Published in final edited form as:

Epilepsia. 2016 January ; 57(Suppl 1): 17–25. doi:10.1111/epi.13232.

Sudden unexpected death in epilepsy genetics: Molecular diagnostics and prevention

Alica M. Goldman[*], **Elijah R. Behr**[†], **Christopher Semsarian**[‡], **Richard D. Bagnall**[‡], **Sanjay Sisodiya**[§], and **Paul N. Cooper**[¶,#]

[*]Department of Neurology, Baylor College of Medicine, Houston, Texas, U.S.A

[†]Cardiac Research Centre, ICCS, St George's University of London, London, United Kingdom

[‡]Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

[§]Institute of Neurology, University College London, London, United Kingdom

[¶]Department of Neurology, Greater Manchester Neurosciences Centre, Salford, United Kingdom

[#]University of Manchester, Manchester, United Kingdom

Summary

Epidemiologic studies clearly document the public health burden of sudden unexpected death in epilepsy (SUDEP). Clinical and experimental studies have uncovered dynamic cardiorespiratory dysfunction, both interictally and at the time of sudden death due to epilepsy. Genetic analyses in humans and in model systems have facilitated our current molecular understanding of SUDEP. Many discoveries have been informed by progress in the field of sudden cardiac death and sudden infant death syndrome. It is becoming apparent that SUDEP genomic complexity parallels that of sudden cardiac death, and that there is a pauci1ty of analytically useful postmortem material. Because many challenges remain, future progress in SUDEP research, molecular diagnostics, and prevention rests in international, collaborative, and transdisciplinary dialogue in human and experimental translational research of sudden death.

Keywords

Sudden unexpected death in epilepsy (SUDEP); genetics; Sudden cardiac death; Sudden infant death syndrome; Molecular autopsy; Prevention

Individual risk prediction remains challenging: A particular concern is that patients with relatively well-controlled epilepsy, including those with infrequent seizures, remain at risk for sudden death.[1] The focus of this article is to explore the role of genetic factors in sudden

Address correspondence to Alica M. Goldman, Department of Neurology, Baylor College of Medicine, One Baylor Plaza, NB222, Houston, Texas 77030, U.S.A. agoldman@bcm.edu.

Disclosure of Conflicts of Interest

None of the remaining authors has any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

unexpected death in epilepsy (SUDEP). In this, we draw on research in sudden cardiac death (SCD) and sudden infant death syndrome (SIDS).

Lessons from Research on the Genetics of Sudden Cardiac Death

The annual rate of SCD is estimated at 50–100,000 in the United Kingdom and 300,000 in the United States.[2] Sudden arrhythmic death syndrome (SADS) refers to SCDs that remain unexplained despite a comprehensive autopsy and toxicology, and are presumed to be due to genetic causes such as familial long-QT syndrome (LQTS) and Brugada syndrome (BrS).[3,4] This accounts for 4% of SCDs in patients younger than 64 years of age and up to 40% in patients younger than 35.[5] Much is known about these monogenic conditions and their presentation.[6] Yet, it is increasingly evident that oligogenicity (interactive influence of a small number of genes) and common genetic variation may modify pathogenesis of these disorders and the risk of SCD.[7–10]

Evidence for a genetic basis for SCD in the young

Structural cardiac disease accounts for approximately 60% of sudden death in that occurs in the young before 35 years of age.[11] In the presence of familial disease, candidate gene testing will identify mutations in ~60% hypertrophic, 25% dilated, and 40% arrhythmogenic right ventricular cardiomyopathies.[12] Diagnostic yield in patients with SADS rests in the profiling of genes responsible for LQTS, BrS, and catecholaminergic polymorphic ventricular tachycardia (CPVT): cardiac potassium channel alpha and beta subunits *KCNQ1*, *KCNH2*, *KCNE1*, and *KCNE2*; the cardiac sodium channel alpha subunit *SCN5A*; and the sarcoplasmic reticulum calcium release channel, the Ryanodine receptor (RyR2),[5,13] respectively. The mutation prevalence in these genes is estimated at around 15–20%.[5,14] Careful cardiologic evaluation of the family can increase the detection rate from 22% to 53%.[15,16] It is now known that those at greatest risk may carry multiple genetic variants.[12] Multiple mutation carriers represent approximately 7% of LQTS probands, and they present with more severe disease.[17]

It has been established that even acquired arrhythmic risk is genetically influenced; in the Paris prospective study, the risk of SCD in middle-aged men was doubled in the presence of a parental SCD history.[18] Investigation focused on common nonsynonymous single nucleotide polymorphisms (SNPs) found association of the S*CN5A-S1103Y* with an eightfold increased risk of SCD due to any cause in African Americans.[19] Moreover, the *S1103Y* allele carriers had 8.4 (2.1–28.6) relative risk (RR) for SADS compared to noncardiac death and *S1103Y* homozygosity in infancy carried an odds ratio (OR) of 24.4 in SIDS risk.[20,21]

Evidence for a genetic basis to coronary SCD: Synonymous common genetic variation

In a large Dutch cohort, cardiac arrest due to ventricular fibrillation (VF) following a first acute ST-elevation myocardial infarction (STEMI) was threefold more common in those with a family history for SCD.[22] Genome-wide association studies (GWAS) of 972 STEMI cases, of which 515 had a cardiac arrest, associated the risk of VF with the common polymorphism *rs2824292* next to a coxsackievirus v receptor gene *CXADR*,[10] which can

increased arrhythmogenicity in the setting of ischemia through altered cardiac conduction.[23] GWAS in a 1,268 SCDs identified and replicated the association of the rs4665058 common variant near the *BAZ2B* gene (bromodomain adjacent zinc finger domain 2B),[9] with as yet unclear functional significance. GWAS of electrocardiographic phenotypes linked to SCD risk found the strongest association with the *NOS1AP* (nitric oxide synthase 1 adaptor protein) gene[24] that has been linked to the risk of SCD in the general population as well as in congenital LQTS.[25,26]

Repolarization reserve: An example of genetic susceptibility to SCD

Acquired LQTS is an idiosyncratic and rare adverse drug reaction that causes both QT prolongation and torsades de pointes (TdP), the polymorphic ventricular tachycardia characteristic of congenital LQTS. It is an important issue in drug safety and development. A rare LQTS genetic variant is detected in approximately10% of cases.[27] Much of the risk associated with S1103Y in African Americans in the early study by Splawski et al.[19] was related to medications known to prolong the QT interval. S1103Y prolongs late sodium current that in turn delays cardiac repolarization. *KCNE1*-D85N, is another example of a common SNP associated with an eightfold increased risk of drug-induced TdP in people taking QT-prolonging drugs.[28] Noncoding SNPs of the *NOS1AP* gene were also linked to the risk of drug-induced TdP in patients taking amiodarone, a commonly used antiarrhythmic agent.[8] These data support the hypothesis of the “repolarization reserve,” a physiologic redundancy of capacity to repolarize the myocardium. Overt congenital LQTS is caused by rare functionally severe mutations while some rare or common genetic variations underlie a concealed genetic reduction of repolarization reserve, which prolongs the QT interval to a minimal extent.[29] The risk of “acquired” LQTS increases with exposure to insults, such as QT-prolonging medications, hypokalemia, or subarachnoid hemorrhage, particularly as such factors may be additive. In addition, women tend to have longer QT intervals and are thus at higher risk for either congenital or acquired LQTS.

Implications for future research

Genetic testing due to SCD concern is relevant not only in suspected cardiomyopathy or arrhythmias but also in people with other disorders. The potential overlap with genetic risk in SUDEP remains to be explored. For example, the seizure-induced bradycardia, acidosis, and autonomic dysfunction may represent an insult to repolarization reserve. However, misdiagnosis of epilepsy also needs to be considered. Cerebral anoxia secondary to a cardiac arrhythmia may be responsible for the seizure phenotype, particularly in the young adult who dies after one, or only a few, seizures, or has exertion-related seizures. This clinical presentation of an arrhythmia syndrome must not be forgotten given the implications of risk to the family. Although only relevant to patients with some genetic epilepsies, there is also the possibility that the same genetic abnormality predisposing to epilepsy predisposes to SCD as discussed below. Finally, although molecular autopsy has started to be applied in SUDEP cases on a research basis, family assessment for SCD genetic risk may also be a good avenue to explore.

The Genetic Spectrum of SUDEP

The panel of candidate SUDEP genes has been growing rapidly, and discoveries have been facilitated by progress in the field of SCD and SIDS, and by translational research in sophisticated animal models.

Arrhythmia genes

The discovery of cardiac voltage-gated sodium channel *SCN5A* in brain limbic regions provided the first link between genetically predisposed cardiac arrhythmias and epilepsy.[30] Subsequent clinical case studies supported the concept of a combined neurocardiac phenotype triggered by mutations in ion channels dually expressed in the brain and in the heart.[31,32] This was followed by the report of epilepsy, cardiac arrhythmias, and SUDEP in transgenic mice carrying the human knock-in mutations in the most common *LQT* gene, the potassium channel *KCNQ1*.[33] The observed model SUDEP event mirrored a previously described human case report,[34] and the study uncovered some of the candidate networks and mechanisms involved in the lethal epilepsy outcome. Consequently, a seizure phenotype was identified in 28% of cases with confirmed LQTS caused by pathogenic variants in the *KCNH2*, *KCNQ1*, and *SCN5A* genes,[35–37] and variants of suspected functional significance were uncovered in 10% of 48 SUDEP cases.[38] Yet, the molecular underpinnings of neurocardiac interactions extend beyond the *LQT* gene family; a catecholaminergic polymorphic ventricular tachycardia (CPVT) is a dysrhythmia presenting with stress-induced syncope[39] and a high 30–50% mortality rate before the age of 30[39] due to a defect in the ryanodine receptor (*RYR2*).[40] The mouse model carrying the human mutation R2474S displayed exercise-induced ventricular arrhythmia and early onset spontaneous convulsive seizures, and lethal arrhythmia triggered sudden death.[41] The combined phenotype of arrhythmias and seizures was also observed in 12 of 24 of Dutch CPVT families affected by *RYR2* mutations[39] and a missense variant *RYR2*-G4936A was found in an 8-year-old SUDEP case with history of epilepsy and recurrent, exercise-induced syncope with normal resting electrocardiography (ECG).[42] The hyperpolarization-activated cyclic nucleotide-gated ion channels *HCN1-4* are implicated in epilepsy and cardiac arrhythmias, owing to their involvement in the generation of the cation (Na+ and K+)–triggered I_h depolarizing current that facilitates action potential and a spontaneous rhythmic activity in the neurons and pacemaking cardiomyocytes.[43–48] The *HCN2*-deficient mouse displays absence epilepsy and sinus arrhythmia,[49] albeit without evidence of a reduced life span. A clinically confirmed phenotype of epilepsy and arrhythmia in humans has not yet been observed, although *HCN* coding variants of suspected functional significance were uncovered in a mutational screen of 48 SUDEP cases.[50] Therefore, the involvement of HCN channels in clinically manifest arrhythmia or epilepsy justifies the consideration of this gene family in candidate SUDEP genes.

Epilepsy genes

Many ion channel genes regulating the central control of cardiac and respiratory function are also expressed within the brain networks thought to underlie epilepsy. For example, the voltage-gated potassium channel *KCNA1* is expressed in brain and in the vagus nerve. The *Kcna1* null mice show seizures, cardiac arrhythmias, vagal hyperexcitability, and premature

death.[51] This channel was also clinically validated in a SUDEP case affected by epileptic encephalopathy and suspected cardiac dysrhythmias carrying de novo and novel *KCNA1* intragenic duplication.[52] The report of familial SUDEP in a kindred affected by the genetic epilepsy syndrome generalized epilepsy with febrile seizures plus (GEFS+) while segregating a novel variant in *SCN1A* gene brought attention to this sodium channel subunit,[53] a principal gene underlying the Dravet syndrome (DS). Patients with DS face an increased risk of premature mortality currently estimated to affect about 4–12% of children,[54–56] and they seem predisposed to autonomic dysfunction, as evidenced by depressed heart rate variability (HRV)[57,58] and increased P- and QT-interval dispersion.[58] The *Scn1a* deficient models mirror the complex human phenotype, exhibiting spontaneous seizures, autonomic instability, and seizure-driven vagal activation preceding sudden death.[59,60] Administration of parasympatholytics reduced the incidence of ictal bradycardia and SUDEP in the model.[60] A knock-in mouse model carrying the human mutation *SCN1A-R1407X*[61,62] displayed a 21% premature death rate, spontaneous seizures, and a prolonged QT interval due to the increased sodium channel–dependent cardiac current in cardiomyocytes.[62] Cardiac arrhythmias in this model often preceded apparent convulsive seizures, thus indicating that some *SCN1A* variants might predispose to sudden death through neurocardiac or sole cardiac mechanisms.[62] There is also experimental evidence that mortality risk in DS is influenced by the affected neuronal cell type and regionally specific differences in *Scn1a* brain expression; selective $Na_v1.1$ deficiency in inhibitory γ-aminobutyric acid (GABA)ergic neurons led to a more severe epileptic phenotype and early and frequent sudden death as compared to mice with constitutive *Scn1a* deficiency.[61] *Scn1a* deficiency restricted to forebrain excitatory neurons combined with global $Na_v1.1$ deficiency in inhibitory GABAergic neurons mitigated the seizure phenotype and lessened the incidence of model SUDEP.[61] The discoveries linking *KCNA1* and *SCN1A* to SUDEP brought attention to other epilepsy genes. The *SCN1B* gene encodes a voltage-gated sodium channel (VGSC) β subunit critical for proper gating and cell surface expression of the VGSC complex.[63] *SCN1B* mutations are linked to GEFS+, temporal lobe epilepsy, as well as DS.[64–66] The *Scn1b* null mouse model displays spontaneous seizures, prolonged QT and RR intervals, and early mortality.[67,68] Spontaneous epilepsy and >30% premature mortality was also observed in a mouse deficient in the glutamic acid decarboxylase isoform *GAD65*.[69] Confirmation of *SCN1B* and *GAD65* in human SUDEP awaits discovery. Comprehensive genomic profiling is certain to facilitate the finding of novel molecular candidates as shown by the detection of a functionally active de novo variant in the *SCN8A* channel gene in a child affected by epileptic encephalopathy and SUDEP.[70–72] SUDEP was also reported in children affected by epilepsy due to variants in the *KCNQ2* gene.[73]

Genes involved in respiration and arousal

Animal models[74–77] and translational human studies[78] have uncovered the critical role of 5-hydroxytryptamine (5-HT) in respiration and arousal[79] and they are discussed in detail elsewhere in this supplement. Mice deficient in the 5-HT2c receptor develop epileptic seizures and are susceptible to premature death,[74] and the genetically engineered Lmx1bf/f/p mice depleted of all 5-HT neurons have severe apnea, hypoventilation, diminished hypercapnic response, compromised arousal from sleep, and premature mortality.[80] There are known alterations in expression levels of several 5-HT receptors in the DBA/2

audiogenic seizure model with ictally induced respiratory arrest and sudden death.[81] These discoveries have led to early pharmacologic intervention exploring the possible beneficial effect of the widely available serotonin reuptake inhibitors (SSRIs) on SUDEP risk. Administration of SSRI in the DBA/1 model ameliorated ictally induced respiratory arrest and death and the effect was age dependent.[82,83] Clinical observations reflected the animal data, as people with epilepsy chronically exposed to SSRIs were less likely to experience profound oxygen desaturation with partial, but not secondarily generalized, seizures.[78]

Complex genetics of human SUDEP

There is growing evidence that variant functional properties along with complex genetic interactions influence the phenotypic expressions of cardiac arrhythmias,[12,84,85] epilepsy,[52,86,87] and SUDEP.[52] Although *SCN8A* gain-of-function mutations are implicated in epileptic encephalopathies and SUDEP,[70,86,88] animal models carrying loss-of-function variants exhibit milder seizure phenotype.[71,72] In addition, *Kcna1* SUDEP model crossed with a *Cacna1a* absence seizure mouse has mild seizure phenotype and improved survival.[89] Furthermore, modulation of neuronal hyperexcitability and premature mortality extends beyond genetic interactions of the ion channel network; the deficiency of the microtubule-binding protein tau in the *Kcna1* knockout mouse not only reduced the seizure frequency and severity, but also improved survival.[90] A human example of genomic complexity in SUDEP was recently illustrated by a pediatric case with DS, frequent ictal apnea, and suspected cardiac arrhythmias.[52] Detailed genomic analysis uncovered interesting combinations of SNPs and copy number variants in genes expressed in both neurocardiac and respiratory control pathways, including *SCN1A*, *KCNA1*, *RYR3*, and *HTR2C*.

Understanding SUDEP Genetics in Populations—The Australian Experience

Tu et al.[38,50] carried out a retrospective review of postmortem reports performed at a single forensic center between 1993 and 2009, identifying 68 cases: the cause of death was “SUDEP” or “possible SUDEP” in 22 and 46 cases, respectively. Postmortem blood was available in 48 cases, and DNA was screened for variants in the most common *LQTS* genes,[38] *KCNQ1, KCNH2*, and *SCN5A*, as well in the *HCN* gene family.[43,44,50] There was a *KCNH2* Arg176Trp and Arg1047Leu missense variation in one and four SUDEP cases, respectively, a single Ala572Asp, Pro1090Leu, and Pro2006Ala missense variation in *SCN5A* in three SUDEP cases[38] and nine nonsynonymous HCN genic variants.[50]

The Arg176Trp variant in *KCNH2* is a nonconservative substitution in a highly conserved N-terminal region of the protein. According to bioinformatic (in silico) analysis, it is probably damaging. The *KCNH2* 176Trp allele is a common founder mutation associated with a prolonged QT interval in Finnish LQTS families.[91–93] It is also reported in a case of sudden unexplained death.[94] In vitro functional studies have shown that the Arg176Trp substitution alters ion channel function, causing accelerated channel deactivation and reduced potassium current density, resulting in a prolonged QT interval.[92] Collectively, these results implicate the *KCNH2* Arg176Trp variant in prolongation of the QT interval, a likely trigger of a fatal arrhythmia in the SUDEP case, a 35-year-old man, reportedly diagnosed with epilepsy 5 years prior to death who had 10 episodes requiring hospitalization;

neuropathology examination reported left hippocampal sclerosis. *KCNH2* Arg1047Leu is a common variant found in 2.9% SUDEP cases (2.9%). One patient with SUDEP, a 52-year-old woman with a history of controlled epilepsy, carried the *KCNH2* Arg1047Leu polymorphism in addition to the rare *SCN5A* Ala572Asp variant that has been reported previously in LQTS and in a case of sudden cardiac death.[95,96] Neuropathology reported microdysgenesis in the left hippocampus. As discussed earlier,[7] it is plausible that the combined effect of these two protein-changing variants raised the risk of sudden death in this patient. *SCN5A* Pro2006Ala is a rare variant with a minor allele frequency (MAF) of 0.1%, reported previously in a case of unexplained cardiac arrest and LQTS.[97,98] This variant was found in a 43-year-old man who died of SUDEP who had nocturnal seizures. The *SCN5A* Pro1090Leu variation shows ethnically variable MAF of 0.008% in European and African ancestry but 2% in an Asian subpopulation. It is considered an Asian-specific polymorphism.[99,100] This variant was found in a 23-year-old from China with a history of poorly controlled epilepsy. *HCN2* Phe738Cys is a nonconservative substitution in the carboxyl-cytoplasmic tail of the *HCN2* protein, predicted by in silico to be possibly damaging. It was detected in a 52-year-old man, a carrier of the common *KCNH2* Arg1047Leu polymorphism. The patient had infrequent seizures since the age of 16 years. *HCN2* Pro802Ser is a nonconservative substitution in the carboxyl-cytoplasmic tail, predicted to be benign. It was detected in a 43-year-old man, also a carrier of the *SCN5A* Pro2006Ala variant, and who had a witnessed nocturnal seizure. *HCN4* Gly973Arg is a nonconservative substitution found in a 44-year-old man with reportedly regular seizures prior to death.

Genetic analysis of the Australian SUDEP cohort supports the hypothesis that genes encoding K^+, Na^+, and Ca^{2+} ion channels expressed both in neuronal and/or cardiac cells are likely to play an important role in the predisposition of epilepsy patients to SUDEP.[38,50] It remains to be determined whether these ion channel variants are the genetic cause in some SUDEP cases or an accompanying risk factor in the sudden death of patients with epilepsy. The variants may act in isolation or require the presence of a second genetic factor or environmental influence, such as uncontrolled seizures, QT-prolonging AEDs, or noncompliance with AED therapy, to predispose epilepsy patients to malignant arrhythmias and sudden death. Screening candidate genes, one at a time, limits the scope of genetic studies. Furthermore, although postmortem blood offers an ideal source of DNA for genetic studies in SUDEP, it is of finite supply, and not always available. Recent major advances in DNA enrichment and “next-generation” sequencing technologies have provided a new and powerful approach to identify mutations responsible for genetic disorders. The ability to enrich and sequence all of the protein coding exons (the exome) reduces the target region to 1.5% of the genome, while retaining the sequences most likely to harbor the majority of variations with high penetrance.[101]

Genetics of SUDEP: Tissue Collection and Utilization

Genetic variation likely contributes to SUDEP risk, but it is unclear how such variation might best be identified; in particular what samples are needed, what methods and analyses might be used, and how potential genetic leads might be followed through.

DNA collection for genetic studies in epilepsy is well established. Worldwide, tens of thousands of DNA samples have now been collected, and many thousands genotyped[102] or exome sequenced. The genetic study of SUDEP clearly provides a different level of challenge, as SUDEP cannot be predicted and there is no “target” population, although some groups of patients might be considered at greater risk. Collection in life for SUDEP studies is challenging, although greater SUDEP awareness[103] could facilitate this. Collection after SUDEP is difficult to systematize. The logistic difficulties of obtaining postmortem material require an awareness of the need and the processes, appropriate consent, and an established infrastructure. Up until now, most genetic studies of SUDEP have been of single cases or small series. In view of this, Klassen et al.[104] investigated the possibility of using other sources for DNA in SUDEP. They were able to extract DNA that could be used for at least some studies from blood spots on Guthrie cards, buccal scrapes on Guthrie cards, and from fingernails. In the field of oncology, it is now a well-established practice to undertake candidate gene or genome-wide whole exome sequencing from formalin-fixed paraffin-embedded samples, including brain. This has opened up large archival collections for research.

Advancing technology now allows for genetic studies using ever-smaller samples of DNA. A recent pathologic study of 143 archived brain samples[105] established the potential of this approach which in future could use prospectively collected samples from both postmortem and surgical cases, SUDEP and otherwise, to generate a regulated and approved resource for further research into, among other areas, SUDEP.

Clinical Implications

It is difficult at this time to translate genetic advances into pragmatic advice for patients, particularly as SUDEP tragically affects a wide range of individuals with epilepsy. Indeed there may be distinct separate populations at risk of SUDEP, with potentially different mechanisms. One group of individuals, typically young adults, with no significant prior known comorbidities and infrequent seizures, who die suddenly might represent a different population from those with severe epilepsy who manifest with frequent generalized convulsions. In the former group, genetic susceptibility to epilepsy may be associated with a genetic susceptibility to sudden cardiac death.[106] In the latter group, there may be complex additive interactions between polygenetic factors, medication, and the consequences of frequent severe seizures. In SUDEP, there is currently no evidence to guide practice for routine genetic testing. However, with genetic screening for long-QT–associated mutations, once confined to the research laboratory, now clinically available as diagnostic tests,[107] any SUDEP case should have a careful review of the family history, and any concern should result in a molecular genetics study.

The first priority in epilepsy practice is to ensure that patients do have epilepsy, rather than a cardiac disorder.[108] All new epilepsy patients must undergo a careful cardiac history and a detailed family history, particularly asking about sudden cardiac death and unexplained deaths in infancy. All patients, indeed anyone who has a blackout, should have an electrocardiogram (Table 1). Modern automated ECG machines may help screen for cardiac disorders, but a cardiologist, experienced in the relevant abnormalities, must review any

abnormalities identified as potentially abnormal. Epilepsy patients with an abnormal or equivocal ECG study, or any suspicious family history, should undergo specialist cardiac review. A specialist cardiac review should also be arranged for any patients who report suspicious symptoms including exercise-related seizures, or where there is witnessed profound pallor during seizures. Such patients should be assessed for possible prolonged monitoring, ideally with an implantable event recorder (IER) (Table 1). It is likely that at present barriers to arranging such specialist assessments result more from lack of awareness among neurologists rather than from resistance from cardiology services.

Even in expert hands, however, spotting QT abnormalities is problematic, most cardiologists miss them,[109] and IER is costly.[110] It is important that all those who care for people with epilepsy be aware that not only might potentially life-threatening cardiac disorders mimic epilepsy,[111] but also patients with epilepsy might be at increased risk of concurrent cardiac arrhythmias.

Developing the hypothesis that there might be (at least) two distinct populations within SUDEP cases, and considering those with frequent generalized seizures despite medication, the use of IER technology needs to be assessed looking for potential markers of cardiac instability. It has long been recognized that some patients have identifiable cardiac abnormalities in the interictal state,[112] and during seizures,[113,114] including varying degrees and types of heart block. In addition, such patients may have disturbances of autonomic function, both when untreated,[115] and also possibly associated with treatment[116]; withdrawal of treatment may exacerbate these abnormalities.[117] These interictal and ictal cardiac disturbances might be of particular significance in those with severe medically intractable epilepsies, and in this group, therefore, the results of prolonged cardiac monitoring might be used to guide drug choices, including nonepilepsy drugs, could help with counseling about other potentially modifiable risk factors, and might result in implantable devices to protect selected patients.[113]

These proposals represent significant changes to current routine practice, and require an increased awareness of the risks of SUDEP for patients. Highlighting these risks to patients has implications.[103] Furthermore, the proposals require increased engagement among neurologists regarding the need for review of cardiac risk factors. An informal survey of United Kingdom cardiac electrophysiologists by one of the authors (PC) suggests that cardiologists already acknowledge the need to investigate such patients. Many young adults who die of SUDEP are not dissimilar to young adults who die of SCD. Increased public awareness of SCD has improved its prevention. It is hoped that increased public awareness of the risks of epilepsy might do the same for SUDEP.

Acknowledgments

Elijah R. Behr has received unrestricted research support from Biotronik.

Biography

Alica M. Goldman is an associate professor of Neurology at Baylor College of Medicine in Houston, Texas.

References

1. Nashef L, Garner S, Sander JW, et al. Circumstances of death in sudden death in epilepsy: interviews of bereaved relatives. J Neurol Neurosurg Psychiatry. 1998; 64:349–352. [PubMed: 9527147]
2. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task force on sudden cardiac death of the European Society of cardiology. Eur Heart J. 2001; 22:1374–1450. [PubMed: 11482917]
3. Papadakis M, Sharma S, Cox S, et al. The magnitude of sudden cardiac death in the young: a death certificate-based review in England and Wales. Europace. 2009; 11:1353–1358. [PubMed: 19700472]
4. Behr ER, Casey A, Sheppard M, et al. Sudden arrhythmic death syndrome: a national survey of sudden unexplained cardiac death. Heart. 2007; 93:601–605. [PubMed: 17237131]
5. Raju H, Behr ER. Unexplained sudden death, focussing on genetics and family phenotyping. Curr Opin Cardiol. 2013; 28:19–25. [PubMed: 23128498]
6. Bastiaenen R, Behr ER. Sudden death and ion channel disease: pathophysiology and implications for management. Heart. 2011; 97:1365–1372. [PubMed: 21685181]
7. Bezzina CR, Barc J, Mizusawa Y, et al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet. 2013; 45:1044–1049. [PubMed: 23872634]
8. Jamshidi Y, Nolte IM, Dalageorgou C, et al. Common variation in the NOS1AP gene is associated with drug-induced QT prolongation and ventricular arrhythmia. J Am Coll Cardiol. 2012; 60:841–850. [PubMed: 22682551]
9. Arking DE, Junttila MJ, Goyette P, et al. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. PLoS Genet. 2011; 7:e1002158. [PubMed: 21738491]
10. Bezzina CR, Pazoki R, Bardai A, et al. Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction. Nat Genet. 2010; 42:688–691. [PubMed: 20622880]
11. Raju H, Alberg C, Sagoo GS, et al. Inherited cardiomyopathies. BMJ. 2011; 343:d6966. [PubMed: 22106372]
12. Wilde AA, Behr ER. Genetic testing for inherited cardiac disease. Nat Rev Cardiol. 2013; 10:571–583. [PubMed: 23900354]
13. Semsarian C, Hamilton RM. Key role of the molecular autopsy in sudden unexpected death. Heart Rhythm. 2012; 9:145–150. [PubMed: 21816129]
14. Tester DJ, Medeiros-Domingo A, Will ML, et al. Cardiac channel molecular autopsy: insights from 173 consecutive cases of autopsy-negative sudden unexplained death referred for postmortem genetic testing. Mayo Clin Proc. 2012; 87:524–539. [PubMed: 22677073]
15. Behr E, Wood DA, Wright M, et al. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. Lancet. 2003; 362:1457–1459. [PubMed: 14602442]

16. Behr ER, Dalageorgou C, Christiansen M, et al. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. Eur Heart J. 2008; 29:1670–1680. [PubMed: 18508782]
17. Westenskow P, Splawski I, Timothy KW, et al. Compound mutations: a common cause of severe long-QT syndrome. Circulation. 2004; 109:1834–1841. [PubMed: 15051636]
18. Jouven X, Desnos M, Guerot C, et al. Predicting sudden death in the population: the Paris Prospective Study I. Circulation. 1999; 99:1978–1983. [PubMed: 10209001]
19. Splawski I, Timothy KW, Tateyama M, et al. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. Science. 2002; 297:1333–1336. [PubMed: 12193783]
20. Burke A, Creighton W, Mont E, et al. Role of SCN5A Y1102 polymorphism in sudden cardiac death in blacks. Circulation. 2005; 112:798–802. [PubMed: 16061744]
21. Plant LD, Bowers PN, Liu Q, et al. A common cardiac sodium channel variant associated with sudden infant death in African Americans, SCN5A S1103Y. J Clin Invest. 2006; 116:430–435. [PubMed: 16453024]
22. Dekker LR, Bezzina CR, Henriques JP, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. Circulation. 2006; 114:1140–1145. [PubMed: 16940195]
23. Marsman RF, Bezzina CR, Freiberg F, et al. Coxsackie and adenovirus receptor is a modifier of cardiac conduction and arrhythmia vulnerability in the setting of myocardial ischemia. J Am Coll Cardiol. 2014; 63:549–559. [PubMed: 24291282]
24. Arking DE, Pulit SL, Crotti L, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. Nat Genet. 2014; 46:826–836. [PubMed: 24952745]
25. Crotti L, Monti MC, Insolia R, et al. NOS1AP is a genetic modifier of the long-QT syndrome. Circulation. 2009; 120:1657–1663. [PubMed: 19822806]
26. Kao WH, Arking DE, Post W, et al. Genetic variations in nitric oxide synthase 1 adaptor protein are associated with sudden cardiac death in US white community-based populations. Circulation. 2009; 119:940–951. [PubMed: 19204306]
27. Behr ER, Roden D. Drug-induced arrhythmia: pharmacogenomic prescribing? Eur Heart J. 2013; 34:89–95. [PubMed: 23091201]
28. Kaab S, Crawford DC, Sinner MF, et al. A large candidate gene survey identifies the KCNE1 D85N polymorphism as a possible modulator of drug-induced torsades de pointes. Circ Cardiovasc Genet. 2012; 5:91–99. [PubMed: 22100668]
29. Roden DM. Taking the “idio” out of “idiosyncratic”: predicting torsades de pointes. Pacing Clin Electrophysiol. 1998; 21:1029–1034. [PubMed: 9604234]
30. Hartmann HA, Colom LV, Sutherland ML, et al. Selective localization of cardiac SCN5A sodium channels in limbic regions of rat brain. Nat Neurosci. 1999; 2:593–595. [PubMed: 10404176]
31. Aurlien D, Leren TP, Tauboll E, et al. New SCN5A mutation in a SUDEP victim with idiopathic epilepsy. Seizure. 2009; 18:158–160. [PubMed: 18752973]
32. Heron SE, Hernandez M, Edwards C, et al. Neonatal seizures and long QT syndrome: a cardiocerebral channelopathy? Epilepsia. 2010; 51:293–296. [PubMed: 19863579]
33. Goldman AM, Glasscock E, Yoo J, et al. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci Transl Med. 2009; 1:2ra6.
34. Bird J, Dembny KAT, Sandeman D, et al. Sudden unexplained death in epilepsy: an intracranially monitored case. Epilepsia. 1997; 38(Suppl. 11):S52–S56. [PubMed: 9092961]
35. Anderson JH, Bos JM, Cascino GD, et al. Prevalence and spectrum of electroencephalogram-identified epileptiform activity among patients with long QT syndrome. Heart Rhythm. 2014; 11:53–57. [PubMed: 24103226]
36. Keller DI, Grenier J, Christe G, et al. Characterization of novel KCNH2 mutations in type 2 long QT syndrome manifesting as seizures. Can J Cardiol. 2009; 25:455–462. [PubMed: 19668779]
37. Partemi S, Cestele S, Pezzella M, et al. Loss-of-function KCNH2 mutation in a family with long QT syndrome, epilepsy, and sudden death. Epilepsia. 2013; 54:e112–e116. [PubMed: 23899126]

38. Tu E, Bagnall RD, Duflou J, et al. Post-mortem review and genetic analysis of sudden unexpected death in epilepsy (SUDEP) cases. Brain Pathol. 2011; 21:201–208. [PubMed: 20875080]
39. Postma AV, Denjoy I, Kamblock J, et al. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. J Med Genet. 2005; 42:863–870. [PubMed: 16272262]
40. Liu N, Priori SG. Disruption of calcium homeostasis and arrhythmogenesis induced by mutations in the cardiac ryanodine receptor and calsequestrin. Cardiovasc Res. 2008; 77:293–301. [PubMed: 18006488]
41. Lehnart SE, Mongillo M, Bellinger A, et al. Leaky Ca^{2+} release channel/ryanodine receptor 2 causes seizures and sudden cardiac death in mice. J Clin Invest. 2008; 118:2230–2245. [PubMed: 18483626]
42. Johnson JN, Tester DJ, Bass NE, et al. Cardiac channel molecular autopsy for sudden unexpected death in epilepsy. J Child Neurol. 2010; 25:916–921. [PubMed: 20395638]
43. Noam Y, Bernard C, Baram TZ. Towards an integrated view of HCN channel role in epilepsy. Curr Opin Neurobiol. 2011; 21:873–879. [PubMed: 21782415]
44. Benarroch EE. HCN channels: function and clinical implications. Neurology. 2013; 80:304–310. [PubMed: 23319474]
45. Monteggia LM, Eisch AJ, Tang MD, et al. Cloning and localization of the hyperpolarization-activated cyclic nucleotide-gated channel family in rat brain. Brain Res Mol Brain Res. 2000; 81:129–139. [PubMed: 11000485]
46. Meuth SG, Kanyshkova T, Meuth P, et al. Membrane resting potential of thalamocortical relay neurons is shaped by the interaction among TASK3 and HCN2 channels. J Neurophysiol. 2006; 96:1517–1529. [PubMed: 16760342]
47. Marionneau C, Couette B, Liu J, et al. Specific pattern of ionic channel gene expression associated with pacemaker activity in the mouse heart. J Physiol. 2005; 562(Pt 1):223–234. [PubMed: 15498808]
48. Stieber J, Wieland K, Stockl G, et al. Bradycardic and proarrhythmic properties of sinus node inhibitors. Mol Pharmacol. 2006; 69:1328–1337. [PubMed: 16387796]
49. Ludwig A, Budde T, Stieber J, et al. Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. EMBO J. 2003; 22:216–224. [PubMed: 12514127]
50. Tu E, Waterhouse L, Duflou J, et al. Genetic analysis of hyperpolarization-activated cyclic nucleotide-gated cation channels in sudden unexpected death in epilepsy cases. Brain Pathol. 2011; 21:692–698. [PubMed: 21615589]
51. Glasscock E, Yoo JW, Chen TT, et al. Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy. J Neurosci. 2010; 30:5167–5175. [PubMed: 20392939]
52. Klassen TL, Bomben VC, Patel A, et al. High-resolution molecular genomic autopsy reveals complex sudden unexpected death in epilepsy risk profile. Epilepsia. 2014; 55:e6–e12. [PubMed: 24372310]
53. Hindocha N, Nashef L, Elmslie F, et al. Two cases of sudden unexpected death in epilepsy in a GEFS+ family with an SCN1A mutation. Epilepsia. 2008; 49:360–365. [PubMed: 18251839]
54. Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. Epilepsia. 2011; 52(Suppl. 2):S44–S49.
55. Skluzacek JV, Watts KP, Parsy O, et al. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. Epilepsia. 2011; 52(Suppl. 2):S95–S101.
56. Sakauchi M, Oguni H, Kato I, et al. Retrospective multiinstitutional study of the prevalence of early death in Dravet syndrome. Epilepsia. 2011; 52:1144–1149. [PubMed: 21480880]
57. Delogu AB, Spinelli A, Battaglia D, et al. Electrical and autonomic cardiac function in patients with Dravet syndrome. Epilepsia. 2011; 52(Suppl. 2):S55–S58.
58. Ergul Y, Ekici B, Tatli B, et al. QT and P wave dispersion and heart rate variability in patients with Dravet syndrome. Acta Neurol Belg. 2013; 113:161–166. [PubMed: 23065439]

59. Cheah CS, Yu FH, Westenbroek RE, et al. Specific deletion of NaV1.1 sodium channels in inhibitory interneurons causes seizures and premature death in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A. 2012; 109:14646–14651. [PubMed: 22908258]
60. Kalume F, Westenbroek RE, Cheah CS, et al. Sudden unexpected death in a mouse model of Dravet syndrome. J Clin Invest. 2013; 123:1798–1808. [PubMed: 23524966]
61. Ogiwara I, Iwasato T, Miyamoto H, et al. Nav1.1 haploinsufficiency in excitatory neurons ameliorates seizure-associated sudden death in a mouse model of Dravet syndrome. Hum Mol Genet. 2013; 22:4784–4804. [PubMed: 23922229]
62. Auerbach DS, Jones J, Clawson BC, et al. Altered cardiac electrophysiology and SUDEP in a model of Dravet syndrome. PLoS ONE. 2013; 8:e77843. [PubMed: 24155976]
63. Brackenbury WJ, Yuan Y, O'Malley HA, et al. Abnormal neuronal patterning occurs during early postnatal brain development of Scn1b-null mice and precedes hyperexcitability. Proc Natl Acad Sci U S A. 2013; 110:1089–1094. [PubMed: 23277545]
64. Wallace RH, Wang DW, Singh R, et al. Febrile seizures and generalized epilepsy associated with a mutation in the Na^+-channel beta1 subunit gene SCN1B. Nat Genet. 1998; 19:366–370. [PubMed: 9697698]
65. Scheffer IE, Harkin LA, Grinton BE, et al. Temporal lobe epilepsy and GEFS+ phenotypes associated with SCN1B mutations. Brain. 2007; 130:100–109. [PubMed: 17020904]
66. Ogiwara I, Nakayama T, Yamagata T, et al. A homozygous mutation of voltage-gated sodium channel beta(I) gene SCN1B in a patient with Dravet syndrome. Epilepsia. 2012; 53:e200–e203. [PubMed: 23148524]
67. Chen C, Westenbroek RE, Xu X, et al. Mice lacking sodium channel beta1 subunits display defects in neuronal excitability, sodium channel expression, and nodal architecture. J Neurosci. 2004; 24:4030–4042. [PubMed: 15102918]
68. Lopez-Santiago LF, Meadows LS, Ernst SJ, et al. Sodium channel Scn1b null mice exhibit prolonged QT and RR intervals. J Mol Cell Cardiol. 2007; 43:636–647. [PubMed: 17884088]
69. Kash SF, Johnson RS, Tecott LH, et al. Epilepsy in mice deficient in the 65-kDa isoform of glutamic acid decarboxylase. Proc Natl Acad Sci U S A. 1997; 94:14060–14065. [PubMed: 9391152]
70. Veeramah KR, O'Brien JE, Meisler MH, et al. De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. Am J Hum Genet. 2012; 90:502–510. [PubMed: 22365152]
71. Hawkins NA, Martin MS, Frankel WN. Neuronal voltage-gated ion channels are genetic modifiers of generalized epilepsy with febrile seizures plus. Neurobiol Dis. 2011; 41:655–660. [PubMed: 21156207]
72. O'Brien JE, Meisler MH. Sodium channel SCN8A (Nav1.6): properties and de novo mutations in epileptic encephalopathy and intellectual disability. Front Genet. 2013; 4:213. [PubMed: 24194747]
73. Weckhuysen S, Ivanovic V, Hendrickx R, et al. Extending the KCNQ2 encephalopathy spectrum: clinical and neuroimaging findings in 17 patients. Neurology. 2013; 81:1697–1703. [PubMed: 24107868]
74. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. Nature. 1995; 374:542–546. [PubMed: 7700379]
75. Tupal S, Faingold CL. Evidence supporting a role of serotonin in modulation of sudden death induced by seizures in DBA/2 mice. Epilepsia. 2006; 47:21–26. [PubMed: 16417527]
76. Richerson GB, Buchanan GF. The serotonin axis: shared mechanisms in seizures, depression, and SUDEP. Epilepsia. 2011; 52(Suppl. 1):S28–S38.
77. Sowers LP, Massey CA, Gehlbach BK, et al. Sudden unexpected death in epilepsy: fatal post-ictal respiratory and arousal mechanisms. Respir Physiol Neurobiol. 2013; 189:315–323. [PubMed: 23707877]
78. Bateman LM, Li CS, Lin TC, et al. Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy. Epilepsia. 2010; 51:2211–2214. [PubMed: 20491872]

79. Massey CA, Sowers LP, Dlouhy BJ, et al. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. Nat Rev Neurol. 2014; 10:271–282. [PubMed: 24752120]
80. Hodges MR, Wehner M, Aungst J, et al. Transgenic mice lacking serotonin neurons have severe apnea and high mortality during development. J Neurosci. 2009; 29:10341–10349. [PubMed: 19692608]
81. Uteshev VV, Tupal S, Mhaskar Y, et al. Abnormal serotonin receptor expression in DBA/2 mice associated with susceptibility to sudden death due to respiratory arrest. Epilepsy Res. 2010; 88:183–188. [PubMed: 20018491]
82. Faingold CL, Randall M. Effects of age, sex, and sertraline administration on seizure-induced respiratory arrest in the DBA/1 mouse model of sudden unexpected death in epilepsy (SUDEP). Epilepsy Behav. 2013; 28:78–82. [PubMed: 23666465]
83. Faingold CL, Tupal S, Randall M. Prevention of seizure-induced sudden death in a chronic SUDEP model by semichronic administration of a selective serotonin reuptake inhibitor. Epilepsy Behav. 2011; 22:186–190. [PubMed: 21783426]
84. Mullally J, Goldenberg I, Moss AJ, et al. Risk of life-threatening cardiac events among patients with long QT syndrome and multiple mutations. Heart Rhythm. 2013; 10:378–382. [PubMed: 23174487]
85. Yoshikane Y, Yoshinaga M, Hamamoto K, et al. A case of long QT syndrome with triple gene abnormalities: digenic mutations in KCNH2 and SCN5A and gene variant in KCNE1. Heart Rhythm. 2013; 10:600–603. [PubMed: 23237912]
86. Veeramah KR, Johnstone L, Karafet TM, et al. Exome sequencing reveals new causal mutations in children with epileptic encephalopathies. Epilepsia. 2013; 54:1270–1281. [PubMed: 23647072]
87. Epi4K Consortium; Epilepsy Phenome/Genome Project. De novo mutations in epileptic encephalopathies. Nature. 2013; 501:217–221. [PubMed: 23934111]
88. Carvill GL, Heavin SB, Yendle SC, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. Nat Genet. 2013; 45:825–830. [PubMed: 23708187]
89. Glasscock E, Qian J, Yoo JW, et al. Masking epilepsy by combining two epilepsy genes. Nat Neurosci. 2007; 10:1554–1558. [PubMed: 17982453]
90. Holth JK, Bomben VC, Reed JG, et al. Tau loss attenuates neuronal network hyperexcitability in mouse and Drosophila genetic models of epilepsy. J Neurosci. 2013; 33:1651–1659. [PubMed: 23345237]
91. Swan H, Viitasalo M, Piippo K, et al. Sinus node function and ventricular repolarization during exercise stress test in long QT syndrome patients with KvLQT1 and HERG potassium channel defects. J Am Coll Cardiol. 1999; 34:823–829. [PubMed: 10483966]
92. Fodstad H, Swan H, Laitinen P, et al. Four potassium channel mutations account for 73% of the genetic spectrum underlying long-QT syndrome (LQTS) and provide evidence for a strong founder effect in Finland. Ann Med. 2004; 36(Suppl. 1):53–63. [PubMed: 15176425]
93. Larsen LA, Andersen PS, Kanters J, et al. Screening for mutations and polymorphisms in the genes KCNH2 and KCNE2 encoding the cardiac HERG/MiRP1 ion channel: implications for acquired and congenital long Q-T syndrome. Clin Chem. 2001; 47:1390–1395. [PubMed: 11468227]
94. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. J Am Coll Cardiol. 2007; 49:240–246. [PubMed: 17222736]
95. Kapplinger JD, Tester DJ, Salisbury BA, et al. Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION long QT syndrome genetic test. Heart Rhythm. 2009; 6:1297–1303. [PubMed: 19716085]
96. Albert CM, Nam EG, Rimm EB, et al. Cardiac sodium channel gene variants and sudden cardiac death in women. Circulation. 2008; 117:16–23. [PubMed: 18071069]
97. Krahn AD, Healey JS, Chauhan V, et al. Systematic assessment of patients with unexplained cardiac arrest: cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER). Circulation. 2009; 120:278–285. [PubMed: 19597050]
98. Priori SG, Napolitano C, Schwartz PJ, et al. The elusive link between LQT3 and Brugada syndrome: the role of flecainide challenge. Circulation. 2000; 102:945–947. [PubMed: 10961955]

99. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011; 8:1308–1339. [PubMed: 21787999]
100. Iwasa H, Itoh T, Nagai R, et al. Twenty single nucleotide polymorphisms (SNPs) and their allelic frequencies in four genes that are responsible for familial long QT syndrome in the Japanese population. J Hum Genet. 2000; 45:182–183. [PubMed: 10807545]
101. Bagnall RD, Das KJ, Duflou J, et al. Exome analysis based molecular autopsy in cases of sudden unexplained death in the young. Heart Rhythm. 2014; 11:655–662. [PubMed: 24440382]
102. International League Against Epilepsy Consortium on Complex Epilepsies. Electronic address e-auea. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. Lancet Neurol. 2014; 13:893–903. [PubMed: 25087078]
103. Jeffs TC, Donner EJ. Our epilepsy story: SUDEP aware. Epilepsia. 2015; 56:9–11. [PubMed: 24754270]
104. Klassen TL, von Ruden EL, Drabek J, et al. Comparative analytical utility of DNA derived from alternative human specimens for molecular autopsy and diagnostics. J Mol Diagn. 2012; 14:451–457. [PubMed: 22796560]
105. Novy J, Belluzzo M, Caboclo LO, et al. The lifelong course of chronic epilepsy: the Chalfont experience. Brain. 2013; 136:3187–3199. [PubMed: 23824485]
106. Nashef L, Hindocha N, Makoff A. Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms. Epilepsia. 2007; 48:859–871. [PubMed: 17433051]
107. Tester DJ, Ackerman MJ. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. Circulation. 2011; 123:1021–1037. [PubMed: 21382904]
108. Zaidi A, Clough P, Cooper P, et al. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. J Am Coll Cardiol. 2000; 36:181–184. [PubMed: 10898432]
109. Viskin S, Rosovski U, Sands AJ, et al. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. Heart Rhythm. 2005; 2:569–574. [PubMed: 15922261]
110. Davis S, Westby M, Petkar S, et al. Tilt testing is more cost-effective than implantable loop recorder monitoring as a means of directing pacing therapy in people with recurrent episodes of suspected vasovagal syncope that affect their quality of life or present a high risk of injury. Heart. 2013; 99:805–810. [PubMed: 23236029]
111. Chadwick D, Jelen P, Almond S. Life and death diagnosis. Pract Neurol. 2010; 10:155–159. [PubMed: 20498188]
112. Russell AE. Cessation of the pulse during the onset of epileptic fits,: with remarks on the mechanism of fits. Lancet. 1906; 168:152–154.
113. Rugg-Gunn FJ, Simister RJ, Squirrell M, et al. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. Lancet. 2004; 364:2212–2219. [PubMed: 15610808]
114. Nashef L, Walker F, Allen P, et al. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. J Neurol Neurosurg Psychiatry. 1996; 60:297–300. [PubMed: 8609507]
115. Persson H, Ericson M, Tomson T. Heart rate variability in patients with untreated epilepsy. Seizure. 2007; 16:504–508. [PubMed: 17493840]
116. Ansakorpi H, Korpelainen JT, Suominen K, et al. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. Epilepsia. 2000; 41:42–47. [PubMed: 10643922]
117. Lossius MI, Erikssen JE, Mowinckel P, et al. Changes in autonomic cardiac control in patients with epilepsy after discontinuation of antiepileptic drugs: a randomized controlled withdrawal study. Eur J Neurol. 2007; 14:1022–1028. [PubMed: 17718695]

Key Points

- Evidence suggests likely genomic complexity and a degree of overlap among among sudden cardiac death, sudden infant death syndrome, and SUDEP
- In some genetic epilepsies, a mutation may also predispose to sudden death, whereas in acquired epilepsies, coexisting genetic variants may increase susceptibility
- For patients with epilepsy, a cardiac history and an electrocardiogram should be obtained, as well as a careful family history for sudden or unexplained deaths
- Awareness that life-threatening cardiac disorders can mimic epilepsy and that patients with epilepsy might be at increased risk of cardiac arrhythmias is needed
- Many challenges remain, and future progress requires collaborative transdisciplinary research

Table 1

Suggested minimum cardiac assessment for individuals with seizures

All patients
ECG with computer analysis
Careful history of events, specifically questioning cardiac features
Exercise-related events
Reported profound pallor at time of seizures
Family history for
Sudden unexplained, or established cardiac deaths, especially <40 years age
Sudden infant death syndrome (SIDS)
Relative with SUDEP
If any of the above, including any uncertainty
Consider ECG studies of first-degree relatives, with computer analysis
Formal specialist cardiology assessment
Consider exercise ECG and/or pharmacologic provocation
Consider implantable event recorder
Consider genetic referral for molecular genetics study including family members