure First Aid.* (2015). Available online at: https://www.cdc.gov/epilepsy/basics/first-aid.htm (accessed January 7, 2021).
21. Schachter S, Shafer PO. *Seizure First Aid*. Landover, MD: Epilepsy Foundation of America (2019). Available online at: http://www.epilepsy.com/get-help/seizure-first-aid (accessed January 7, 2021).
22. Goodman JH, Stewart M, Drislane FW. Chapter 190: Autonomic disturbances. In: Engel J, Pedley TA, editors, *Epilepsy: A Comprehensive Textbook*, Vol. 2, 2nd edn. Philadelphia, PA: Lippincott Williams and Wilkins (2008), p. 1999–2005.
23. Sakamoto K, Saito T, Orman R, Koizumi K, Lazar J, Salciccioli L, et al. Autonomic consequences of kainic acid-induced limbic cortical seizures in rats: peripheral autonomic nerve activity, acute cardiovascular changes, and death. *Epilepsia.* (2008) 49:982–96. doi: 10.1111/j.1528-1167.2008.01545.x
24. Sowers LP, Massey CA, Gehlbach BK, Granner MA, Richerson GB. Sudden unexpected death in epilepsy: fatal post-ictal respiratory and arousal mechanisms. *Respir Physiol Neurobiol.* (2013) 189:315–23. doi: 10.1016/j.resp.2013.05.010
25. Faingold CL, Randall M, Tupal S. DBA/1 mice exhibit chronic susceptibility to audiogenic seizures followed by sudden death associated with respiratory arrest. *Epilepsy Behav.* (2010) 17:436–40. doi: 10.1016/j.yebeh.2010.02.007
26. Faingold CL, Kommajosyula SP, Long X, Plath K, Randall M. Serotonin and sudden death: differential effects of serotonergic drugs on seizure-induced respiratory arrest in DBA/1 mice. *Epilepsy Behav.* (2014) 37:198–203. doi: 10.1016/j.yebeh.2014.06.028
27. Villiere SM, Nakase K, Kollmar R, Silverman J, Sundaram K, Stewart M. Seizure-associated central apnea in a rat model: evidence for resetting the respiratory rhythm and activation of the diving reflex. *Neurobiol Dis.* (2017) 101:8–15. doi: 10.1016/j.nbd.2017.01.008

28. Canteras NS, Swanson LW. Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: a PHAL anterograde tract-tracing study in the rat. *J Comp Neurol.* (1992) 324:180–94. doi: 10.1002/cne.903240204
29. Geerling JC, Shin JW, Chimenti PC, Loewy AD. Paraventricular hypothalamic nucleus: axonal projections to the brainstem. *J Comp Neurol.* (2010) 518:1460–99. doi: 10.1002/cne.22283
30. Massey CA, Sowers LP, Dlouhy BJ, Richerson GB. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. *Nat Rev Neurol.* (2014) 10:271–82. doi: 10.1038/nrneurol.2014.64
31. Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. *J Neurol Neurosurg Psychiatry.* (1996) 60:297–300. doi: 10.1136/jnnp.60.3.297
32. Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain.* (2008) 131(Pt 12):3239–45. doi: 10.1093/brain/awn277
33. Blum AS. Respiratory physiology of seizures. *J Clin Neurophysiol.* (2009) 26:309–15. doi: 10.1097/WNP.0b013e3181b7f14d
34. Seyal M, Bateman LM. Ictal apnea linked to contralateral spread of temporal lobe seizures: intracranial EEG recordings in refractory temporal lobe epilepsy. *Epilepsia.* (2009) 50:2557–62. doi: 10.1111/j.1528-1167.2009.02245.x
35. Bateman LM, Spitz M, Seyal M. Ictal hypoventilation contributes to cardiac arrhythmia and SUDEP: report on two deaths in video-EEG-monitored patients. *Epilepsia.* (2010) 51:916–20. doi: 10.1111/j.1528-1167.2009.02513.x
36. Seyal M, Bateman LM, Albertson TE, Lin TC, Li CS. Respiratory changes with seizures in localization-related epilepsy: analysis of periictal hypercapnia and airflow patterns. *Epilepsia.* (2010) 51:1359–64. doi: 10.1111/j.1528-1167.2009.02518.x
37. Singh K, Katz ES, Zarowski M, Loddenkemper T, Llewellyn N, Manganaro S, et al. Cardiopulmonary complications during pediatric seizures: a prelude to understanding SUDEP. *Epilepsia.* (2013) 54:1083–91. doi: 10.1111/epi.12153
38. Sivathamboo S, Constantino TN, Chen Z, Sparks PB, Goldin J, Velakoulis D, et al. Cardiorespiratory and autonomic function in epileptic seizures: a video-EEG monitoring study. *Epilepsy Behav.* (2020) 111:107271. doi: 10.1016/j.yebeh.2020.107271
39. Stewart M. The urethane/kainate seizure model as a tool to explore physiology and death associated with seizures. In: Lathers CM, Schraeder PL, Bungo ME, Leetsma JE, editors. *Sudden Death in Epilepsy: Forensic and Clinical Issues*. Boca Raton, FL: Taylor and Francis Group (2011), p. 627–44.
40. Willott JF, Henry KR. Roles of anoxia and noise-induced hearing loss in the postictal refractory period for audiogenic seizures in mice. *J Comp Physiol Psychol.* (1976) 90:373–81. doi: 10.1037/h0077204
41. Venit EL, Shepard BD, Seyfried TN. Oxygenation prevents sudden death in seizure-prone mice. *Epilepsia.* (2004) 45:993–6. doi: 10.1111/j.0013-9580.2004.02304.x
42. Uteshev VV, Tupal S, Mhaskar Y, Faingold CL. Abnormal serotonin receptor expression in DBA/2 mice associated with susceptibility to sudden death due to respiratory arrest. *Epilepsy Res.* (2010) 88:183–8. doi: 10.1016/j.eplepsyres.2009.11.004
43. Schraeder PL, Lathers CM. Cardiac neural discharge and epileptogenic activity in the cat: an animal model for unexplained death. *Life Sci.* (1983) 32:1371–82. doi: 10.1016/0024-3205(83)90813-5
44. Paydarfar D, Eldridge FL, Scott SC, Dowell RT, Wagner PG. Respiratory responses to focal and generalized seizures in cats. *Am J Physiol.* (1991) 260(5 Pt 2), R934–R40. doi: 10.1152/ajpregu.1991.260.5.R934
45. Johnston SC, Horn JK, Valente J, Simon RP. The role of hypoventilation in a sheep model of epileptic sudden death. *Ann Neurol.* (1995) 37:531–7. doi: 10.1002/ana.410370416
46. Johnston SC, Siedenberg R, Min JK, Jerome EH, Laxer KD. Central apnea and acute cardiac ischemia in a sheep model of epileptic sudden death. *Ann Neurol.* (1997) 42:588–94. doi: 10.1002/ana.410420409
47. Rheims S, Alvarez BM, Alexandre V, Curot J, Maillard L, Bartolomei F, et al. Hypoxemia following generalized convulsive seizures: risk factors and effect of oxygen therapy. *Neurology.* (2019) 92:e183–e93. doi: 10.1212/WNL.0000000000006777
48. Tavee J, Morris H 3rd. Severe postictal laryngospasm as a potential mechanism for sudden unexpected death in epilepsy: a near-miss in an EMU. *Epilepsia.* (2008) 49:2113–7. doi: 10.1111/j.1528-1167.2008.01781.x
49. Amir J, Ashkenazi S, Schonfeld T, Weitz R, Nitzan M. Laryngospasm as a single manifestation of epilepsy. *Arch Dis Child.* (1983) 58:151–3. doi: 10.1136/adc.58.2.151
50. Terndrup TE, Gregory ME, Fordyce WE. The role of the upper airway in contributing to respiratory responses during experimental seizures in piglets. *Pediatr Res.* (1995) 38:61–6. doi: 10.1203/00006450-199507000-00011
51. Terndrup TE, Kadison A, Woo P. Glottal patency during experimental seizures in piglets. *Pediatr Res.* (1995) 38:932–7. doi: 10.1203/00006450-199512000-00017
52. Leaming JM, Terndrup TE, Ognibene S. Glottal patency during experimental cortical seizures in piglets. *Acad Emerg Med.* (1999) 6:682–7. doi: 10.1111/j.1553-2712.1999.tb00435.x
53. Antoniuk SA, Oliva LV, Bruck I, Malucelli M, Yabumoto S, Castellano JL. Sudden unexpected, unexplained death in epilepsy autopsied patients. *Arq Neuropsiquiatr.* (2001) 59:40–5. doi: 10.1590/S0004-282X2001000100009
54. Morentin B, Alcaraz R. [Sudden unexpected death in epilepsy in children and adolescents]. *Rev Neurol.* (2002) 34:462–5. doi: 10.33588/rn.3405.2001408
55. Salmo EN, Connolly CE. Mortality in epilepsy in the west of Ireland: a 10-year review. *Ir J Med Sci.* (2002) 171:199–201. doi: 10.1007/BF03170280
56. Mooney S, Kollmar R, Gurevich R, Tromblee J, Banerjee A, Sundaram K, et al. An oxygen-rich atmosphere or systemic fluoxetine extend the time to respiratory arrest in a rat model of obstructive apnea. *Neurobiol Dis.* (2020) 134:104682. doi: 10.1016/j.nbd.2019.104682
57. So EL, Sam MC, Lagerlund TL. Postictal central apnea as a cause of SUDEP: evidence from near-SUDEP incident. *Epilepsia.* (2000) 41:1494–7. doi: 10.1111/j.1528-1157.2000.tb00128.x
58. Vilella L, Lacuey N, Hampson JP, Rani MRS, Sainju RK, Friedman D, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). *Neurology.* (2019) 92:e171–e82. doi: 10.1212/WNL.0000000000006785
59. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med.* (2012) 8:597–619. doi: 10.5664/jcsm.2172
60. Berry RB, Ryals S, Girdhar A, Wagner MH. Use of chest wall electromyography to detect respiratory effort during polysomnography. *J Clin Sleep Med.* (2016) 12:1239–44. doi: 10.5664/jcsm.6122
61. Bain AR, Drvis I, Dujic Z, MacLeod DB, Ainslie PN. Physiology of static breath holding in elite apneists. *Exp Physiol.* (2018) 103:635–51. doi: 10.1113/EP086269
62. Joffe AM. Use your SMARTs (Some Kind of Multidisciplinary Airway Response Team) for emergent airway management outside the operating room. *Anesth Analg.* (2015) 121:11–3. doi: 10.1213/ANE.0000000000000723
63. Mark LJ, Herzer KR, Cover R, Pandian V, Bhatti NI, Berkow LC, et al. Difficult airway response team: a novel quality improvement program for managing hospital-wide airway emergencies. *Anesth Analg.* (2015) 121:127–39. doi: 10.1213/ANE.0000000000000691
64. Tsai AC, Krisciunas GP, Brook C, Basa K, Gonzalez M, Crimlisk J, et al. Comprehensive Emergency Airway Response Team (EART) Training and Education: impact on team effectiveness, personnel confidence, and protocol knowledge. *Ann Otol Rhinol Laryngol.* (2016) 125:457–63. doi: 10.1177/0003489415619178
65. Erlandson MJ, Clinton JE, Ruiz E, Cohen J. Cricothyrotomy in the emergency department revisited. *J Emerg Med.* (1989) 7:115–8. doi: 10.1016/0736-4679(89)90254-0
66. Visvanathan T, Kluger MT, Webb RK, Westhorpe RN. Crisis management during anaesthesia: laryngospasm. *Qual Saf Health Care.* (2005) 14:e3. doi: 10.1136/qshc.2002.004275
67. Salem MR, Crystal GJ, Nimmagadda U. Understanding the mechanics of laryngospasm is crucial for proper treatment. *Anesthesiology.* (2012) 117:441–2. doi: 10.1097/ALN.0b013e31825f02b4
68. Runciman WB, Kluger MT, Morris RW, Paix AD, Watterson LM, Webb RK. Crisis management during anaesthesia: the development of an anaesthetic crisis management manual. *Qual Saf Health Care.* (2005) 14:e1. doi: 10.1136/qshc.2002.004101
69. Borshoff D. *Anaesthetic Crisis Manual*. Cambridge: Cambridge University Press (2011).

70. Larson CP Jr. Laryngospasm–the best treatment. *Anesthesiology.* (1998) 89:1293–4. doi: 10.1097/00000542-199811000-00056
71. Fink BR. The etiology and treatment of laryngeal spasm. *Anesthesiology.* (1956) 17:569–77. doi: 10.1097/00000542-195607000-00007
72. Naggar I, Uchida S, Kamran H, Lazar J, Stewart M. Autonomic boundary conditions for ventricular fibrillation and their implications for a novel defibrillation technique. *J Physiol Sci.* (2012) 62:479–92. doi: 10.1007/s12576-012-0225-8
73. Naggar I, Lazar J, Kamran H, Orman R, Stewart M. Relation of autonomic and cardiac abnormalities to ventricular fibrillation in a rat model of epilepsy. *Epilepsy Res.* (2014) 108:44–56. doi: 10.1016/j.eplepsyres.2013.10.018
74. Devinsky O. Sudden, unexpected death in epilepsy. *N Engl J Med.* (2011) 365:1801–11. doi: 10.1056/NEJMra1010481
75. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. *Lancet.* (2011) 378:2028–38. doi: 10.1016/S0140-6736(11)60176-1
76. Bardai A, Lamberts RJ, Blom MT, Spanjaart AM, Berdowski J, van der Staal SR, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. *PLoS One.* (2012) 7:e42749. doi: 10.1371/journal.pone.0042749
77. Stecker EC, Reinier K, Uy-Evanado A, Teodorescu C, Chugh H, Gunson K, et al. Relationship between seizure episode and sudden cardiac arrest in patients with epilepsy: a community-based study. *Circ Arrhythm Electrophysiol.* (2013) 6:912–6. doi: 10.1161/CIRCEP.113.000544
78. Lamberts RJ, Blom MT, Novy J, Belluzzo M, Seldenrijk A, Penninx BW, et al. Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. *J Neurol Neurosurg Psychiatry.* (2015) 86:309–13. doi: 10.1136/jnnp-2014-307772

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 11 February 2021
doi: 10.3389/fneur.2021.609236

Myocardial Iron Overload in an Experimental Model of Sudden Unexpected Death in Epilepsy

*Enes Akyuz[1], Zuleyha Doganyigit[2], Ece Eroglu[3], Franco Moscovicz[4], Amalia Merelli[4], Alberto Lazarowski[4] and Jerónimo Auzmendi[4,5]**

[1] Department of Biophysics, Medical School, Yozgat Bozok University, Yozgat, Turkey, [2] Department of Histology and Embryology, Medical School, Yozgat Bozok University, Yozgat, Turkey, [3] Medical School, Yozgat Bozok University, Yozgat, Turkey, [4] Department of Clinical Biochemistry, School of Pharmacy and Biochemistry, Pathophysiology and Clinical Biochemistry Institute (INFIBIOC), University of Buenos Aires, Buenos Aires, Argentina, [5] National Council of Science and Technology (CONICET), Buenos Aires, Argentina

Uncontrolled repetitive generalized tonic-clonic seizures (GTCS) are the main risk factor for sudden unexpected death in epilepsy (SUDEP). GTCS can be observed in models such as Pentylenetetrazole kindling (PTZ-K) or pilocarpine-induced Status Epilepticus (SE-P), which share similar alterations in cardiac function, with a high risk of SUDEP. Terminal cardiac arrhythmia in SUDEP can develop as a result of a high rate of hypoxic stress-induced by convulsions with excessive sympathetic overstimulation that triggers a neurocardiogenic injury, recently defined as "Epileptic Heart" and characterized by heart rhythm disturbances, such as bradycardia and lengthening of the QT interval. Recently, an iron overload-dependent form of non-apoptotic cell death called ferroptosis was described at the brain level in both the PTZ-K and SE-P experimental models. However, seizure-related cardiac ferroptosis has not yet been reported. Iron overload cardiomyopathy (IOC) results from the accumulation of iron in the myocardium, with high production of reactive oxygen species (ROS), lipid peroxidation, and accumulation of hemosiderin as the final biomarker related to cardiomyocyte ferroptosis. Iron overload cardiomyopathy is the leading cause of death in patients with iron overload secondary to chronic blood transfusion therapy; it is also described in hereditary hemochromatosis. GTCS, through repeated hypoxic stress, can increase ROS production in the heart and cause cardiomyocyte ferroptosis. We hypothesized that iron accumulation in the "Epileptic Heart" could be associated with a terminal cardiac arrhythmia described in the IOC and the development of state-potentially in the development of SUDEP. Using the aforementioned PTZ-K and SE-P experimental models, after SUDEP-related repetitive GTCS, we observed an increase in the cardiac expression of hypoxic inducible factor 1α, indicating hypoxic-ischemic damage, and both necrotic cells and hemorrhagic areas were related to the possible hemosiderin production in the PTZ-K model. Furthermore, we demonstrated for the first time an accumulation of hemosiderin in the heart in the SE-P model. These results suggest that uncontrolled recurrent seizures, as described in refractory epilepsy, can give rise to high hypoxic stress in the heart, thus inducing

OPEN ACCESS

Edited by:
Rohit Shankar, Cornwall Partnership NHS Foundation Trust, United Kingdom

Reviewed by:
Michael Kinney, Belfast Health and Social Care Trust, United Kingdom
Charlotte Lawthom, Aneurin Bevan University Health Board, United Kingdom

***Correspondence:**
Jerónimo Auzmendi
jeronimo.auzmendi@gmail.com

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *22 September 2020*
Accepted: *04 January 2021*
Published: *11 February 2021*

Citation:
Akyuz E, Doganyigit Z, Eroglu E, Moscovicz F, Merelli A, Lazarowski A and Auzmendi J (2021) Myocardial Iron Overload in an Experimental Model of Sudden Unexpected Death in Epilepsy. Front. Neurol. 12:609236. doi: 10.3389/fneur.2021.609236

hemosiderin accumulation as in IOC, and can act as an underlying hidden mechanism contributing to the development of a terminal cardiac arrhythmia in SUDEP. Because iron accumulation in tissues can be detected by non-invasive imaging methods, cardiac iron overload in refractory epilepsy patients could be treated with chelation therapy to reduce the risk of SUDEP.

Keywords: SUDEP, epilepsy, heart failure, iron overload cardiomyopathy, ferroptosis

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is the single leading cause of premature death in people with epilepsy, affecting ∼1 in 1,000 patients (1). One of the most important clinical risk factors related to SUDEP is a high frequency of uncontrolled generalized tonic-clonic seizures (GTCS) that result in an increased risk of death in patients with refractory epilepsy (2–4).

Although the mechanism that triggers sudden death is unknown, several lines of evidence suggest that SUDEP could be due to a terminal cardiac arrhythmia as a consequence of a highly frequent seizure-triggered hypoxic-stress plus excessive sympathetic overstimulation that triggers neurocardiogenic injury and affects electrical properties of the myocardium resulting in a propensity for severe bradycardia, and fatal cardiac arrhythmia (5). In this sense, the alteration in cardiomyocytes such as vacuolization and nucleus displacement by vacuole was described as a reversible pathological condition.

However, diffuse interstitial fibrosis with multiple areas of cardiomyocyte replacement by connective tissue and perivascular fibrosis were also observed and interpreted as irreversible pathological changes (6). Although, cardiac fibrosis was reported to be more frequently detected in SUDEP cases, a more recent study demonstrated that this cardiac pathology was less severe in SUDEP cases than sudden arrhythmic death (7). The lower level of cardiac damage observed in SUDEP suggests that sudden death is not primarily related to anatomical abnormalities but to functional abnormalities secondary to chronic and persistent hypoxic stress. In this way, exceeding a cumulative stress threshold, a further seizure could trigger a fatal cardiac arrhythmia.

In this regard, autonomic cardiac neural discharges have been characterized after pentylenetetrazol (PTZ)-induced epileptogenic activity (8). In this sense, cardiac hypertrophy seems to be related to the autonomic changes that arise from seizures, suggesting that the heart could be structurally affected, as observed in a chronic epileptic rat model (9). Structural cardiac pathologies can provide more insight into the SUDEP heterogeneous mechanisms (10).

Experimental data obtained from a Dravet Syndrome model showed that cardiomyocytes exhibited increased excitability, prolonged action potential duration, and triggered activity. In this model, continuous radiotelemetric electrocardiographic (ECG) recordings showed QT-interval (QT) prolongation, ventricular ectopic foci, idioventricular rhythms, beat-to-beat variability, ventricular fibrillation, and focal bradycardia that were associated with spontaneous deaths in mice (11). Accordingly, QT prolongation and heart rate alteration were reported after a single pilocarpine-induced status epilepticus (SE) in rats, whereas subsequent SE was associated with an increased SUDEP frequency and a worsening of electrophysiology (12). Furthermore, upregulation of P-glycoprotien (P-gp) and downregulation of inward-rectifier potassium channels (Kir) have been proposed to alter the electrical properties and contractibility of cardiomyocytes (13, 14). It has recently been demonstrated that the expression of ubiquitin-specific peptidase 15 (USP15) was upregulated in a PTZ-kindled (PTZ-K) rat model of epilepsy. USP15 upregulation was associated with increased levels of intracellular reactive oxygen species (ROS) and enhanced superoxide dismutase (SOD) activity (15). SOD, which converts superoxide (O_2^-) into hydrogen peroxide (H_2O_2) and dioxygen (O_2), can act through a reaction called disproportionation as the front line of defense against ROS-mediated injuries (16).

Oxidative stress is assumed to be a major factor in IOC. Reduced free iron ions (Fe^{2+}) participate in the ROS formation via Haber-Weiss and Fenton reactions. Because cardiac tissue contains high levels of functional L-type voltage-gated Ca^{2+} channels, hypoxic conditions can turn cardiac tissue especially susceptible to free iron overload (17, 18). Additionally, divalent transporters such as the zinc transporter ZIP_8 and ZIP_{14} provide an active pathway for Fe^{2+} entry that can lead to multiple deleterious effects (19, 20). In a hypoxia-inducible factor 1α (HIF-1α)-dependent manner, hypoxia will also upregulate the expression of transferrin receptor (Tfr-R) through which more iron will enter the cell, resulting in various structural damage and functional alterations, such as impaired excitation contraction coupling. Furthermore, impaired relaxation and subsequent contractility, lipid peroxidation, mitochondrial dysfunction with reduced ATP production, and direct DNA damage can be observed (17, 21). In this regard, a feedback mechanism has been described between the participation of oxidative stress with inflammation and excitotoxicity in refractory epilepsy (22, 23). We suspect that those could also be present in the heart as a consequence of repetitive and/or severe seizures.

These functional changes were also described in conditions of cardiac hypoxia, where the oxidative environment promotes iron deposition that is associated with a slow mechanism of cell death called ferroptosis (24). We hypothesize that in refractory epilepsy, recurrent episodes of hypoxia and oxidative stress will induce a progressive accumulation of iron in cardiomyocytes as a ferroptosis hallmark of Iron Overload Cardiomyopathy (IOC) and propensity to terminal cardiac arrhythmia associated with

SUDEP. The aim of this study was to evaluate the presence of hemosiderin deposits in the heart in an experimental model of SUDEP secondary to SE.

MATERIALS AND METHODS

Experimental Model

Pentylenetetrazole Kindling Model

The PTZ-K epilepsy model was induced using an established protocol (25). The rats were injected intraperitoneally with a subconvulsive dose of PTZ (35 mg/kg) three times a week (Monday, Wednesday, and Friday) for 1 month until kindling occurred. After each injection, the rats were placed alone in an isolated transparent Plexiglas cage and their convulsive behavior was independently monitored for 30 min. Records were blindly analyzed to determine seizure stage, onset latency, and duration. Seizure severity was scored using Racine's classification (25) as follows: no response (Score 0); facial movements, ear, and whisker twitching (Score 1); myoclonic convulsions without rearing (Score 2); myoclonic jerks, upright position with clonic forelimb convulsions (Score 3); clonic-tonic convulsions (Score 4); generalized clonic-tonic seizures with loss of postural control (Score 5) and finally death (Score 6).

Lithium-Pilocarpine Paradigm

SE was induced weekly for 3 weeks as previously described (12). Briefly, 200–250 g male Wistar rats were maintained at 20–25°C, 60% humidity, 12/12 h light/dark cycle, and food *ad libitum*. Rats were administered lithium chloride (33 mEq/kg i.p.) 18 h prior to pilocarpine treatment (30 mg/kg i.p.). Convulsive behavior was assessed using the Racine scale described above and only animals that were kept for at least 5 min with GTCS were included in this study. SE was limited with diazepam (20 mg/kg i.p.) at 20 min. All rats were supplied with 1 ml of H_2O i.p. every 12 h. The rats were allowed recovery periods of 48 h after SE in which vital signs were closely monitored.

Tissue Preparation

Fixation and Cryostat Preservation

Animals exposed to the pilocarpine paradigm were routinely fixed as previously described (12). Briefly, the rats were anesthetized with ketamine/xylazine (k/x: 90/10 mg/kg, i.p.). After thoracic surgery, the heart was exposed and the blood was then flushed by perfusion from the left ventricle using a 21G butterfly needle. Reverse circulation was achieved by cutting the right atrium and then applying 60 ml of saline plus heparin (50 UI/ml). A first fixation step was carried out applying 60 ml of 4% paraformaldehyde (PFA) in cold phosphate buffer saline (PBS). The final fixation step was performed using 300 ml of 4%PFA applied by gravity. After fixation, hearts were removed and fixed after 12 h and then washed with PBS. Finally, the hearts were snap-frozen and stored at −20°C until cryostat processing. Frozen hearts were serially cut into 30-micron coronal sections and then placed into one of 20 slices each. In this way, each slice contains a section separated by 600 microns.

Fixation and Paraffin Inclusion

Tissue samples obtained from rats exposed to the kindling model were determined with a 10% formaldehyde solution for use in histological examinations. After the detection process, routine tissue follow-up steps were applied to the tissues and embedded in paraffin to perform the paraffin blocks (10).

Cytochemistry

Perls Staining

Slices containing a 30 μm thick frozen section at the coronal incidence were used for iron deposition determination. One out of 10 consecutive sections was stained and analyzed for hemosiderin aggregates. Briefly, the slices were incubated with a solution of 10 g/l potassium ferrocyanide in 0.1 mol/l HCl for 10 min at room temperature. Then the slices were washed well under running tap water for at least 20 min. The slices were contrast-stained using a dilute safranin solution (1% v/v) for 1 min. To prevent false-positive Perls staining, all materials used in this technique were washed with 1 M HCl for 24 h.

Hematoxylin-Eosin Staining

Tissue sections (5 μm) were obtained from the paraffin blocks and then placed on polylysine-coated slices for morphological analysis. The prepared slides were left in the oven for a certain period using standard histological methods as described in Akyuz et al. (10). Xylene and paraffin were removed and passed through a graded alcohol series and diluted. After being covered with Entellan® (107,960 Sigma-Aldrich), cardiac tissues were examined with the Olympus BX53 microscope. With the ImageJ program, 25 cell lengths from each group were measured.

Immunohistochemistry

The Avidin-Biotin-peroxidase method was used immunohistochemically for the determination of cardiac anti-HIF-1α ([H1alpha67] (ab1) Abcam) immunoreactivity. The 5 μm thick sections taken from paraffin blocks were kept in an oven at 60°C overnight and then passed through xylene and decreasing graded alcohol series. Then, after washing with distilled water, it was treated with citrate buffer for antigen recovery. Hydrogen peroxide was applied after washing with PBS and the Large Volume Detection System kit (NB100-479, Novus Biologicals, USA) was used. After that, serum block application was performed for 5 min. After blocking the serum, HIF-1α was applied at 4°C overnight as the primary antibody. Secondary streptavidin-HRP (TP-125-HL; Thermo Scientific) and DAB chromogen with Biotin were applied, contrast staining with Gill Hematoxylin. Finally, it was passed through the gradually increasing alcohol-xylene series and closed with Entellan. Images obtained with the DP71 digital camera under the Olympus BX53 brand light microscope were analyzed for image differences using Image J 1.48v software.

Data and Statistical Analysis

The free software of the National Institute of Health Image-J was used to measure the immunoreactivity of 25 areas of the images taken from the 5 preparations of each group. In the same way, the length of 25 cardiomyocytes per group was analyzed.

The positive Perls reactions of 15–30 non-consecutive coronal sections were analyzed for each heart in the control and three SE groups. The Graphpad Prism 8.0 program was used for statistical analysis. Results are shown as the mean standard deviation. The independent sample *T*-test was used for intergroup comparison. A statistical value of $p < 0.05$ was considered significant.

RESULTS

Pentylenetetrazol Kindling Model

After the 13th PTZ injection, all rats developed chronic epilepsy-like behavior with spontaneous generalized tonic-clonic seizures (stage 5). The mean degree of phase of all injections was 5.31 ± 0.58 and the duration of the seizures was 308 ± 95 s. Moreover, we did not observe a significant difference in body weight between the corresponding experimental group. Cardiomyocytes showed a clear difference in HIF-1α immunoreactivity between the control group and the kindled group. The HIF-1α immunoreactivity increased in the cardiomyocytes from 81.58 ± 10.12 μm^2 -control- to 117.39 ± 5.69 μm^2 -kindling- ($p = 0.0001$) (**Figure 1**). This result is in the same way as our previous report on HIF-1α immunoreactivity in cardiomyocytes under SE (12).

Furthermore, we found morphological differences between the cardiomyocytes of the controls and the kindled rats (**Figure 2**). PTZ treatment increased cardiomyocyte length by ∼20% (26.60 ± 5.02 μm -control- vs. 32.29 ± 6.35 μm - kindled - $p = 0.003$). Additionally, in the rat heart of the PTZ-K model, large hemorrhagic areas (**Figure 2** black arrows) and necrotic cells (**Figure 2** yellow arrows) were observed. Interestingly, both morphological alterations are related to iron deposits such as hemosiderin accumulation (26).

Status Epilepticus Induced by the Pilocarpine Paradigm

Taking into account that the kindling model induces hypoxic cardiac stress similar to that we previously reported under SE (12), we analyzed the iron deposition in the heart after severe convulsive stress produced by three consecutive weekly-induced SE. We used Perls staining to visualize the iron deposit as a blue precipitate (**Figure 3**) and found 2.5 folds that increased a positive blue mark (18.33% ±9.28 -control- vs. 48.39% ±6.73−3 SE- $p = 0.0427$).

DISCUSSION

Sudden unexpected death in epilepsy is the most important cause of death in people with epilepsy. Although different conditions that predispose to SUDEP have been described, clinical and experimental studies show that high frequency of GTCS is the most important risk factor, which explains why refractory epilepsies have a higher risk of SUDEP. Despite the fact that SUDEP is assumed to be a neurocardiorespiratory injury, the intrinsic mechanism that triggers sudden death is still unknown. Additionally, obstructive apnea has also been proposed as a key factor because of ictal involvement of brainstem structures producing laryngospasm (27, 28). In this sense, it has recently been reported that an oxygen-rich atmosphere, as well as selective serotonergic reuptake inhibitors, could prevent seizure-associated death and lead to a recovery of respiratory function after the seizure in mice (29). In association with these experimental data, a clinical study called MORTEMUS (Mortality Monitoring Unit Study in Epilepsy) suggests that the potential SUDEP mechanism could be centrally mediated and, therefore, alter respiratory and cardiac functions as a consequence of GTCS (30). Furthermore, some controversial concepts between SUDEP and sudden cardiac death during epilepsy have yet to be resolved.

In a previous report we described for the first time, a direct relationship between repetitive seizures with progressive P-gp overexpression in the heart and brain parenchyma, which is associated with SUDEP (14). Later we also described that repetitive convulsive stress acts as a general hypoxic condition that promotes P-gp overexpression associated with HIF-1α nuclear translocation in both the heart and brain parenchyma (12, 31). In the same way, in an independent experiment, we also showed that epileptic/hypoxic stress reduces the expression of the inward rectifier potassium channel 3.1 (kir3.1) (32), and we speculated that the inverse relationship between the expression of P-gp and Kir3.1 could be in part responsible for the depolarization of the cardiomyocyte membrane, and the aforementioned arrhythmia (13). Recent studies have shown that the mTOR pathway can also play an important role in SUDEP-associated cardiac disturbance in a HIF-1α-dependent manner (33).

In the present research, we show evidence that subconvulsive PTZ doses applied in a kindling model promoted cardiac hypoxic stress by increasing the HIF-1α stabilization in a similar way to that previously observed in SE (12). In addition, large hemorrhagic areas were observed. Some experimental and clinical studies have shown that intramyocardial hemorrhage often occurs in acute myocardial ischemia-reperfusion or infarction, resulting in iron accumulation and hemosiderin deposits that can be detected by magnetic resonance imaging with a long-lasting persistence (34–37). Likewise, we reported cardiomyocyte hypertrophy that could indicate overstimulation of the sympathetic system, as is also observed in chronic arterial hypertension, acute myocardial infarction, genetic cardiomyopathy, myocarditis, heart valve disease, thyroid disorders, obesity, diabetes, aging, among others (38). Interestingly, cardiomyocyte hypertrophy along with decreased gap junction and mitochondrial dysfunction was described as the most common cause of cardiac-related sudden death (39). Furthermore, the imbalance of iron metabolism and oxidative stress are also major factors for the evolution of cardiac hypertrophy, cardiac arrhythmia, and aging-associated pathological changes in the heart (40).

Additionally, convulsive/hypoxic stress will promote a tissue oxidative environment with ROS formation associated with free Fe^{+2}, the Haber-Weiss and Fenton reactions, and iron overload as the main mechanism of cell death, called ferroptosis, that leads to tissue injury (24). This altered iron homeostasis allows uncontrolled entry and deposition of iron into different organs, including the heart, and leads to progressive damage with severe

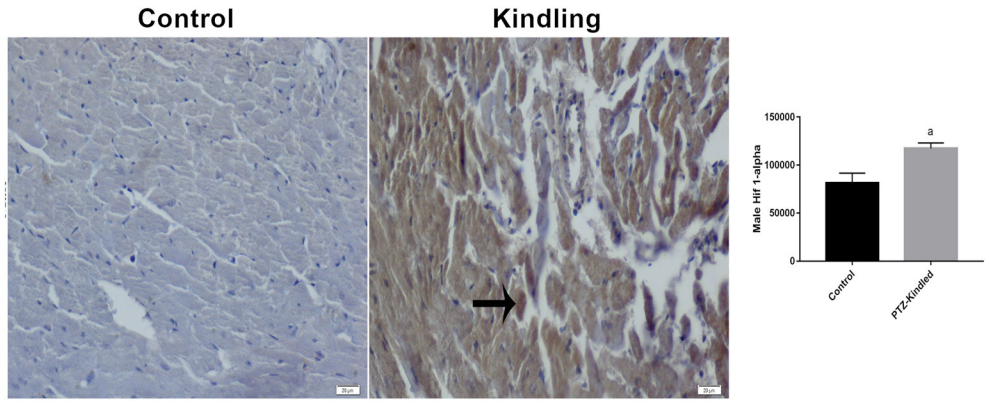


FIGURE 1 | Hif 1-α immunoreactivity staining images and graphics. Immunoreactive areas are shown with a black arrow. Compared with the control, $^{a}p < 0.05$ was considered significant. x400.

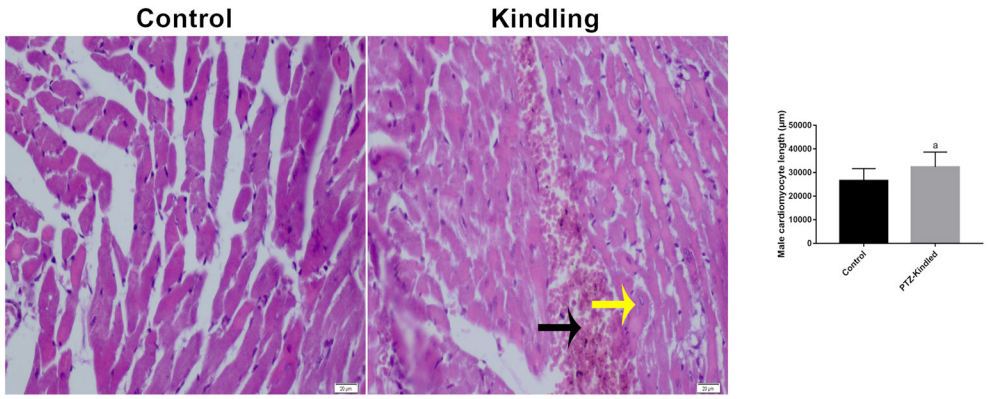


FIGURE 2 | Plots of Hematoxylin-eosin staining image and cardiomyocyte length. Necrotic cells are shown with a yellow arrow and hemorrhagic areas with a black arrow. Compared with the control $^{a}p < 0.05$ was considered significant.

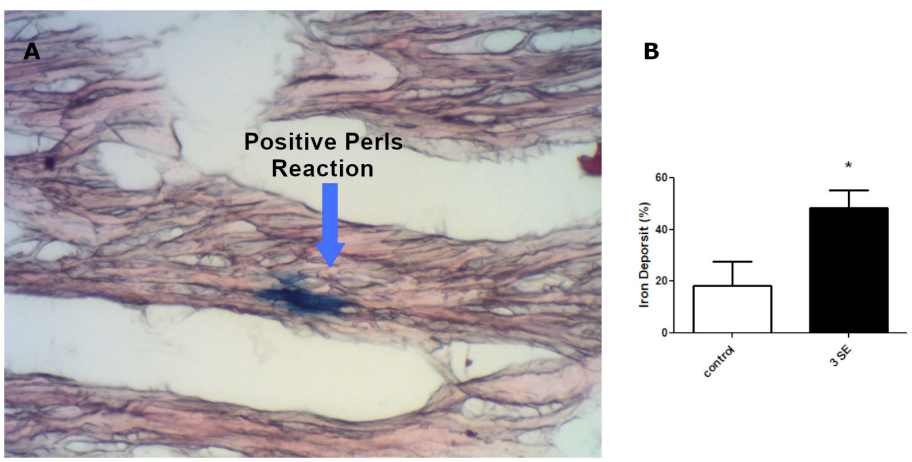


FIGURE 3 | Iron deposition in cardiomyocytes. **(A)** Micrograph at x400 showing cardiomyocites (red) and iron deposition (blue). **(B)** Quantitation of positive iron deposition in myocardial coronal sections of four rats after the third SE $^{*}p < 0.05$.

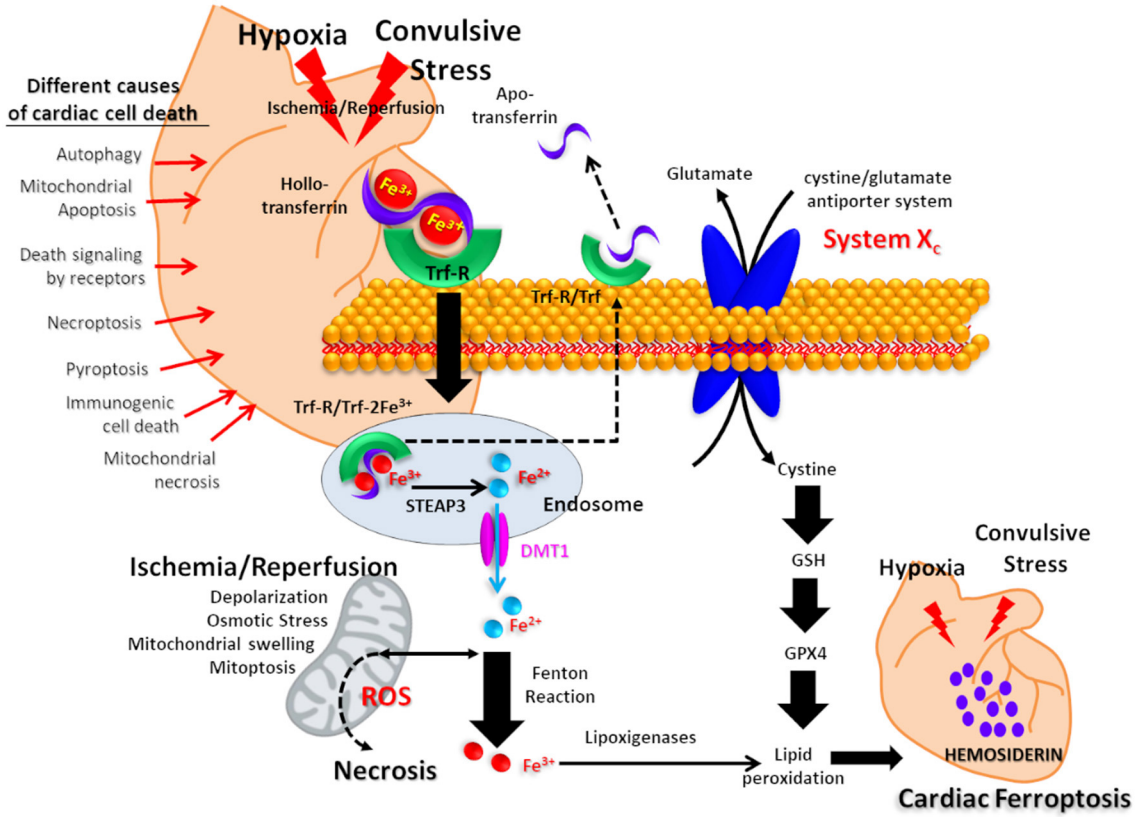


FIGURE 4 | Proposed mechanism for cardiac iron overload related to postconvulsive hypoxia-ischemia. Iron transported by holotransferrin is recognized by the plasma membrane receptor (Trf-R). After endocytosis, Fe^{3+} is reduced to Fe^{2+} in endosomes by the metalloreductase six-transmembrane epithelial antigen of prostate 3 (Steap3) and released from endosomes by divalent metal transporter 1 (DMT1). After the Fenton reaction, iron promotes lipid peroxidation via the activation of lipoxygenases, resulting in hemosiderin accumulation. On the other hand, the axis composed of the cystine/glutamate antiporter system X_c, Glutation (GSH) and Glutation peroxidase 4 (GPX4) is as a key regulator for tissue iron overload and ferroptosis. Other possible mechanisms of cardiomyocyte death are listed on the left side of the picture.

failure of affected organs (41, 42). Moreover, heme metabolism after tissue hemorrhage will produce hemosiderin accumulations for prolonged periods (43). Based on the different mechanisms described for cell death, ferroptosis is characterized by iron accumulation with deleterious effects on the functions of cells or organs.

In this scenario, the hemosiderin deposits could be interpreted as an iron-scar indicating the site where a cell has died, after severe ischemia-reperfusion and oxidative stress processes. This complex mechanism could develop in the heart after repetitive convulsive/hypoxic stress. The finding of hemosiderin in the cardiomyocytes of our experimental SUDEP model suggests that ferroptosis has been present as a potential intrinsic mechanism that led to fatal cardiac arrhythmia (**Figure 4**) (44).

The accumulation of iron in the myocardium can result in a heart dysfunction known as *"Iron Overload Cardiomyopathy"* (IOC), which mainly described in certain inherited diseases related to alterations of iron/hemoglobin metabolism (hemochromatosis and thalassemia major, respectively), as well as secondary to a high rate of red blood cell transfusions (45). Furthermore, an adult patient with hereditary spherocytosis died after atrial tachycardia and cardiogenic shock, and the endomyocardial biopsy of the right ventricle revealed multiple myocardial hemosiderin deposits (46). Currently, IOC is assumed to be the most common cause of mortality in patients with secondary iron overload and is a major comorbidity in patients with genetic hemochromatosis (47, 48). IOC has been characterized by remodeling of the left ventricle (LV) with chamber dilation and reduced LV ejection fraction (LVEF) (49).

Recently, the concept of "Epileptic Heart" was defined as a heart and coronary vasculature damaged by chronic epilepsy as a result of repeated catecholamine surges and hypoxemia leading to electrical and mechanical dysfunction (50). In the "Epileptic Heart" syndrome several cardiological anomalies like ventricular hypertrophy, dilated cardiomyopathy, myocardial fibrosis, cardiomegaly, structural changes or dysfunction, higher levels of left ventricular stiffness, left ventricular filling pressures (by echocardiography), greater left atrial volume determined (by echocardiography), increased left ventricular filling pressure, end-systolic diameter, end-systolic volume, atrial fibrillation, and abnormal cardiac conduction have been reported. Interestingly, some of these same features were also described in the IOC.

Based on these data, we wonder if a potential "Epileptic Heart" might also exhibit iron overload in cardiomyocytes as described in the IOC syndromes. To our knowledge, this is the first experimental evidence showing increased iron overload in rat heart after induced SE, suggesting that repetitive severe seizures could lead to a fatal IOC-like syndrome.

POTENTIAL CLINICAL APPLICATIONS RELATED TO THIS RESEARCH

In IOC, iron can be stored in myocytes in the form of ferritin, hemosiderin, and labile cell iron (free iron), the latter being the most active, but hemosiderin can be detected by imaging studies such as the cardiovascular magnetic resonance T2* (CMR-derived T2*). The increase in heart iron burden is inversely related to the relaxation time T2*. Thus, T2* values <20 ms, indicative of myocardial siderosis, have an inverse correlation with the LVEF, while T2* values <10 ms, indicative of severe iron overload, are associated with an increased annual risk of developing arrhythmias (51, 52). This non-invasive imaging method has revolutionized the clinical management of patients with hemoglobinopathies and other iron overload conditions.

CMR-derived T2* enables accurate diagnosis and quantification of myocardial and hepatic iron deposition, and hence the tailoring and monitoring of iron chelation therapy, thereby improving survival as in cases of thalassemia major (45, 53). Similarly, the topical application of the biological chelator lactoferrin to ulcerated legs of patients with ulcerative hemosiderinic dyschromia of chronic venous insufficiency, significantly reduced hemosiderin deposits, thus favoring the clearance of the iron deposition in the ulcerated legs as well as a complete ulcer scarring (54). Consistent with the possible use of CMR-derived T2* determining the iron heart, magnetic resonance imaging (MRI) with T1 mapping can distinguish fibrosis, edema, lipid accumulation, and iron and amyloid deposition (55). These changes included higher sympathetic drive, myocardial catecholaminergic toxicity, and cardiac fibrosis, and patients with refractory epilepsy may therefore have an arrhythmogenic phenotype. Cardiac imaging tools could help to identify cardiac injury as a biomarker of SUDEP risk.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The animal study was reviewed and approved by CICUAL committee of the School of Medicine, University of Buenos Aires.

AUTHOR CONTRIBUTIONS

EA, ZD, EE, FM, AM, AL, and JA contributed to the experimental design and produce the results. EA, ZD, EE, FM, and JA analyzed the data. EA, AL, and JA wrote the text. All authors contributed to the article and approved the submitted version.

FUNDING

The source that applied to this research was UBACyT 20720170200024BA (AM and AL).

REFERENCES

1. Verducci C, Hussain F, Donner E, Moseley BD, Buchhalter J, Hesdorffer D, et al. SUDEP in the North American SUDEP registry: the full spectrum of epilepsies. *Neurology*. (2019) 93:E227–36. doi: 10.1212/WNL.0000000000007778
2. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. *Neurology*. (2005) 64:1131–3. doi: 10.1212/01.WNL.0000156352.61328.CB
3. Shankar R, Donner EJ, McLean B, Nashef L, Tomson T. Sudden unexpected death in epilepsy (SUDEP): what every neurologist should know. *Epileptic Disord*. (2017) 19:1–9. doi: 10.1684/epd.2017.0891
4. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol*. (2008) 7:1021–31. doi: 10.1016/S1474-4422(08)70202-3
5. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia*. (2012) 53:227–33. doi: 10.1111/j.1528-1167.2011.03358.x
6. Natelson BH, Suarez RV, Terrence CF, Turizo R. Patients with epilepsy who die suddenly have cardiac disease. *Arch Neurol*. (1998) 55:857–60. doi: 10.1001/archneur.55.6.857
7. Devinsky O, Kim A, Friedman D, Bedigian A, Moffatt E, Tseng ZH. Incidence of cardiac fibrosis in SUDEP and control cases. *Neurology*. (2018) 91:e55–61. doi: 10.1212/WNL.0000000000005740
8. Lathers CM, Schraeder PL. Autonomic dysfunction in epilepsy: characterization of autonomic cardiac neural discharge associated with pentylenetetrazol-induced epileptogenic activity. *Epilepsia*. (1982) 23:633–47. doi: 10.1111/j.1528-1157.1982.tb05079.x
9. Naggar I, Lazar J, Kamran H, Orman R, Stewart M. Relation of autonomic and cardiac abnormalities to ventricular fibrillation in a rat model of epilepsy. *Epilepsy Res*. (2014) 108:44–56. doi: 10.1016/j.eplepsyres.2013.10.018
10. Akyuz E, Polat K, Ates S, Unalmis D, Tokpinar A, Yilmaz S, et al. Investigating cardiac morphological alterations in a pentylenetetrazol-kindling model of epilepsy. *Diagnostics*. (2020) 10:388. doi: 10.3390/diagnostics10060388
11. Auerbach DS, Jones J, Clawson BC, Offord J, Lenk GM, Ogiwara I, et al. Altered cardiac electrophysiology and sudep in a model of dravet syndrome. *PLoS ONE*. (2013) 8:e77843. doi: 10.1371/journal.pone.0077843
12. Auzmendi J, Buchholz B, Salguero J, Cañellas C, Kelly J, Men P, et al. Pilocarpine-induced status epilepticus is associated with P-glycoprotein induction in cardiomyocytes, electrocardiographic changes, and sudden death. *Pharmaceuticals*. (2018) 11:21. doi: 10.3390/ph11010021
13. Auzmendi J, Akyüz E, Lazarowski A. The role of P-glycoprotein (P-gp) and inwardly rectifying potassium (Kir) channels in sudden unexpected death in epilepsy (SUDEP). *Epilepsy Behav*. (2019). doi: 10.1016/j.yebeh.2019.106590. [Epub ahead of print].
14. Auzmendi J, Merelli A, Girardi E, Orozco-Suarez S, Rocha L, Lazarowski A. Progressive heart P-glycoprotein (P-gp) overexpression after experimental repetitive seizures (ERS) associated with fatal status epilepticus (FSE). Is it related with SUDEP? *Mol Cell Epilepsy*. (2014) 1:43–51. doi: 10.14800/mce.66
15. Chen X, Bao G, Liu F. Inhibition of USP15 prevent glutamate-induced oxidative damage by activating Nrf2/HO-1 signaling pathway in HT22 cells. *Cell Mol Neurobiol*. (2020) 40:999–1010. doi: 10.1007/s10571-020-00789-3

16. Kangralkar V, Patil S, Bandivadekar R. Oxidative stress and diabetes: a review. *Int J Pharm Appl*. (2010) 1:38–45. doi: 10.1176/pn.45.23.psychnews_45_23_048
17. Oudit GY, Sun H, Trivieri MG, Koch SE, Dawood F, Ackerley C, et al. L-type Ca^{2+} channels provide a major pathway for iron entry into cardiomyocytes in iron-overload cardiomyopathy. *Nat Med*. (2003) 9:1187–94. doi: 10.1038/nm920
18. Tsushima RG, Wickenden AD, Bouchard RA, Oudit GY, Liu PP, Backx PH. Modulation of iron uptake in heart by L-type Ca^{2+} channel modifiers: possible implications in iron overload. *Circ Res*. (1999) 84:1302–9. doi: 10.1161/01.RES.84.11.1302
19. Bodiga VL, Thokala S, Kovur SM, Bodiga S. Zinc dyshomeostasis in cardiomyocytes after acute hypoxia/reoxygenation. *Biol Trace Elem Res*. (2017) 179:117–29. doi: 10.1007/s12011-017-0957-7
20. Knutson MD. Non-transferrin-bound iron transporters. *Free Radic Biol Med*. (2019) 133:101–11. doi: 10.1016/j.freeradbiomed.2018.10.413
21. Das SK, Wang W, Zhabyeyev P, Basu R, Mclean B, Fan D, et al. Iron-overload injury and cardiomyopathy in acquired and genetic models is attenuated by resveratrol therapy. *Sci Rep*. (2015) 5:18132. doi: 10.1038/srep18132
22. Pearson-Smith JN, Patel M. Metabolic dysfunction and oxidative stress in epilepsy. *Int J Mol Sci*. (2017) 18:2365. doi: 10.3390/ijms18112365
23. Lorigados L, Morales LM, Orozco-Suárez S, Gallardo JM, Díaz-Hung ML, González ME, et al. *Oxidative stress in pharmacoresistant epilepsy*. (2016) 33:2101–7. Available online at: https://www.who.int/mediacen (accessed September 19, 2020).
24. Yang WS, Stockwell BR. Ferroptosis: death by lipid peroxidation. *Trends Cell Biol*. (2016) 26:165–76. doi: 10.1016/j.tcb.2015.10.014
25. Racine RJ. Modification of seizure activity by electrical stimulation II. Motor seizure. *Electroencephalogr Clin Neurophysiol*. (1972) 32:281–94. doi: 10.1016/0013-4694(72)90177-0
26. Whittaker P, Hines FA, Robl MG, Dunkel VC. Histopathological evaluation of liver, pancreas, spleen, and heart from iron-overloaded sprague-dawley rats*1,2. *Toxicol Pathol*. (1996) 24:558–63. doi: 10.1177/019262339602400504
27. Stewart M, Kollmar R, Nakase K, Silverman J, Sundaram K, Orman R, et al. Obstructive apnea due to laryngospasm links ictal to postictal events in SUDEP cases and offers practical biomarkers for review of past cases and prevention of new ones. *Epilepsia*. (2017) 58:e87–90. doi: 10.1111/epi.13765
28. Nakase K, Kollmar R, Lazar J, Arjomandi H, Sundaram K, Silverman J, et al. Laryngospasm, central and obstructive apnea during seizures: defining pathophysiology for sudden death in a rat model. *Epilepsy Res*. (2016) 128:126–39. doi: 10.1016/j.eplepsyres.2016.08.004
29. Mooney S, Kollmar R, Gurevich R, Tromblee J, Banerjee A, Sundaram K, et al. An oxygen-rich atmosphere or systemic fluoxetine extend the time to respiratory arrest in a rat model of obstructive apnea. *Neurobiol Dis*. (2020) 134:104682. doi: 10.1016/j.nbd.2019.104682
30. 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) 12:966–77. doi: 10.1016/S1474-4422(13)70214-X
31. Merelli A, Czornyj L, Lazarowski A. Erythropoietin as a new therapeutic opportunity in brain inflammation and neurodegenerative diseases. *Int J Neurosci*. (2015) 125:793–7. doi: 10.3109/00207454.2014.989321
32. Akyüz E, Mega Tiber P, Beker M, Akbaş F. Expression of cardiac inwardly rectifying potassium channels in pentylenetetrazole kindling model of epilepsy in rats. *Cell Mol Biol*. (2018) 64:47–54. doi: 10.14715/cmb/2017.64.15.8
33. Sharma S, Mazumder AG, Rana AK, Patial V, Singh D. Spontaneous recurrent seizures mediated cardiac dysfunction *via* mTOR pathway upregulation: a putative target for SUDEP management. *CNS Neurol Disord - Drug Targets*. (2019) 18:555–65. doi: 10.2174/1871527318666190801112027
34. Cokic I, Wawrowsky K, Kali A, Yang H-J, Tang R, Francis J, et al. Acute and stable ischemic heart disease myocardial hemorrhage after coronary ischemia-reperfusion leads to an iron-mediated, self-perpetuating loop of foam cell and ceroid accumulation. *J Am Coll Cardiol*. (2017) 69(Suppl. 11):197. doi: 10.1016/S0735-1097(17)33586-6
35. Kumar A, Green JD, Sykes JM, Ephrat P, Carson JJL, Mitchell AJ, et al. Detection and quantification of myocardial reperfusion hemorrhage using T2 (*)-weighted CMR. *JACC Cardiovasc Imaging*. (2011) 4:1274–83. doi: 10.1016/j.jcmg.2011.08.016
36. Van Den Bos EJ, Baks T, Moelker AD, Kerver W, Van Geuns RJ, Van Der Giessen WJ, et al. Magnetic resonance imaging of haemorrhage within reperfused myocardial infarcts: possible interference with iron oxide-labelled cell tracking? *Eur Heart J*. (2006) 27:1620–6. doi: 10.1093/eurheartj/ehl059
37. Anderson LJ, Westwood MA, Holden S, Davis B, Prescott E, Wonke B, et al. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. *Br J Haematol*. (2004) 127:348–55. doi: 10.1111/j.1365-2141.2004.05202.x
38. Maillet M, Van Berlo JH, Molkentin JD. Molecular basis of physiological heart growth: fundamental concepts and new players. *Nat Rev Mol Cell Biol*. (2013) 14:38–48. doi: 10.1038/nrm3495
39. Mansueto G, Benincasa G, Capasso E, Graziano V, Russo M, Niola M, et al. Autoptic findings of sudden cardiac death (SCD) in patients with arrhythmogenic ventricular cardiomiopathy (AVC) from left ventricle and biventricular involvement. *Pathol-Res Pract*. (2020) 216:153269. doi: 10.1016/j.prp.2020.153269
40. Kumar V, Santhosh Kumar TR, Kartha CC. Mitochondrial membrane transporters and metabolic switch in heart failure. *Heart Fail Rev*. (2019) 24:255–67. doi: 10.1007/s10741-018-9756-2
41. Buja LM, Roberts WC. Iron in the heart. Etiology and clinical significance. *Am J Med*. (1971) 51:209–21. doi: 10.1016/0002-9343(71)90240-3
42. Hentze MW, Muckenthaler MU, Andrews NC. Balancing acts: molecular control of mammalian iron metabolism. *Cell*. (2004) 117:285–97. doi: 10.1016/S0092-8674(04)00343-5
43. Felberg RA, Grotta JC, Shirzadi AL, Strong R, Narayana P, Hill-Felberg SJ, et al. Cell death in experimental intracerebral hemorrhage: the "black hole" model of hemorrhagic damage. *Ann Neurol*. (2002) 51:517–24. doi: 10.1002/ana.10160
44. Del Re DP, Amgalan D, Linkermann A, Liu Q, Kitsis RN. Fundamental mechanisms of regulated cell death and implications for heart disease. *Physiol Rev*. (2019) 99:1765–817. doi: 10.1152/physrev.00022.2018
45. Kremastinos DT, Farmakis D. Iron overload cardiomyopathy in clinical practice. *Circulation*. (2011) 124:2253–63. doi: 10.1161/CIRCULATIONAHA.111.050773
46. Fujino T, Inoue S, Katsuki S, Higo T, Ide T, Oda Y, et al. Fatal cardiac hemochromatosis in a patient with hereditary spherocytosis. *Int Heart J*. (2018) 59:427–30. doi: 10.1536/ihj.17-160
47. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. *J Card Fail*. (2010) 16:888–900. doi: 10.1016/j.cardfail.2010.05.009
48. Pennell DJ, Udelson JE, Arai AE, Bozkurt B, Cohen AR, Galanello R, et al. Cardiovascular function and treatment in β-thalassemia major: a consensus statement from the american heart association. *Circulation*. (2013) 128:281–308. doi: 10.1161/CIR.0b013e31829b2be6
49. Albakri A. Iron overload cardiomyopathy: a review of literature on clinical status and meta-analysis of diagnostic and clinical management using iron chelators. *Intern Med Care*. (2018) 2. doi: 10.15761/IMC.1000117
50. Verrier RL, Pang TD, Nearing BD, Schachter SC. The epileptic heart: concept and clinical evidence. *Epilepsy Behav*. (2020) 105:106946. doi: 10.1016/j.yebeh.2020.106946
51. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation*. (2009) 120:1961–8. doi: 10.1161/CIRCULATIONAHA.109.874487
52. He T. Cardiovascular magnetic resonance T2* for tissue iron assessment in the heart. *Quant Imaging Med Surg*. (2014) 4:407–12. doi: 10.3978/j.issn.2223-4292.2014.10.05
53. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the

UK and relation to T2* cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. (2008) 10:42. doi: 10.1186/1532-429X-10-42

54. Brizzio E, Castro M, Narbaitz M, Borda N, Carbia C, Correa L, et al. Ulcerated hemosiderinic dyschromia and iron deposits within lower limbs treated with a topical application of biological chelator. *Veins Lymphat*. (2012) 1:18–26. doi: 10.4081/vl.2012.e6
55. Fialho GL, Wolf P, Walz R, Lin K. Epilepsy and ultra-structural heart changes: the role of catecholaminergic toxicity and myocardial fibrosis. What can we learn from cardiology? *Seizure*. (2019) 71:105–9. doi: 10.1016/j.seizure.2019.07.002

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 12 February 2021
doi: 10.3389/fneur.2021.643916

Seizure Clusters, Seizure Severity Markers, and SUDEP Risk

Manuela Ochoa-Urrea[1,2], Nuria Lacuey[1,2], Laura Vilella[1,2], Liang Zhu[3], Shirin Jamal-Omidi[1,2], M. R. Sandhya Rani[1,2], Johnson P. Hampson[1,2], Mojtaba Dayyani[1,2], Jaison Hampson[1,2], Norma J. Hupp[1,2], Shiqiang Tao[1,2], Rup K. Sainju[1,4], Daniel Friedman[1,5], Maromi Nei[1,6], Catherine Scott[1,7], Luke Allen[1,7], Brian K. Gehlbach[1,4], Victoria Reick-Mitrisin[8], Stephan Schuele[1,9], Jennifer Ogren[1,10], Ronald M. Harper[1,10], Beate Diehl[1,7], Lisa M. Bateman[1,11], Orrin Devinsky[1,5], George B. Richerson[1,4], Guo-Qiang Zhang[1,2] and Samden D. Lhatoo[1,2]*

[1] National Institute of Neurological Disorders and Stroke Center for Sudden Unexpected Death in Epilepsy Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, United States, [2] Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, United States, [3] Biostatistics & Epidemiology Research Design Core, Division of Clinical and Translational Sciences, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, United States, [4] University of Iowa Carver College of Medicine, Iowa City, IA, United States, [5] New York University Langone School of Medicine, New York, NY, United States, [6] Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, United States, [7] Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, London, United Kingdom, [8] Case Western Reserve University, Cleveland, OH, United States, [9] Feinberg School of Medicine, Northwestern University, Chicago, IL, United States, [10] Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles (UCLA), Los Angeles, CA, United States, [11] Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA, United States

Rationale: Seizure clusters may be related to Sudden Unexpected Death in Epilepsy (SUDEP). Two or more generalized convulsive seizures (GCS) were captured during video electroencephalography in 7/11 (64%) patients with monitored SUDEP in the MORTEMUS study. It follows that seizure clusters may be associated with epilepsy severity and possibly with SUDEP risk. We aimed to determine if electroclinical seizure features worsen from seizure to seizure within a cluster and possible associations between GCS clusters, markers of seizure severity, and SUDEP risk.

Methods: Patients were consecutive, prospectively consented participants with drug-resistant epilepsy from a multi-center study. Seizure clusters were defined as two or more GCS in a 24-h period during the recording of prolonged video-electroencephalography in the Epilepsy monitoring unit (EMU). We measured heart rate variability (HRV), pulse oximetry, plethysmography, postictal generalized electroencephalographic suppression (PGES), and electroencephalography (EEG) recovery duration. A linear mixed effects model was used to study the difference between the first and subsequent seizures, with a level of significance set at $p < 0.05$.

Results: We identified 112 GCS clusters in 105 patients with 285 seizures. GCS lasted on average 48.7 ± 19 s (mean 49, range 2–137). PGES emerged in 184 (64.6%) seizures and postconvulsive central apnea (PCCA) was present in 38 (13.3%) seizures. Changes in seizure features from seizure to seizure such as seizure and convulsive phase durations appeared random. In grouped analysis, some seizure features underwent significant deterioration, whereas others improved. Clonic phase and postconvulsive central apnea (PCCA) were significantly shorter in the fourth seizure compared to the first. By contrast, duration of decerebrate posturing and ictal central apnea were longer. Four SUDEP cases in the cluster cohort were reported on follow-up.

OPEN ACCESS

Edited by:
Brian Darryl Moseley,
University of Cincinnati, United States

Reviewed by:
James Tao,
University of Chicago, United States
Marina Trivisano,
Bambino Gesù Children Hospital (IRCCS), Italy
Jeff Kennedy,
UC Davis Medical Center, United States

***Correspondence:**
Manuela Ochoa-Urrea
manuela.ochoaurrea@uth.tmc.edu

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: 19 December 2020
Accepted: 25 January 2021
Published: 12 February 2021

Citation:
Ochoa-Urrea M, Lacuey N, Vilella L, Zhu L, Jamal-Omidi S, Rani MRS, Hampson JP, Dayyani M, Hampson J, Hupp NJ, Tao S, Sainju RK, Friedman D, Nei M, Scott C, Allen L, Gehlbach BK, Reick-Mitrisin V, Schuele S, Ogren J, Harper RM, Diehl B, Bateman LM, Devinsky O, Richerson GB, Zhang G-Q and Lhatoo SD (2021) Seizure Clusters, Seizure Severity Markers, and SUDEP Risk. Front. Neurol. 12:643916. doi: 10.3389/fneur.2021.643916

Conclusion: Seizure clusters show variable changes from seizure to seizure. Although clusters may reflect epilepsy severity, they alone may be unrelated to SUDEP risk. We suggest a stochastic nature to SUDEP occurrence, where seizure clusters may be more likely to contribute to SUDEP if an underlying progressive tendency toward SUDEP has matured toward a critical SUDEP threshold.

Keywords: SUDEP, seizure cluster, generalized convulsive seizure, epilepsy, video-EEG (VEEG) monitoring

INTRODUCTION

Seizure clusters occur frequently in patients with epilepsy (PWE). Their frequency ranges from 22–43% in an outpatient setting (1, 2) and occurs in up to 83% in inpatient settings (3). Frequency also depends on the definition used and the population targeted (4). Seizure clusters are usually defined as repetitive and closely grouped seizures whose pattern of occurrence deviates from an expected distribution (5, 6). However, a unified operational definition has not been established (4, 6) Definitions vary from study to study, including: ≥3 seizures in 24 h (1, 2, 4, 7–13), ≥2 in 24 h (14), and 2–4 seizures in <48 h (15). Seizure clusters are associated with an increased risk of status epilepticus and hospitalizations, and are deleterious for quality of life of PWE (7, 16). In addition, seizure clusters are associated with increased mortality and are seen as an adverse event in the epilepsy monitoring unit (EMU) (2, 17, 18).

In the landmark mortality in epilepsy monitoring unit study (MORTEMUS), two or more generalized convulsive seizures (GCS) were captured during video electroencephalography (VEEG) in 7/11 (64%) patients with VEEG monitored SUDEP, and in 3/9 (33%) patients in near-SUDEP (19). Thus, the occurrence of a cluster of GCS has been speculated to be a risk factor for SUDEP. We hypothesized that if GCS clusters are a SUDEP risk factor, electroclinical scrutiny of consecutive GCS may indicate increasing seizure severity. We aimed to determine if there is worsening of electroclinical seizure features from seizure to seizure within a cluster and possible associations between GCS clusters, markers of seizure severity, and SUDEP risk.

METHODS

Patient Selection

Patients were consecutive, prospectively consented participants in the National Institute of Neurological Disorders and Stroke (NINDS) Center for SUDEP Research's Autonomic and Imaging Biomarkers of SUDEP multicenter project (U01- NS090407), its preliminary phase, the Prevention and Risk Identification of SUDEP Mortality (PRISM) project (P20NS076965) and, prospectively consented participants from Memorial Hermann Hospital Epilepsy Monitoring Unit (Houston, Texas). Patients with drug-resistant epilepsy (failure of adequate trials of ≥2 antiepileptic medications) (20) undergoing VEEG evaluation in the EMU of participating centers from September 2011 until April 2020 were studied. We included patients with VEEG recorded GCS clusters, including generalized tonic clonic seizures, focal to bilateral tonic-clonic seizures, and focal-onset motor bilateral clonic seizures (21). Exclusion criteria were status epilepticus and obscured or unavailable video.

Data Collection and Definitions

Demographic and clinical data were collected. A GCS cluster was defined as two or more GCS in a 24 h period (14). Epileptogenic zone was classified as generalized (genetic generalized epilepsy in all cases), focal, both, or unknown (22). State of consciousness was defined as either awake or asleep according to Tatum, 2014 (23). Clinical seizure duration was determined by the time between first and last semiological ictal sign, and EEG duration was determined by the time between EEG onset and offset. GCS duration was defined as time from onset of bilateral motor signs of tonicity or clonicity to clinical seizure end. The duration of GCS was further divided into phases according to ictal semiology as previously described (24): a tonic phase, a jittery phase (also called vibratory period) and a clonic phase. In addition, tonic phase semiology was classified into 4 categories, based on a modified classification proposed by previous authors, (25) in ictal decerebrate, decorticate, hemi-decerebrate and absence of tonic phase. Early nursing intervention was defined as oxygen administration or suction applied during the seizure or within 5 s of seizure termination (25). The impact of anti-seizure medication (ASM) changes on electroclinical features was assessed. ASM changes were collected as tapering (gradual decrease in medication), withdrawal (complete cessation of medication), increase or resumption of medication, and no change. Administration of rescue medication was determined as the administration of IV benzodiazepines and/or IV bolus of ASM during or after a seizure.

Patients underwent prolonged surface VEEG monitoring with the 10–20 international electrode system or invasive VEEG with subdural electrodes, depth electrodes or stereoEEG. Peripheral capillary oxygen saturation (SpO_2) and heart rate were monitored. SpO_2 <90% was considered hypoxemia. Breathing rate was assessed between 2 min pre-ictally and 3 min after clinical seizure end through careful composite analysis of inductance plethysmography, EEG breathing artifact, visually inspected thoracoabdominal excursions, and auditory breathing information. Central apnea was defined as ≥1 missed breaths without any other explanation (i.e., speech, movement, or intervention). Ictal central apnea (ICA) was defined as apnea during non-convulsive seizure or apnea occurring in the pre-convulsive phase of GCS (26). Post-convulsive central apnea (PCCA) referred to apnea after a GCS (26). Postictal generalized EEG suppression (PGES) was defined according to Lhatoo

et al. (27). Presence and duration of postictal generalized EEG suppression (PGES) were determined by visual analysis. Presence and duration of postictal EEG burst suppression were also determined. Combined PGES and burst suppression, following PGES, made up the EEG recovery duration. Heart rate variability (HRV) was assessed using the LabChart HRV module (LabChart Pro 8 software; ADInstruments, Sydney, Australia). For a detailed description of the data collection and definitions please refer to the **Supplementary Material**.

Statistical Analysis

Summary statistics were reported as mean ± standard deviation (SD), median with range, and frequency with percentage. For continuous outcomes, linear mixed effects models were used to study the difference between the first and subsequent seizures while accounting for the within-cluster correlation. Empirical covariance estimators were used for robust inferences. For binary outcomes, generalized linear mixed effects models were used, with binary distribution and logit link. Each model was adjusted for sex, age, epilepsy duration, epileptogenic zone, early nursing intervention (early O_2 administration and suction) and administration of rescue medication. Because the percentage of clusters composed of five and seven seizures was low, we performed the mixed model until the 4th seizure and excluded the 5th, 6th, and 7th seizures from the analysis. The level of significance was set at $p < 0.05$. Statistical analysis was done with SAS software version 9.4 (Cary, NC).

RESULTS

One hundred and twelve GCS clusters were identified in 105 patients with 285 seizures. Three patients had two clusters and two patients had three clusters during different EMU admissions. The remainder had one cluster only. Thirteen (11.6%) clusters occurred during invasive EEG. Mean age was 35.9 ± 14 years (median 33, range 12–69), 47% were female, and mean epilepsy duration was 16.3 ± 11.6 (14, 0.08–43) years. Fifty-six (53.33%) patients had ≥3 GCS per year, and 35 (33.33%) had <3 GCS per year. Sixteen (15.2%) patients had a history of seizure clusters. Fifty-nine percent of seizures occurred during sleep. The mean inter-seizure interval was 6.52 h ± 6.12 (3.78, 0.05–23.62). The epileptogenic zone was most frequently temporal lobe, followed by frontal lobe (**Table 1**). Average clinical seizure duration was 93.6 ± 44.7 s (84.5, 28–393), average EEG seizure duration was 105.7 s ± 50.5 s (94, 38–516) and the GCS phase lasted on average 48.7 ± 19 s (49, 2–137). PGES was present in 184 (64.6%) seizures, lasting on average 36.84 s ± 20.98 (35, 2–135) and PCCA was present in 38 (13.33%) seizures lasting 10.74 s ± 6.99 (8, 3–26). Electroclinical seizure features and their respective durations are shown in **Table 2**.

There were 70 clusters (66.67%) with two seizures, 30 (28.57%) with three seizures, six clusters (5.71%) with four seizures, five clusters (4.76%) with five seizures and one cluster (0.95%) with seven seizures.

TABLE 1 | Epileptogenic zone.

Variable	Patients, $n = 105$ (%)	Cluster, $n = 112$ (%)
Epileptogenic zone		
Generalized	10 (9.5)	10 (8.9)
Focal	93 (88.6)	100 (89.3)
Temporal	37 (39.8)	38 (38)
Bitemporal	13 (13.9)	13 (13)
Frontal	19 (20.4)	22 (22)
Parietal	1 (1)	1 (1)
Insula	1 (1)	1 (1)
Multifocal	13 (13.9)	13 (13)
Lateralized	9 (9.7)	12 (12)
Unknown	2 (1.9)	2 (1.8)
Lateralization of epilepsy		
Left	40 (38.1)	43 (38.4)
Right	26 (24.8)	29 (25.9)
Generalized	10 (9.5)	10 (8.9)
Bilateral	27 (25.7)	28 (25)
Unknown	2 (1.9)	2 (1.8)

n, number.

TABLE 2 | Seizure features and their durations.

Seizure feature	Seizures $n = 285$ (%)	Average duration (s)	SD (s)	Range (s)
Tonic phase	181 (63.5)	7.66	3.96	(2, 22)
Jittery phase	230 (80.7)	10.30	7.50	(1, 41)
Clonic phase	284 (99.6)	37.08	17.09	(5, 130)
Decerebration	130 (45.6)	16.07	11.58	(1, 54)
Decortication	65 (22.8)	15.89	11.19	(2, 50)
PGES	183 (64.2)	36.84	21.04	(2, 135)
Hypoxemia postGCS	84 (29.5)	83.31	46.71	(4, 310)
EEG recovery	185 (64.9)	74.88	60.46	(2, 354)
PCCA	35 (12.3)	10.74	7.09	(3, 37)
ICA	72 (38.9)	17.54	12.95	(5, 74)

s, seconds; n, number; PGES, post-ictal generalized electroencephalographic suppression; EEG, electroencephalographic; PCCA, post-convulsive central apnea; ICA, ictal central apnea.

Electroclinical Characteristics

We did a group analysis to compare electroclinical features of the first seizure with subsequent seizures, adjusting for sex, age, epilepsy duration, epileptogenic zone, administration of rescue medication, early administration of oxygen and early suctioning (early nursing intervention). No significant differences were found in clinical or EEG seizure duration, tonic phase duration, GCS duration, PGES duration and EEG recovery (**Table 3**). Concerning HRV, there were no statistically significant differences between seizures. In addition, state of consciousness (awake or asleep), SpO_2 recovery, presence of decerebrate posturing, total hypoxemia duration, and presence of PGES did not show differences between seizures. Seizure-to-seizure comparisons of clinical seizure durations and GCS

TABLE 3 | Comparison of electroclinical features of first seizure with each subsequent seizure in a cluster.

Seizure feature	Seizure #	Estimate	Standard Error	*p*-value
Clinical duration	1	0		
	2	1.91	5.39	0.725
	3	−0.62	5.51	0.911
	4	2.04	6.96	0.770
EEG duration	1	0		
	2	−1.57	7.05	0.824
	3	0.48	7.24	0.948
	4	−0.49	7.97	0.951
Decerebration duration	1	0		
	2	1.06	1.21	0.386
	3	0.79	2.10	0.710
	4	7.22	1.15	**<0.0001**
Tonic phase duration	1	0		
	2	0.75	0.60	0.219
	3	1.87	1.07	0.087
	4	5.96	3.15	0.064
Clonic phase duration	1	0		
	2	−2.19	2.54	0.390
	3	−6.05	3.17	0.059
	4	−11.87	3.63	**0.002**
GCS duration	1	0		
	2	−0.62	2.35	0.792
	3	−2.68	2.97	0.369
	4	−5.41	3.86	0.164
PGES duration	1	0		
	2	−2.35	3.77	0.535
	3	−5.43	3.69	0.147
	4	−10.98	17.26	0.527
EEG recovery	1	0		
	2	−18.63	10.81	0.091
	3	−11.54	16.29	0.482
	4	−49.71	26.09	0.062
PCCA duration	1	0		
	2	−2.13	4.30	0.654
	3	0.94	1.63	0.606
	4	−7.49	1.70	**0.022**
ICA duration	1	0		
	2	3.16	2.72	0.255
	3	5.42	4.14	0.201
	4	10.79	3.53	**0.005**

EEG, electroencephalographic; GCS, generalized convulsive seizure; PGES, post-ictal generalized electroencephalographic suppression; PCCA, post-convulsive central apnea; ICA, ictal central apnea. Bold values indicate p < 0.05.

durations showed apparently random variations representing either improvement, deterioration or no change. We depicted the variation in seizure duration for clinical seizure duration and GCS duration as an example (**Figure 1**). As inferred from the graphs in the figure, seizures tended to have the same or random durations throughout the cluster.

Duration of clonic phase and PCCA duration were significantly shorter in the 4th seizure as compared to the first one (**Table 3**), $p = 0.002$ and $p = 0.022$, respectively. On the other hand, duration of decerebrate posturing ($p < 0.0001$) and ictal central apnea (ICA) ($p = 0.005$) were longer in the 4th seizure. With both parameters we found a progressive increase in duration with subsequent seizures.

Anti-seizure Medications

For 217 (76%) seizures we had information on changes in anti-seizure medications (ASM) during the EMU admission. Of these, 80 (36.9%) seizures occurred during medication taper, 68 (31.3%) during medication withdrawal, 66 (30.4%) during resumption or increase of ASM and three (1.38%) seizures occurred with no change in ASM. We grouped the changes in ASM into those who had taper or withdrawal and those who had increase or no change. We compared both groups and found no statistically significant differences with regards to electroclinical features (**Supplementary Table 1**). However, the group with taper or withdrawal of ASM were less likely to have PGES. Rescue medication, either a benzodiazepine, an intravenous bolus of ASM or both, was given after 34 seizures in 25 clusters.

SUDEP Cases

Four cases of definite/probable SUDEP were established during follow-up. They died between 9 months and 5.5 years after admission. Two of them were found unresponsive in bedroom and for the other two there is no current information about the circumstances of death. Of these cases, only one had a known history of seizure clusters before the EMU evaluation. Average age was 49.25 ± 10.15 years (51.5, 33–61) with a duration of epilepsy of 34.5 ± 7.5 years (35.5, 24–43). They had between 12 and 24 GCS in the prior year. There were no consistent electroclinical characteristics among them. However, two had PGES >50 s. The mean intra-cluster inter-seizure interval for SUDEP patients was 5.14 ± 5.02 h (3.24, 1.63–14.82). In comparison with patients who did not die, there was no difference in the inter-seizure interval ($p = 0.59$).

DISCUSSION

Our prospective study of GCS in the EMU suggest that the markers of seizure severity in seizure clusters, in each consecutive seizure, change randomly. Some markers show improvement while others either stay the same or deteriorate with subsequent seizures. This heterogeneity suggests that clusters alone may not predispose to SUDEP, but that their timing in relation to the overall course of a patient's epilepsy may be more important for mortality risk. Thus, the course of SUDEP may be a stochastic, rather than probabilistic process, where an underlying progressive increase in SUDEP risk accrues over time. Seizure clusters early in this progression pose less risk than clusters late in the process (**Figure 2**, model B). The MORTEMUS study suggested that seizure clusters were important premortem phenomena (19), although this was not a controlled observation, and no electroclinical characterization of seizure clusters was carried out. Our study suggests that seizure clusters in themselves

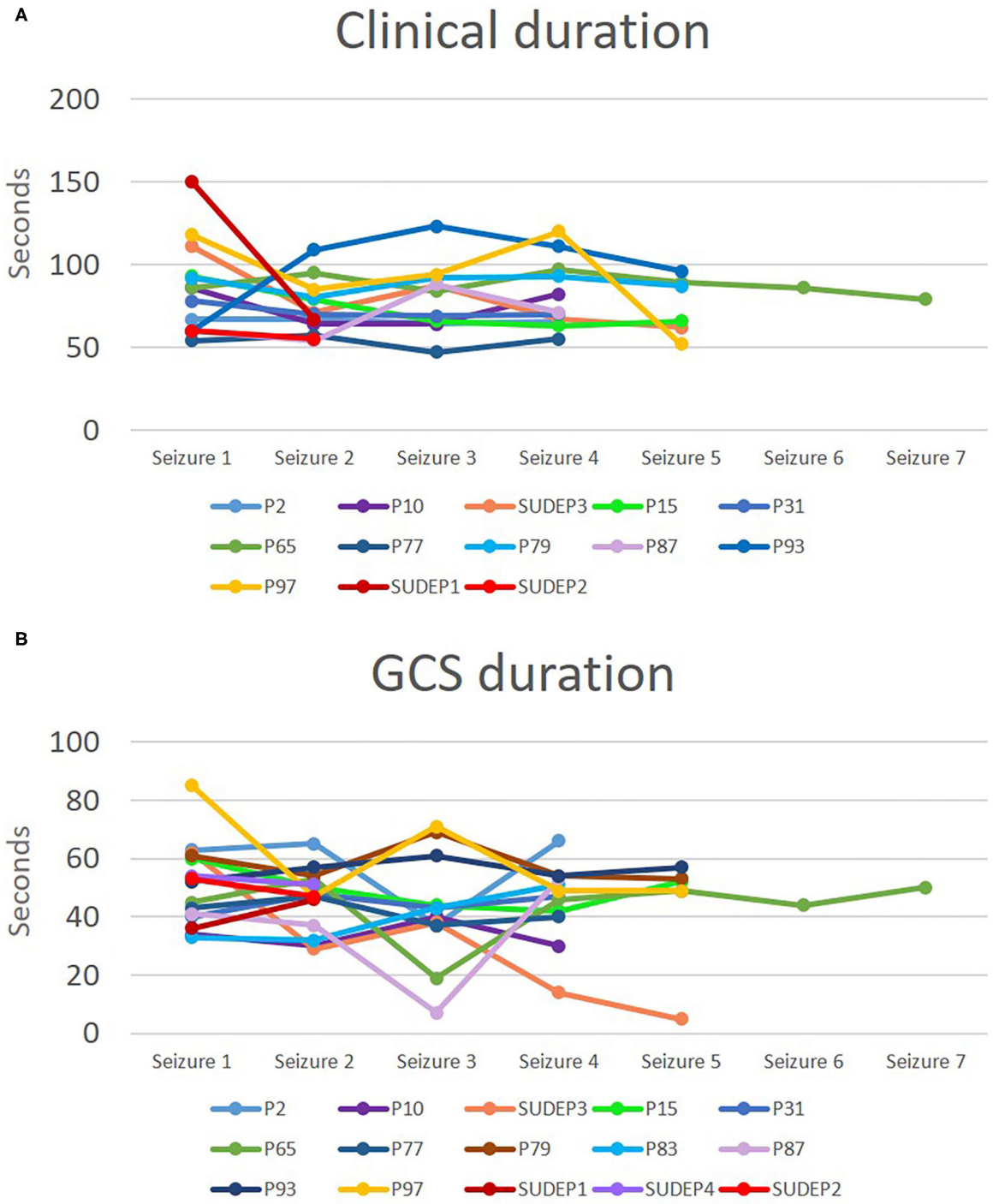


FIGURE 1 | Clinical seizure and convulsive phase durations in patients with at least four seizures in a cluster and for SUDEP cases. Durations for clinical seizure **(A)** and for GCS **(B)** are depicted. Each line represents a cluster and each point represents the duration in seconds for a specific seizure in the cluster.

may not be risk factors for death. Known risk factors of younger age of onset of epilepsy and longer duration of epilepsy may indicate that the underlying tendency toward SUDEP is a progressive phenomenon (28–30). We found no significant effect of duration of epilepsy and age of onset of epilepsy on tendency to worsening of electroclinical markers of seizure severity. Supporting the notion that clusters may not be related to SUDEP risk is the PCDH19-Related Epilepsy Syndrome. It

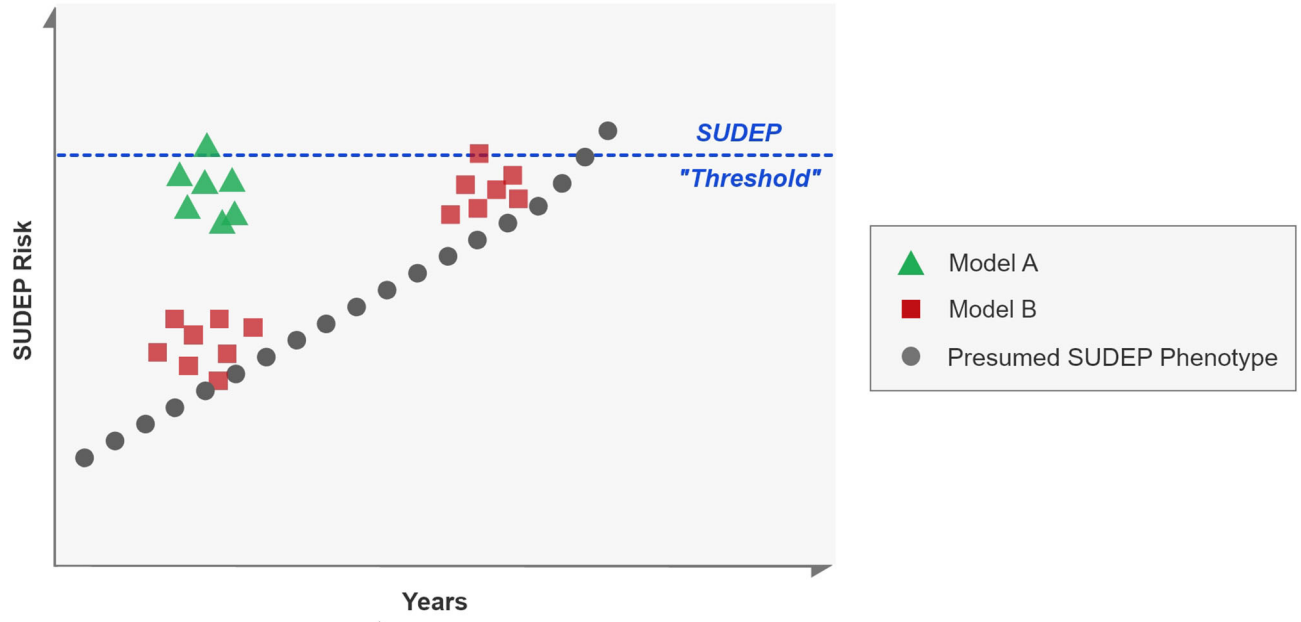


FIGURE 2 | Models of seizure clusters and SUDEP risk. Each square, dot or triangle represents a seizure. A proposed SUDEP phenotype is represented in black, where sporadic seizures occur over years, eventually culminating in SUDEP. Model A proposes that clusters are important for risk of SUDEP, regardless of underlying tendency whereas Model B denotes that risk is only enhanced if the underlying risk has also progressed toward a hypothetical SUDEP "threshold." Our data suggests that model B may be more likely than model A.

is a childhood onset epilepsy syndrome characterized by seizure clusters (31). To the best of our knowledge, no case of SUDEP related to PCDH19 has been reported in the literature.

The four prospectively ascertained SUDEP patients in our study had very long durations of epilepsy (24–43 years), and the time from recorded clusters to SUDEP ranged from 9 months to 5.5 years. None of the patients were reported to have seizure clusters around the time of SUDEP. Two patients had a very high frequency of GCS (up to 24 per year) and two had prolonged PGES (>50 s); both have been proposed as risk factors for SUDEP (27, 32). However, the clusters in our SUDEP cases behaved very similarly to clusters in the rest of our study population.

GCS are the most important risk factor for SUDEP (32). A recent study suggested that GCS become dramatically lethal when they occur under circumstances such as in night time, sleeping alone, living alone and prone position (33). In addition, if risk factors such as living alone and the presence of GCS could be modified, a great proportion (69%) of SUDEP cases could be prevented (34). These observations suggest that GCS clusters occurring in well-supervised environments such as the EMU, like in this study, are unlikely to cause SUDEP.

On examination of electroclinical seizure features, we found no progressive increase in clinical or electrographic seizure duration. There was also no increase in various seizure severity markers such as tonic phase and convulsive phase durations, presence of decerebrate posturing, hypoxemia duration, SpO_2 recovery, and presence of PGES. Some patients showed no significant changes in seizure features from seizure to seizure, whereas others either improved or deteriorated. Within individuals, each subsequent seizure could either show improvement or deterioration in seizure severity, suggesting random variations.

On the other hand, in grouped analysis, durations of clonic phase and PCCA were significantly shorter in subsequent seizures. These findings may indicate faster recovery with subsequent seizures, from a clinical and respiratory standpoint, and thus an adaptive process that is perhaps protective against SUDEP risk. It is possible that seizure termination mechanisms are enhanced with repetitive seizures (35, 36), and lead to faster recovery of respiratory drive and to a shorter clonic phase. However, in contrast to a previous study that found the last seizure in a cluster to be longer, we failed to find significant differences in terms of clinical and EEG seizure duration between the first and the fourth seizure (3) (**Figure 1**). The difference in these findings could reflect dissimilarities in seizure cluster definition and the type of seizures explored. We only included GCS in our study, while other studies have included non-convulsive seizures within the cluster (3). We chose to include only GCS since these events are directly related to SUDEP risk (32, 37). In addition, a study found that in patients who later developed SUDEP, heart rate tended to increase with subsequent seizures in a clusters (38). We evaluated HRV and we did not find any changes in these parameters with subsequent seizures within a cluster.

Interestingly, in grouped analysis, we found some seizure features to worsen, namely duration of decerebrate posturing and ICA duration. Both decerebrate posturing duration and ICA duration are putative markers of seizure severity (39,

40). Decerebrate posturing has been associated with PGES, a proposed SUDEP biomarker (40). Similarly, prolonged ICA (>60 s) has been associated with severe hypoxemia (39). Although, ICA was longer with each seizure, the average duration of ICA was short (17.54 s). Thus, a much larger number of seizure clusters and patients may be needed for study to throw light on the apparently contradictory improvements in some seizure features and deterioration in others.

With regards to ASM, we found that tapering or withdrawal did not influence electroclinical features of a seizure. PGES was more likely to happen in the group with increase or no change in medication. However, PGES duration did not show any difference.

Limitations of our study include difficulty in using a standardized definition of seizure clusters since no consensus currently exists. We chose the definition of two or more GCS in 24 h since the MORTEMUS study observed that patients with SUDEP had two or more seizures before death (19). Clusters in our sample were created by medication discontinuation in the EMU and so they may not behave as seizure clusters in ambulatory PWE. Thus, these may be biologically distinct phenomena. In addition, we did not include in the analysis non-convulsive seizures. Hence, it is not possible to ascertain whether other seizure types could potentially affect the severity of physiologic changes seen in a cluster that also include GCS. We acknowledge that there was a low number of SUDEP cases in our sample.

CONCLUSIONS

If there is no evidence of convincing, progressive deterioration of seizure severity parameters with subsequent seizures, then, is there a role for clusters in SUDEP? The findings of this study suggest that the occurrence of clusters alone does not set the stage for SUDEP with each successive seizure, in quantifiable terms. We therefore hypothesize that SUDEP may be the culmination of underlying disease progression (41) that reaches a critical SUDEP threshold; seizure clusters may only become important for enhanced mortality risk if they occur around this threshold.

In conclusion, clustering failed to show evidence of clinical or electroencephalographic deterioration with each seizure that would explain why seizure clusters may lead to SUDEP, as found by the MORTEMUS study (19). Although clusters may reflect epilepsy severity, their occurrence by themselves may be unrelated to SUDEP risk, and may require underlying progression toward a SUDEP threshold before finally leading to SUDEP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Case Western Reserve University and University Hospitals, as part of NIH/NINDS Center for SUDEP Research study (U01 NS090405, U01 NS090406, U01 NS090407). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MO-U: major role in the acquisition and analysis of data, design and conceptualized the study, interpreted the data, and drafted the manuscript for intellectual content. NL and SL: design and conceptualized study, interpreted the data, and revised the manuscript for intellectual content. LV, SJ-O, MR, JPH, MD, JH, NH, VR-M, CS, JO, and ST: data acquisition. LZ: analysis of data, statistical analysis, and reviewed the manuscript for intellectual content. RS, DF, MN, LA, BG, SS, RH, BD, LB, OD, GR, and G-QZ: revised the manuscript for intellectual content.

FUNDING

This study was funded by the Center for SUDEP Research: NIH/NINDS U01-NS090405, U01 NS090406, and U01 NS090407.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.643916/full#supplementary-material

REFERENCES

1. Haut SR, Lipton RB, LeValley AJ, Hall CB, Shinnar S. Identifying seizure clusters in patients. *Neurology*. (2005) 19:1313–5. doi: 10.1212/01.wnl.0000180685.84547.7f
2. Sillanpää M, Schmidt D. Seizure clustering during drug treatment affects seizure outcome and mortality of childhood-onset epilepsy. *Brain*. (2008) 131:938–44. doi: 10.1093/brain/awn037
3. Ferastraoaru V, Schulze-Bonhage A, Lipton RB, Dümpelmann M, Legatt AD, Blumberg J, et al. Termination of seizure clusters is related to the duration of focal seizures. *Epilepsia*. (2016) 57:889–95. doi: 10.1111/epi.13375
4. Haut SR. Seizure clusters: characteristics and treatment. *Curr Opin Neurol*. (2015) 28:143–50. doi: 10.1097/WCO.0000000000000177
5. Dreifuss FE, Rosman NP, Cloyd JC, Pellock JM, Kuzniecky RI, Lo WD, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med*. (1998) 338:1869–75. doi: 10.1056/NEJM199806253382602
6. Jafarpour S, Hirsch LJ, Gaínza-Lein M, Kellinghaus C, Detyniecki K. Seizure cluster: definition, prevalence, consequences, and management. *Seizure*. (2019) 68:9–15. doi: 10.1016/j.seizure.2018.05.013
7. Haut SR, Shinnar S, Moshé SL. Seizure clustering: risks and outcomes. *Epilepsia*. (2005) 46:146–9. doi: 10.1111/j.0013-9580.2005.29004.x

8. Scholly J, Bartolomei F, Valenti-Hirsch MP, Boulay C, De Saint Martin A, Timofeev A, et al. Atonic seizures in children with surgically remediable epilepsy: a motor system seizure phenotype? *Epileptic Disord*. (2017) 19:315–26. doi: 10.1684/epd.2017.0930
9. Yen D-J, Chen C, Shih Y-H, Guo Y-C, Liu L-T, Yu H-Y, et al. Antiepileptic drug withdrawal in patients with temporal lobe epilepsy undergoing presurgical video-EEG monitoring. *Epilepsia*. (2008) 42:251–5. doi: 10.1046/j.1528-1157.2001.15100.x
10. Chen B, Choi H, Hirsch LJ, Katz A, Legge A, Wong RA, et al. Prevalence and risk factors of seizure clusters in adult patients with epilepsy. *Epilepsy Res*. (2017) 133:98–102. doi: 10.1016/j.eplepsyres.2017.04.016
11. Rose AB, McCabe PH, Gilliam FG, Smith BJ, Boggs JG, Ficker DM, et al. Occurrence of seizure clusters and status epilepticus during inpatient video-EEG monitoring. *Neurology*. (2003) 60:975–8. doi: 10.1212/01.WNL.0000053748.83309.28
12. Di Gennaro G, Picardi A, Sparano A, Mascia A, Meldolesi GN, Grammaldo LG, et al. Seizure clusters and adverse events during pre-surgical video-EEG monitoring with a slow anti-epileptic drug (AED) taper. *Clin Neurophysiol*. (2012) 123:486–8. doi: 10.1016/j.clinph.2011.08.011
13. Martinez C, Sullivan T, Hauser WA. Prevalence of acute repetitive seizures (ARS) in the United Kingdom. *Epilepsy Res*. (2009) 87:137–43. doi: 10.1016/j.eplepsyres.2009.08.006
14. Fisher RS, Bartfeld E, Cramer JA. Use of an online epilepsy diary to characterize repetitive seizures. *Epilepsy Behav*. (2015) 47:66–71. doi: 10.1016/j.yebeh.2015.04.022
15. Asadi-Pooya AA, Nei M, Sharan A, Sperling MR. Seizure clusters in drug-resistant focal epilepsy. *Epilepsia*. (2016) 57:e187–90. doi: 10.1111/epi.13465
16. Penovich PE, Buelow J, Steinberg K, Sirven J, Wheless J. Burden of seizure clusters on patients with epilepsy and caregivers. *Neurologist*. (2017) 22:207–14. doi: 10.1097/NRL.0000000000000140
17. Fahoum F, Omer N, Kipervasser S, Bar-Adon T, Neufeld M. Safety in the epilepsy monitoring unit: a retrospective study of 524 consecutive admissions. *Epilepsy Behav*. (2016) 61:162–7. doi: 10.1016/j.yebeh.2016.06.002
18. Rheims S, Ryvlin P. Patients' safety in the epilepsy monitoring unit. *Curr Opin Neurol*. (2014) 27:213–8. doi: 10.1097/WCO.0000000000000076
19. 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) 12:966–77. doi: 10.1016/S1474-4422(13)70214-X
20. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. (2009) 51:1069–77. doi: 10.1111/j.1528-1167.2009.02397.x
21. Fisher RS, Cross JH, French JA, Higurashi N, Peltola J, Roulet E, et al. Operational classification of seizure types by the International League Against Epilepsy : position paper of the ILAE commission for classification and terminology. *Epilepsia*. (2017) 58:522–30. doi: 10.1111/epi.13670
22. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia*. (2017) 58:512–21. doi: 10.1111/epi.13709
23. Tatum WO. Normal adult EEG. In: Ebersole JS, Husain AM, Nordli DR Jr, editors. *Current Practice of Clinical Electroencephalography*. 4th ed. Philadelphia: Wolters Kluwer (2014). p. 90–124.
24. Lhatoo SD, Luders HO. Secondary generalized tonic–clonic seizures (54b). In: Luders HO, editor. *Textbook of Epilepsy Surgery*. London, UK: Informa Healthcare (2008). p. 492–500.
25. Alexandre V, Mercedes B, Valton L, Maillard L, Bartolomei F, Szurhaj W, et al. Risk factors of postictal generalized EEG suppression in generalized convulsive seizures. *Neurology*. (2015) 85:1598–603. doi: 10.1212/WNL.0000000000001949
26. Vilella L, Lacuey N, Hampson JP, Rani MRS, Loparo K, Sainju RK, et al. Incidence, recurrence, and risk factors for peri-ictal central apnea and sudden unexpected death in epilepsy. *Front Neurol*. (2019) 10:1–13. doi: 10.3389/fneur.2019.00166
27. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. *Ann Neurol*. (2010) 68:787–96. doi: 10.1002/ana.22101
28. Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: a search for risk factors. *Epilepsy Behav*. (2007) 10:138–41. doi: 10.1016/j.yebeh.2006.11.010
29. Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, et al. Incidence and risk factors in sudden unexpected death in epilepsy. *Neurology*. (2001) 56:519–25. doi: 10.1212/WNL.56.4.519
30. Nilsson L, Farahmand B, Persson P-G, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case control study. *Lancet*. (1999) 353:888–93. doi: 10.1016/S0140-6736(98)05114-9
31. Samanta D. PCDH19-related epilepsy syndrome: a comprehensive clinical review. *Pediatr Neurol*. (2020) 105:3–9. doi: 10.1016/j.pediatrneurol.2019.10.009
32. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors. *Neurology*. (2017) 88:1674–80. doi: 10.1212/WNL.0000000000003685
33. Sveinsson O, Andersson T, Carlsson S, Tomson T. Circumstances of SUDEP: a nationwide population-based case series. *Epilepsia*. (2018) 59:1074–82. doi: 10.1111/epi.14079
34. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP. *Neurology*. (2020) 94:e419–29. doi: 10.1212/WNL.0000000000008741
35. Lado FA, Moshé SL. How do seizures stop? *Epilepsia*. (2008) 49:1651–64. doi: 10.1111/j.1528-1167.2008.01669.x
36. Timofeev I, Steriade M. Neocortical seizures: initiation, development and cessation. *Neuroscience*. (2004) 123:299–336. doi: 10.1016/j.neuroscience.2003.08.051
37. Faingold CL, Evans MS. Pathophysiology of generalized tonic-clonic seizures. In: Panayiotopoulos CP, editor. *Atlas of Epilepsies*. London: Springer London (2010). p. 243–6.
38. Nei M, Ho RT, Abou-Khalil BW, Drislane FW, Liporace J, Romeo A, et al. EEG and ECG in sudden unexplained death in epilepsy. *Epilepsia*. (2004) 45:338–45. doi: 10.1111/j.0013-9580.2004.05503.x
39. Lacuey N, Zonjy B, Hampson JP, Rani MRS, Zaremba A, Sainju RK, et al. The incidence and significance of periictal apnea in epileptic seizures. *Epilepsia*. (2018) 59:573–82. doi: 10.1111/epi.14006
40. Vilella L, Lacuey N, Hampson JP, Zhu L, Omidi S, Ochoa-Urrea M, et al. Association of peri-ictal brainstem posturing with seizure severity and breathing compromise in patients with generalized convulsive seizures. *Neurology*. (2021) 96:e352–65. doi: 10.1212/WNL.0000000000011274
41. Simeone KA, Hallgren J, Bockman CS, Aggarwal A, Kansal V, Netzel L, et al. Respiratory dysfunction progresses with age in Kcna1-null mice, a model of sudden unexpected death in epilepsy. *Epilepsia*. (2018) 59:345–57. doi: 10.1111/epi.13971

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 16 February 2021
doi: 10.3389/fneur.2021.636045

Seizure Clusters: Morbidity and Mortality

*Kristie Bauman and Orrin Devinsky**

Department of Neurology, NYU Grossman School of Medicine and NYU Langone Comprehensive Epilepsy Center, New York, NY, United States

Seizure clusters, an intermediate between single seizure and status epilepticus, are associated with morbidity, impaired quality of life, and premature mortality. The relationship between seizure clusters and sudden unexplained death in epilepsy (SUDEP) is poorly understood. Here, we define seizure clusters; review comorbid psychiatric disorders and memory deficits associated with seizure clusters; and review cases of witnessed SUDEP for which seizure frequency prior to death is available. Patients with a history of seizure clusters have a 2.5 fold increased risk for SUDEP, and one third of patients with monitored in hospital SUDEP experienced a cluster of generalized tonic clonic seizures prior to death. Understanding the effects of seizure frequency and duration on SUDEP risk could yield new insights in SUDEP pathophysiology and new targets for intervention.

Keywords: seizure, seizure cluster, SUDEP (sudden unexplained death in epilepsy), morbidity, mortality

OPEN ACCESS

Edited by:
Brian Darryl Moseley, University of Cincinnati, United States

Reviewed by:
Marina Trivisano, Bambino Gesù Children Hospital (IRCCS), Italy
Manuel Toledo, Vall d'Hebron University Hospital, Spain

****Correspondence:***
Orrin Devinsky
od4@nyu.edu
orcid.org/0000-0003-0044-4632

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *08 December 2020*
Accepted: *25 January 2021*
Published: *16 February 2021*

Citation:
Bauman K and Devinsky O (2021) Seizure Clusters: Morbidity and Mortality. Front. Neurol. 12:636045. doi: 10.3389/fneur.2021.636045

INTRODUCTION

Seizure duration forms a continuous range from brief single seizures to refractory status epilepticus with seizure clusters as intermediate, whose durations, number of discrete events and severities vary widely. The border between single seizure, seizure cluster and status epilepticus is obscured by overlapping biological phenomena and the lack of a precise, readily quantified, or widely accepted definition of a seizure cluster. Seizure clusters are typically defined by the number of seizures over a specific interval or as an increased seizure frequency above baseline recognizable by patient or family (1–5). For many patients, seizure clusters impair quality of life and increase morbidity (hospitalization, status epilepticus, postictal psychosis), and mortality (6–11).

The relationship between seizure clusters and sudden unexplained death in epilepsy (SUDEP) remains poorly defined. The borders between SUDEP, death following seizure clusters, and death from status epilepticus are unclear. Terminologies vary widely among and between epileptologists focused on clinical care and those focused on SUDEP research, and forensic pathologists/medical examiners. Because >99% of SUDEPs occur out of hospital and ∼90% are unwitnessed, the presence, types and durations of seizures preceding death are poorly characterized (12, 13). Current SUDEP criteria exclude documented status epilepticus, although in individual cases, it is often impossible to determine if status preceded death. Here, we examine the definitions of seizure clusters, and relationships between premature death and seizure frequency and between seizure clusters and SUDEP.

TABLE 1 | Clinical definitions of seizure clusters.

References	Time Interval	Seizure Number and Type
Di Gennaro et al. (1) Noe and Drazkowski (18) Haut et al. (8) Rose et al. (4) Haut et al. (3) Yen et al. (5) Haut et al. (9)	24 h	> 3 focal impaired awareness seizures
Martinez et al. (17) Sillanpää and Schmidt (11)	24 h	> 3 focal or generalized seizures (excluding absence and myoclonic seizures)
Penovich et al. (20) Fisher et al. (19)	24 h	> 2 seizures of any type
Detyniecki et al. (22) Detyniecki et al. (21)	6 h	> 2 seizures of any type
Di Gennaro et al. (1) Noe and Drazkowski (18) Rose et al. (4)	4 h	> 3 focal impaired awareness seizures

WHAT ARE SEIZURE CLUSTERS?

Seizure clusters lack a uniformly accepted clinical (see **Table 1**) or statistical definition (14, 15). Many studies have proposed clinical definitions of seizure clusters as a number of seizures over a unit of time. This is founded on the finding that seizures that recur within 8 h are more likely to come from a concordant focus and are therefore not independent of each other (7, 16). Thus, many define seizure clusters as > 3 seizures over 24 h since the average interictal period is ≤ 8 h (1, 3–5, 8, 9, 11, 17, 18). Others have broadened the definition to 2 or more seizures in 24 h to allow easier patient recall of seizure clusters (19, 20). More recent studies have both shortened the time interval and decreased the number of seizures required to define a cluster to > 2 seizures in 6 h (21, 22). This change encourages earlier recognition of seizure clusters and earlier use of rescue medication but misses clusters which occur over a longer period of time.

It is important to also consider which seizure types should be counted when defining seizure clusters. Seizure severity is one factor to consider as some seizure types may have a greater effect on quality of life, morbidity, and mortality. Many studies in presurgical patients have therefore included only focal impaired awareness and focal to bilateral tonic clonic seizures in their definitions of seizure clusters (1, 3–5, 8, 9, 18). While some suggest including all seizure types for ease of patient recall and reporting (19), this may overestimate the prevalence of clinically relevant seizure clusters if seizures which typically occur at high frequencies are included. Many therefore exclude absence and myoclonic seizures (11, 17). Similarly, many excluded generalized epilepsy syndromes which are associated with a high seizure burden such as West Syndrome and Lennox Gastaut since typical seizure frequency in these patients often far exceeds the numeric seizure threshold for clustering (11). However, these patients can still have a clinically relevant increase in seizure frequency above baseline which should also be considered seizure clusters.

Statistical definitions of seizure clusters may be more applicable in some scenarios than definitions which focus on seizure number and interval alone. Bauer and Burr (23) proposed one of the most inclusive statistical definitions for clusters: "those time periods during which seizure occurrence is significantly increased compared to the rate expected from an individual mean." Others defined clusters as a threefold increase in the patient's typical seizure frequency over a three day period (24).

Both clinical and statistical definitions fail to capture clinically relevant clusters in subsets of patients. A clinical definition > 2 seizures in 6 h encourages earlier use of rescue medication and may decrease incidence of adverse events due to clustering, but may miss patients whose clusters occur over longer periods of time. A definition of 3 seizures in a 24 h period captures these patients, but may overestimate seizure clusters in patients with high seizure frequency. On the other end of the spectrum, statistical definition of clusters such as a three fold increase in seizure frequency overestimates clusters in patients with low seizure frequency, such as a single breakthrough seizure in a previously seizure free patient. These definitions have the potential to overestimate seizure frequency due to the failure to account for random variations in seizure frequency. More recently, the algorithm *ClusterCalc* has been proposed to improve sensitivity and specificity in identifying seizure clusters by accounting for random variation (25). This algorithm demonstrated that 37–59% of clusters identified by traditional definitions may have occurred due to chance (25).

Seizure clusters also reflect an ongoing debate whether "seizures beget seizures" (26). Although this maxim is often considered from the perspective of seizures dispersed more widely in time (e.g., a boy has convulsive seizures at age 8, 11, 12, and 12.5—the shortening interval possibly reflecting another maxim), it is also consistent with recurrent seizures over a brief interval (i.e., seizure cluster). Both interpretations are also consistent with Hebb's maxim that "neurons that fire together wire together" (27).

The prevalence of seizure clusters varies by population. Among inpatients with drug resistant epilepsy undergoing anti-seizure medication (ASM) withdrawal for pre-surgical evaluations, 39 to 61% experience seizure clusters over a 24 h period during a study lasting 2–12 days (1, 3, 4, 9). Among outpatients, seizure clusters are less frequent, occurring in 22 to 34% of patients over years (11, 21, 28, 29). However, after excluding patients who are seizure free, the rates of clustering among those with active epilepsy is higher at 52% and even higher at 71% among those with > 4 seizures per year (21).

Seizure clusters are associated with significant morbidity. Depending on the individual, the severity and frequency of seizures within a cluster, and other factors, seizure clusters may predispose to acute or more long-lasting psychiatric, cognitive or physical disorders. Postictal psychosis is more common after clustering. Case series and case- control cohort studies of patients with postictal psychosis showed a trend toward high rates of seizure clustering before postictal psychosis, though this did not reach statistical significance in these underpowered studies

(6, 10). Clusters may cause long term disability through the development of interictal psychosis. In one case series, 13.4% of patients with postictal psychosis developed interictal psychosis (30). Seizure clusters may drive changes in neuronal networks that lower the threshold for psychosis and depress normal neuronal function over time (30). Despite their association with psychosis, seizure clusters are not associated with higher rates of anxiety or depression (8).

The effect of seizure clusters on memory is not well defined as we lack well-powered prospective case-control studies. Our data cannot distinguish the direct adverse effects of clusters from progression of epileptogenesis or the underlying disorder, medication effects and other factors (e.g., head injury from seizures, depression). While postictal and interictal psychosis are associated with memory and other cognitive impairments, seizure clusters could theoretically have beneficial cognitive effects by increasing the inter-seizure interval and allowing longer periods of brain "rest" with seizure freedom.

Compared to those with weekly, or daily seizures ($N = 32$), those with seizure clusters with seizure free intervals of at least 2 weeks ($N = 8$) had significantly higher IQ, arithmetic, and reading comprehension scores (31). However, this study did not quantify total seizure number and cannot distinguish the effect of seizure frequency or seizure number on cognition.

Patients with seizure clusters have higher rates of several adverse outcomes, including failure to achieve seizure remission during treatment (i.e., treatment-resistant epilepsy) (11), high seizure frequencies (8, 11) and more frequent hospitalizations (8). Seizure clusters also affect many aspects of quality of life with a majority of patients reporting negative effects on their career, independence, ability to drive, extracurricular, and social activities, and ability to travel (20). Evidence supports and refutes an association between seizure clusters and status epilepticus (3, 8, 9). The burden of prolonged seizures and status epilepticus among seizure cluster patients is likely underestimated since many patients live alone and have no recall for clusters or status. Further, changing definitions of clusters and status epilepticus (e.g., 10 vs. 30 min) limits comparisons across studies. Seizure clusters affect large portions of the epilepsy population and likely contribute directly to some deaths.

SEIZURE CLUSTERS AND MORTALITY

In one population study, people with epilepsy had an 11 fold higher odds of premature death compared to matched general population controls (32). The risk of sudden unexplained death is even higher. A Danish cohort of children and young adults with epilepsy had a 27 fold higher risk of sudden unexplained death, which remained elevated at 16 times higher risk even after adjusting for comorbidities associated with epilepsy (33). Although many deaths result from the underlying cause of epilepsy (e.g., neoplasms, stroke, perinatal disorders), 15.8% were caused by external causes. Individuals with epilepsy were more likely to die from suicide, assault, motor vehicle accidents, and non-vehicle accidents such as falls and drowning (32). This risk accrues with increasing seizure frequency, seizure clustering, and time since epilepsy diagnosis. In a Finnish cohort of childhood onset epilepsy patients followed for ∼40 years found that patients with seizure clusters had a 3.5-fold greater frequency of premature death (42%) than those without seizure clusters (14%) (11). This risk may be modifiable as patients with seizure clusters who subsequently had better seizure control did not have an increased risk of death (11). Seizure control strongly influenced SUDEP risk. Adult patients with childhood onset epilepsy with poor seizure control had a 5-fold increased risk of SUDEP (34). However, the relationship between seizure clusters and SUDEP is poorly understood.

SEIZURE CLUSTERS AND SUDEP

Nearly 90% of SUDEPs are unwitnessed. Our understanding of the relationship between SUDEP and seizure duration and frequency is limited to witnessed out of hospital SUDEPs and SUDEPs which recorded by video EEG. While status epilepticus cases are excluded from SUDEP, it is difficult and often impossible to differentiate seizure clusters during sleep from status epilepticus without video EEG since observers cannot distinguish ongoing nonconvulsive seizures, postictal sedation, and normal sleep. Here, we review the existing case series and case reports of witnessed SUDEP and the seizure frequency prior to death as available.

A series of 15 witnessed out-of-hospital SUDEP found that 12 were preceded by GTC, one by focal seizure, and two by post-ictal state due to seizure of unknown semiology (35). While status epilepticus cases (seizures >30 min or multiple seizures without return to baseline) were excluded, the identification of seizure clusters or status epilepticus was severely limited in this population since most patients were found in bed (35). Thus, recognition of seizure could be delayed and family members or caregivers may only observe the seizure after they awaken (e.g., at 6 a.m.) or when they hear noises associated with a seizure, which again may correspond with lighter stages of sleep. Thus, even in witnessed cases, the true seizure frequency or duration during the hours before death is rarely known with certainty. While seizure number in the 24 h before death could identify seizure cluster cases, this data is limited by recall bias and memory lapses due to delays in interviewing family members after SUDEP occurred.

Other studies used historical seizure frequency to characterize seizure frequency before SUDEP. In the Finnish pediatric cohort followed prospectively for ∼40 years, 22% of patients had >1 lifetime seizure cluster (11). SUDEP was >2.5-fold more frequent among those with seizure clusters than those without (8 vs. 3%), but the small sample size limited statistical power (11). The effect of seizure clusters on SUDEP risk in epileptic encephalopathies is poorly understood. Seizure clusters are common in several developmental epileptic encephalopathies, including Dravet and PCDH19 syndromes, in which clusters are often provoked by fever. Although seizure clusters occur in more than 90% of PCDH19 patients (36), SUDEP is rarely reported. By contrast, patients with Dravet syndrome often have nocturnal clusters of tonic or tonic-clonic seizures, especially between ages 4–11 years of age (37). It is possible that a tendency to more severe

seizure clusters in sleep contributes to SUDEP risk in Dravet syndrome, although further study, ideally including a spectrum of developmental epileptic encephalopathies would be helpful in identifying relevant factors.

The MORTality in Epilepsy Monitoring Unit Study (38), reviewed 29 cardiorespiratory arrests in patients observed in epilepsy monitoring units. This landmark study provided important insights into SUDEP pathophysiology. These cases may differ in some ways from out of hospital SUDEP since most had anti-seizure medication withdrawal before death, although the majority of out-of-hospital SUDEPs were found to have subtherapeutic or undetectable anti-seizure medication levels or did not take their last dose of medication, suggesting many underwent medication withdrawal (12, 13, 39). MORTEMUS included 16 cases of definite or probable SUDEP, 2 fatal near SUDEP, 7 non-fatal near SUDEP, and 4 deaths due to other causes (38). Like other studies, nearly all SUDEPs occurred overnight, limiting data in cases where the patient not being monitored when death occurred. All 11 monitored SUDEP cases were preceded by a GTC. Among these cases, 7 cases had only the one terminal GTC in the 12 h preceding death. Of the remaining four cases, two patients had 5 GTCs, one had 4 GTCs, and one had 2 GTCs in the 12 h preceding death. Unfortunately, seizure duration was not reported, and while no deaths resulted from status epilepticus, the definition of status epilepticus was not explicitly defined and series spanned a period in which diagnostic criteria for status epilepticus changed. Further, most SUDEPs occurred in sleep, making it uncertain if patients returned to baseline between seizures, which makes it impossible to distinguish a cluster from status epilepticus. Also, non-GTCs were not quantified and the number of patients with clusters of focal and generalized seizures before death is unknown. In MORTEMUS, 36% of patients had clusters of 2 or more GTCs in the 24 h prior to death, but the true prevalence of seizure clusters with focal unaware and focal aware seizures is likely higher (38).

CONCLUSION

Although epilepsy is associated with morbidity and mortality, these risks appear to be higher in individuals with a seizure cluster. People with epilepsy have an 11 times higher risk of premature death (32), and patients with seizure clusters are at even higher risk with one cohort finding a 3.5 fold higher risk of premature death in those with seizure clusters compared to those without (11).

Poor seizure control and seizure medication withdrawal are risk factors for SUDEP (12, 13, 34, 39). This could suggest that seizure clusters, which may be more frequent in these groups, are also a risk factor for SUDEP. Patients with a history of seizure clusters during their lifetime had a 2.5 fold increased risk of SUDEP, though this study was underpowered due to small sample size (11). Among cases of monitored in hospital SUDEP, 36% had clusters of GTCs in the 24 h prior to death (38). The rates of focal seizure clusters in this population is unknown, and the prevalence of both focal and generalized seizure clusters prior to SUDEP is likely higher.

The greatest limitation in our understanding of the pathophysiology and effects of seizure clusters is the lack of a consensus definition (14, 15). Existing definitions are often tailored to the patient population being studied: $>$ 2 seizures in 24 h for outpatient seizure diary studies which require patient recall (19, 20), $>$ 2 seizures in 6 h for studies examining efficacy of rescue medications (22), or statistical definitions for those with high seizure frequency such as in Lennox Gastaut Syndrome. While these definitions each have strengths within specific patient populations, the variation limits comparisons of studies and generalizability of findings. The consensus definition for seizure clusters should aim to identify seizure clusters as soon as possible to allow earlier intervention while also striving to not over or underestimate clinically relevant seizure clusters. Algorithms such as *ClusterCalc* identify clusters while accounting for randomness in inter-seizure interval variation and may improve our ability to study clinically significant seizure clusters (25). Further research in this area may help determine when clusters are more likely to self-terminate, continue, or result in status epilepticus or SUDEP and allow targeted early intervention to prevent adverse effects of seizure clusters.

The effect of seizure clusters on SUDEP risk remains poorly understood. Research in this area has been limited by multiple factors: (1) $>$99% of SUDEPs occur out of hospital, (2) $\sim$90% of SUDEPs are unwitnessed, and (3) recall bias and memory lapses due to delays in interviewing witnesses of SUDEP. While the effect of the first two factors is difficult to overcome, the third may be a target for intervention in future studies. The rise of electronic seizure diaries could offer new insights into seizure frequency and duration in the hours to days prior to SUDEP. Similarly, seizures captured through responsive neurostimulation may be readily quantified, though this population is limited and remains small at this time. Understanding the effects of seizure frequency and duration on SUDEP risk could offer insights in the SUDEP pathophysiology and new targets for intervention.

AUTHOR CONTRIBUTIONS

Both authors, KB and OD, contributed on conception, design and drafting the article or revising it critically for important intellectual content. They both approved the final version.

REFERENCES

1. Di Gennaro G, Picardi A, Sparano A, Mascia A, Meldolesi GN, Grammaldo LG, et al. Seizure clusters and adverse events during pre-surgical video-EEG monitoring with a slow anti-epileptic drug (AED) taper. *Clin Neurophysiol.* (2012) 123:486–8. doi: 10.1016/j.clinph.2011.08.011
2. Haut SR. Seizure clusters: characteristics and treatment. *Curr Opin Neurol.* (2015) 28:143–50. doi: 10.1097/wco.0000000000000177
3. Haut SR, Swick C, Freeman K, Spencer S. Seizure clustering during epilepsy monitoring. *Epilepsia.* (2002) 43:711–5. doi: 10.1046/j.1528-1157.2002.26401.x

4. Rose AB, McCabe PH, Gilliam FG, Smith BJ, Boggs JG, Ficker DM, et al. Occurrence of seizure clusters and status epilepticus during inpatient video-EEG monitoring. *Neurology.* (2003) 60:975–8. doi: 10.1212/01.wnl.0000053748.83309.28
5. Yen DJ, Chen C, Shih YH, Guo YC, Liu LT, Yu HY, et al. Antiepileptic drug withdrawal in patients with temporal lobe epilepsy undergoing presurgical video- EEG monitoring. *Epilepsia.* (2001) 42:251–5. doi: 10.1046/j.1528-1157.2001.15100.x
6. Alper K, Kuzniecky R, Carlson C, Barr WB, Vorkas CK, Patel JG, et al. Postictal psychosis in partial epilepsy: a case-control study. *Ann Neurol.* (2008) 63:602–10. doi: 10.1002/ana.21341
7. Haut SR. Seizure clustering. *Epilepsy Behav.* (2006) 8:50–5. doi: 10.1016/j.yebeh.2005.08.018
8. Haut SR, Shinnar S, Moshé SL. Seizure clustering: risks and outcomes. *Epilepsia.* (2005) 46:146–9. doi: 10.1111/j.0013-9580.2005.29004.x
9. Haut SR, Shinnar S, Moshé SL, O'Dell C, Legatt AD. The association between seizure clustering and convulsive status epilepticus in patients with intractable complex partial seizures. *Epilepsia.* (1999) 40:1832–4. doi: 10.1111/j.1528-1157.1999.tb01607.x
10. Logsdail SJ, Toone BK. Post-ictal psychoses. A clinical and phenomenological description. *Br J Psychiatry.* (1988) 152:246–52. doi: 10.1192/bjp.152.2.246
11. Sillanpää M, Schmidt D. Seizure clustering during drug treatment affects seizure outcome and mortality of childhood-onset epilepsy. *Brain.* (2008) 131:938–44. doi: 10.1093/brain/awn037
12. Pollanen MS, Kodikara S. Sudden unexpected death in epilepsy: a retrospective analysis of 24 adult cases. *Forensic Sci Med Pathol.* (2012) 8:13–8. doi: 10.1007/s12024-011- 9263-4
13. Verducci C, Hussain F, Donner E, Moseley BD, Buchhalter J, Hesdorffer D, et al. SUDEP in the North American SUDEP Registry: the full spectrum of epilepsies. *Neurology.* (2019) 93:e227–e36. doi: 10.1212/wnl.0000000000007778
14. Gidal B, Klein P, Hirsch LJ. Seizure clusters, rescue treatments, seizure action plans: Unmet needs and emerging formulations. *Epilepsy Behav.* (2020) 112:107391. doi: 10.1016/j.yebeh.2020.107391
15. Jafarpour S, Hirsch LJ, Gaínza-Lein M, Kellinghaus C, Detyniecki K. Seizure cluster: Definition, prevalence, consequences, and management. *Seizure.* (2019) 68:9–5. doi: 10.1016/j.seizure.2018.05.013
16. Haut SR, Legatt AD, O'Dell C, Moshé SL, Shinnar S. Seizure lateralization during EEG monitoring in patients with bilateral foci: the cluster effect. *Epilepsia.* (1997) 38:937–40. doi: 10.1111/j.1528-1157.1997.tb01260.x
17. Martinez C, Sullivan T, Hauser WA. Prevalence of acute repetitive seizures (ARS) in the United Kingdom. *Epilepsy Res.* (2009) 87:137–43. doi: 10.1016/j.eplepsyres.2009.08.006
18. Noe KH, Drazkowski JF. Safety of long-term video-electroencephalographic monitoring for evaluation of epilepsy. *Mayo Clin Proc.* (2009) 84:495–500. doi: 10.1016/s0025-6196(11)60580-6
19. Fisher RS, Bartfeld E, Cramer JA. Use of an online epilepsy diary to characterize repetitive seizures. *Epilepsy Behav.* (2015) 47:66–71. doi: 10.1016/j.yebeh.2015.04.022
20. Penovich PE, Buelow J, Steinberg K, Sirven J, Wheless J. Burden of seizure clusters on patients with epilepsy and caregivers: survey of patient, caregiver, clinician perspectives. *Neurologist.* (2017) 22:207–14. doi: 10.1097/nrl.0000000000000140
21. Detyniecki K, O'Bryan J, Choezom T, Rak G, Ma C, Zhang S, et al. Prevalence and predictors of seizure clusters: a prospective observational study of adult patients with epilepsy. *Epilepsy Behav.* (2018) 88:349–56. doi: 10.1016/j.yebeh.2018.09.035
22. Detyniecki K, Van Ess PJ, Sequeira DJ, Wheless JW, Meng TC, Pullman WE. Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters-a randomized, double-blind, placebo-controlled trial. *Epilepsia.* (2019) 60:1797–808. doi: 10.1111/epi.15159
23. Bauer J, Burr W. Course of chronic focal epilepsy resistant to anticonvulsant treatment. *Seizure.* (2001) 10:239–46. doi: 10.1053/seiz.2000.0499
24. Newmark ME, Dubinsky S. The significance of seizure clustering: a review of 343 outpatients in an epilepsy clinic. In: Dreifuss FE, editor. *Chronopharmacology in Therapy of the Epilepsies*. New York, NY: Raven Press (1990). p. 89–103.
25. Chiang S, Haut SR, Ferastraoaru V, Rao VR, Baud MO, Theodore WH, et al. Individualizing the definition of seizure clusters based on temporal clustering analysis. *Epilepsy Res.* (2020) 163:106330. doi: 10.1016/j.eplepsyres.2020.106330
26. Gowers WR. *Epilepsy and Other Chronic Convulsive Disorders: Their Causes, Symptoms and Treatment*. London: JandA Churchill. (1881).
27. Keysers C, Gazzola V. Hebbian learning and predictive mirror neurons for actions, sensations and emotions. *Philos Trans R Soc Lond B Biol Sci.* (2014) 369:20130175. doi: 10.1098/rstb.2013.0175
28. Bauer J, Ghane Y, Flügel D, Wildt L, Stefan H. Etiology, follow-up and therapy of seizure clusters in temporal lobe epilepsy and catamenial epileptic seizures. *Schweiz Arch Neurol Psychiatr.* (1992) 143:117–34.
29. Manford M, Fish DR, Shorvon SD. An analysis of clinical seizure patterns and their localizing value in frontal and temporal lobe epilepsies. *Brain.* (1996) 119:17–40. doi: 10.1093/brain/119.1.17
30. Tarulli A, Devinsky O, Alper K. Progression of postictal to interictal psychosis. *Epilepsia.* (2001) 42:1468–71. doi: 10.1046/j.1528-1157.2001.10701.x
31. Smith ML, Elliott IM, Lach L. Cognitive skills in children with intractable epilepsy: comparison of surgical and nonsurgical candidates. *Epilepsia.* (2002) 43:631–7. doi: 10.1046/j.1528-1157.2002.26101.x
32. Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet.* (2013) 382:1646–54. doi: 10.1016/s0140-6736(13)60899-5
33. Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, Haunsø S, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. *Epilepsia.* (2013) 54:1613–20. doi: 10.1111/epi.12328
34. Sillanpä M, Shinnar S. Long-term mortality in childhood-onset epilepsy. *N Engl J Med.* (2010) 363:2522–2529. doi: 10.1056/NEJMoa0911610
35. Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. *J Neurol Neurosurg Psychiatry.* (2000) 68:211–3. doi: 10.1136/jnnp.68.2.211
36. Smith L, Singhal N, El Achkar CM, Truglio G, Rosen Sheidley B, Sullivan J, et al. PCDH19-related epilepsy is associated with a broad neurodevelopmental spectrum. *Epilepsia.* (2018) 59:679–89. doi: 10.1111/epi.14003
37. Losito E, Kuchenbuch M, Chemaly N, Laschet J, Chiron C, Kaminska A, et al. Age-related "Sleep/nocturnal" tonic and tonic clonic seizure clusters are underdiagnosed in patients with Dravet Syndrome. *Epilepsy Behav.* (2017) 74:33–40. doi: 10.1016/j.yebeh.2017.05.037
38. 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) 12:966–77. doi: 10.1016/s1474-4422(13)70214-x
39. Ngugi AK, Bottomley C, Fegan G, Chengo E, Odhiambo R, Bauni E, et al. Premature mortality in active convulsive epilepsy in rural Kenya: causes and associated factors. *Neurology.* (2014) 82:582–9. doi: 10.1212/wnl.0000000000000123

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 12 March 2021
doi: 10.3389/fneur.2021.642645

Ictal and Interictal Cardiac Manifestations in Epilepsy. A Review of Their Relation With an Altered Central Control of Autonomic Functions and With the Risk of SUDEP

Laure Mazzola[1,2†] *and Sylvain Rheims*[2,3*†]

[1] Neurology Department, University Hospital, Saint-Étienne, France, [2] Lyon Neuroscience Research Center, INSERM U 1028, CNRS UMR, Lyon, France, [3] Department of Functional Neurology and Epileptology, Hospices Civils de Lyon and University of Lyon, Lyon, France

OPEN ACCESS

Edited by:
Brian Darryl Moseley,
University of Cincinnati, United States

Reviewed by:
Kheng Seang Lim,
University of Malaya, Malaysia
Luiz E. Mello,
Federal University of São Paulo, Brazil

***Correspondence:**
Sylvain Rheims
sylvain.rheims@chu-lyon.fr

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: 16 December 2020
Accepted: 19 February 2021
Published: 12 March 2021

Citation:
Mazzola L and Rheims S (2021) Ictal and Interictal Cardiac Manifestations in Epilepsy. A Review of Their Relation With an Altered Central Control of Autonomic Functions and With the Risk of SUDEP. Front. Neurol. 12:642645. doi: 10.3389/fneur.2021.642645

There is a complex interrelation between epilepsy and cardiac pathology, with both acute and long-term effects of seizures on the regulation of the cardiac rhythm and on the heart functioning. A specific issue is the potential relation between these cardiac manifestations and the risk of Sudden and Unexpected Death in Epilepsy (SUDEP), with unclear respective role of centrally-control ictal changes, long-term epilepsy-related dysregulation of the neurovegetative control and direct effects on the heart function. In the present review, we detailed available data about ictal cardiac changes, along with interictal cardiac manifestations associated with long-term functional and structural alterations of the heart. Pathophysiological mechanisms of these cardiac changes are discussed, with a specific focus on central mechanisms and the investigation of a possible deregulation of the central control of autonomic functions in addition to the role of catecholamine and hypoxemia on heart.

Keywords: epilepsy, sudden unexpected death in epilepsy, heart rate variability, ictal asystole, ictal tachycardia and bradycardia

INTRODUCTION

Since the description of the first ictal asystole more than 100 years ago (1), a large number of studies have investigated the complex inter-relationship between the brain and the heart in patients with epilepsy (2). Epilepsy-related cardiac manifestations can occur during seizures, but also in the inter-ictal period and can be associated with long-term functional and structural alterations of the heart. Over the past years, the scientific interest in these complex heart-brain interactions in patients with epilepsy have been reinforced by two main clinical reasons:

- The first corresponds to the issue of sudden unexpected death in patients with epilepsy (SUDEP). Among the causes of premature deaths in patients with epilepsy, SUDEP represents a major cause, especially in young adults with uncontrolled seizures with an incidence of about 0.5%/year of uncontrolled epilepsy (3). SUDEP is a non-traumatic and non-drowning death in patients with epilepsy, unrelated to a documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomic cause of death (3, 4). Although the exact pathophysiological mechanisms that lead to SUDEP remain unknown (5, 6), experimental and clinical data strongly suggest that most SUDEP result from a postictal central respiratory dysfunction progressing to terminal apnea, later followed by cardiac arrest (3). However, additional evidence suggests occurrence of an overall seizure-related failure of neuro-vegetative control (7), reinforcing the need of better understanding of the impact of seizures on cardiovascular function.
- The second aspect is the development of seizure detection devices, especially in order to alert the patients' caregivers and improve their safety. Because of the close relationship between seizures and changes in heart rate, cardiac monitoring has been proposed as a variable of choice for optimizing the detection rate of these devices (8).

Several reviews of the literature have analyzed the relationship between heart and epilepsy. Some have focused on ictal or interictal cardiac changes (9–12). Recently, Verrier et al. (13) proposed the concept of the "Epileptic Heart" as "a heart and coronary vasculature damaged by chronic epilepsy as a result of repeated surges in catecholamines and hypoxemia leading to electrical and mechanical dysfunction." Others focused on new insights into possible pathways from epilepsy, catecholaminergic toxicity, subtle cardiac changes and sudden death (14), or on the implication of treatment (15).

In this review, the characteristics of ictal and interictal cardiac manifestations will be successively detailed. We will focus more particularly on their respective physiopathology, especially on central mechanisms with the investigation of a possible deregulation of the central control of autonomic functions, studied in functional imaging and using intracranial stimulations/recordings, in addition to the role of catecholamine and hypoxemia on heart which have already been reviewed elsewhere (13, 14). Their potential relations with SUDEP pathophysiology and implications in clinical practice, including for seizure detection, will be discussed.

CHARACTERISTICS OF SEIZURE-RELATED CARDIAC MANIFESTATIONS

Ictal Cardiac Manifestations

Heart Rate Changes

Tachycardia is the most common ictal cardiac manifestation. It is reported in 82% of patients on average, with some intra-individual variability, since not all seizures in a patient with ictal tachycardia will necessarily lead to tachycardia (9).

In the literature, changes in heart rate during seizures correspond on average to an increase of 30 bpm or more than 50% compared to the interictal heart rate. They mainly occur in the pre-ictal period or within 30 s after the beginning of the seizure, the maximal heart rate being achieved for a majority of seizures within the first 60 s (9, 16). However, most studies suggesting modifications of the heart rate in the pre-ictal period have been performed in patients investigated with scalp EEG, raising the possibility that concomitant ictal EEG discharge might have not been visible. In a study using intracranial electrodes, ictal tachycardia was always concomitant to an increase in unilateral ictal high frequency epileptic activity restricted to anterior hippocampus and amygdala (17). In addition, tachycardia is also frequently observed in the post-ictal period, particularly after tonic-clonic seizures (9, 18).

The percentage of seizures associated with a change in heart rate appears to be similar for generalized tonic-clonic seizures (64%) and for focal seizures (71%), although it is likely that the magnitude of the change is increased as the focal seizure progresses to bilateral tonic-clonic seizure (9, 19). In patients with focal epilepsies, tachycardia is more commonly seen during temporal lobe seizures than extra-temporal seizures (9, 20, 21). However, as most of studies have been performed in patients with temporal lobe epilepsy, a selection bias cannot be excluded. Although preferential right lateralization of seizures with tachycardia has been suggested, most studies do not find an association with the laterality of epileptic discharges (9, 20, 22).

Seizures with bradycardia or ictal asystole are much rarer. Ictal asystole, defined as a sinusal pause of at least 3 s occurring during a seizure, usually has a duration of $<$60 s, and is spontaneously reversible (23–27). They are only reported in focal seizures, and in 90% of cases they correspond to drug-resistant seizures with altered consciousness of temporal origin, without clear preferential lateralization. Incidence of ictal asystole in drug-resistant focal epilepsy is estimated at 12 per 100 patient-years (23–27). Distinguishing syncope related to ictal asystole from cardiac asystole might be difficult (28), and use of implantable loop recorder can sometimes be required in the diagnostic process. Older age at onset, occurrence during wakefulness, and brief duration of the events have been suggested to be in favor of cardiac asystole (29). Only rare patients with ictal asystole have undergone cardiopulmonary resuscitation (30), suggesting that the vast majority of seizures with asystole resolve spontaneously, without the need for resuscitation (18). However, the risk of recurrence is high (28). Unlike ictal tachycardia, ictal bradycardia, or asystole can be symptomatic with syncope and sometimes traumatic falls. Importantly, ictal bradycardia or asystole should be distinguished from post-ictal conduction or rhythm cardiac disorders. These complications, in particular severe bradycardia, asystole, or ventricular fibrillation, are closely related to post-ictal hypoxemia following central peri-ictal respiratory disorders (7, 31). After a generalized seizure, the risk of asystole is therefore greater in patients with severe post-ictal apnea (32). In the MORTEMUS study, which investigated respiratory and electrocardiogram (EKG) data from patients who died from SUDEP during long-term video-EEG, abnormal heart

rhythms were observed after the onset of apnea in all deceased patients (33).

Other cardiac arrhythmias and conduction abnormalities, during or after seizures, have been reported in patients with drug-resistant focal epilepsy. Atrioventricular block, atrial fibrillation, supraventricular tachycardia, atrial, or ventricular premature depolarisations, ventricular fibrillation, and QT interval shortening or prolongation can thus be observed (9, 18).

Direct Cardiac Effects

Myocardial ischemia can be caused by seizures, especially in patients with cardiovascular risk factors. Up to 40% of seizures could be associated with ST segment depression (34). However, troponin remains normal in most patients (35, 36), suggesting that this transient myocardial ischemia does not generally result in severe acute ischemic myocardial injury. Seizures, especially generalized tonic-clonic seizures and status epilepticus, are also a well-known cause of Takotsubo syndrome, the clinical, EKG, and laboratory presentation of which may mimic that of acute ischemic heart disease (2). These complications have been linked to the release of catecholamines induced by seizures (36).

Interictal Cardiac Manifestations

Changes in Myocardial Structure

It has been suggested both in experimental models and in patients, that recurrence of seizures can progressively lead to cardiac fibrosis, potentially through catecholaminergic toxicity (14). Compared to healthy matched controls, patients with temporal lobe epilepsy have higher left ventricular rigidity, linked to cardiac fibrosis by deposits in the extracellular matrix, which in turn promotes systolic and diastolic dysfunction and arrhythmogenesis (37). Although the relationship between these long-term structural changes and the risk of ictal arrhythmias remains to be determined, several studies have reported an association between cardiac fibrosis and the risk of SUDEP (38, 39).

Channelopathies

More recently, it has also been shown that repetition of seizures can alter the expression of cardiac ion channels. Epilepsy-related alterations in the cardiac expression of sodium (Nav1.1/1.5), potassium (Kv4.2/4.3), calcium (NCX1), and cationic (HCN2/4) channels have thus been reported in animal models (40). It remains to be determined whether or not this mechanism is associated with impaired vegetative regulation in patients with epilepsy and especially, with the risk of SUDEP.

Heart Rate Variability (HRV)

HRV is the change in the time interval between two heart beats. HRV reflects the balance between sympathetic and parasympathetic activity of the autonomic nervous system. HRV is thus an index of activity of the neurovegetative system, whose decrease is a strong predictor of sudden death in patients with heart disease (41). Overall, increased heart rate variability indicates a shift toward parasympathetic dominance, while lower heart rate variability is seen in times of high sympathetic output (42). In patients with epilepsy, HRV is usually decreased, suggesting a shift toward sympathetic dominance (42). This has been shown in various types of epilepsy, including temporal lobe epilepsy (43, 44), frontal lobe epilepsy (45), idiopathic generalized epilepsy (44), epileptic spasms (46), or in Dravet Syndrome, where patients have extremely depressed parasympathetic function (10, 47), even in comparison with other types of epilepsy. In addition, it has been suggested that alteration of HRV might be precipitated and/or aggravated by insular resection in patients undergoing epilepsy surgery (48). However, the exact relationship between these chronic alterations of HRV and the risk of SUDEP remains unclear (7). Some studies reported association between risk of SUDEP and severe alteration of HRV (10, 49–51) whereas others did not confirm this observation (52). Furthermore, the alterations of HRV might also be associated with other risk SUDEP factors, including post-ictal generalized EEG suppression (53).

In addition, many studies have examined peri-ictal changes in HRV (10, 54). The results are sometimes heterogeneous, but overall seem to show an increase in sympathetic activity during the seizure, regardless of the type of seizure, but more markedly for temporal seizures and generalized seizures (7). Recovery occurs gradually, as post-ictal changes that can be prolonged, up to several hours. Changes in HRV can precede clinical onset of seizure by several seconds and have therefore been studied for the development of seizure detection tools.

PATHOPHYSIOLOGICAL MECHANISMS

The mechanisms underlying the emergence of these cardiac alterations remain poorly understood and several hypotheses need to be considered. These hypotheses may coexist in the same patients, interacting with each other.

Deregulation of Central Control of Vegetative Functions

Some of the most important integrative control centers for autonomic nervous system functions are located in the brainstem (55, 56). However, many animal and human studies support that cortical regions are involved in autonomic function and modulation in response to environment changes (55, 57–60). In 1993, Benarroch proposed the term of "Central Autonomic Network" (CAN) to describe a group of forebrain, brainstem, and limbic regions involved in the generation of an appropriate autonomic functional state (55). In 2000, Thayer and Lane (61) proposed a model of neurovisceral integration, permitting to link cardiac regulation to emotional or cognitive tasks through activation of the CAN. In addition to the autonomic nuclei of the brainstem and limbic structures such as the amygdala and the insula, their model also includes the cingulate and medial prefrontal cortex. Cortical regions, particularly medial prefrontal cortex, would exert a top-down control on cingulate, anterior insula and amygdala, which form an interconnected network, and modulate activity of subcortical and brainstem regions. These later regions would in turn finalize the autonomic output to the body by modulating the parasympathetic/sympathetic balance. In accordance with this model, recent meta-analysis of

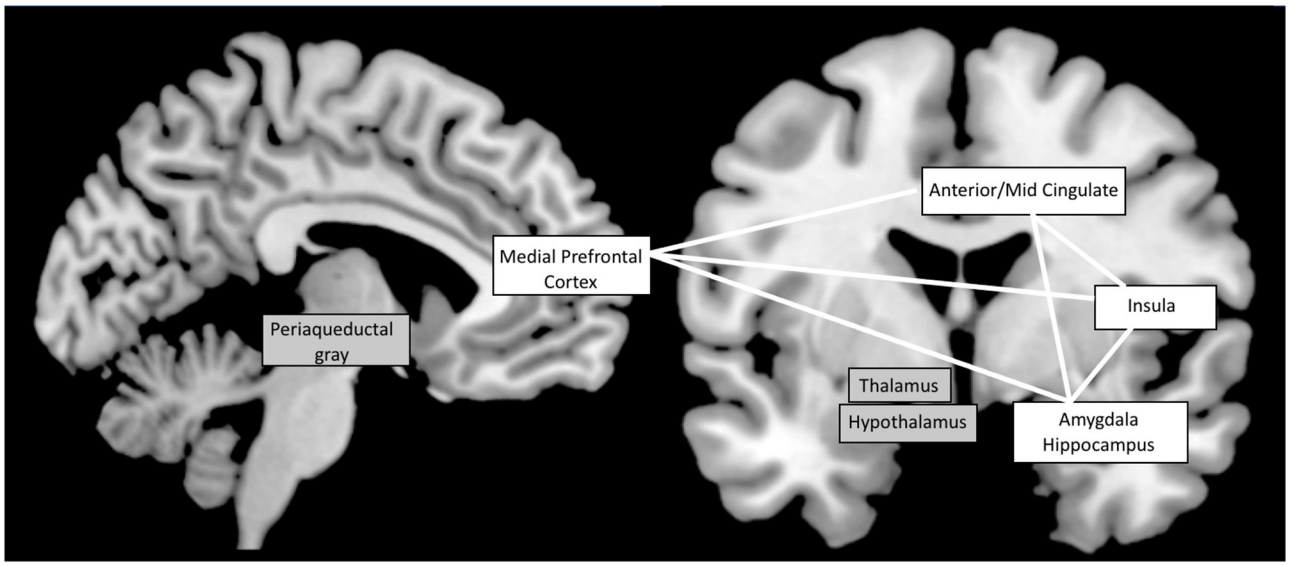


FIGURE 1 | The Central Autonomic Network: most implicated brain regions according to functional neuro-imaging studies (57, 60, 62). Cortical structures are shown on a white background while subcortical structures are on a gray background. White lines symbolize the functional connectivity between cortical regions.

human neuroimaging experiments evaluating central autonomic cardiovascular processing identified several consistently implicated brain regions, consisting of cortical areas, including the anterior and mid-cingulate cortices, insula, amygdala, hippocampus, medial prefrontal cortex; and subcortical structures such as thalamus, hypothalamus, periaqueductal gray matter (57, 60, 62) (see **Figure 1**). Orbitofrontal cortex is also mentioned by some authors (60, 62). Analysis of functional connectivity has revealed functional connectivity between the medial prefrontal cortex and other structures of the CAN, particularly the amygdala and the hippocampus (63, 64). Parcellation of orbitofrontal cortex and hypothalamus has shown specificity for functional connectivity between the medial orbito-frontal cortex and the medial hypothalamus (65, 66). In their meta-analysis, Thayer et al. (66), established a link between mainly amygdala and ventromedial prefrontal cortex activation, during several cognitive and affective tasks, and heart rate variation. De la Cruz et al. (67) recently investigated the relationship between heart rate and functional connectivity of brain regions involved in autonomic control. Subjects with slow heart rate exhibited significantly increased functional connectivity between amygdala, insula, prefrontal cortex, anterior cingulate, hippocampus, and hypothalamus compared to subjects with medium or fast heart rate.

Some studies suggested the possibility of a lateralization of insular cortex in terms of cardiac function, the right insula being more involved in sympathetic regulation, and the left one in parasympathetic cardiac regulation [see (60, 68) for a review]. On the contrary, others did not conclude to any lateralization (57).

Very few studies have investigated the effects of cortical stimulation on heart rate in humans. Electrical stimulation of limbic structures, especially the amygdala and peri-amygdaloid pyriform cortex, have been reported to produce autonomic changes, including cardiovascular responses, mediated by either sympathetic or parasympathetic pathways (69). Autonomic responses (including heart rate changes) are also mentioned after stimulation of the cingulate cortex (70, 71) and orbito-frontal cortex (72). Several data support the pivotal role of the insula in this central autonomic network, sometimes with contradictory experimental results. In animals, stimulation of rat posterior insula (58, 73) and primate antero-ventral insula (74, 75) have induced heart rate changes. In humans, Oppenheimer et al. (59) were the first to report heart rate changes after 70 intraoperative stimulations of the insula in five patients. Bradycardia was observed more frequently after stimulations of the left insula, whereas tachycardia was more often elicited after stimulation of the right insular cortex. More recently, Chouchou et al. (76) confirmed the role of insula in regulation of cardiac activity, based on responses to direct electrical stimulation performed during stereo-electro-encephalography. Out of 100 insular stimulations, almost 50% induced a modification of heart rate. Insular representation of tachycardia was more posterior than that of bradycardia and both types of cardiac responses were equally represented in right and left insula. Tachycardiac responses were underpinned by sympathetic reactivity, and bradycardia by parasympathetic control.

Likewise, Catenoix et al. (77) reported an insular seizure with ictal asystole. The electrode implanted in the left posterior long gyrus showed a high frequency discharge starting 2 s before asystole, underlying the possibility of a proper role of insula in some dysautonomic seizures. However, a recent SEEG study exploring 37 temporal lobe seizures in 9 patients, showed that tachycardia was concomitant to an increase in epileptic activity in anterior hippocampus and amygdala, but was independent of ictal insular activity (17), suggesting that insula implication is not necessary to evoke cardiac changes.

Sympathetic or parasympathetic ictal changes could so result from direct activation by epileptic discharge of the central autonomic network (78), whose activation by the discharge would modify the activity of the autonomic nervous system during the seizure. In addition, like the data which show a progressive alteration of the brainstem structures involved in respiratory control (79), it could be possible that the repetition of the seizures could modify the subcortical nuclei in charge of vegetative regulation. Thus, the repetitive stimulation of central autonomic network by epileptic discharges may lead to chronic dysfunction of the autonomic nervous system leading at least in part to interictal disorders.

Genetic Background

Several ion channel genes whose mutations are involved in cardiac arrhythmias are also expressed in the brain. For example, the SCN5A gene, whose mutation is associated with long QT syndrome, is also expressed in the brain and is associated with epilepsy (80). Some cardiac events, including sudden deaths, may therefore be linked to genetic risk factors common to epilepsy and cardiac arrhythmias.

A growing body of evidence points to a genetic susceptibility to cardiorespiratory and autonomic dysfunction in epilepsy. In an analysis of the entire exome sequencing of 61 SUDEP cases, mutations known to cause long QT syndrome were found in 7% of cases and an additional 15% had candidate variants in potentially predisposing genes to malignant cardiac arrhythmias (81). Similarly, the effect of the SCN1A mutation on heart function may partly explain the increased risk of mortality in Dravet syndrome (82–84).

Roles of Epilepsy Treatments

Several anti-seizure drugs have been associated with conduction abnormalities or arrhythmias. This has been particularly reported with sodium channel blockers (2), including risk of atrioventricular block with carbamazepine (85), sinus pause and hypotension with rapid administration of phenytoin (86) or atrioventricular block or atrial fibrillation with lacosamide (87–89). However, no formal relationship has been established between these drug-related adverse events and ictal arrhythmias (2). Importantly, a pooled analysis did not find a significant association between the treatments and an increased risk of SUDEP when adjusting the frequency of generalized tonic-clonic seizures (90).

The effect of vagus nerve stimulation (VNS) on autonomic function remains uncertain. Heart changes associated with VNS are rare. Few cases of VNS-induced bradycardia have been reported. In addition, data on the alterations in parasympathetic tone of the cardiovascular system induced by VNS are contradictory (91).

Finally, while the data concerning the relationship between some antiepileptic treatments, in particular enzyme inducers, and the destabilization of lipid metabolism are numerous (92), the real impact of these modulations on the risk of atherosclerosis and a fortiori on the risk of the occurrence of cardiovascular events remain debated (93–95). In a study based on an insurance registry from several states in the United States, the risk of having a stroke with enzyme inducer antiepileptics compared to other treatments was 1.22 (0.90–1.65) (94). A large British study used the GPRD database and studied 252,407 patients over the age of 18 who received antiepileptic therapy between 1990 and 2013 (95). Among them, 5,069 strokes (ischemic or hemorrhagic) and 3,636 myocardial infarctions have been reported. The use of enzyme-inducing therapy was not associated with a significant increase in the risk of stroke, including ischemic stroke. In contrast, the use of an inducer for more than 24 months was associated with a significantly increased risk of myocardial infarction [1.46 (1.15–1.85)] (95). Nevertheless, translated into annual risk, this difference remained very low, with a difference in risk of occurrence of 1.39 / 1,000 patients per year (0.33–2.45).

POTENTIAL RELATIONS WITH PATHOPHYSIOLOGY OF SUDEP

Epilepsy-related cardiac dysfunction may be associated with increased risk of premature mortality, because of a relation either with the risk of SUDEP or with the risk of heart diseases. As discussed in details by Verrier et al. the issue of long-term risk of heart diseases might be predominant in terms of incidence and should deserve a specific attention (13). This risk might be primarily related to the direct effects of seizures on the heart, the genetic background and/or the long-term adverse events of antiseizure drugs (13). In contrast, the exact relation between these cardiac symptoms and the risk of SUDEP remains to be clarified.

The data suggesting that the ictal cardiac dysfunction plays a key leading role in the initiation of the cascade of events that lead to SUDEP are limited. As discussed above, the possibility that the main event is a serious heart rhythm disorder seems unlikely or may represent a minority of SUDEP (5, 27). Although severe bradycardia, transient asystole or an episode of ventricular tachycardia was observed in all monitored SUDEP in the MORTEMUS study, these events followed chronologically the apnea (33). Even in Dravet syndrome, in which it is possible that the channelopathy also has a cardiac effect, available data are conflicting. In some rodent model of Dravet Syndrome, altered cardiac electrical function contributed to susceptibility to arrhythmogenesis and SUDEP (82). However, in others, asystole was shown to be also triggered by postictal respiratory dysfunction, possibly by a direct effect of hypoxemia on heart muscle (96).

Accordingly, an important aspect might be the interrelations between the central regulation of respiratory function and the one of neurovegetative functions, including the central regulation of cardiac rhythm. Brain areas involved in these regulations are highly connected to each other, both at the cortical level and in the brainstem, and each of them is partly regulated by the other. Brain regions involved in the regulation of the arterial pressure as well as in breathing control thus overlap with the Central Autonomic Network involved in the regulation of heart rhythm, both at the cortical level and in the brainstem. Direct electrical cortical stimulation of the subcallosal neocortex resulted in consistent decreases in systolic blood pressure (97).

The latter was interpreted as a reduction in sympathetic drive, resulting in a reduction in cardiac output (97). Similarly, direct electrical cortical stimulation of several areas of the Central Autonomic Network reliably induces apnea. This has mostly been reported in the amygdala or the hippocampus (98–100) but also in the cingulate and orbitofrontal cortex (101). In addition direct electrical stimulation of the perisylvian cortex can result in significant decrease of SpO_2 (102). In this context, it might be speculated that acute disorganization of these cortical regions by an epileptic discharge might precipitate simultaneous alterations of the cortical drive of respiration, cardiac rhythm, and arterial pressure. Some clues obtained during seizures might be in favor of this hypothesis. It has thus been shown that ictal autonomic dysfunction is correlated with seizure-related respiratory dysfunction in temporal lobe seizures, with prolonged impairment of parasympathetic tone associated with postictal hypoxemia (54). In generalized convulsive seizures, there is a close relationship between post-ictal severe respiratory dysfunction and post-ictal conduction or rhythm cardiac disorders (32, 33). In this seizure type, which is the main risk factor of SUDEP (103), the cortical dysfunction of neurovegetative regulation and breathing control, might be reinforced by the dysfunction of brainstem control, resulting from the spreading depolarization in the brainstem. In a rodent model of SUDEP, pharmacological-induction in the brainstem of electroencephalographic suppression resulted in apnea, bradycardia, and asystole, similar to the events seen in monitored SUDEP (104). Furthermore, respiratory regulation following a seizure is modulated by norepinephrine pathway (105). In patients, the occurrence and/or severity of post-ictal EEG suppression is associated with post-ictal respiratory dysfunction (106) as well as with both sympathetic activation and parasympathetic suppression (53).

Despite these preliminary data, the hypothesis of a leading role of post-ictal central neurovegetative breakdown in the SUDEP requires additional evidence. In addition, the exact relationship between these potential peri-ictal alterations of the Central Autonomic Network, long-term alterations of respiration and long-term alteration of cardiac regulation, especially HRV, remains an open question. Whether or not the risk of severe of post-ictal neurovegetative breakdown, and eventually SUDEP, might be higher in patients with combined alterations of respiratory and cardiac controls is unknown. Better understanding how these issues interact with each other and if they share pathophysiological mechanisms might be of key importance for unraveling SUDEP biomarker with greater predictive value than those currently available (7), a critical aspect in the perspective of SUDEP prevention (107).

IMPLICATIONS IN CLINICAL PRACTICE

Diagnostic and Management of Epilepsy-Related Cardiac Disorders

Identification of interictal cardiac changes should allow the prevention, early detection, and possible treatment of cardiac co-morbidities. It could also guide the choice of anti-seizures drugs according to the patient profile, in order to avoid the appearance or worsening of arrhythmia or cardiac conduction disorders. An EKG should therefore be performed in all patient with newly-diagnosed epilepsy, especially to exclude long-QT syndrome, but it should then be reprocessed regularly in the follow up. Some studies have suggested the interest of prolonged routine EKG recordings (108).

Similarly, identification of patients with severe ictal heart rate changes is important. Although ictal asystole are typically self-limiting events, they can expose to severe injuries. Considering the risk of seizure-related traumatisms and the risk of recurrence, aggressive treatment, including pacemaker implantation, should be discussed if seizure freedom cannot be achieved (28). Because active management of antiseizure drugs might reduce the risk of SUDEP (109), whether or not identification of post-ictal cardiac arrythmias after generalized convulsive seizure (32) should be taken into account in therapeutic decision is an open question.

Seizure Detection Devices

Over the past 10 years, there has been a growing interest in the potential applications of mobile health technologies for seizure detection, with the objective of faster caregivers' intervention and decreased risk of seizure-related injuries. Basically, three physiological variables can be used for non-EEG based seizure detection: detection of body movements, eye movements, and seizure-related modification of vegetative functions, including the cardiac rhythm (110). While detection of generalized tonic-clonic seizures has shown promising results with utilization either alone or in combination of accelerometers, automatic video detection, surface EMG, and bed alarms (8, 111), these approaches are much less sensitive for focal seizures. In contrast, the main approach consists in detection of seizure-induced autonomic changes, especially cardiac rhythm changes. While first studies showed disappointing results with high rate of false-alarm, recent data were more encouraging. In a recent study using a wearable EKG device, the overall sensitivity was low at 54% but raised to 90.5% for non-convulsive seizures in the 53.5% of patients in whom more than 66% of seizures were detected (112). An ictal change in HR of more than 50 bpm (increase or decrease) predicted responders with a predictive positive value of 87% (95% CI 69.9–95.4%) and a negative predictive value of 90% (95% CI 70.4–97.2%) (112).

Beyond detecting ictal tachycardia to alert caregivers about the occurrence of a seizure, an additional question will be how these devices can be used to detect post-ictal arrythmia and/or asystole. Such approach might be used to alert patients family or the rescue services of a severe post-ictal arrythmia with high risk of immediate SUDEP, especially in patients with frequent nocturnal convulsive seizures and who sleep alone (113).

CONCLUSION

Much progress has been made in recent years in the characterization of ictal and interictal cardiac manifestations in epilepsy. Although their pathophysiology remains debated, improving knowledge could lead us to improve the care of our patients. Their identification should allow the prevention

and possible treatment of cardiac co-morbidities, and also guide the choice of anti-epileptic treatments, in order to prevent the appearance or worsening of conduction or rhythm cardiac disorders. In addition, monitoring EKG and HRV, which are biomarkers easy to record and measure, could allow the development of increasingly precise non-invasive seizure detection tools for monitoring and possibly for the early treatment of seizures. However, a key remains to better understand the exact relation between these cardiac manifestations and the risk of SUDEP. Further studies are required to decipher the respective role of centrally-control ictal changes, long-term dysregulation and direct effects on the heart function.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Russell AE. Cessation of the pulse during the onset of epileptic fits, with remarks on the mechanism of fits. *Lancet*. (1906) 168:152–54. doi: 10.1016/S0140-6736(01)30477-4
2. Shmuely S, van der Lende M, Lamberts RJ, Sander JW, Thijs RD. The heart of epilepsy: current views and future concepts. *Seizure*. (2017) 44:176–83. doi: 10.1016/j.seizure.2016.10.001
3. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. *Lancet Neurol*. (2016) 15:1075–88. doi: 10.1016/S1474-4422(16)30158-2
4. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia*. (2012) 53:227–33. doi: 10.1111/j.1528-1167.2011.03358.x
5. Devinsky O. Sudden, unexpected death in epilepsy. *N Engl J Med*. (2011) 365:1801–11. doi: 10.1056/NEJMra1010481
6. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. *Lancet*. (2011) 378:2028–38. doi: 10.1016/S0140-6736(11)60176-1
7. Ryvlin P, Rheims S, Lhatoo SD. Risks and predictive biomarkers of sudden unexpected death in epilepsy patient. *Curr Opin Neurol*. (2019) 32:205–12. doi: 10.1097/WCO.0000000000000668
8. Rheims S. Wearable devices for seizure detection: Is it time to translate into our clinical practice. *Rev Neurol*. (2020) 176:480–84. doi: 10.1016/j.neurol.2019.12.012
9. Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. *Seizure*. (2014) 23:496–505. doi: 10.1016/j.seizure.2014.02.012
10. Myers KA, Bello-Espinosa LE, Symonds JD, Zuberi SM, Clegg R, Sadleir LG, et al. Heart rate variability in epilepsy: a potential biomarker of sudden unexpected death in epilepsy risk. *Epilepsia*. (2018) 59:1372–80. doi: 10.1111/epi.14438
11. Ufongene C, El Atrache R, Loddenkemper T, Meisel C. Electrocardiographic changes associated with epilepsy beyond heart rate and their utilization in future seizure detection and forecasting methods. *Clin Neurophysiol*. (2020) 131:866–79. doi: 10.1016/j.clinph.2020.01.007
12. Bruno E, Biondi A, Richardson MP, RADAR-CNS Consortium. Pre-ictal heart rate changes: a systematic review and meta-analysis. *Seizure*. (2018) 55:48–56. doi: 10.1016/j.seizure.2018.01.003
13. Verrier RL, Pang TD, Nearing BD, Schachter SC. The epileptic heart: concept and clinical evidence. *Epilepsy Behav*. (2020) 105:106946. doi: 10.1016/j.yebeh.2020.106946
14. Fialho Guilherme L, Wolf Peter, Walz Roger, Lin Katia. Epilepsy and ultra-structural heart changes: the role of catecholaminergic toxicity and myocardial fibrosis. What can we learn from cardiology. *Seizure*. (2019) 71:105–9. doi: 10.1016/j.seizure.2019.07.002
15. Zaccara G and Lattanzi S. Comorbidity between epilepsy and cardiac arrhythmias: Implication for treatment. *Epilepsy Behav*. (2019) 97:304–12. doi: 10.1016/j.yebeh.2019.05.038
16. Marshall DW, Westmoreland BF, Sharbrough FW. Ictal tachycardia during temporal lobe seizures. *Mayo Clin Proc*. (1983) 58:443–46.
17. Chouchou F, Bouet R, Pichot V, Catenoix H, Mauguière F, Jung J. The neural bases of ictal tachycardia in temporal lobe seizures. *Clin Neurophysiol*. (2017) 128:1810–19. doi: 10.1016/j.clinph.2017.06.033
18. 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. doi: 10.1016/j.autneu.2015.07.066
19. Blumhardt LD, Smith PE, Owen L. Electrocardiographic accompaniments of temporal lobe epileptic seizures. *Lancet*. (1986) 1:1051–56. doi: 10.1016/S0140-6736(86)91328-0
20. Leutmezer F, Schernthaner C, Lurger S, Pötzelberger K, Baumgartner C. Electrocardiographic changes at the onset of epileptic seizures. *Epilepsia*. (2003) 44:348–54. doi: 10.1046/j.1528-1157.2003.34702.x
21. Weil S, Arnold S, Eisensehr I, Noachtar S. Heart rate increase in otherwise subclinical seizures is different in temporal vs. extratemporal seizure onset: support for temporal lobe autonomic influence. *Epileptic Disord*. (2005) 7:199–204. doi: 10.1017/CBO9780511781780.015
22. Mayer H, Benninger F, Urak L, Plattner B, Geldner J, Feucht M. EKG abnormalities in children and adolescents with symptomatic temporal lobe epilepsy. *Neurology*. (2004) 63:324–28. doi: 10.1212/01.WNL.0000129830.72973.56
23. Rocamora R, Kurthen M, Lickfett L, Von Oertzen J, Elger CE. Cardiac asystole in epilepsy: clinical and neurophysiologic features. *Epilepsia*. (2003) 44:179–85. doi: 10.1046/j.1528-1157.2003.15101.x
24. Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. *Lancet*. (2004) 364:2212–19. doi: 10.1016/S0140-6736(04)17594-6
25. Schuele SU, Bermeo AC, Alexopoulos AV, Locatelli ER, Burgess RC, Dinner DS, Foldvary-Schaefer N. Video-electrographic and clinical features in patients with ictal asystole. *Neurology*. (2007) 69:434–41. doi: 10.1212/01.wnl.0000266595.77885.7f
26. Scott CA and Fish DR. Cardiac asystole in partial seizures. *Epileptic Disord*. (2000) 2:89–92.
27. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol*. (2008) 7:1021–31. doi: 10.1016/S1474-4422(08)70202-3
28. Hampel KG, Thijs RD, Elger CE, Surges R. Recurrence risk of ictal asystole in epilepsy. *Neurology*. (2017) 89:785–91. doi: 10.1212/WNL.0000000000004266
29. Sankaranarayanan M, Makhija P, Gopinath S, Mathew N, Radhakrishnan K. Comparison of clinical and electrophysiological characteristics between ictal and cardiac asystole encountered during video-EEG monitoring. *Epileptic Disord*. (2019) 21:337–6. doi: 10.1684/epd.2019.1085
30. Lanz M, Oehl B, Brandt A, Schulze-Bonhage A. Seizure induced cardiac asystole in epilepsy patients undergoing long term video-EEG monitoring. *Seizure*. (2011) 20:167–72. doi: 10.1016/j.seizure.2010.11.017
31. Rheims S, Alvarez BM, Alexandre V, Curot J, Maillard L, Bartolomei F, et al. Hypoxemia following generalized convulsive seizures: risk factors and effect of oxygen therapy. *Neurology*. (2019) 92:e183–93. doi: 10.1212/WNL.0000000000006777
32. Vilella L, Lacuey N, Hampson JP, Rani MS, Sainju RK, Friedman D, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy. (SUDEP). *Neurology*. (2019) 92:e171–82. doi: 10.1212/WNL.0000000000006785
33. 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) 12:966–77. doi: 10.1016/S1474-4422(13)70214-X

34. Tigaran S, Mølgaard H, McClelland R, Dam M, and Jaffe AS. Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients. *Neurology*. (2003) 60:492–95. doi: 10.1212/01.WNL.0000042090.13247.48
35. Woodruff BK, Britton JW, Tigaran S, Cascino GD, Burritt MF, McConnell JP, et al. Cardiac troponin levels following monitored epileptic seizures. *Neurology*. (2003) 60:1690–92. doi: 10.1212/01.WNL.0000065881.46964.4F
36. Nass RD, Motloch LJ, Paar V, Lichtenauer M, Baumann J, Zur B, et al. Blood markers of cardiac stress after generalized convulsive seizures. *Epilepsia*. (2019) 60:201–10. doi: 10.1111/epi.14637
37. Fialho GL, Pagani AG, Wolf P, Walz R, Lin K. Echocardiographic risk markers of sudden death in patients with temporal lobe epilepsy. *Epilepsy Res*. (2018) 140:192–97. doi: 10.1016/j.eplepsyres.2018.01.016
38. Zhuo L, Zhang Y, Zielke HR, Levine B, Zhang X, Chang L, et al. Sudden unexpected death in epilepsy: evaluation of forensic autopsy cases. *Forensic Sci Int*. (2012) 223:171–75. doi: 10.1016/j.forsciint.2012.08.024
39. Devinsky O, Kim A, Friedman D, Bedigian A, Moffatt E, Tseng ZH. Incidence of cardiac fibrosis in SUDEP and control cases. *Neurology*. (2018) 91:e55–61. doi: 10.1212/WNL.0000000000005740
40. Li Michael CH, O'Brien Terence J, Todaro M, Powell KL. Acquired cardiac channelopathies in epilepsy: evidence, mechanisms, and clinical significance. *Epilepsia*. (2019) 60:1753–67. doi: 10.1111/epi.16301
41. Tsuji H, Venditti FJ, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation*. (1994) 90:878–83. doi: 10.1161/01.CIR.90.2.878
42. Myers KA, Sivathamboo S, Perucca P. Heart rate variability measurement in epilepsy: How can we move from research to clinical practice. *Epilepsia*. (2018) 59:2169–78. doi: 10.1111/epi.14587
43. Massetani R, Strata G, Galli R, Gori S, Gneri C, Limbruno U, et al. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability. *Epilepsia*. (1997) 38:363–69. doi: 10.1111/j.1528-1157.1997.tb01129.x
44. Tomson T, Ericson M, Ihrman C, and Lindblad LE. Heart rate variability in patients with epilepsy. *Epilepsy Res*. (1998) 30:77–83. doi: 10.1016/S0920-1211(97)00094-6
45. do Nascimento Vinholes L, Sousa da Silva A, Marinho Tassi E, Corrêa Borges de Lacerda G. Heart rate variability in frontal lobe epilepsy: association with SUDEP risk. *Acta Neurol Scand*. (2020) 143:62–70. doi: 10.1111/ane.13330
46. Møller MM, Høgenhaven H, Uldall P, Ballegaard M. Heart rate variability in infants with West syndrome. *Seizure*. (2015) 27:10–5. doi: 10.1016/j.seizure.2015.02.003
47. Delogu AB, Spinelli A, Battaglia D, Dravet C, De Nisco A, Saracino A, et al. Electrical and autonomic cardiac function in patients with Dravet syndrome. *Epilepsia*. (2011) 52(Suppl 2):55–8. doi: 10.1111/j.1528-1167.2011.03003.x
48. Lacuey N, Garg V, Bangert B, Hampson JP, Miller J, Lhatoo S. Insular resection may lead to autonomic function changes. *Epilepsy Behav*. (2019) 97:260–64. doi: 10.1016/j.yebeh.2019.04.035
49. DeGiorgio CM, Miller P, Meymandi S, Chin A, Epps J, Gordon S, et al. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 Inventory. *Epilepsy Behav*. (2010) 19:78–81. doi: 10.1016/j.yebeh.2010.06.011
50. Drake ME, Andrews JM, Castleberry CM. Electrophysiologic assessment of autonomic function in epilepsy. *Seizure*. (1998) 7:91–96. doi: 10.1016/S1059-1311(98)80062-9
51. Novak JL, Miller PR, Markovic D, Meymandi SK, DeGiorgio CM. Risk assessment for sudden death in epilepsy: the SUDEP-7 inventory. *Front Neurol*. (2015) 6: 252. doi: 10.3389/fneur.2015.00252
52. Baysal-Kirac L, Serbest NG, Sahin E, Dede HÖ, Gürses C, Gökyigit A, et al. Analysis of heart rate variability and risk factors for SUDEP in patients with drug-resistant epilepsy. *Epilepsy Behav*. (2017) 71:60–4. doi: 10.1016/j.yebeh.2017.04.018
53. Poh MZ, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Madsen JR, et al. Autonomic changes with seizures correlate with postictal EEG suppression. *Neurology*. (2012) 78:1868–76. doi: 10.1212/WNL.0b013e318258f7f1
54. Szurhaj W, Troussière AC, Logier R, Derambure P, Tyvaert L, Semah F, et al. Ictal changes in parasympathetic tone: prediction of postictal oxygen desaturation. *Neurology*. (2015) 85:1233–39. doi: 10.1212/WNL.0000000000001994
55. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin Proc*. (1993) 68:988–1001. doi: 10.1016/S0025-6196(12)62272-1
56. Guyenet PG. The sympathetic control of blood pressure. *Nat Rev Neurosci*. (2006) 7:335–46. doi: 10.1038/nrn1902
57. Beissner F, Meissner K, Bär KJ, and Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J Neurosci*. (2013) 33:10503–11. doi: 10.1523/JNEUROSCI.1103-13.2013
58. Oppenheimer SM and Cechetto DF. Cardiac chronotropic organization of the rat insular cortex. *Brain Res*. (1990) 533:66–72. doi: 10.1016/0006-8993(90)91796-J
59. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology*. (1992) 42:1727–32. doi: 10.1212/WNL.42.9.1727
60. Ruiz Vargas E, Sörös P, Shoemaker JK, Hachinski V. Human cerebral circuitry related to cardiac control: a neuroimaging meta-analysis. *Ann Neurol*. (2016) 79:709–16. doi: 10.1002/ana.24642
61. Thayer JF and Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord*. (2000) 61:201–16. doi: 10.1016/S0165-0327(00)00338-4
62. Sklerov M, Dayan E, Browner N. Functional neuroimaging of the central autonomic network: recent developments and clinical implications. *Clin Auton Res*. (2019) 29:555–66. doi: 10.1007/s10286-018-0577-0
63. Norton KN, Luchyshyn TA, Kevin Shoemaker J. Evidence for a medial prefrontal cortex-hippocampal axis associated with heart rate control in conscious humans. *Brain Res*. (2013) 1538:104–15. doi: 10.1016/j.brainres.2013.09.032
64. Sakaki M, Yoo HJ, Nga L, Lee TH, Thayer JF, Mather M. Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. *Neuroimage*. (2016) 139:44–52. doi: 10.1016/j.neuroimage.2016.05.076
65. Hirose S, Osada T, Ogawa A, Tanaka M, Wada H, Yoshizawa Y, et al. Lateral-medial dissociation in orbitofrontal cortex-hypothalamus connectivity. *Front Hum Neurosci*. (2016) 10:244. doi: 10.3389/fnhum.2016.00244
66. Thayer JF, Ahs F, Fredrikson M, Sollers JJ, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev*. (2012) 36:747–56. doi: 10.1016/j.neubiorev.2011.11.009
67. de la Cruz F, Schumann A, Köhler S, Reichenbach JR, Wagner G, Bär KJ. The relationship between heart rate and functional connectivity of brain regions involved in autonomic control. *Neuroimage*. (2019) 196:318–28. doi: 10.1016/j.neuroimage.2019.04.014
68. Oppenheimer S, Cechetto D. The insular cortex and the regulation of cardiac function. *Compr Physiol*. (2016) 6:1081–33. doi: 10.1002/cphy.c140076
69. Gloor P. Physiology of the limbic system. *Adv Neurol*. (1975) 11:27–55.
70. Pool JL, Ransohoff J. Autonomic effects on stimulating rostral portion of cingulate gyri in man. *J Neurophysiol*. (1949) 12:385–92. doi: 10.1152/jn.1949.12.6.385
71. Caruana F, Gerbella M, Avanzini P, Gozzo F, Pelliccia V, Mai R, et al. Motor and emotional behaviours elicited by electrical stimulation of the human cingulate cortex. *Brain*. (2018) 141:3035–51. doi: 10.1093/brain/awy219
72. Van buren JM, Bucknam CA, Pritchard WL. Autonomic representation in the human orbitotemporal cortex. *Neurology*. (1961) 11:214–24. doi: 10.1212/WNL.11.3.214
73. Marins FR, Iddings JA, Fontes MA, Filosa JA. Evidence that remodeling of insular cortex neurovascular unit contributes to hypertension-related sympathoexcitation. *Physiol Rep*. (2017) 5:13156. doi: 10.14814/phy2.13156
74. Hoffman BL and Rasmussen T. Stimulation studies of insular cortex of Macaca mulatta. *J Neurophysiol*. (1953) 16:343–51. doi: 10.1152/jn.1953.16.4.343
75. Kaada BR. Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of rhinencephalic and other structures in primates, cat, and dog; a study of responses from the limbic, subcallosal, orbito-insular, piriform and temporal cortex, hippocampus-fornix and amygdala. *Acta Physiol Scand Suppl*. (1951) 24:1–262.

76. Chouchou F, Mauguière F, Vallayer O, Catenoix H, Isnard J, Montavont A, et al. How the insula speaks to the heart: cardiac responses to insular stimulation in humans. *Hum Brain Mapp*. (2019) 40:2611–22. doi: 10.1002/hbm.24548
77. Catenoix H, Mauguière F, Guénot M, Isnard J, and Ryvlin P. Recording the insula during ictal asystole. *Int J Cardiol*. (2013) 169:e28–30. doi: 10.1016/j.ijcard.2013.08.100
78. Sevcencu C, Struijk JJ. Autonomic alterations and cardiac changes in epilepsy. *Epilepsia*. (2010) 51:725–37. doi: 10.1111/j.1528-1167.2009.02479.x
79. Patodia S, Somani A, O'Hare M, Venkateswaran R, Liu J, Michalak Z, et al. The ventrolateral medulla and medullary raphe in sudden unexpected death in epilepsy. *Brain*. (2018) 141:1719–33. doi: 10.1093/brain/awy078
80. Hartmann HA, Colom LV, Sutherland ML, Noebels JL. Selective localization of cardiac SCN5A sodium channels in limbic regions of rat brain. *Nat Neurosci*. (1999) 2:593–95. doi: 10.1038/10147
81. Bagnall RD, Crompton DE, Petrovski S, Lam L, Cutmore C, Garry SI, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. *Ann Neurol*. (2016) 79:522–34. doi: 10.1002/ana.24596
82. Auerbach DS, Jones J, Clawson BC, Offord J, Lenk GM, Ogiwara I, et al. Altered cardiac electrophysiology and SUDEP in a model of Dravet syndrome. *PLoS ONE*. (2013) 8:e77843. doi: 10.1371/journal.pone.0077843
83. Frasier CR, Zhang H, Offord J, Dang LT, Auerbach DS, Shi H, et al. Channelopathy as a SUDEP biomarker in dravet syndrome patient-derived cardiac myocytes. *Stem Cell Reports*. (2018) 11:626–34. doi: 10.1016/j.stemcr.2018.07.012
84. Kalume F, Westenbroek RE, Cheah CS, Yu FH, Oakley JC, Scheuer T, Catterall WA. Sudden unexpected death in a mouse model of Dravet syndrome. *J Clin Invest*. (2013) 123:1798–808. doi: 10.1172/JCI66220
85. Kasarskis EJ, Kuo CS, Berger R, Nelson KR. Carbamazepine-induced cardiac dysfunction. Characterization of two distinct clinical syndromes. *Arch Intern Med*. (1992) 152:186–91. doi: 10.1001/archinte.152.1.186
86. Randazzo DN, Ciccone A, Schweitzer P, Winters SL. Complete atrioventricular block with ventricular asystole following infusion of intravenous phenytoin. *J Electrocardiol*. (1995) 28:157–59. doi: 10.1016/S0022-0736(05)80287-0
87. Nizam A, Mylavarapu K, Thomas D, Briskin K, Wu B, Saluja D, et al. Lacosamide-induced second-degree atrioventricular block in a patient with partial epilepsy. *Epilepsia*. (2011) 52:e153–5. doi: 10.1111/j.1528-1167.2011.03212.x
88. Chinnasami S, Rathore C, Duncan JS. Sinus node dysfunction: an adverse effect of lacosamide. *Epilepsia*. (2013) 54:e90–3. doi: 10.1111/epi.12108
89. Degiorgio CM. Atrial flutter/atrial fibrillation associated with lacosamide for partial seizures. *Epilepsy Behav*. (2010) 18:322–24. doi: 10.1016/j.yebeh.2010.04.043
90. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Subcommission on mortality. do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. *Epilepsia*. (2012) 53:249–52. doi: 10.1111/j.1528-1167.2011.03354.x
91. Garamendi I, Acera M, Agundez M, Galbarriatu L, Marinas A, Pomposo I, et al. Cardiovascular autonomic and hemodynamic responses to vagus nerve stimulation in drug-resistant epilepsy. *Seizure*. (2017) 45:56–60. doi: 10.1016/j.seizure.2016.11.018
92. Mintzer S. Metabolic consequences of antiepileptic drugs. *Curr Opin Neurol*. (2010) 23:164–69. doi: 10.1097/WCO.0b013e32833735e7
93. Ding D, Wang W, Wu J, Ma G, Dai X, Yang B, et al. Premature mortality in people with epilepsy in rural China: a prospective study. *Lancet Neurol*. (2006) 5:823-27. doi: 10.1016/S1474-4422(06)70528-2
94. Patorno E, Glynn RJ, Hernandez-Diaz S, Avorn J, Wahl PM, Bohn RL, et al. Risk of ischemic cerebrovascular and coronary events in adult users of anticonvulsant medications in routine care settings. *J Am Heart Assoc*. (2013) 2:e000208. doi: 10.1161/JAHA.113.000208
95. Renoux C, Dell'Aniello S, Saarela O, Filion KB, Boivin JF. Antiepileptic drugs and the risk of ischaemic stroke and myocardial infarction: a population-based cohort study. *BMJ Open*. (2015) 5:e008365. doi: 10.1136/bmjopen-2015-008365
96. Kim Y, Bravo E, Thirnbeck CK, Smith-Mellecker LA, Kim SH, Gehlbach BK, et al. Severe peri-ictal respiratory dysfunction is common in Dravet syndrome. *J Clin Invest*. (2018) 128:1141–53. doi: 10.1172/JCI94999
97. Lacuey N, Hampson JP, Theeranaew W, Zonjy B, Vithala A, Hupp NJ, et al. Cortical structures associated with human blood pressure control. *JAMA Neurol*. (2018) 75:194. doi: 10.1001/jamaneurol.2017.3344
98. Lacuey N, Zonjy B, Londono L, Lhatoo SD. Amygdala and hippocampus are symptomatogenic zones for central apneic seizures. *Neurology*. (2017) 88:701–5. doi: 10.1212/WNL.0000000000003613
99. Lacuey N, Hampson JP, Harper RM, Miller JP, Lhatoo S. Limbic and paralimbic structures driving ictal central apnea. *Neurology*. (2019) 92:e655–69. doi: 10.1212/WNL.0000000000006920
100. Nobis WP, Schuele S, Templer JW, Zhou G, Lane G, Rosenow JM, et al. Amygdala-stimulation-induced apnea is attention and nasal-breathing dependent. *Ann Neurol*. (2018) 83:460–71. doi: 10.1002/ana.25178
101. Klinger D, Gloor P. The connections of the amygdala and of the anterior temporal cortex in the human brain. *J Comp Neurol*. (1960) 115:333–69. doi: 10.1002/cne.901150305
102. Loizon M, Ryvlin P, Chatard B, Jung J, Bouet R, Guenot M, et al. Transient hypoxemia induced by cortical electrical stimulation: a mapping study in 75 patients. *Neurology*. (2020) 94:e2323–36. doi: 10.1212/WNL.0000000000009497
103. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. (2017) 88:1674–80. doi: 10.1212/WNL.0000000000003685
104. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. *Sci Transl Med*. (2015) 7:282ra46. doi: 10.1126/scitranslmed.aaa4050
105. Kruse SW, Dayton KG, Purnell BS, Rosner JI, Buchanan GF. Effect of monoamine reuptake inhibition and α_1 blockade on respiratory arrest and death following electroshock-induced seizures in mice. *Epilepsia*. (2019) 60:495–507. doi: 10.1111/epi.14652
106. Alexandre V, Mercedes B, Valton L, Maillard L, Bartolomei F, Szurhaj W, et al. Risk factors of postictal generalized EEG suppression in generalized convulsive seizures. *Neurology*. (2015) 85:1598–603. doi: 10.1212/WNL.0000000000001949
107. Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: a realistic goal. *Epilepsia*. (2013) 54(Suppl 2):23–8. doi: 10.1111/epi.12180
108. Pang TD, Nearing BD, Krishnamurthy KB, Olin B, Schachter SC, Verrier RL. Cardiac electrical instability in newly diagnosed/chronic epilepsy tracked by Holter and ECG patch. *Neurology*. (2019) 93:450–58. doi: 10.1212/WNL.0000000000008077
109. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol*. (2011) 10:961–68. doi: 10.1016/S1474-4422(11)70193-4
110. Van de Vel A, Cuppens K, Bonroy B, Milosevic M, Jansen K, Van Huffel S, et al. Non-EEG seizure detection systems and potential SUDEP prevention: state of the art: Review and update. *Seizure*. (2016) 41:141–53. doi: 10.1016/j.seizure.2016.07.012
111. Beniczky S, Jeppesen J. Non-electroencephalography-based seizure detection. *Curr Opin Neurol*. (2019) 32:198–204. doi: 10.1097/WCO.0000000000000658
112. 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. doi: 10.1111/epi.16343
113. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: a nationwide population-based case-control study. *Neurology*. (2019) 94:e419–29. doi: 10.1212/WNL.0000000000008741

Conflict of Interest: SR received consultant and/or speaker fees from EISAI, UCB Pharma, Livanova, GW Pharma, Arvelles therapeutics, Idiorsia.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 28 April 2021
doi: 10.3389/fneur.2021.661391

Atrioventricular Conduction in Mesial Temporal Lobe Seizures

Max C. Pensel[1†], *Luca M. Basili*[2†], *Arthur Jordan*[3] *and Rainer Surges*[3*]

[1] Department of Psychiatry, University Hospital Bonn, Bonn, Germany, [2] Department of Neurology and Psychiatry, Sapienza University Rome, Rome, Italy, [3] Department of Epileptology, University Hospital Bonn, Bonn, Germany

Purpose: Asymmetric cerebral representation of autonomic function could help to stratify cardiac complications in people with epilepsy, as some seizures are associated with potentially deleterious arrhythmias including bradycardia and atrioventricular (AV) conduction block. We investigated seizure-related changes in AV conduction and ascertained whether these alterations depend on the hemisphere in mesial temporal lobe epilepsy (mTLE).

Methods: EEG and ECG data of people with pharmacoresistant mTLE undergoing pre-surgical video-EEG telemetry with seizures independently arising from both hippocampi, as determined by intracranial depths electrodes were reviewed. RR and PR intervals were measured using one-lead ECG. Statistics were done with paired student's *t*-tests and linear regression analysis. Data are given as mean ± SD.

Results: Fifty-six seizures of 14 patients (5 men, age 34.7 ± 9.8 years) were included (2 seizures per hemisphere and patient). There were no differences of absolute PR intervals and HR before and during unilateral ictal activity between left- and right-sided hippocampal seizures. Peri-ictal modulation of AV conduction, however, appeared greater with left-sided seizures, as the slope of the PR/HR correlations was significantly steeper with seizures originating in the left hippocampus. PR lengthening >200 ms or full block did not occur in any seizure.

Conclusions: Our data show that on average, PR intervals shortens with mesial temporal lobe seizures with more prominent effects in seizures with left-sided onset, supporting the notion of lateralized cerebral control of cardiac function. The clinical relevance of this subtle finding is unclear but may indicate a lateralized susceptibility to seizure-related AV node dysfunction in mTLE.

Keywords: atrioventricular conduction, mesial temporal lobe epilepsy, cardiac arrhythmia, pre-surgical evaluation, video-EEG monitoring, intracranial depth electrodes

OPEN ACCESS

Edited by:
Brian Darryl Moseley, University of Cincinnati, United States

Reviewed by:
Kais Gadhoumi, Duke University, United States
Selim R. Benbadis, University of South Florida, United States

***Correspondence:**
Rainer Surges
rainer.surges@ukbonn.de

[†] *These authors have contributed equally to this work*

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *30 January 2021*
Accepted: *06 April 2021*
Published: *28 April 2021*

Citation:
Pensel MC, Basili LM, Jordan A and Surges R (2021) Atrioventricular Conduction in Mesial Temporal Lobe Seizures. Front. Neurol. 12:661391. doi: 10.3389/fneur.2021.661391

INTRODUCTION

Given the intricate overlap of regions involved in the central autonomic nervous system (CAN) and networks that generate or maintain epileptic activity, seizures are frequently accompanied by alterations of cardiac properties and heart activity (1, 2). These changes are mostly benign and may be used to detect and count epileptic seizures using wearable devices (3). Potentially lethal cardiac arrhythmias such as ventricular tachycardia or sustained asystole are rare and contribute to the elevated risk of premature mortality and sudden cardiac death in people with epilepsy (2, 4).

Previous studies have predominantly reported increases and decreases of sinus node activity with subsequent changes in heart rate (HR) as well as lengthening or shortening of cardiac repolarization and QT intervals in association with seizures (4, 5). Whilst ictal bradyarrhythmias and asystole occur rarely and almost exclusively in temporal lobe seizures spreading to the contralateral hemisphere, ictal increases of HR is a frequent phenomenon in temporal and frontal lobe epilepsies of both hemispheres (2). In focal seizures of patients with mesial temporal lobe epilepsy (mTLE), however, QT intervals were lengthened to a greater extent and more often beyond abnormal limits during seizures originating in the left hippocampus, indicating that cerebral control of cardiac repolarization may be asymmetrically represented (6). Little is known about seizure-related alterations of atrioventricular (AV) conduction. In all twelve cases with ictal AV block reported so far, seizures emanated from the left hemisphere (mostly from the temporal lobe), suggesting that delay or inhibition AV conduction is preferentially controlled by CAN networks of the left hemisphere (2, 7). However, direct investigations of changes of PR-Intervals related to seizure activity and hemisphere are lacking so far.

In view of these observations, we hypothesized that seizure-related modulation of AV conduction depends on the side of ictal activity. Such an asymmetric representation of AV node control may serve as lateralizing hint during assessment of seizure-onset zone, but may also help to identify people at an elevated risk for ictal AV block and asystole. In the present study, we investigated seizure-related changes in AV conduction in patients with medically refractory bilateral mTLE who underwent intracranial video-EEG telemetry for pre-surgical diagnostics.

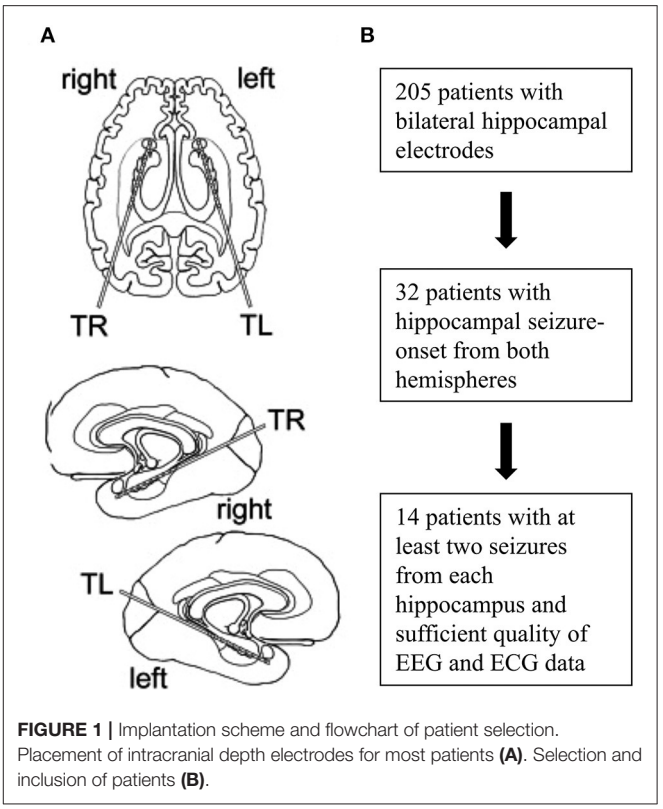


FIGURE 1 | Implantation scheme and flowchart of patient selection. Placement of intracranial depth electrodes for most patients **(A)**. Selection and inclusion of patients **(B)**.

MATERIALS AND METHODS

This study is a retrospective audit of EEG and ECG data recorded during standard clinical procedures and was approved as such by the local medical ethics committee (Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn, No. 352/12). Patient data of a 12-year period (2000–2011) collected at our tertiary epilepsy center (Department of Epileptology, University Hospital Bonn) were reviewed. All patients suffered from pharmacoresistant mTLE and underwent pre-surgical video-EEG telemetry, with seizures arising from both hippocampi, as assessed by intracranial EEG recordings with depth electrodes. Patients with known cardiac diseases were excluded.

A total of 205 patients with bilateral hippocampal electrodes was eligible. Of these, 32 patients displayed hippocampal seizures with onsets from both hemispheres and 14 patients showed at least two seizures from each hippocampus and had EEG- and ECG-recordings of sufficient quality (especially regarding readability of PR intervals) to be included in the final analysis (**Figure 1**, **Table 1**). Two seizures originating from each hippocampus per patient were visually analyzed. If more than two seizures per hemisphere occurred, the two seizures with the greatest HR changes were chosen. All analyzed seizures showed a clear unilateral start. Twelve patients had one 10-contacts hippocampal depth electrode per side stereotactically implanted via a posterior approach (Adtech®, Racine, WI, USA), 1 patient had four 5-contacts depth electrodes implanted from lateral into each hemisphere, covering the amygdala, the hippocampus, the entorhinal cortex and the parahippocampal gyrus. The remaining patient had two 5-contacts electrodes on each side (amygdala and hippocampus), implanted from a lateral approach (**Figure 2**). Electrode position was confirmed via MRI after implantation. The presurgical assessment included cerebral MRI (1.5 or 3 Tesla), scalp EEG (10–20 system with additional electrodes) and neuropsychological testing, prior to invasive video-EEG telemetry. The EEG data were recorded with a video-synchronized digital system (Stellate Harmonie, Version 5.4, Schwarzer GmbH/Natus, Germany), using up to 128 channels, a 200 Hz sampling rate and a 16-bit digital converter. Band pass filter was applied below 0.016 and above 70 Hz. Seizure onset was defined by the occurrence of ictal EEG pattern. The ECG tracing was recorded simultaneously to the iEEG registration via I-lead ECG, with one electrode placed below each clavicle.

RR and PR intervals were manually determined at different timepoints (*preictal*: 1 min before EEG seizure-onset, *early ictal*: within the first seconds of seizure activity and *late ictal*: at the end of the unilateral course of the seizure, before spread to the contralateral side or seizure termination). The respective values of RR and PR interval were calculated as a mean of 2–3 successive ECG intervals. After calculating HR values from RR intervals, statistical analyses were performed to compare preictal and ictal data of seizures originating from the left and right hippocampus

TABLE 1 | Clinical features of patients included in this study.

Patient no.	Sex	Age[a]/epilepsy duration[b]/ handedness	MRI finding	Surgery	Intracranial electrodes	FU[c]/OC[d]
1	M	32/32/R	HS B	No	HC: 1 depth electrode (10 c.) on each side ExHC: None	n.a.
2	M	28/23/L	HS L	SAHE L	HC: 1 depth electrode (10 c.) on each side ExHC: 1 temporo-lateral (16 c.) and 2 temporo-basal (4 c.) strip electrodes on each side	48/I
3	F	24/4/R	HS B	No	HC: 1 depth electrode (10 c.) on each side ExHC: 1 temporo-lateral (4 c.) and 2 temporo-basal (4 c.) strip electrodes on each side	n.a.
4	F	55/33/R	HS B	SAHE R	HC: 1 depth electrode (10 c.) on each side ExHC: 1 temporo-lateral (6 c.) and 2 temporo-basal (4 c.) strip electrodes on each side	53/II
5	M	45/39/L	None	No	HC: 1 depth electrode (10 c.) on each side ExHC: 1 temporo-lateral (4 c.) and 2 temporo-basal (4 c.) strip electrodes on each side	n.a.
6	F	47/7/R	HS B	No	HC: 1 depth electrode (10 c.) on each side ExHipp: None	n.a.
7	F	46/33/R	HS R	SAHE R	HC: 1 depth electrode (10 c.) on each side ExHC: 1 temporo-lateral (6 c.) and 2 temporo-basal (4 c.) strip electrodes on each side	18/II
8	M	22/15/L	None	SAHE L	HC: 1 depth electrode (10 c.) on each side ExHC: 2 temporo-basal (4 c.) strip electrodes on each side, 1 temporo-lateral strip electrode (6 c.) on right side and 1 grid electrode (32 c.) on left side covering Wernicke's area	24/I
9	F	35/30/R	HS B	No	HC: 1 depth electrode (10 c.) on each side ExHC: None	n.a.
10	F	31/30/R	HS B	AHE, TL-resection L	HC: 1 depth electrode (10 c.) on each side ExHC: None	No FU
11	F	34/14/R	HS B	No	HC: 1 depth electrode (10 c.) on each side ExHC: None	n.a.
12	F	28/25/L	HS R	No	HC: 2 depth electrodes (8 c.) on each side ExHC: 2 temporo-basal (4 c.) strip electrodes on each side	n.a.
13	F	31/29/R	HS B	No	HC: 1 depth electrode (10 c.) on each side ExHC: 1 temporo-lateral (6 c.) and 2 temporo-basal (4 c.) strip electrodes on each side	n.a.
14	M	28/15/R	HS L	No	HC: 5 depths electrodes (10 c.) on each side (implanted from lateral). ExHC: 2 frontal strip electrodes (8 c.) on each side	n.a.

[a]At telemetry [Y], [b][Y], [c]Follow Up [m], [d]Outcome [Engel Classification]. B, bilateral; c, electrode contacts; ExHC, extrahippocampal; HC, hippocampal; HS, hippocampal sclerosis; L, left; n.a., not applicable; R, right; SAHE, selective amygdala-hippocampectomy; TL, temporal lobe.

using paired student's *t*-tests. Furthermore, a bivariate linear regression of HR and PR intervals for right and left-sided seizures was performed. Resulting correlations were considered as a measure of peri-ictal modulation of AV conduction. Analyses and graphs were generated using GraphPad Prism 4 (San Diego, CA 92108, USA). The data underlying the study are available from the corresponding author on reasonable request.

RESULTS

Recordings of 56 seizures (2 seizures per hemisphere and patient) in 14 patients with refractory mTLE (5 men, age 34.7 ± 9.8 years, epilepsy duration 23.5 ± 10.7 years) were analyzed. Hippocampal sclerosis was found in 12 patients (bilateral in 8 cases), 2 patients had no apparent lesions (**Table 1**).

Changes of HR were observed during all seizures (**Figure 2A**). In 64.3% of the seizures HR increases alone occurred, whereas HR increase followed by HR decrease, HR decrease alone, or HR decrease followed by HR increase were observed in 12.5, 12.5, and 10.7%, respectively. Overall, there were statistically significant increases of HR in left (pre-ictal 84 ± 15 bpm, late ictal 107 ± 21 bpm, $t = -7.34$, df = 27, $p < 0.001$) and right-sided (pre-ictal 83 ± 13 bpm, late ictal 102 ± 18 bpm, $t = -6.48$, df = 27, $p < 0.001$) hippocampal seizures.

At the level of individual patients, PR intervals during seizures were consistently shortened (in all 2 seizures per hemisphere and patient) in right-hippocampal seizures of 4 patients and left-hippocampal seizures of 3 patients. Consistent lengthening of PR intervals was found in right-hippocampal seizures of 5 patients and left-hippocampal seizures of 4 patients. Consistent

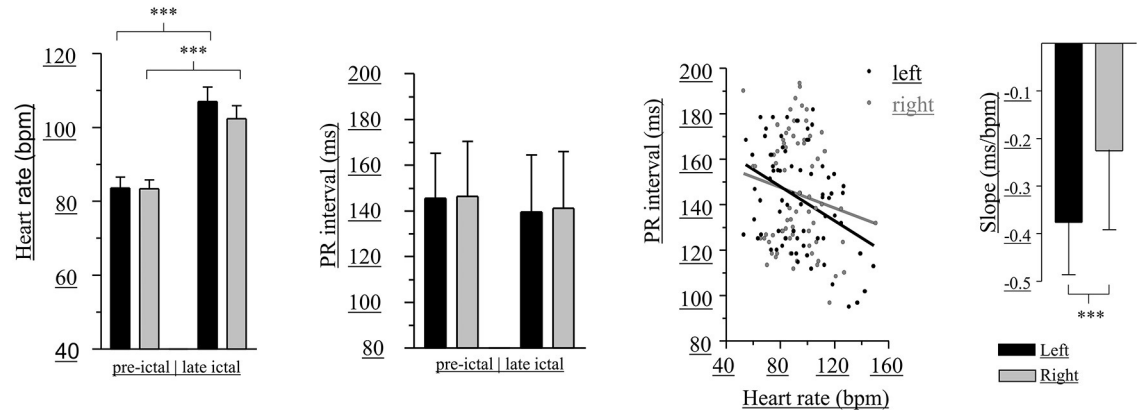


FIGURE 2 | Modulation of PR intervals is greater with left-hippocampal seizures. Heart rate before (left bars) and during (right bars) unilateral hippocampal seizures **(A)**. PR interval before (left bars) and during (right bars) unilateral hippocampal seizures **(B)**. PR interval/HR correlations and slopes (inset) **(C)**. A total of 56 seizures (black bars, left-sided seizures; gray bars, right-sided seizures) of 14 patients was included. ***$p < 0.001$.

shortening of PR intervals of all seizures of both sides was not observed in any patients, whereas consistent lengthening of PR intervals in all 4 seizures was seen in 1 patient.

At the group level (pooled data), there were no significant differences between left- and right-sided hippocampal seizures regarding absolute PR intervals and HR before (PR intervals: left 146 ± 20 ms, right 146 ± 24 ms, $t = -0.13$, df = 54, $p = 0.894$; HR: left 84 ± 15 bpm, right 83 ± 13 bpm, $t = 0.07$, df = 54, $p = 0.947$) as well as during early (PR intervals: left 143 ± 24 ms, right 146 ± 25 ms, $t = -0.40$, df = 54, $p = 0.689$; HR: left 93 ± 23 bpm, right 92 ± 14 bpm, $t = 0.31$, df = 54, $p = 0.756$) or late (PR intervals: left 138 ± 27 ms, right 141 ± 25 ms, $t = -0.43$, df = 54, $p = 0.669$; HR: left 107 ± 21 bpm, right 102 ± 18 bpm, $t = 0.90$, df = 54, $p = 0.373$) unilateral seizure activity (**Figure 2B**). Peri-ictal modulation of AV conduction, however, appeared greater during left-sided seizures, as the negative correlation between HR and PR intervals was significantly different than that of right-sided seizures (left: −0.38 ± 0.11 ms/bpm, $r^2 = 0.14$; right: −0.23 ± 0.17 bpm, $r^2 = 0.02$; $t = 6.98$, df = 97, $p < 0.0001$; **Figure 2C**).

DISCUSSION

In this retrospective clinical study, peri-ictal PR intervals and HR were assessed in patients with pharmacoresistant bilateral mTLE. Importantly, these patients were bilaterally implanted and at least two seizures per side were registered, allowing a comparison between left-and right-hippocampal seizure-related changes of PR intervals, and minimizing the effects of inter- and intra-individual variability. Moreover, the simultaneous iEEG-ECG recording provides optimal ECG resolution regarding time and localization of seizure onsets. While this investigation of seizure and hemisphere related changes of PR-Intervals follows an original approach, it does not come without limitations. Firstly, several other regions involved in the CAN such as the insular cortex, hypothalamus, thalamus and cingulate gyrus were not covered by intracranial EEG electrodes, so that spreading of ictal activity could not be recorded and excluded (8). Secondly, all patients had bilateral mTLE and mostly in association with structurally altered hippocampal tissue, which may modify the contribution of the affected hippocampi to the regulation of autonomic function. Whether our findings apply also to other patient groups remains thus to be elucidated. Thirdly, a systematic electrical stimulation of the implanted electrodes and analysis of ECG alterations was not done, which could have complemented and strengthened our subtle findings.

As expected, all seizures were associated with alterations of HR, mainly chronotropic changes with tachycardia, or mixed patterns, supporting the notion of the hippocampus as an important element within the CAN. Overall, the absolute changes of HR and PR intervals were similar in seizures originating from the left and right hippocampus. Previous studies in apparently healthy subjects revealed an inverse correlation between PR intervals and HR, i.e., PR intervals shorten with increasing HR (9). Intriguingly, when considering the correlation between PR intervals and HR in our patients, PR interval shortening was significantly greater during left-hippocampal seizures, although absolute PR intervals and PR interval changes were within normal limits (4, 9). This subtle finding is unlikely to have a clinical meaning, but may reflect a lateralized representation of the CAN with the left hemisphere being more important in the control of AV conduction. This assumption is also underscored by the finding that AV blocks were exclusively reported with left-sided seizures (although this effect is opposite to the enhanced shortening of PR intervals per HR observed in this study) (2, 7). *In-vivo* experiments in rodents and neuroimaging studies in humans provide structural correlates that link the left mesial temporal lobe to the control of cardiac properties. At the brain stem level, the nucleus ambiguus and raphe nuclei are involved in the modulation of AV conduction (10–12) which, in turn, are connected to structures of the medial temporal lobe (particularly to the subiculum, amygdala, entorhinal cortex, and hippocampus) via the lateral forebrain bundle (1). A meta-analysis of neuroimaging data has highlighted the contribution of the left amygdala to central processing of autonomic function (13), which may explain our finding of a

greater impact of left-sided mesial temporal lobe seizures on PR interval shortening.

In conclusion, left-hippocampal seizures appear to be linked to greater changes in cardiac repolarization and AV conduction (6). These alterations are subtle, but underscore the notion of asymmetric lateralization of cortical heart control, which in turn may reflect an elevated risk of disturbed AV conduction in people with left mTLE.

DATA AVAILABILITY STATEMENT

The data underlying the study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medinizische Fakultaet Bonn. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LMB and AJ have collected and analyzed data. MP has analyzed the data and drafted the manuscript. RS has designed and supervised the study. All authors have reviewed the draft.

REFERENCES

1. Edlow BL, McNab JA, Witzel T, Kinney HC. The structural connectome of the human central homeostatic network. *Brain Connect.* (2016) 6:187–200. doi: 10.1089/brain.2015.0378
2. 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. doi: 10.1016/j.autneu.2015.07.066
3. Ryvlin P, Cammoun L, Hubbard I, Ravey F, Beniczky S, Atienza D. Noninvasive detection of focal seizures in ambulatory patients. *Epilepsia.* (2020) 61 (Suppl. 1):S47–S54. doi: 10.1111/epi.16538
4. Surges R, Shmuely S, Dietze C, Ryvlin P, Thijs RD. Identify patients with epilepsy at high risk of cardiac death: recognize signs, risk factors and initial management of high risk of cardiac death. *Epileptic Disord.* (2021) 23:17-39. doi: 10.1684/epd.2021.1254
5. Ufongene C, El Atrache R, Loddenkemper T, Meisel C. Electrocardiographic changes associated with epilepsy beyond heart rate and their utilization in future seizure detection and forecasting methods. *Clin Neurophysiol.* (2020) 131:866–79. doi: 10.1016/j.clinph.2020.01.007
6. Surges R, Jordan A, Elger CE. Ictal modulation of cardiac repolarization, but not of heart rate, is lateralized in mesial temporal lobe epilepsy. *PLoS ONE.* (2013) 8:e64765. doi: 10.1371/journal.pone.0064765
7. Allana SS, Ahmed HN, Shah K, Kelly AF. Ictal bradycardia and atrioventricular block: a cardiac manifestation of epilepsy. *Oxf Med Case Rep.* (2014) 2014:33–5. doi: 10.1093/omcr/omu015
8. Jobst BC, Gonzalez-Martinez J, Isnard J, Kahane P, Lacuey N, Lahtoo SD, et al. The insula and its epilepsies. *Epilepsy Curr.* (2019) 19:11–21. doi: 10.1177/1535759718822847
9. Carruthers SG, McCall B, Cordell BA, Wu R. Relationships between heart rate and PR interval during physiological and pharmacological interventions. *Br J Clin Pharmacol.* (1987) 23:259–65. doi: 10.1111/j.1365-2125.1987.tb03043.x
10. Salo LM, Campos RR, McAllen RM. Differential control of cardiac functions by the brain. *Clin Exp Pharmacol Physiol.* (2006) 33:1255–8. doi: 10.1111/j.1440-1681.2006.04520.x
11. Salo LM, Nalivaiko E, Anderson CR, McAllen RM. Control of cardiac rate, contractility, and atrioventricular conduction by medullary raphe neurons in anesthetized rats. *Am J Physiol Heart Circ Physiol.* (2009) 296:H318–24. doi: 10.1152/ajpheart.00951.2008
12. Sampaio KN, Mauad H, Michael Spyer K, Ford TW. Chronotropic and dromotropic responses to localized glutamate microinjections in the rat nucleus ambiguus. *Brain Res.* (2014) 1542:93–103. doi: 10.1016/j.brainres.2013.10.035
13. Beissner F, Meissner K, Bär KJ, Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J Neurosci.* (2013) 33:10503–11. doi: 10.1523/JNEUROSCI.1103-13.2013

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 11 May 2021
doi: 10.3389/fneur.2021.669517

Automated Analysis of Risk Factors for Postictal Generalized EEG Suppression

Xiuhe Zhao[1†], Laura Vilella[2,3†], Liang Zhu[4], M. R. Sandhya Rani[2,3], Johnson P. Hampson[2,3], Jaison Hampson[2,3], Norma J. Hupp[2,3], Rup K. Sainju[2,5], Daniel Friedman[2,6], Maromi Nei[2,7], Catherine Scott[2,8], Luke Allen[2,8], Brian K. Gehlbach[2,5], Stephan Schuele[2,9], Ronald M. Harper[2,10], Beate Diehl[2,8], Lisa M. Bateman[2,11], Orrin Devinsky[2,6], George B. Richerson[2,5], Guo-Qiang Zhang[2,3], Samden D. Lhatoo[2,3] and Nuria Lacuey[2,3]*

[1] Department of Neurology, Qilu Hospital of Shandong University, Jinan, China, [2] National Institute of Neurological Disorders and Stroke (NINDS) Center for Sudden Unexpected Death in Epilepsy (SUDEP) Research, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, United States, [3] Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, United States, [4] Biostatistics and Epidemiology Research Design Core, Division of Clinical and Translational Sciences, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, United States, [5] Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, IA, United States, [6] New York University (NYU) Grossman School of Medicine, New York, NY, United States, [7] Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, United States, [8] Department of Neurology, Institute of Neurology, University College London, London, United Kingdom, [9] Feinberg School of Medicine, Northwestern University, Chicago, IL, United States, [10] Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles, Los Angeles, CA, United States, [11] Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA, United States

OPEN ACCESS

Edited by:
Brian Darryl Moseley,
University of Cincinnati, United States

Reviewed by:
Elena Gardella,
University of Southern Denmark, Denmark
James Tao,
University of Chicago, United States

***Correspondence:**
Laura Vilella
lvilellabertran@gmail.com

[†] These authors share first authorship

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: 19 February 2021
Accepted: 13 April 2021
Published: 11 May 2021

Citation:
Zhao X, Vilella L, Zhu L, Rani MRS, Hampson JP, Hampson J, Hupp NJ, Sainju RK, Friedman D, Nei M, Scott C, Allen L, Gehlbach BK, Schuele S, Harper RM, Diehl B, Bateman LM, Devinsky O, Richerson GB, Zhang G-Q, Lhatoo SD and Lacuey N (2021) Automated Analysis of Risk Factors for Postictal Generalized EEG Suppression. Front. Neurol. 12:669517. doi: 10.3389/fneur.2021.669517

Rationale: Currently, there is some ambiguity over the role of postictal generalized electro-encephalographic suppression (PGES) as a biomarker in sudden unexpected death in epilepsy (SUDEP). Visual analysis of PGES, known to be subjective, may account for this. In this study, we set out to perform an analysis of PGES presence and duration using a validated signal processing tool, specifically to examine the association between PGES and seizure features previously reported to be associated with visually analyzed PGES.

Methods: This is a prospective, multicenter epilepsy monitoring study of autonomic and breathing biomarkers of SUDEP in adult patients with intractable epilepsy. We studied videoelectroencephalogram (vEEG) recordings of generalized convulsive seizures (GCS) in a cohort of patients in whom respiratory and vEEG recording were carried out during the evaluation in the epilepsy monitoring unit. A validated automated EEG suppression detection tool was used to determine presence and duration of PGES.

Results: We studied 148 GCS in 87 patients. PGES occurred in 106/148 (71.6%) seizures in 70/87 (80.5%) of patients. PGES mean duration was 38.7 ± 23.7 (37; 1–169) seconds. Presence of tonic phase during GCS, including decerebration, decortication and hemi-decerebration, were 8.29 (CI 2.6–26.39, $p = 0.0003$), 7.17 (CI 1.29–39.76, $p = 0.02$), and 4.77 (CI 1.25–18.20, $p = 0.02$) times more likely to have PGES, respectively. In addition, presence of decerebration ($p = 0.004$) and decortication ($p = 0.02$), older age ($p = 0.009$), and hypoxemia duration ($p = 0.03$) were associated with longer PGES durations.

Conclusions: In this study, we confirmed observations made with visual analysis, that presence of tonic phase during GCS, longer hypoxemia, and older age are reliably associated with PGES. We found that of the different types of tonic phase posturing, decerebration has the strongest association with PGES, followed by decortication, followed by hemi-decerebration. This suggests that these factors are likely indicative of seizure severity and may or may not be associated with SUDEP. An automated signal processing tool enables objective metrics, and may resolve apparent ambiguities in the role of PGES in SUDEP and seizure severity studies.

Keywords: PGES, generalized convulsive seizure, epilepsy, SUDEP, mortality, post-ictal generalized EEG suppression, sudden unexpected death in epilepsy

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) incidence ranges from 1.1 to 5.9 per 1,000 patient-years in epilepsy clinic populations to 6.3–9.3 per 1,000 patients with intractable epilepsy, posing a significant public health problem (1). Risk factors that increase risk include ≥3 generalized convulsive seizure (GCS) per year, younger age of onset of epilepsy and longer duration of epilepsy (2–4). In a case-control study (5), duration of postictal generalized electroencephalographic suppression (PGES) was significantly longer in patients who later died of SUDEP; duration >50 s was significantly associated with a higher risk of SUDEP (5). All patients in the Mortality in Epilepsy Monitoring Units Study (MORTEMUS) had PGES in the agonal seizure (6). However, a case control study of patients who later died of SUDEP did not find PGES predictive (7). Although several observations have been made on factors associated with PGES, seizure severity, and potential SUDEP risk, almost all of have been made with visual analysis of PGES, which we now know to be subjective and perhaps unreliable. This may explain apparent ambiguity over the role of PGES in SUDEP (8–10). In this study, we set out to perform an analysis of PGES presence and duration using a validated signal processing tool (11), specifically to examine the association between PGES and seizure features previously reported to be associated with visually analyzed PGES.

METHODS

All patients were prospectively consented participants in the National Institute of Neurological Disorders and Stroke (NINDS) Center for SUDEP Research's (CSR) Autonomic and Imaging Biomarkers of SUDEP multicenter project (U01-NS090407) and its preliminary phase, the Prevention and Risk Identification of SUDEP Mortality (PRISM) project (P20NS076965). We studied video-electroencephalogram (vEEG) recordings of GCS in a cohort of patients who underwent long-term monitoring in the epilepsy monitoring unit (EMU). Generalized convulsive seizures (GCS) included generalized tonic-clonic seizures, focal to bilateral tonic-clonic seizures, and focal-onset motor bilateral clonic seizures (12).

The cohort included a total of 87 patients who had 148 GCS, in whom inductance plethysmography (abdominal and thoracic belts) and vEEG recording were carried out during the evaluation in EMU. EEGs were recorded on Nihon Kohden EEG acquisition software with a 1,000 Hz sampling rate using conventional bipolar and common average referenced 10–20 montages. Chest and abdominal excursions were recorded using inductance plethysmography (Ambu, Ballerup, Denmark). Peripheral capillary oxygen saturation (SpO_2) and heart rate (HR) were monitored using pulse oximetry (NellcorOxiMax N-600x, Covidien, Minneapolis, MN, USA). The cardiopulmonary data were time-synchronized with the EEG data.

A validated automated EEG suppression detection tool (11) was used to determine presence and duration of PGES and supplemented by two-experienced clinical epileptologists (SL and NL) who reviewed the EEG records with differences resolved by consensus when the tool gave no solution.

Collection of Variables

The following data were collected and analyzed: Age on admission and at epilepsy onset, gender, body mass index (BMI), duration of epilepsy, previous epilepsy surgery and number of GCS in the preceding 12 months (classified as ≥3 and <3), seizure semiological presentation and duration, body position at seizure end before nursing intervention (supine, prone, lateral, sitting, or undetermined), state prior to seizure onset (awake/sleep and sleep state [N1, N2, N3, and R]).

Tonic phase was defined as tonicity in both arms, further classified into decerebration (both upper limbs straight symmetric), decortication (both upper limbs flexed symmetrically) or hemi-decerebration (tonic extension of one arm with flexion of contralateral arm without progression to decortication or decerebration). Postictal generalized electroencephalographic suppression (PGES), postictal burst suppression and EEG recovery in the post-convulsive period were identified. The EEG signal-processing algorithm was trained to recognize PGES as in previous studies (5, 13): an immediate postictal (within 30 s after GCS) generalized absence of electroencephalographic activity >10 μV in amplitude, lasting at minimum 1 s. Duration of PGES referred to the time interval from PGES onset to the appearance of burst suppression or continuous slowing. Burst Suppression (BS) was defined as generalized, intermittent slowing during the post-convulsive period, alternating with PGES. Combined PGES and burst suppression made up the EEG recovery duration.

TABLE 1 | Seizure-specific demographic, clinical characteristics and MRI neuroimaging details.

		Total ($n = 148$)	PGES ($n = 106$)	No PGES ($n = 42$)
Demographics		***N***	***N***	***N***
Gender	Male	67	49	18
	Female	81	57	24
Age at admission (mean), years		37.37	38.12	36.02
Age at epilepsy onset (mean), years		19.71	19.56	16.64
BMI		28.99	29.62	27.38
History				
Duration of epilepsy (mean), years		17.54	17.58	16.69
Previous epilepsy surgery		16	8	8
Frequency of GCS in the previous year	<3	33	22	11
	≥3	100	72	28
Epileptogenic zone				
Temporal		37	34	3
Frontal		23	15	8
Parietal		1	1	0
Occipital		1	1	0
Multifocal		23	13	10
Generalized		28	23	5
Lateralized		20	11	9
Bitemporal		12	5	7
Unknown		3	3	0
Lateralization of seizure onset				
Left		49	36	13
Right		33	26	7
Generalized		28	23	5
Bilateral		35	18	17
State at seizure onset	Awake	72	53	19
	Sleep	73	53	20
Sleep stage at seizure onset	R	1	1	0
	N1	22	14	8
	N2	49	38	11
	N3	1	0	1
Neuroimaging findings on MRI				
Negative		90	59	13
Positive				
Tumor		10	7	3
Encephalomalacia		8	7	1
Hippocampal asymmetry		6	5	1
Vascular malformation		4	3	2
Temporal horn asymmetry		4	2	2
Mesial temporal sclerosis		2	0	2
Malformation of cortical development		6	6	0
Temporal horn asymmetry		4	2	2
Unavailable		18	17	1
AED				
Number of AED on admission (mean)		2	1.88	2.31
	No AED	1	1	0
	One	38	33	5
	Two	75	54	21
	Three	28	14	14
	Four	6	4	2
AED changes before GTCS				
	Tapering	69	40	29
	Withdrawal	70	61	9
	Increase	2	1	1
	No change	7	4	3
Early nursing interventions				
	O_2 administration	84	59	25
	Oral suction	62	49	13

EEG, electroencephalogram; PGES, postictal generalized EEG suppression; GCS, generalized clonic seizure; BMI, body mass index; AED, antiepileptic drugs; R, REM.

Localization of the putative epileptogenic zone was defined based on clinical history, seizure semiology, neuroimaging, and EEG. High-resolution magnetic resonance imaging (MRI) or computed tomography (CT) results were collected (**Table 1**). The number of antiepileptic drugs (AED) on admission and changes of AED before the recorded GCS (tapering, withdrawal, increase or no change) were recorded. Early nursing intervention was defined as oxygen administration or oral suctioning applied during the seizure or within 5 s of seizure termination. Respiratory data included peripheral arterial oxygen saturation (SpO_2) at preictal baseline, GCS onset, SpO_2 nadir, duration of hypoxemia (<90%, from GCS onset to 3 min postictal), and presence of central apnea (pre-GCS or post-GCS) were collected using respiratory inductance plethysmography and finger pulse oximetry. Central apnea was defined as ≥1 missed breaths without any other explanation (i.e., speech, movement, or intervention). In some cases whose respiratory data were missing, review of the video to assess respiratory effort helped in differentiating obstructive from central apnea.

Statistical Analysis

Descriptive statistics were provided for seizure-specific demographic and clinical variables (**Table 1**). Generalized estimating equation (GEE) method was used to model the presence of PGES or PGES duration on different demographic and clinical variables. Variables with a $p < 0.1$ were employed in the multivariate models. For the binary variable presence of PGES, a binary distribution and a logit link were specified in GEE and odds ratios, 95% confidence intervals, and p-values were reported (**Table 3**). For the continuous variable PGES duration,

TABLE 2 | Seizure-specific electroclinical features and cardiorespiratory data of the patients.

		Total ($n = 148$)	PGES ($n = 106$)	No PGES ($n = 42$)
Seizure semiology				
Duration of generalized seizure (mean), s		49.22	47.35	51.88
Duration of tonic phase (mean), s		8.74	8.38	10.2
Duration of clonic phase (mean), s		34.97	33.12	38.12
Tonic phase semiology				
	Hemi-decerebration	13	13	0
	Decerebration	66	59	7
	Decortication	29	21	8
	No tonic	40	13	27
Body position (at seizure end)				
	Supine	98	73	25
	Prone	4	1	3
	Lateral	41	27	14
	Sitting	1	1	0
	Undermined	4	4	0
EEG				
PGES duration (mean), s		38.73		
Burst suppression		62	56	6
EEG recovery (mean), s		83.44	82.07	92.14
Respiratory data				
SpO_2 at baseline (mean), %		95.46	94.35	95.55
SpO_2 at GCS onset (mean),%		92.55	93.1	90.68
SpO_2 nadir (mean), %		59.64	57.07	67.22
Duration of hypoxemia (mean), s		130.82	132.34	126.33
Central apnea				
	Ictal	49	36	13
	Postictal	31	27	4

Values are given as numbers of GCS unless otherwise indicated.
EEG, electroencephalogram; PGES, postictal generalized EEG suppression; GCS, generalized clonic seizure; SpO_2, peripheral capillary oxygen saturation.

TABLE 3 | Multivariate analysis of electroclinical seizure features and cardiorespiratory data with PGES presence.

		OR	Confidence interval	*P*-value
Tonic phase semiology	Decerebration	8.29	2.60–26.39	**0.0003**
	Decortication	4.77	1.25–18.20	**0.02**
	Hemi-decerebration	7.17	1.29–39.76	**0.02**
	No tonic	–	–	–
Lateralization of seizure onset	Right	0.90	0.23–3.51	0.88
	Generalized	0.93	0.17–5.21	0.93
	Bilateral	0.40	0.12–1.32	0.13
	Left	–	–	–
Post-convulsive central apnea (PCCA)	Yes	1.32	0.44-3.98	0.62
	No	–	–	–
BMI		1.04	0.97–1.11	0.24

Bold value indicates the statistically significant ($p < 0.05$).

TABLE 4 | Multivariate analysis of electroclinical seizure features and cardiorespiratory data with PGES duration.

		Estimate	SE	*p*-value
Tonic phase semiology	Decerebration	34.97	12.15	**0.004**
	Decortication	23.85	10.41	**0.02**
	Hemi-decerebration	17.29	12.70	0.17
	No tonic	–	–	–
Position at GCS end	Supine/Sitting	12.21	5.92	**0.039**
	Lateral	–	–	–
Age		0.77	0.29	**0.009**
GCS Onset O_2		−0.42	0.34	0.22
Hypoxemia duration		0.10	0.04	**0.03**
State	Sleep	−13.54	4.21	**0.001**
	Awake	–	–	–
BMI		0.07	0.25	0.77

GCS, generalized convulsive seizure; BMI, body mass index. Bold value indicates the statistically significant ($p < 0.05$).

covariate coefficient estimates, standard error, and corresponding *p*-values from GEE method were provided (**Table 4**). $P < 0.05$ in the final models were considered significant. All analyses were performed in SAS 9.4 (Cary, NC).

RESULTS

Data from 148 GCS in 87 patients were collected. These patients were previously reported in a paper studying breathing changes as biomarkers of SUDEP (13). Details of seizure-specific demographics, clinical characteristics and MRI neuroimaging details are presented in **Table 1**. Seizure-specific electroclinical seizure features and cardiorespiratory data are shown in **Table 2**.

Mean age on admission was 37.4 ± 14.1 (34; 18–77) years and at epilepsy onset was 19.7 ± 16.06 (16–67) years. Epilepsy duration was 17.5 ± 12.2 (15; 0.08–45) years, with 65% more than 10 years. Mean body mass index was 28.7 ± 6.6 kg/m^2 (28.1; 15.1–45.8 kg/m^2). Twenty-six patients had <3 GCS in the last year and 52 had ≥3. Frequency of GCS was unknown in nine patients. Sixteen (10.8%) had previous epilepsy surgery. Ninety (60.8%) of the seizures were recorded from 50 patients who had negative neuroimaging (details seen in **Table 1**).

Seizures were of temporal onset in 37(25%), generalized in 28(18.9%), frontal in 23(15.5%), multifocal in 23(15.5%), lateralized but not localized in 20 (13.5%), bitemporal in 12(8.1%), occipital in one (0.7%), and parietal in one (0.7%). Seizure onset could not be localized or lateralized in the

remaining three seizures. Seizure onset was left in 49 (33.1%), right in 33 (22.3%), bilateral in 35 (23.6%), and generalized in 28 (18.9%). The remaining three were undetermined. At the time of the recorded seizure, patients were on three or more AEDs in 23% seizures, on two in 50.7%, on one in 25.7%, and 0.7% on no AEDs. Oral suctioning was used in 62/148 (41.89%) seizures and oxygen administration on 84/148 (56.76%).

Tonic semiology was seen in 108/148 (72.9%) seizures, with decerebration in 66/148 (44.6%), decortication in 29/148 (19.6%), and hemi-decerebration in 13/148 (8.8%) (**Table 2**) The mean duration of tonic phase was 8.7 (8.50, 1–23) seconds (s). The mean duration of the clonic phase was 34.9 (32–110) seconds and of the entire GCS, 49.22 (48, 5–126) seconds, **Table 2**.

Seventy-two seizures occurred during wakefulness, 73 during sleep, and the remaining three (in one patient) during postictal stupor due to a seizure cluster. Out of 72 seizures that occurred during wakefulness, 53 had PGES. Out of 73 seizures that occurred during sleep, 52 had PGES. The duration of PGES in seizures arising from awake state was 41.52 (2–169) seconds, and 35.83 (1–119) seconds when asleep. Supine posture was seen after 98/148 (66%) seizures with mean PGES duration of 38.89 (2–169). Lateral posture was seen after 41/148 (28%) seizures with mean PGES duration of 31.25 (23–36) seconds. Prone posture was seen in 4/148 (28%) with mean PGES duration of 38.00 (28–42) seconds. Sitting posture was grouped with supine due to the small number (one patient), and undetermined was excluded from analysis (**Table 2**).

Mean baseline SpO_2 was 95.46 ± 2.35 (96; 89–100)%. The SpO_2 nadir mean was 59.64 ± 14.10 (60; 22–87)%. In 33% (49/148) seizures, central apnea occurred before GCS (ictal central apnea, ICA) and in 21% (31/148), apnea occurred postictally (post-convulsive central apnea, PCCA) (**Table 2**).

PGES (Postictal Generalized EEG Suppression)

PGES occurred in 106/148 (71.6%) seizures and 70/87 (80.5%) patients (57 female). Mean duration was 38.7 ± 23.7 (37; 1–169) seconds (s). PGES duration ≥50 s occurred in 18% (19/106). EEG recovery duration was 83.4 + 119.2 (54; 1–1,091) seconds. In univariate analysis, we found that older age was associated with longer PGES duration ($p = 0.03$) and higher BMI was associated with the presence of PGES ($p = 0.04$). Gender, age at epilepsy onset, epilepsy duration, previous epilepsy surgery, and the number of GCS within 12 months prior to admission were not associated with PGES. Epileptogenic zone and imaging abnormalities were not associated with occurrence or duration of PGES. During EMU monitoring, most patients had changes in AEDs (tapering: 46.6%, withdrawal: 47.3%).The number of AEDs at admission or changes before recorded GCS were not correlated with PGES presence or duration. Similarly, presence or duration of PGES were not associated with early nursing intervention (oxygen administration or oral suctioning).

In univariate analysis, presence of decerebration ($p < 0.01$), decortication ($p = 0.01$), and hemidecerebration ($p < 0.0001$) during tonic phase were all associated with PGES presence. In addition, decerebration was associated with longer PGES duration ($p = 0.009$). Duration of GCS, tonic or clonic phase were not associated with PGES incidence ($p = 0.39$; $p = 0.54$; $p = 0.26$, respectively) or PGES duration ($p = 0.46$; $p = 0.37$; $p = 0.35$). Sleep ($p = 0.1$) and lateral posture ($p = 0.04$) were inversely correlated to duration of PGES. Severe hypoxemia (SpO_2 <75%) was associated with PGES presence ($p = 0.007$) and duration ($p = 0.003$); hypoxemia duration in turn was associated with PGES duration ($p = 0.03$). For central apnea, there was no association with occurrence of ICA or PCCA and PGES.

In multivariate analysis, presence of decerebration, decortication and hemi-decerebration during the tonic phase, were 8.29 (CI 2.6–26.39, $p < 0.001$), 7.17 (CI 1.29–39.76, $p = 0.02$), and 4.77 (CI 1.25–18.20, $p = 0.02$) times more likely to have PGES, respectively, compared to absence of tonic phase (**Table 3**). In addition, decerebration presence ($p = 0.004$), decortication presence ($p = 0.02$), older age ($p = 0.009$), and hypoxemia duration ($p = 0.03$) were associated with longer PGES durations. Sleep state (as opposed to awake) was associated with shorter PGES duration ($p = 0.001$; **Tables 3, 4**).

DISCUSSIONS

We confirmed, using an objective method for analysis of PGES, that several variables indicated by visual analysis were indeed associated with this phenomenon. PGES is a common phenomenon following GCS, with an incidence of 72%, and has an average duration of 38.7 s. PGES occurrence is associated with presence of a tonic phase during GCS and presence of severe hypoxemia. In addition, longer durations of tonic phase and hypoxemia, older age and postictal supine and sitting position (compared to lateral) are associated with longer PGES duration.

Reports of PGES incidences are variable, ranging from 29 to 74% after GCS (5, 7–10, 14–17). Variability may be due to observer subjectivity, heterogeneous patient populations, and different criteria for diagnosis (7, 18). Differences in visual analysis may be significant; we now know this to be subjective and perhaps unreliable. Our results (72%) indicate PGES to be reliably common. Average PGES duration in our study was 38.7 s. This is roughly concordant with previous studies where PGES duration ranged from 33 to 53 s (8, 10, 17), with a median of 28 s (8). Only 18% of GCS had PGES duration longer than >50 s, suggesting prolonged obtundation is usually infrequent. Prolonged PGES has been suggested as a SUDEP risk factor (5) and associated with more severe postictal coma (17), although other studies have not confirmed this relationship (7, 8). One study found that patients who died of SUDEP had significantly shorter PGES duration compared to living controls (19). In our prospective cohort, two near SUDEP cases occurred (13), with PGES lasting 169 and 75 s, respectively, although no conclusions can be drawn from this observation alone. Analysis of the overall CSR study (of which this report is a part) is currently under way.

We found that presence of tonic phase is associated with both appearance and longer duration of PGES confirming studies based on visual analysis on tonic phase presence (9, 10, 16, 17, 20) and tonic phase duration (9). Different types of tonic phase posturing had varying impact, such that decerebration had

the strongest association, followed by decortication, followed by hemi-decerebration. We found that lateral posture (compared to supine) at seizure end is inversely correlated with PGES duration, suggesting briefer obtundation. Although SUDEP cases are more likely to be found in a prone position (21, 22), we could not assess possible associations due to the limited number of prone individuals [4/148 (2.7%)] in our cohort. Sleep state at seizure onset was inversely associated with PGES duration. This is in contrast to other studies that have noted direct association between sleep and increased PGES (8, 10, 23), although others have not (19, 20, 24). Deep sleep before seizure onset, including REM (R) and N3 sleep only occurred in one patient each, and hence the relationship between sleep state and PGES is unresolved here.

In our study, we found that older age at admission was correlated with longer PGES. This is consistent with previous studies (25, 26), but not with others (8–10). We did not find any association between temporal lobe seizure onsets and occurrence of PGES, concordant with some studies (8, 10), but not with others (7, 17) Consistent with all previous studies, we found no association between PGES and GCS frequency, total duration of GCS, gender, epilepsy duration or presence of MRI abnormalities (8–10, 15, 24, 27). AED reduction has been said to increase risk of PGES five-fold (8). Our results suggest that AED reduction did not influence PGES, consistent with a previous study (16), although this lack or relationship may reflect a very small number who did not have medications decreased. Early periictal nursing intervention (14) and O_2 administration (10) are reportedly been associated with reduced PGES duration. Other studies found intervention, including early O_2 mask administration to have no effect (19, 20, 28), consistent with our current findings. However, hypoxemia duration was associated with PGES duration, reflecting the finding that O_2 administration was local EMU protocol driven (regardless of hypoxemia extent) rather than governed by the extent of hypoxemia encountered. This interpretation is in line with ictally triggered severe hypoxemia and hypercapnia previously observed with PGES (14, 15, 29, 30).

One of the main limitations of our study is that the results are largely confirmatory of prior results achieved by visual analysis, and lacks of novel findings. However, the reproducibility of the results may be an indicator that the automated PGES tool is reliable for research studies in order to eliminate the inter-rater variability in PGES assessment in a time-sparing manner.

CONCLUSIONS

In this study, with a custom signal-processing tool for PGES analysis, we confirmed observations made with visual analysis, that presence of a tonic phase during GCS, longer hypoxemia, older age and postictal supine or sitting position (compared to lateral) are reliably associated with PGES. The findings suggest that these factors are likely indicative of seizure severity and may or may not be associated with SUDEP. We found that of the different types of tonic phase posturing, decerebration has the strongest association with PGES, followed by decortication, followed by hemi-decerebration. Part of the variability in the literature could result from heterogeneous patient populations, different research methodologies, anti-epileptic medications, or seizure frequency. However, use of visual analysis of PGES detection and quantification, likely plays a part. An automated signal-processing tool enables objective metrics, and may resolve apparent ambiguities in the role of PGES in SUDEP and seizure severity studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the studies involving human participants were reviewed and approved by Case Western Reserve University and University Hospitals, as part of NIH/NINDS Center for SUDEP Research study (U01 NS090405, U01 NS090406, and U01 NS090407). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ and LV were major role in data acquisition, data analysis and interpretation, and drafted manuscript for intellectual content. NL designed and conceptualized the study, interpretation of the data, and drafted manuscript for intellectual content. SL designed and conceptualized the study, and revised the manuscript for intellectual content. RS, DF, MN, BG, SS, RH, BD, LB, OD, GR, and G-QZ revised the manuscript for intellectual content. JoH, JaH, MR, NH, CS, and LA were involved in the data acquisition and management. LZ was involved in the statistical analysis. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the Center for SUDEP Research: NIH/NINDS U01-NS090405, U01 NS090406, and U01 NS090407.

REFERENCES

1. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol.* (2008) 7:1021–31. doi: 10.1016/S1474-4422(08)70202-3

2. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. *Epilepsia.* (2012) 53:249–52. doi: 10.1111/j.1528-1167.2011.03354.x

3. Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, Haunso S, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. *Epilepsia.* (2013) 54:1613–20. doi: 10.1111/epi.12328
4. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study. *Neurology.* (2017) 89:170–7. doi: 10.1212/WNL.0000000000004094
5. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. *Ann Neurol.* (2010) 68:787–96. doi: 10.1002/ana.22101
6. Ryvlin P, Nashef L, Lhatoo S, Bateman L, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol.* (2013) 12:966–77. doi: 10.1016/s1474-4422(13)70214-x
7. Surges R, Strzelczyk A, Scott C, Walker M, Sander JJE. Postictal generalized electroencephalographic suppression is associated with generalized seizures. *Epilepsy Behav*. (2011) 21:271–4. doi: 10.1016/j.yebeh.2011.04.008
8. Lamberts RJ, Gaitatzis A, Sander JW, Elger CE, Surges R, Thijs RD. Postictal generalized EEG suppression: an inconsistent finding in people with multiple seizures. *Neurology*. (2013) 81:1252–6. doi: 10.1212/WNL.0b013e3182a6cbeb
9. Tao JX, Yung I, Lee A, Rose S, Jacobsen J, Ebersole JS. Tonic phase of a generalized convulsive seizure is an independent predictor of postictal generalized EEG suppression. *Epilepsia.* (2013) 54:858–65. doi: 10.1111/epi.12094
10. Alexandre V, Mercedes B, Valton L, Maillard L, Bartolomei F, Szurhaj W, et al. Risk factors of postictal generalized EEG suppression in generalized convulsive seizures. *Neurology.* (2015) 85:1598–603. doi: 10.1212/WNL.0000000000001949
11. Theeranaew W, McDonald J, Zonjy B, Kaffashi F, Moseley BD, Friedman D, et al. Automated detection of postictal generalized EEG suppression. *IEEE Trans Biomed Eng.* (2018) 65:371–7. doi: 10.1109/TBME.2017.2771468
12. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE commission for classification and terminology. *Epilepsia.* (2017) 58:522–30. doi: 10.1111/epi.13670
13. Vilella L, Lacuey N, Hampson JP, Rani MRS, Sainju RK, Friedman D, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). *Neurology.* (2019) 92:e171–82. doi: 10.1212/wnl.0000000000006785
14. Seyal M, Bateman L, Li CJE. Impact of periictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility. *Epilepsia.* (2013) 54:377–82. doi: 10.1111/j.1528-1167.2012.03691.x
15. Seyal M, Hardin K, Bateman LJE. Postictal generalized EEG suppression is linked to seizure-associated respiratory dysfunction but not postictal apnea. *Epilepsia.* (2012) 53:825–31. doi: 10.1111/j.1528-1167.2012.03443.x
16. Freitas J, Kaur G, Fernandez G, Tatsuoka C, Kaffashi F, Loparo K, et al. Age-specific periictal electroclinical features of generalized tonic-clonic seizures and potential risk of sudden unexpected death in epilepsy (SUDEP). *Epilepsy Behav*. (2013) 29:289–94. doi: 10.1016/j.yebeh.2013.08.010
17. Xu J, Jin B, Yan J, Wang J, Hu J, Wang Z, et al. Postictal generalized EEG suppression after generalized convulsive seizures: a double-edged sword. *Clin Neurophysiol.* (2016) 127:2078–84. doi: 10.1016/j.clinph.2015.10.064
18. Tilz C, Stefan H, Hopfengaertner R, Kerling F, Genow A, Wang-Tilz Y. Influence of levetiracetame on ictal and postictal EEG in patients with partial seizures. *Eur J Neurol.* (2006) 13:1352–8. doi: 10.1111/j.1468-1331.2006.01516.x
19. Kang JY, Rabiei AH, Myint L, Nei M. Equivocal significance of post-ictal generalized EEG suppression as a marker of SUDEP risk. *Seizure.* (2017) 48:28–32. doi: 10.1016/j.seizure.2017.03.017
20. Asadollahi M, Noorbakhsh M, Simani L, Ramezani M, Gharagozli K. Two predictors of postictal generalized EEG suppression: tonic phase duration and postictal immobility period. *Seizure.* (2018) 61:135–8. doi: 10.1016/j.seizure.2018.08.009
21. Lamberts R, Thijs R, Laffan A, Langan Y, Sander JJE. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia.* (2012) 53:253–7. doi: 10.1111/j.1528-1167.2011.03360.x
22. Zhuo L, Zhang Y, Zielke H, Levine B, Zhang X, Chang L, et al. Sudden unexpected death in epilepsy: Evaluation of forensic autopsy cases. *Forensic Sci Int*. (2012) 223:171–5. doi: 10.1016/j.forsciint.2012.08.024
23. Lamberts R, Laranjo S, Kalitzin S, Velis D, Rocha I, Sander J, et al. Postictal generalized EEG suppression is not associated with periictal cardiac autonomic instability in people with convulsive seizures. *Epilepsia.* (2013) 54:523–9. doi: 10.1111/epi.12021
24. Lee A, Wu S, Zhou X, Liebenthal J, Rose S, Tao JX. Periictal autonomic dysfunction and generalized postictal EEG suppression in convulsive seizures arising from sleep and wakefulness. *Epilepsy Behav.* (2013) 28:439–43. doi: 10.1016/j.yebeh.2013.06.010
25. Pavlova M, Singh K, Abdennadher M, Katz E, Dworetzky B, White DP, et al. Comparison of cardiorespiratory and EEG abnormalities with seizures in adults and children. *Epilepsy Behav.* (2013) 29:537–41. doi: 10.1016/j.yebeh.2013.09.026
26. Sarkis RA, Thome-Souza S, Poh MZ, Llewellyn N, Klehm J, Madsen JR, et al. Autonomic changes following generalized tonic clonic seizures: an analysis of adult and pediatric patients with epilepsy. *Epilepsy Res.* (2015) 115:113–8. doi: 10.1016/j.eplepsyres.2015.06.005
27. Moseley B, DeGiorgio CM. The SUDEP risk inventory: association with postictal generalized EEG suppression. *Epilepsy Res.* (2015) 117:82–4. doi: 10.1016/j.eplepsyres.2015.09.006
28. Wu S, Issa N, Rose S, Ali A, Tao JX. Impact of periictal nurse interventions on postictal generalized EEG suppression in generalized convulsive seizures. *Epilepsy Behav*. (2016) 58:22–5. doi: 10.1016/j.yebeh.2016.02.025
29. Moseley B, So E, Wirrell E, Nelson C, Lee R, Mandrekar J, et al. Characteristics of postictal generalized EEG suppression in children. *Epilepsy Res*. (2013) 106:123–7. doi: 10.1016/j.eplepsyres.2013.05.007
30. Kuo J, Zhao W, Li C, Kennedy J, Seyal MJE. Postictal immobility and generalized EEG suppression are associated with the severity of respiratory dysfunction. *Epilepsia.* (2016) 57:412–7. doi: 10.1111/epi.13312

Conflict of Interest: OD receives grant support from NINDS, NIMH, MURI, CDC, and NSF. He has equity and/or compensation from the following companies: Tilray, Receptor Life Sciences, Qstate Biosciences, Tevard Biosciences, Script Biosciences, Regel Biosciences, Empatica, Papa & Barkley, Rettco, Silver Spike, and California Cannabis Enterprises (CCE).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 24 November 2021
doi: 10.3389/fneur.2021.623358

Distinct Patterns of Brain Metabolism in Patients at Risk of Sudden Unexpected Death in Epilepsy

Benjamin P. Whatley[1,2*], *Joel S. Winston*[3,4,5,6], *Luke A. Allen*[1,7,8], *Sjoerd B. Vos*[7,8,9,10], *Ashwani Jha*[11], *Catherine A. Scott*[1,8], *April-Louise Smith*[12], *Fahmida A. Chowdhury*[1], *Jamshed B. Bomanji*[12], *Samden D. Lhatoo*[8,13,14], *Ronald M. Harper*[8,15,16] *and Beate Diehl*[1,7,8]

[1] *Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, United Kingdom,* [2] *Division of Neurology, Dalhousie University, Halifax, NS, Canada,* [3] *Department of Clinical Neurophysiology, National Hospital for Neurology and Neurosurgery, London, United Kingdom,* [4] *Wellcome Trust Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, United Kingdom,* [5] *Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom,* [6] *Department of Clinical Neurophysiology, King's College Hospital, London, United Kingdom,* [7] *Epilepsy Society MRI Unit, Chalfont St Peter, United Kingdom,* [8] *The Center for SUDEP Research, National Institutes of Neurological Disorders and Stroke, Bethesda, MD, United States,* [9] *Neuroradiological Academic Unit, Queen Square Institute of Neurology, University College London, London, United Kingdom,* [10] *Centre for Medical Image Computing, University College London, London, United Kingdom,* [11] *Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, London, United Kingdom,* [12] *Institute of Nuclear Medicine, University College London, London, United Kingdom,* [13] *Epilepsy Center, Neurological Institute, University Hospitals Case Medical Center, Cleveland, OH, United States,* [14] *Department of Neurology, University of Texas Health Sciences Center at Houston, Houston, TX, United States,* [15] *Brain Research Institute, University of California, Los Angeles, Los Angeles, CA, United States,* [16] *Department of Neurobiology, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, United States*

OPEN ACCESS

Edited by:
Rohit Shankar,
University of Plymouth,
United Kingdom

Reviewed by:
Rhys Thomas,
Newcastle University, United Kingdom
Zachary Threlkeld,
Stanford University, United States

****Correspondence:***
Benjamin P. Whatley
b.whatley@ucl.ac.uk

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *29 October 2020*
Accepted: *25 October 2021*
Published: *24 November 2021*

Citation:
Whatley BP, Winston JS, Allen LA, Vos SB, Jha A, Scott CA, Smith A-L, Chowdhury FA, Bomanji JB, Lhatoo SD, Harper RM and Diehl B (2021) Distinct Patterns of Brain Metabolism in Patients at Risk of Sudden Unexpected Death in Epilepsy. Front. Neurol. 12:623358. doi: 10.3389/fneur.2021.623358

Objective: To characterize regional brain metabolic differences in patients at high risk of sudden unexpected death in epilepsy (SUDEP), using fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET).

Methods: We studied patients with refractory focal epilepsy at high ($n = 56$) and low ($n = 69$) risk of SUDEP who underwent interictal ^{18}FDG-PET as part of their pre-surgical evaluation. Binary SUDEP risk was ascertained by thresholding frequency of focal to bilateral tonic-clonic seizures (FBTCS). A whole brain analysis was employed to explore regional differences in interictal metabolic patterns. We contrasted these findings with regional brain metabolism more directly related to frequency of FBTCS.

Results: Regions associated with cardiorespiratory and somatomotor regulation differed in interictal metabolism. In patients at relatively high risk of SUDEP, fluorodeoxyglucose (FDG) uptake was increased in the basal ganglia, ventral diencephalon, midbrain, pons, and deep cerebellar nuclei; uptake was decreased in the left planum temporale. These patterns were distinct from the effect of FBTCS frequency, where increasing frequency was associated with decreased uptake in bilateral medial superior frontal gyri, extending into the left dorsal anterior cingulate cortex.

Significance: Regions critical to cardiorespiratory and somatomotor regulation and to recovery from vital challenges show altered interictal metabolic activity in patients with frequent FBTCS considered to be at relatively high-risk of SUDEP, and shed light on the processes that may predispose patients to SUDEP.

Keywords: SUDEP, positron emission tomography, central autonomic regulation, cardiorespiratory regulation, epilepsy, bilateral tonic-clonic seizure

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of premature death in people with epilepsy, and is second only to stroke as a neurological cause of years of life lost in the general population (1). Patients with medically-refractory epilepsy and convulsive seizures are at particularly high risk (2).

The underlying mechanisms of SUDEP are unclear, but a landmark study of physiological changes immediately prior to SUDEP identified a consistent pattern of cardiorespiratory collapse: a bilateral tonic-clonic seizure is followed by a short, variable period of normal cardiovascular and respiratory patterning, and then a combination of central apnoea and bradycardia, ultimately evolving to asystole (3). The absence of intrinsic cardiac pathology or lung disease in these patients points to a failure of central regulatory processes controlling these vital functions, and there is likely overlap with brain areas implicated in other conditions associated with sudden death, such as congenital central hypoventilation syndrome (CCHS) (4), sudden infant death syndrome (5), and heart failure (6).

Biomarkers for SUDEP risk are urgently needed. Sudden unexpected death in epilepsy is a tragic outcome in epilepsy, but sudden death remains sufficiently rare that it is difficult to conduct prospective mechanistic studies in this population. One option is to use a surrogate marker of risk to stratify patients, but no validated risk prediction tools exist. Several SUDEP risk factors have been identified, with frequent convulsive seizures, anti-seizure polytherapy, and increased duration of epilepsy emerging as the strongest predictors (7). However, two risk assessment inventories, the SUDEP-7 (8) and the International League Against Epilepsy (ILAE) combined analysis score (9), fail to distinguish between individuals dying with SUDEP and living patient controls with epilepsy. A recently validated probabilistic prediction score seems promising but is clinically-based and not designed to provide mechanistic insight (10).

Patients who have died of SUDEP demonstrate changes in brain volumes within regions that are key for regulating breathing and cardiovascular functions (11, 12). In these patients, loss of gray matter in both medial and lateral cerebellum, periaqueductal gray (PAG), left medial and posterior thalamus, left hippocampus, and posterior cingulate was demonstrated using retrospective analysis of existent MRI scans. These volume losses are significant, but less marked in patients at high risk of SUDEP, as defined by three or more generalized tonic-clonic seizures (GTCS) per year, and were absent in those patients without GTCS. Gray matter volumes in limbic areas and a subcallosal region (BA25) were increased in patients with high risk and those who died of SUDEP (11, 12). Moreover, functional connectivity between brain sites that regulate breathing and cardiovascular control (including thalamus, brainstem, anterior cingulate, putamen, amygdala, medial/orbitofrontal cortex, insula, hippocampus, caudate, and subcallosal cortex) are affected in patients at high risk of SUDEP (13, 14). We reasoned that interictal metabolic changes within those regions would provide distinct and complementary information about the neurobiological processes mediating SUDEP risk. We therefore analyzed fluorine-18-fluorodeoxyglucose (^{18}FDG) uptake in patients at high and low risk of SUDEP, and sought to identify regions that demonstrate metabolic differences between these groups.

METHODS

Study Design and Patient Selection

We enrolled 135 patients aged >18 years with medically refractory focal epilepsy who were being evaluated in the video telemetry unit at the National Hospital for Neurology and Neurosurgery, London, UK, and who had undergone fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) scans as part of their pre-surgical workup. Patients were excluded if original PET data could not be retrieved, if there were significant structural abnormalities seen on MRI, or if there were missing demographic or clinical data critical to the analyses. Patients enrolled between April 2015 and December 2018 provided written informed consent to participate in a prospective study evaluating autonomic, respiratory, and imaging biomarkers of SUDEP. This study was approved by the relevant ethics committees (14/SW/0021 and 19/SW/0071 South West-Central Bristol Ethics Committee).

Frequency of GTCS has emerged as the single most-important risk factor for SUDEP, and the largest increase in risk occurs with three or more of these seizures per year (7). We therefore chose to classify our patients using a binary SUDEP risk score, according to focal to bilateral tonic-clonic seizures (FBTCS) frequency in our group of patients with intractable focal epilepsy undergoing PET for pre-surgical evaluation ≥3 FBTCS per year "high risk," $n = 56$) vs. zero FBTCS per year "low risk," $n = 69$)]. In our previous studies, this approach distinguished >80% of SUDEP cases (11). The screening led to the exclusion of 10 patients at intermediate risk. We used this cutoff as a conservative marker of SUDEP risk, as having ≥3 FBTCS per year confers the highest risk of SUDEP. Sudden Unexpected Death in Epilepsy is a GTCS-related event (3, 15), and therefore the low risk group was restricted to those with zero FBTCS in the previous year.

All clinical data used for risk assessment and/or as covariates were extracted from multidisciplinary team meeting notes via chart review, and from a local database capturing autonomic, respiratory, and imaging biomarkers of SUDEP. Mann-Whitney-*U* and Chi-squared tests were used to compare demographic, clinical, and PET signal characteristics across the high- and low-risk groups, implemented in MATLAB 2018b (Mathworks).

PET Acquisition Parameters

Patients were asked to fast for a minimum of six hours prior to scanning. All scans were acquired at the Institute of Nuclear Medicine, University College London Hospitals, on either a Discovery VCT (140 kV, 80 mA, 0.8 s) or Discovery 710 PET/CT (120 kV, 170 mA, 0.8 s) (GE Healthcare). Patients were injected with a target activity of 250 MBq and an uptake time of 30–45 min. Scans were acquired for 15 min per bed (slice thickness: 3.27 mm) and reconstructed (3 iterations, 20 subsets, post-filtering: Hanning, 4 mm). Time-of-flight imaging was used for

those scans acquired on the GE Discovery 710. Reconstructed images were exported as DICOM files, and converted to NifTi format for further pre-processing.

Image Processing and Statistics—Voxel-Wise Analysis

Images were processed and analyzed using SPM12 (Wellcome Center for Human Neuroimaging) implemented in MATLAB 2018b (Mathworks). Details of our adapted voxel-based morphometry methodology (16) have previously been published (17). Individual PET scans were non-linearly normalized to an FDG-PET template in ICBM/MNI space that has been validated in a dementia cohort in the presence of brain atrophy (18, 19). Image intensity was modulated during normalization to account for non-linear spatial warping during modulation. Normalized images were resliced to 3 mm isotropic voxels.

We were primarily interested in the gray matter signal; thus, a binary optimal-threshold mask was created to include only consistently high-intensity voxels in the spatially-normalized scans. Compared to the standard SPM method for creating binary masks, this strategy minimizes the risk of excluding regions with very low intensity that may bear some physiological relevance, particularly in the context of brain atrophy (20). This mask was then applied to all spatially-normalized ^{18}FDG-PET images. As the final step prior to statistical analysis, images were smoothed with a 6 mm FWHM Gaussian filter.

Several scanning and patient factors can introduce between-subject signal variation in ^{18}FDG-PET images, many of which have no physiological bearing. These factors include the individual pharmacodynamics of the ^{18}FDG levels, and the timing and dosage of ^{18}FDG relative to the imaging acquisition. To account for these variations, we estimated the background ^{18}FDG-PET signal per scan for later use in our statistical models, using voxel intensities extracted from high-intensity areas, ventricular compartment, and white matter compartment. High-intensity activity was indexed as the summed intensities of all raw ^{18}FDG-PET counts within the optimal-threshold mask, ventricular and white matter activity as the summed intensities of the voxels falling within the CSF and white matter tissue compartments, respectively (based on the Neuromorphometrics atlas included with SPM).

Statistical parametric mapping was used to explore whole brain differences in ^{18}FDG uptake between the groups (21, 22). Sudden Unexpected Death in Epilepsy risk (the binary covariate of interest) was entered as an independent variable into a general linear model, with additional covariates to control for confounding including age, sex, and weight, and total high-intensity activity, white matter activity and CSF intensity. A planned *t*-test was used to estimate the effect of SUDEP risk, the effect of interest. In keeping with standard methodology, the resultant map of *t*-statistics was first thresholded at a cluster-forming threshold of $p < 0.001$. Then, the cluster-level threshold for statistical significance was set at $p < 0.05$ after family-wise error correction for multiple comparisons across all brain voxels. Figures were thresholded at $p < 0.001$ uncorrected, with a cluster extent threshold of $k = 110$ voxels to aid visualization.

TABLE 1 | Group characteristics of patients with high and low SUDEP risk.

	Low risk ($n = 69$)	High risk ($n = 56$)	*p*
Age, years, median, IQR	33.2, 23.5–41.1	31.1, 26.3–37.5	0.51[a]
Sex, M:F	35:34	33:23	0.36[b]
Weight, kg, median, IQR	75.0, 65.0–89.2	78.5, 67.5–95.5	0.27[a]
Height, m, median, IQR	1.70, 1.63–1.80	1.73, 1.64–1.81	0.36[a]
Epilepsy duration, years, median, IQR	17.5, 12.0–26.6	16.9, 9.8–25.2	0.50[a]
Number of AEDs, median, IQR	3, 2–3	3, 2–3	0.39[a]
Frequency of FBTCS (per year), median, IQR	0, 0	24, 12–52	–
Frequency of all seizure types (per year), median, IQR	208.0, 78.0–527.8	243.0, 116.5–525.0	0.50[a]
MRI lesion, yes:no	16:53	14:42	0.81[b]
PET results (normal/temporal/other)	21:39:9	10:30:16	0.06[b]

IQR, interquartile range.
[a] *Mann-Whitney-U.*
[b] *Pearson chi-square.*

Image Analysis—Role of FBTCS Frequency

Given that our binary SUDEP risk score was based on FBTCS frequency threshold, we explored whether regional differences in ^{18}FDG uptake were more directly related to convulsion frequency rather than our surrogate score for SUDEP risk. This analysis was undertaken within the 63 participants who had at least one FBTCS in the previous year. FBTCS frequency was $\log_{10}$-transformed to obtain a normal distribution and entered into a general linear model with similar additional confounding covariates as the primary SUDEP risk analysis. The effect of interest, FBTCS frequency, was estimated with a planned *t*-test, and statistical thresholds were set as previously described.

RESULTS

Patient Characteristics

High- and low-risk SUDEP groups did not differ significantly for age, sex, weight, height, duration of epilepsy, number of anti-epileptic drugs, epilepsy duration, frequency of all seizure types, presence of MRI lesions, or final nuclear medicine impression of the PET scans (**Table 1**). Measures used to estimate the background signal of the PET scans did not significantly differ between the two risk groups (**Table 2**).

Altered Glucose Uptake in High vs. Low SUDEP Risk Subjects

Whole-brain analysis demonstrated that high FBTCS burden—and therefore high SUDEP risk—was associated with a large cluster of increased FDG uptake that included the right cerebellar deep nuclei, cerebellar vermis, pontine tegmentum, dorsal midbrain/PAG, bilateral ventral diencephalon, bilateral thalamus, bilateral pallidum, left putamen, and left claustrum

TABLE 2 | Estimates of background PET signal.

	Low risk ($n = 69$)	High Risk ($n = 56$)	p
Sum of high intensity voxel intensities (median, IQR, $\times 10^8$)	7.18, 5.72–8.63	6.95, 5.99–8.35	0.53[a]
Sum of ventricular compartment voxel intensities (median, IQR, $\times 10^6$)	6.10, 4.93–7.93	5.99, 4.69–7.23	0.53[a]
Sum of white matter compartment voxel intensities (median, IQR, $\times 10^8$)	1.89, 1.52–2.33	1.83, 1.57–2.18	0.49[a]

IQR, interquartile range.
[a] *Mann-Whitney-U.*

(**Figure 1**, depicted in orange). These high-risk subjects also showed a cluster of decreased activity in the left planum temporale (**Figure 1**, depicted in blue).

Effect of Frequency of FBTCS

A whole-brain regression analysis evaluating the effect of frequency of FBTCS on ^{18}FDG uptake found that increasing frequency of FBTCS was associated with a cluster of decreased FDG-uptake in the bilateral medial superior frontal gyrus, with extension including dorsal aspects of the left anterior cingulate gyrus (**Figure 2**, depicted in blue).

DISCUSSION

Overview

Our principal finding is that multiple brain regions known to be involved in cardiovascular, breathing, and aspects of somatomotor regulation show altered metabolism in patients with a relatively high frequency of FBTCS. These patients are known to be at relatively high risk of SUDEP. Increased metabolic activity appeared in the basal ganglia, ventral diencephalon, midbrain, pontine tegmentum, and deep cerebellar structures, as detailed below. To be sure, these regions subserve a vast array of functions. However, the functions that they have in common are related to regulation of cardiorespiratory function, including autonomic regulation, motor initiation and coordination, respiratory timing, integration of hypoxia and hypercarbia with breathing patterns, adrenergic regulation, modulation of awareness, interactions of breathing with blood pressure, and dampening of apnoea and blood pressure extremes. Decreased metabolism appeared in the left planum temporale.

To establish at the overlap between our results and known autonomic regions, we queried the online Neurosynth database (https://neurosynth.org/analyses/terms/autonomic, acquired May 16, 2021). An automated meta-analysis of human functional neuroimaging studies (23), yielded a map of activations more likely to appear in publications referencing the term "autonomic" than those not referencing this term. The resulting map demonstrates activations in nine of the twelve regions identified in the present study—including the right cerebellum, cerebellar vermis, pontine tegmentum, dorsal midbrain/PAG, bilateral ventral diencephalon, left thalamus, left putamen, and left claustrum—and suggests that these regions are consistently implicated in studies of autonomic function. That these regions demonstrate altered metabolism in patients with a high frequency of FBTCS represents an important addition to our understanding of interictal metabolism in patients at the highest risk of SUDEP, which is likely a consequence of centrally-mediated autonomic and cardiorespiratory collapse.

Volume vs. Metabolic Changes

In previous work, we demonstrated that patients who have died of SUDEP demonstrate decreased gray matter volumes in the posterior thalami, medial and lateral cerebellum, and PAG—regions known to be critical for cardiorespiratory recovery (11, 12). Patients at high-risk of SUDEP—as ascertained by FBTCS frequency—also showed volume loss in the cerebellum and thalamic regions, although to a lesser degree. Disturbance or loss of neuronal elements is typically associated with regional hypometabolism, and in the presence of atrophy, there may be an additional element of artifactual hypometabolism due to partial volume effects (24, 25). At first glance, it may appear surprising that these regions are associated with *increased* FDG-uptake in patients at high risk of SUDEP assessed in this study. However, hypermetabolism has been seen in other conditions marked by loss or dysfunction of neurons. A critical distinction is that glucose uptake does not reflect only neuronal metabolism—under normal circumstances, half of the glucose leaving capillaries is taken up by astrocytes (26). Under neurodegenerative conditions, regional astrocyte and neuroinflammatory cell metabolism may result in areas of relative hypermetabolism (27, 28). In an FDG-PET study of 32 patients with ALS, hypermetabolism appeared in the midbrain and pons, regions in which neurodegeneration of corticospinal neurons is present (29). Subcortical and cerebellar regions of hypermetabolism in a patient with ALS were shown to worsen over 20 months (30), changes that were associated with either an increase, decrease, or no change in cortical thickness, suggesting that atrophy and metabolism need not be coupled. In the present study, areas of increased metabolism may well co-localize with atrophy, and may indicate underlying gliosis and neuronal loss or ongoing inflammatory responses.

Alternatively, the co-occurrence of atrophy and hypermetabolism may suggest an upregulation of neuronal activity. In patients with Alzheimer's disease, a mismatch develops between atrophy and blood flow, with atrophy-corrected cerebral blood flow increased to the hippocampus compared to healthy controls (31). Whether such upregulation may occur in the hypermetabolic regions identified here is not known at this time.

Finally, normalizing PET data to the global mean can result in an artifactual appearance of hypermetabolism in subcortical structures (32). However, in this study, we have not used global normalization, and while the sums of high intensity voxels were included as a covariate, these sums do not differ between the high and low risk groups (**Table 2**). Furthermore, there is no *a priori*

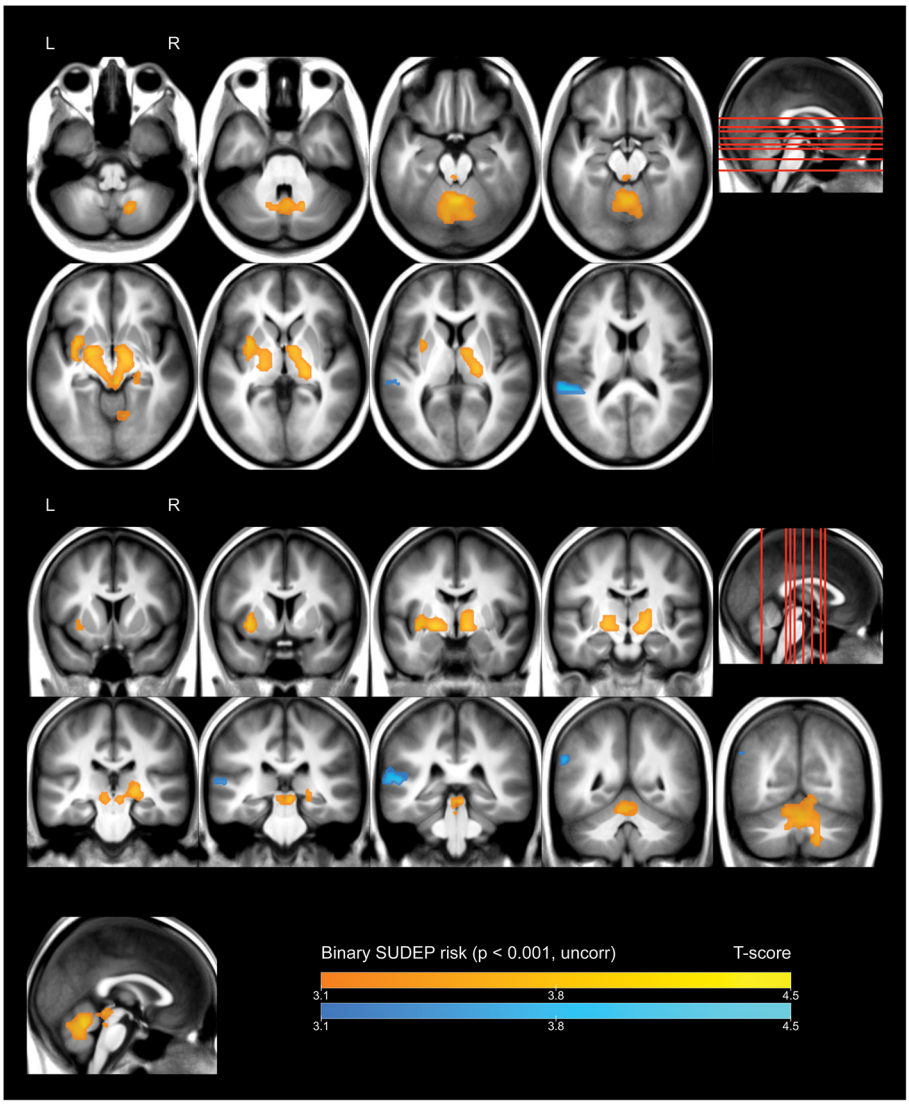


FIGURE 1 | Whole brain SPM results, high vs. low SUDEP risk. Displayed at peak height threshold $T > 3.2$ ($p < 0.001$ uncorrected), with an extent threshold $k = 110$ voxels. Clusters smoothed for display purposes. Covariates included age, sex, weight, and summed intensities of high intensity voxels, ventricular voxels, and white matter voxels. Regions of increased FDG-uptake in patients at high risk of SUDEP are depicted in orange, and regions of decreased FDG-uptake are depicted in blue.

reason to assume that patients at higher risk of SUDEP have lower global mean glucose uptake.

Increased FDG Uptake in Regions Involved in Autonomic Control

Increased FDG uptake within the left putamen, bilateral pallidum, bilateral thalamus, bilateral ventral diencephalon, and left claustrum may reflect a pathological disturbance that contributes to disrupted autonomic functions, i.e., a profound hypotension or altered sympathetic or parasympathetic drive to the heart, placing patients at risk for SUDEP. The basal ganglia patterns are of principal concern because of their significant roles in autonomic control, and especially blood pressure maintenance (33, 34). The posterior thalamus demonstrates deficient responses to hypoxia in patients with CCHS (35), is especially important for control of hypoxic responses during early development (36, 37), and shows increased metabolic activity up to 2 weeks following prolonged hypoxia (38). This region exhibits decreased volume and diminished functional connectivity with brain stem structures in patients at high risk of SUDEP (12, 13), which raises the possibility that it may fail to respond appropriately to hypoxia in this risk group.

The dorsal striatum helps to modulate blood pressure changes (33) and motor program initiation, where "motor program" includes coordination of the upper airway musculature with the diaphragm. The putamen, in particular, participates in initiation of motor action, and demonstrates profound abnormalities in patients with obstructive sleep apnoea, which may contribute to the failure to activate upper airway muscles in a timely fashion before diaphragmatic descent, leading to

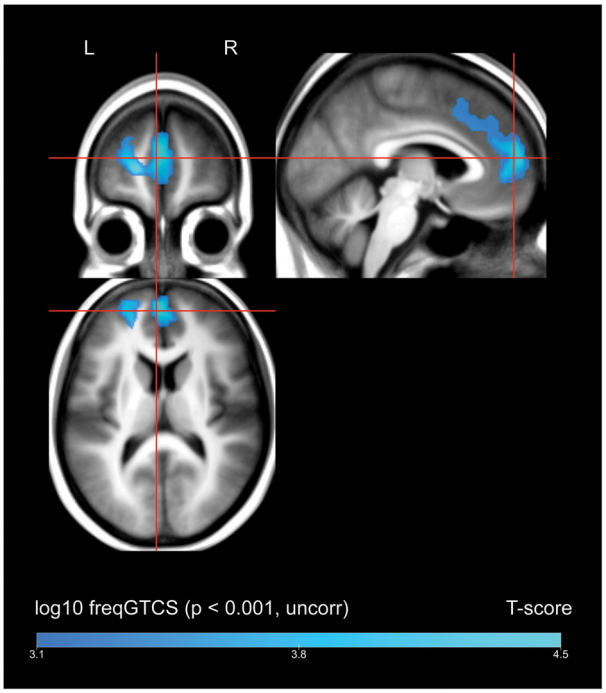


FIGURE 2 | Whole brain SPM results, regression of frequency of FBTCS against FDG-uptake. Displayed at peak height threshold $T > 3.2$ ($p < 0.001$ uncorrected), with an extent threshold $k = 110$ voxels. Clusters smoothed for display purposes. Covariates included age, sex, weight, and summed intensities of high intensity voxels, ventricular voxels, and white matter voxels. Regions of where increasing frequency of FBTCS predicts decreased FDG-uptake are depicted in blue.

airway obstruction in that syndrome (39). Decreased connectivity occurs between the putamen and anterior cingulate cortex, i.e., motor control and autonomic areas in patients at high risk of SUDEP (13), and central apnea respiratory muscle cessation can be induced by blood pressure elevation (40). Changes in putamen/cingulate cortex connectivity may contribute to failure in those interactions.

The ventral diencephalon, which includes the hypothalamus, ventral thalamus, subthalamus, and epithalamus, helps to govern a range of autonomic functions including thermal regulation, and both parasympathetic and sympathetic outflow. This region is extensively damaged in CCHS, obstructive sleep apnoea, and heart failure, all of which are associated with sudden death (41). The ventral diencephalon receives direct inputs from limbic cortical regions via the subiculum and may thus be modulated by seizures (42). Whether the hypothalamus plays a direct role in SUDEP is not yet known, but the structure exerts profound influences on blood pressure; thus, baseline metabolic or structural changes within that area are of concern.

The claustrum is an intriguing region with respect to epilepsy and SUDEP. Situated between the insular cortices and the putamen, the claustrum is involved in sensory integration and consciousness. It has robust connections to almost all cortical areas, as well as subcortical areas including the putamen, globus pallidus, and lateral amygdala (43, 44). The claustrum integrates and modulates widespread neuronal activity, and sustains very focal damage in a subset of cases of refractory status epilepticus (45). There is evidence that the claustrum is a common area involved in ictal and interictal activity across focal epilepsies, and patients with frequent seizures have reduced GABAa receptor binding in this region, as measured by flumenazil-PET (46). With respect to SUDEP risk, altered function of the claustrum may modulate downstream regions involved in autonomic regulation.

A cluster of regions with increased metabolism in patients with a high frequency of FBTCS extended from the midbrain, caudally through the pontine tegmentum, and involved the bilateral cerebellar vermis and right cerebellar deep nuclei. These regions are heavily involved in autonomic and respiratory regulation. Of great relevance for SUDEP, the cerebellar areas serve a "last resort" role to dampen extremes of blood pressure or recover from prolonged apnoea (47–49). Lesions within the cerebellar deep nuclei, for example, will lead to an inability to recover from profound hypotension (48), a significant concern in SUDEP, with a loss of blood pressure in postictal periods providing a circumstance for cardiovascular collapse. The PAG serves critical roles in the control of breathing and the perception of breathlessness (50), and demonstrates decreased volume in patients who have died of SUDEP (11, 51). A recent study demonstrated that when fluoxetine blocks respiratory arrest in an animal model of SUDEP, significantly increased PAG activation results (52), suggesting a potential role in recovery from apnoea. The parabrachial nucleus of the pons, locus coeruleus, and dorsal raphe nucleus are implicated in CO_2-induced arousal (53), and are damaged in CCHS, another condition with a high prevalence of sudden death (41). These nuclei are also damaged in infants who die of SIDS (5), again suggesting their potential importance to the pathophysiology of SUDEP.

Cerebellar areas project heavily to vestibular and brainstem areas which then integrate with autonomic and respiratory areas of the brainstem. Cerebellar structures, and particularly the vermis, provide essential integration for compensatory responses to hypotension, and beat-to-beat maintenance of cardiovascular homeostasis (54). The cerebellum also modulates breathing in response to hypercapnia, particularly via the fastigial nuclei, which project to pontomedullary nuclei and the posterior thalamus, and cerebellar responses to hypercapnia are impaired in patients with CCHS (35, 55). Cerebellar volume loss appears in many patients with epilepsy, but is most marked in patients who have died of SUDEP, even after controlling for anti-epileptic drug exposure (11). Given this volume loss, the present results suggest that, as noted above with respect to patients with ALS, patients at increased risk of SUDEP may have active inflammation or gliosis in these regions.

Decreased Interictal FDG Uptake in Left Planum Temporale

A pronounced decline in FDG-uptake in the high FBTCS group was present in the left planum temporale, a region that constitutes part of Wernicke's area, and is implicated in speech and language processing (56). The relevance of these findings is unclear, though regional interictal hypometabolism may reflect areas of overlapping functional deficit zone in our patient group (57).

FBTCS Frequency as a Proxy for SUDEP Risk

Frequency of FBTCS is the strongest predictor of SUDEP. However, the FDG-PET findings we have reported are directly reflective of the interictal metabolic pattern associated with a propensity to generate FBTCS, and represent an indirect evaluation of SUDEP risk. In this study, two patients died of SUDEP, and both were in the high risk group. As a tertiary referral center engaged in epilepsy surgery evaluations, all of our patients are likely at a higher risk than the general population of people with epilepsy. There is likely a referral bias toward patients with a higher seizure burden, greater number of anti-seizure medications, and refractory epilepsy. Those undergoing FDG-PET are more likely to have MRI-negative focal epilepsy. However, with reference to **Table 1**, our groups do not differ in terms of epilepsy duration, overall seizure frequency, or number of anti-seizure medications. As such, we are confident that our results reflect a difference between those patients with frequent FBTCS vs. those with none.

It is difficult to disentangle the effects of FBTCS and SUDEP risk. However, our additional regression analysis by FBTCS frequency did not identify any overlapping significant clusters. This finding suggests that the interictal metabolic patterns we reported reflect a difference between patients with a propensity to generate FBTCS and those without. If the effects were driven entirely by the occurrence of FBTCS, we might expect to see the same interictal patterns associated with a greater frequency of FBTCS. This was not the case, which suggests that the metabolic patterns for FBTCS frequency and SUDEP risk, as defined by a propensity to produce FBTCS, may be distinct. This caveat, however, can only be addressed fully if a well-calibrated risk score were available.

We note that our high- and low-risk groups did not differ with respect to number of AEDs or duration of epilepsy. These two factors also emerged as important risk factors for SUDEP (7), and might therefore be expected to differ between our groups. However, this finding likely reflects the referral bias at our center toward patients with drug-resistant epilepsy. Furthermore, the adjusted OR for polytherapy (1.95) and duration of epilepsy (1.95) are less marked than the adjusted OR for $\geq$3 FBTCS (15.46) (7).

Risk classification could be improved by including physiological data, such as presence of hypoxia, post-ictal generalized EEG suppression, apnea, and/or heart rate variability. It will also be important to attempt to replicate these findings in patients who died of SUDEP relative to patients with epilepsy deemed to be at low risk of SUDEP. These replications could be done in a case-controlled retrospective manner, allowing for an enriched sample.

CONCLUSIONS

High frequency of FBTCS is associated with hypermetabolism in regions of the diencephalon, cerebellum, midbrain, and pons. These findings suggest a possible association between SUDEP risk and functional changes in brain regions that subserve a variety of critical functions, including cardiorespiratory regulation. Whether these alterations reflect compensatory changes or damage is unknown. It is premature to speculate on the processes underlying altered metabolism in these regions that lead to increased SUDEP risk; it does appear, however, that blood pressure regulation and breathing pattern sites, and especially areas underlying recovery from vital challenges are especially targeted.

There are precedents for using PET abnormalities as a biomarker for future events (58). The remarkable metabolic increases found in the basal ganglia, thalamus, brainstem, and cerebellum raise the possibility that these alterations may be useful to predict SUDEP. Considered within the context of structural changes and functional connectivity alterations determined by earlier MRI procedures, these findings shed light on the processes that pre-dispose patients to SUDEP and suggest targets for interventions to avoid neural conditions that lead to fatal outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by South West-Central Bristol Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BW prepared and analyzed the data and wrote the manuscript. JW, RH, AJ, BD, FC, SL, and LA advised on interpretation of findings. JW, AJ, and LA advised on imaging analysis. CS advised on clinical and neurophysiological issues. SV, JB, and A-LS advised on imaging and methodological issues. All authors contributed editorially.

FUNDING

We are grateful for support from the NIH—National Institute of Neurological Disorders and Stroke (U01-NS090407). BW would like to acknowledge support for his research time through a Samuel R. McLaughlin Fellowship and the University Internal Medicine Research Fund (Dalhousie University, Halifax, Canada), as well as a Detweiler Traveling Fellowship (Royal College of Physicians and Surgeons of Canada, Ottawa, Canada).

ACKNOWLEDGMENTS

We are grateful for support from the Wolfson Foundation and the Epilepsy Society for supporting the Epilepsy Society MRI scanner, and for the support of the National Institute for Health Research University College London Hospitals Biomedical Research Center.

REFERENCES

1. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. *Epilepsia.* (2014) 55:1479–85. doi: 10.1111/epi.12666
2. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol.* (2008) 7:1021–31. doi: 10.1016/S1474-4422(08)70202-3
3. 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) 12:966–77. doi: 10.1016/S1474-4422(13)70214-X
4. Patwari PP, Carroll MS, Rand CM, Kumar R, Harper R, Weese-Mayer DE. Congenital central hypoventilation syndrome and the PHOX2B gene: a model of respiratory and autonomic dysregulation. *Respir Physiol Neurobiol.* (2010) 173:322–35. doi: 10.1016/j.resp.2010.06.013
5. Paine SM, Jacques TS, Sebire NJ. Review: neuropathological features of unexplained sudden unexpected death in infancy: current evidence and controversies. *Neuropathol Appl Neurobiol.* (2014) 40:364–84. doi: 10.1111/nan.12095
6. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. *J Appl Physiol.* (2003) 95:677–84. doi: 10.1152/japplphysiol.00101.2003
7. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. *Epilepsia.* (2011) 52:1150–9. doi: 10.1111/j.1528-1167.2010.02952.x
8. Odom N, Bateman LM. Sudden unexpected death in epilepsy, periictal physiology, and the SUDEP-7 inventory. *Epilepsia.* (2018) 59:e157–60. doi: 10.1111/epi.14552
9. Hesdorffer DC, Tomson T. Sudden unexpected death in epilepsy. Potential role of antiepileptic drugs. *CNS Drugs.* (2013) 27:113–9. doi: 10.1007/s40263-012-0006-1
10. Jha A, Oh C, Hesdorffer D, Diehl B, Devore S, Brodie MJ, et al. Sudden Unexpected Death in Epilepsy: A Personalized Prediction Tool. *Neurology.* (2021) 96:e2627–e2638. doi: 10.1212/WNL.0000000000011849
11. Allen LA, Vos SB, Kumar R, Ogren JA, Harper RK, Winston GP, et al. Cerebellar, limbic, and midbrain volume alterations in sudden unexpected death in epilepsy. *Epilepsia.* (2019) 60:718–29. doi: 10.1111/epi.14689
12. Wandschneider B, Koepp M, Scott C, Micallef C, Balestrini S, Sisodiya SM, et al. Structural imaging biomarkers of sudden unexpected death in epilepsy. *Brain.* (2015) 138(Pt 10):2907–19. doi: 10.1093/brain/awv233
13. Allen LA, Harper RM, Kumar R, Guye M, Ogren JA, Lhatoo SD, et al. Dysfunctional brain networking among autonomic regulatory structures in temporal lobe epilepsy patients at high risk of sudden unexpected death in epilepsy. *Front Neurol.* (2017) 8:544. doi: 10.3389/fneur.2017.00544
14. Allen LA, Harper RM, Guye M, Kumar R, Ogren JA, Vos SB, et al. Altered brain connectivity in sudden unexpected death in epilepsy (SUDEP) revealed using resting-state fMRI. *Neuroimage Clin.* (2019) 24:102060. doi: 10.1016/j.nicl.2019.102060
15. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia.* (2012) 53:253–7. doi: 10.1111/j.1528-1167.2011.03360.x
16. Ashburner J, Friston KJ. Voxel-based morphometry - the methods. *Neuroimage.* (2000) 11:805–21. doi: 10.1006/nimg.2000.0582
17. Jha A, Teotonio R, Smith AL, Bomanji J, Dickson J, Diehl B, et al. Metabolic lesion-deficit mapping of human cognition. *Brain.* (2020) 143:877–90. doi: 10.1093/brain/awaa032
18. Della Rosa PA, Cerami C, Gallivanone F, Prestia A, Caroli A, Castiglioni I, et al. A standardized [18F]-FDG-PET template for spatial normalization in statistical parametric mapping of dementia. *Neuroinformatics.* (2014) 12:575–93. doi: 10.1007/s12021-014-9235-4
19. Perani D, Della Rosa PA, Cerami C, Gallivanone F, Fallanca F, Vanoli EG, et al. Validation of an optimized SPM procedure for FDG-PET in dementia diagnosis in a clinical setting. *Neuroimage Clin.* (2014) 6:445–54. doi: 10.1016/j.nicl.2014.10.009
20. Ridgway GR, Omar R, Ourselin S, Hill DL, Warren JD, Fox NC. Issues with threshold masking in voxel-based morphometry of atrophied brains. *Neuroimage.* (2009) 44:99–111. doi: 10.1016/j.neuroimage.2008.08.045
21. Friston KJ, Worsley KJ, Frackowiak RS, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. *Hum Brain Mapp.* (1994) 1:210–20. doi: 10.1002/hbm.4600 10306
22. Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD. Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage.* (1996) 4:223–35. doi: 10.1006/nimg.1996.0074
23. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. *Nat Methods.* (2011) 8:665–70. doi: 10.1038/nmeth.1635
24. Rapoport SI, Grady CL. Parametric *in vivo* brain imaging during activation to examine pathological mechanisms of functional failure in Alzheimer disease. *Int J Neurosci.* (1993) 70:39–56. doi: 10.3109/00207459309000559
25. Bokde AL, Pietrini P, Ibanez V, Furey ML, Alexander GE, Graff-Radford NR, et al. The effect of brain atrophy on cerebral hypometabolism in the visual variant of Alzheimer disease. *Arch Neurol.* (2001) 58:480–6. doi: 10.1001/archneur.58.3.480
26. Nehlig A, Coles JA. Cellular pathways of energy metabolism in the brain: is glucose used by neurons or astrocytes? *Glia.* (2007) 55:1238–50. doi: 10.1002/glia.20376
27. Backes H, Walberer M, Ladwig A, Rueger MA, Neumaier B, Endepols H, et al. Glucose consumption of inflammatory cells masks metabolic deficits in the brain. *Neuroimage.* (2016) 128:54–62. doi: 10.1016/j.neuroimage.2015.12.044
28. Schroeter M, Dennin MA, Walberer M, Backes H, Neumaier B, Fink GR, et al. Neuroinflammation extends brain tissue at risk to vital peri-infarct tissue: a double tracer [11C]PK11195- and [18F]FDG-PET study. *J Cereb Blood Flow Metab.* (2009) 29:1216–25. doi: 10.1038/jcbfm.2009.36
29. Cistaro A, Valentini MC, Chio A, Nobili F, Calvo A, Moglia C, et al. Brain hypermetabolism in amyotrophic lateral sclerosis: a FDG PET study in ALS of spinal and bulbar onset. *Eur J Nucl Med Mol Imaging.* (2012) 39:251–9. doi: 10.1007/s00259-011-1979-6
30. Rajagopalan V, Pioro EP. Longitudinal (18)F-FDG PET and MRI reveal evolving imaging pathology that corresponds to disease progression in a patient with ALS-FTD. *Front Neurol.* (2019) 10:234. doi: 10.3389/fneur.2019.00234
31. Alsop DC, Casement M, de Bazelaire C, Fong T, Press DZ. Hippocampal hyperperfusion in Alzheimer's disease. *Neuroimage.* (2008) 42:1267–74. doi: 10.1016/j.neuroimage.2008.06.006
32. Borghammer P, Cumming P, Aanerud J, Gjedde A. Artefactual subcortical hyperperfusion in PET studies normalized to global mean: lessons from Parkinson's disease. *Neuroimage.* (2009) 45:249–57. doi: 10.1016/j.neuroimage.2008.07.042
33. Pazo JH, Belforte JE. Basal ganglia and functions of the autonomic nervous system. *Cell Mol Neurobiol.* (2002) 22:645–54.
34. Goldstein DS, Holmes CS, Dendi R, Bruce SR Li ST. Orthostatic hypotension from sympathetic denervation in Parkinson's disease. *Neurology.* (2002) 58:1247–55. doi: 10.1212/wnl.58.8.1247
35. Harper RM, Macey PM, Woo MA, Macey KE, Keens TG, Gozal D, et al. Hypercapnic exposure in congenital central hypoventilation syndrome reveals CNS respiratory control mechanisms. *J Neurophysiol.* (2005) 93:1647–58. doi: 10.1152/jn.00863.2004
36. Koos BJ, Rajaee A, Ibe B, Guerra C, Kruger L. Thalamic mediation of hypoxic respiratory depression in lambs. *Am J Physiol Regul Integr Comp Physiol.* (2016) 310:R586–95. doi: 10.1152/ajpregu.00412.2015
37. Koos BJ, Chau A, Matsuura M, Punla O, Kruger L. Thalamic locus mediates hypoxic inhibition of breathing in fetal sheep. *J Neurophysiol.* (1998) 79:2383–93. doi: 10.1152/jn.1998.79.5.2383
38. Merz TM, Treyer V, Hefti U, Spengler CM, Schwarz U, Buck A, et al. Changes in cerebral glucose metabolism after an expedition to high altitudes. *High Alt Med Biol.* (2006) 7:28–38. doi: 10.1089/ham.2006.7.28
39. Kumar R, Farahvar S, Ogren JA, Macey PM, Thompson PM, Woo MA, et al. Brain putamen volume changes in newly-diagnosed patients with obstructive sleep apnea. *Neuroimage Clin.* (2014) 4:383–91. doi: 10.1016/j.nicl.2014.01.009
40. Trelease RB, Sieck GC, Marks JD, Harper RM. Respiratory inhibition induced by transient hypertension during sleep in unrestrained cats. *Exp Neurol.* (1985) 90:173–86. doi: 10.1016/0014-4886(85)90050-0

41. Harper RM, Kumar R, Macey PM, Harper RK, Ogren JA. Impaired neural structure and function contributing to autonomic symptoms in congenital central hypoventilation syndrome. *Front Neurosci.* (2015) 9:415. doi: 10.3389/fnins.2015.00415
42. Stewart M. An explanation for sudden death in epilepsy (SUDEP). *J Physiol Sci.* (2018) 68:307–20. doi: 10.1007/s12576-018-0602-z
43. Smythies J, Edelstein L, Ramachandran V. Hypotheses relating to the function of the claustrum. *Front Integr Neurosci.* (2012) 6:53. doi: 10.3389/fnint.2012.00053
44. Torgerson CM, Irimia A, Goh SY, Van Horn JD. The DTI connectivity of the human claustrum. *Hum Brain Mapp.* (2015) 36:827–38. doi: 10.1002/hbm.22667
45. Meletti S, Slonkova J, Mareckova I, Monti G, Specchio N, Hon P, et al. Claustrum damage and refractory status epilepticus following febrile illness. *Neurology.* (2015) 85:1224–32. doi: 10.1212/WNL.0000000000001996
46. Laufs H, Richardson MP, Salek-Haddadi A, Vollmar C, Duncan JS, Gale K, et al. Converging PET and fMRI evidence for a common area involved in human focal epilepsies. *Neurology.* (2011) 77:904–10. doi: 10.1212/WNL.0b013e31822c90f2
47. Chen CH, Williams JL, Lutherer LO. Cerebellar lesions alter autonomic responses to transient isovolaemic changes in arterial pressure in anaesthetized cats. *Clin Auton Res.* (1994) 4:263–72. doi: 10.1007/BF01827432
48. Lutherer LO, Lutherer BC, Dormer KJ, Janssen HF, Barnes CD. Bilateral lesions of the fastigial nucleus prevent the recovery of blood pressure following hypotension induced by hemorrhage or administration of endotoxin. *Brain Res.* (1983) 269:251–7. doi: 10.1016/0006-8993(83)90134-8
49. Williams JL, Everse SJ, Lutherer LO. Stimulating fastigial nucleus alters central mechanisms regulating phrenic activity. *Respir Physiol.* (1989) 76:215–27. doi: 10.1016/0034-5687(89)90099-6
50. Faull OK, Subramanian HH, Ezra M, Pattinson KTS. The midbrain periaqueductal gray as an integrative and interoceptive neural structure for breathing. *Neurosci Biobehav Rev.* (2019) 98:135–44. doi: 10.1016/j.neubiorev.2018.12.020
51. Mueller SG, Bateman LM, Laxer KD. Evidence for brainstem network disruption in temporal lobe epilepsy and sudden unexplained death in epilepsy. *Neuroimage Clin.* (2014) 5:208–16. doi: 10.1016/j.nicl.2014.06.010
52. Kommajosyula SP, Faingold CL. Neural activity in the periaqueductal gray and other specific subcortical structures is enhanced when a selective serotonin reuptake inhibitor selectively prevents seizure-induced sudden death in the DBA/1 mouse model of sudden unexpected death in epilepsy. *Epilepsia.* (2019) 60:1221–33. doi: 10.1111/epi.14759
53. Buchanan GF. Impaired CO_2-induced arousal in SIDS and SUDEP. *Trends Neurosci.* (2019) 42:242–50. doi: 10.1016/j.tins.2019.02.002
54. Baker J, Kimpinski K. Reduced brainstem functional connectivity in patients with peripheral autonomic failure. *Neuroimage Clin.* (2019) 23:101924. doi: 10.1016/j.nicl.2019.101924
55. Xu F, Frazier DT. Role of the cerebellar deep nuclei in respiratory modulation. *Cerebellum.* (2002) 1:35–40. doi: 10.1080/14734220275320378
56. Shapleske J, Rossell SL, Woodruff PW, David AS. The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. *Brain Res Brain Res Rev.* (1999) 29:26–49. doi: 10.1016/s0165-0173(98)00047-2
57. Rosenow F, Luders H. Presurgical evaluation of epilepsy. *Brain.* (2001) 124(Pt 9):1683–700. doi: 10.1093/brain/124.9.1683
58. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet.* (2017) 389:834–45. doi: 10.1016/s0140-6736(16)31714-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership