The Heart of Epilepsy:

Cardiac Comorbidity and Sudden Death

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Thesis submitted to UCL for the degree of Doctor of Philosophy

2019

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Declaration

I, Sharon Shmuely, hereby declare that the work presented in this thesis is my own. The work presented here has not been submitted for another degree or qualification. Where information has been derived from other sources, I confirm that this has been indicated by referencing.

Signature: Date: 7 October 2019

Abstract

The research described in this thesis aims to increase understanding of cardiac comorbidities and sudden unexpected death in epilepsy (SUDEP). People with epilepsy have a three-fold increased risk of dying prematurely compared to the general population. Common contributors to this are cardiovascular comorbidities, of which I provide an overview. Cardiovascular conditions and epilepsy can both lead to transient loss of consciousness (TLOC) with overlapping semiology. Particularly, myoclonic jerks which are commonly observed during syncope can be mistaken for signs of epilepsy. A misdiagnosis with detrimental consequences. I provide evidence that a careful analysis of motor phenomena can distinguish the two conditions. SUDEP is the commonest direct epilepsy-related premature death (UK >500 people/year). It typically occurs following convulsive seizures (CS). Most victims are found prone and some suggested people should sleep supine. I assessed video-EEG recordings of 180 CS and demonstrated peri-ictal positions often change, and most ending prone turned during CS. Sleeping supine is thus unlikely to prevent a postictal prone position and reduce risk of SUDEP. Pathomechanisms underlying SUDEP are likely a combination of interacting cardiorespiratory and autonomic factors. People with Dravet syndrome (DS) have a particular high SUDEP risk. I show that 49% of reported deaths in DS are SUDEP cases, most <10 years (78%). In DS, *SCN1A* mutations are mostly found, encoding a sodium channel expressed in brain and heart. DS mouse models suggest a key role for peri-ictal cardiac arrhythmias in SUDEP. I conducted a multicentre observational study and recorded 547 seizures in 45 DS

participants. No major peri-ictal arrhythmias were found. Peri-ictal QTc-lengthening was, however, more common in DS than controls. This may reflect unstable repolarisation and increased propensity for arrhythmias. Prospective data to determine whether these peri-ictal variables can predict SUDEP risk is warranted.

Impact statement

In 2016 I attended the Partners Against Mortality in Epilepsy (PAME) conference where I met many people that lost a loved one to sudden unexpected death in epilepsy (SUDEP). Their devastating stories had great impact on me. The stories were filled with sadness but also frustration as many felt they were not properly informed about the possibility of SUDEP. All shared an eagerness to help improve awareness of SUDEP. I encountered this eagerness again when I started the recruitment for my clinical study. For people with Dravet syndrome (DS) and their carers, SUDEP is a fear they live with every day. They were very willing to participate, even though the study was quite taxing, involving long-term ambulatory measurements which required multiple daily actions. Their dedication made a huge impression on me. As a young researcher I can only hope that my work helps to reduce the number of people that succumb to SUDEP.

In the DS community cardiac arrhythmias are thought to play a crucial role in SUDEP. My study has provided valuable new information but the findings cannot directly help people on an individual level. As I did not find any actionable arrhythmias, there is no need for structural long-term electrocardiography (ECG) measurements in people with DS. An important role for cardiac dysfunction in SUDEP in DS, however, cannot be excluded. Mainly because I recorded nonfatal seizures and not SUDEP. I also found that substantial peri-ictal QTc-lengthening was more common in people with DS than in controls. Whether this variable can predict SUDEP should be explored in future studies.

A relevant additional finding was the large number of (likely convulsive) seizures, mostly nocturnal, which were missed by caregivers. The fact that the study was mainly in a home-based setting, in contrast to epilepsy monitoring units, makes it very useful and it touches on an important issue. It is especially notable to find this in a group of people that are watched closely and in which generally a lot of attention is paid to optimisation of seizure detection. As discussed in this thesis several studies indicated that early signalling of nocturnal convulsive seizures may decrease SUDEP risk. There clearly is an urgent need for improved seizure detection.

Acknowledgements

I would like to thank my supervisors Prof Ley Sander and Dr Roland Thijs for guiding, supporting and encouraging me during the work on these inspiring research projects. I am so grateful to have had two involved, talented teachers who were always approachable and available to answer any questions and queries.

A special thank you to all the people that worked with us on the study on Cardiac Arrhythmias in Dravet syndrome (CADS), Mr Rainer Surges, Prof Helen Cross, Mrs Amy Muggeridge, Dr Hanno Tan, Prof Sanjay Sisodiya, Dr Eva Brilstra, Dr Boudewijn Gunning and Dr Judith Vermeulen. The project would not have been possible without the great dedication and efforts of all participants with Dravet syndrome and their families and carers.

I have been fortunate to have the chance to work with and learn from Prof Gert van Dijk about data collection, scientific writing and presenting, Prof Dick Lindhout whose enthusiasm inspired me and who taught me about the genetics of epilepsy, Dr Gail Bell who supported me by critically evaluating all manuscripts I have produced related to the work in this thesis, and Prof Job van der Palen who helped out with multiple statistical challenges.

I wish to express special gratitude to my fellow PhD-student, desk mate and sparring partner Robert Helling. Your insights, support, humour, and, of course, MATLAB skills were invaluable for me and my work throughout this PhD journey.

I would like to thank all my other colleagues at the Research Department at Stichting Epilepsie Instellingen Nederland (SEIN), especially Anouk,

Evelien, Matteo and Trusjen. You created such a loving environment, where everyone helped each other when needed and we were free to say, share and ask anything. I am very grateful for my predecessors Robert Lamberts and Marije van der Lende, who taught me everything I needed to know get started on my PhD journey.

Most importantly, I am so grateful to have a family who have always supported all my goals and ambitions and helped me keep things in perspective: my parents Ella and Gil, my brother Oran, sister-in-law Rosanne, my beautiful nieces Norah and Yael, who turned my world upside down and made me realise what is most important in life, and my love Omar. With you by my side I feel only excitement for all new adventures that lie ahead.

This work would not have been possible without financial support of the “Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie” and the Dutch Epilepsy Foundation (project number 15-10).

Table of contents

Publications arising from this work

- **Shmuely S**, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: A review. *Epilepsy Behav* 2016; 64: 69-74.
- **Shmuely S**, van der Lende M, Lamberts RJ, Sander JW, Thijs RD. The heart of epilepsy: Current views and future concepts. *Seizure* 2016; 44: 176-83.
- **Shmuely S**, Surges R, Sander JW, Thijs RD. Prone sleeping and SUDEP risk: the dynamics of body positions in nonfatal convulsive seizures. *Epilepsy Behav* 2016; 62:176-9.
- Van der Lende M, **Shmuely S**, Aronica EMA, Thijs RD. Sudden unexpected death in epilepsy (SUDEP). *Tijdschr Neurol Neurochir* 2017; 118: 128-34.
- **Shmuely S**, Thijs RD, Kalitzin SN, Sander JW. Introduction. *Int J Neural Syst* 2016; 26: 1602002. Subject: Autonomous Neuro-Dynamics and its Clinical Translation: an overview.
- **Shmuely S**, Bauer PR, van Zwet EW, van Dijk JG, Thijs RD. Differentiating motor phenomena in tilt-induced syncope and convulsive seizures. *Neurology* 2018; 90: e1339-e46.
- **Shmuely S** and Thijs RD. Epilepsy and Heart Diseases. In: Mula M. The Comorbidities of Epilepsy. London, UK: Academic Press; 2019; 159-76.
- **Shmuely S**, Surges R, Helling R, Gunning WB, Brilstra EH, Verhoeven JS, Cross JH, Sisodiya SM, Tan HL, Sander JW, Thijs RD. Cardiac Arrhythmias in Dravet syndrome (CADS): an observational multicentre study. Manuscript submitted.

- **Shmuely S**, Thijs RD, Surges R. Title. Epilepsy Disorders: Seminars in Epileptology of the International League Against Epilepsy (ILAE). Manuscript in preparation.

Poster and oral presentations

- Dutch Paediatric Neurology Association (Nederlandse Vereniging voor Kinderneurologie, NVKN), annual meeting, Heemstede, the Netherlands, April 2015. Oral presentation: “Dravet syndrome: a mutation with consequences for the brain and the heart?”.
- Dravet syndrome foundation the Netherlands and Belgium conference, Heeze, the Netherlands, September 2015. Oral presentation: “Cardiac arrhythmias in Dravet syndrome”.
- Syncope and Autonomic Disorders Symposium (Werkgroep voor Syncope en Autonome Aandoeningen, WSAA), Utrecht, the Netherlands, November 2015. Oral presentation: “Myoclonic jerks and other motor signs in vasovagal syncope and convulsive seizures”.
- Scientific Research Section of the Dutch League against Epilepsy (Stichting Wetenschappelijk Onderzoek, SWO), midwinter meeting, Amsterdam, the Netherlands, March 2016. Poster presentation: "Prone sleeping and SUDEP risk: the dynamics of body positions in non-fatal convulsive seizures”.
- Partners Against Mortality in Epilepsy (PAME) Conference, Alexandria, Virginia, USA, June 2016. Poster presentations: “Mortality in Dravet Syndrome” and “Can prone sleeping increase risk of sudden unexpected death in epilepsy?”.
- 12th European Congress on Epileptology, Prague, Czech Republic, September 2016. Two presentations: 1) Oral: “Motor phenomena in vasovagal syncope: clinical aspects and comparison with convulsive seizures”, and 2) Poster: "Prone sleeping and SUDEP risk: the dynamics

of body positions in non-fatal convulsive seizures". Presentation was awarded with a 'Highly Commended Abstract Certificate'.

- Dutch Clinical Neurophysiology Association (Nederlandse Vereniging voor Klinische Neurofysiologie, NVKNF), annual meeting, Amsterdam, the Netherlands, November 2016. Oral presentation: "Motor phenomena in vasovagal syncope: clinical and electrophysiological aspects and a comparison with convulsive seizures".
- Dutch Neurology Association (Vereniging voor Neurologie, NVN), annual scientific meeting, Nunspeet, the Netherlands, November 2016. Poster presentation: "Epilepsy and syncope: a shocking comparison".
- European Federation of Autonomic Societies (EFAS) School and Meeting, Innsbruck, Austria, February 2017. Poster and oral presentation: "Motor phenomena in transient loss of consciousness: How to differentiate vasovagal syncope from convulsive seizures". Awarded a travel grand.
- Neurology Conference of the Leiden University Medical Centre (LUMC), Leiden, the Netherlands, February 2017. Oral presentation: "Motor phenomena in transient loss of consciousness: how to differentiate vasovagal syncope from convulsive seizures".
- Scientific Research Section of the Dutch League against Epilepsy (Stichting Wetenschappelijk Onderzoek, SWO), midwinter meeting, Amsterdam, the Netherlands, February 2017. Poster and oral presentation: "Motor phenomena in transient loss of consciousness: How to differentiate vasovagal syncope from convulsive seizures". Presentation was awarded with the 'Best Clinical Research Award'.

- European Academy of Neurology (EAN) Congress, Amsterdam, the Netherlands, June 2017. Oral presentation: "Differentiating motor phenomena in vasovagal syncope and convulsive seizures". A bursary for participation was granted.
- Partners Against Mortality in Epilepsy (PAME) Conference, Alexandria, Virginia, USA, June 2018. Poster presentation: “Cardiac Arrhythmias in Dravet syndrome (CADS): preliminary results”.
- 33rd International Epilepsy Congress, Bangkok, Thailand, June 2019. Poster presentation: “Cardiac Arrhythmias in Dravet syndrome (CADS)”.

List of abbreviations

AAN	American Academy of Neurology
ASM	Antiseizure Medication
AV	Atrioventricular
CI	Confidence Interval
CNS	Central Nervous System
CS	Convulsive Seizure(s), here defined as focal to bilateral tonic-clonic or generalised tonic-clonic
DS	Dravet Syndrome
ECG	Electrocardiography
EEG	Electroencephalography
EMU	Epilepsy Monitoring Unit
FNR	False Negative Rate
FPR	False Positive Rate
GEE	Generalised Estimating Equations
GGE	Generalised Genetic Epilepsy
HRV	Heart Rate Variability
ILAE	International League Against Epilepsy
IQR	Interquartile Range
LQT	Long QT
LR+/-	Likelihood Ratio, positive/negative
LUMC	Leiden University Medical Centre
MCD	Mean Consecutive Differences
NICE	National Institute of Health and Care Excellence
OR	Odds Ratio
PGES	Postictal Generalised EEG Suppression
PNES	Psychogenic Non-Epileptic Seizures

pNN50	Percentage of Consecutive RR Intervals Differing >50 ms
RMSSD	Root Mean Square of Successive Differences of RR Intervals
S	Slow EEG pattern (in syncope)
SD	Standard Deviation
SFS	Slow Flat Slow EEG pattern (in syncope)
SDNN	Standard Deviation of RR Intervals
SE	Status Epilepticus
SEIN	Stichting Epilepsie Instellingen Nederland
SIDS	Sudden Infant Death Syndrome
SMEB	Severe Myoclonic Epilepsy of Infancy Borderline
SMEI	Severe Myoclonic Epilepsy of Infancy
SMR	Standardised Mortality Ratio
SUDEP	Sudden Unexpected Death in Epilepsy
TLOC	Transient Loss of Consciousness
VF	Ventricular Fibrillation
VNS	Vagus Nerve Stimulation
VT	Ventricular Tachycardia

List of tables

List of figures

Figure 12. The 3-lead ECG vest and a textile electrode.

Figure 13. Study flow chart.

Figure 14. Hours of ECG recording, total number of seizures and the proportion of unreported seizures for each subject of the Dravet syndrome group.

Figure 15. Example of how unreported seizures were detected based on the resemblance to heart rate patterns and accelerometery of reported convulsive seizures in two Dravet syndrome cases.

Figure 16. Box plots of peri-ictal heart rates in convulsive seizures of the Dravet syndrome (blue) and historical epilepsy control group (grey).

Figure 17. Heart rate curve during a convulsive seizure of a 14-year-old girl with Dravet syndrome from one minute prior to seizure onset to five minutes after seizure end.

Chapter 1 Introduction

This chapter provides an overview of the theoretical framework leading up to the research projects of this thesis. I will start with a description of the earliest mention of epilepsy and highlight important discoveries made since then. The fascinating connection between epilepsy and the heart is discussed. I will touch upon current epilepsy treatment and important aspects of disease burden. In the next part, the commonest causes of premature mortality directly and indirectly related to epilepsy are outlined. Sudden unexpected death in epilepsy (SUDEP), the most common directly to epilepsy related cause of death, will be described in detail.

1.1 Epilepsy paradigm

Epilepsy is one of the commonest brain conditions, affecting over 70 million people worldwide (Fiest *et al.*, 2017; Ngugi *et al.*, 2011; Thurman *et al.*, 2011). One of the earliest accounts was found on a Babylonian tablet, dating back to around 1,000 BC (Wilson and Reynolds, 1990). On this tablet, epilepsy is called ‘Sakkikku miqt’ (falling disease). The tablet contains a detailed description of seizures as we know them today, the aetiology, however, was ascribed to supernatural evil forces with each seizure type associated with the name of a demon or god. The belief that an attack of a demon or god caused seizures led to the introduction of the term ‘epilepsy’ by the Greek (500-400BC), meaning ‘to seize’ or ‘to attack’ (Chaudhary *et al.*, 2011). Hippocrates was the first to describe epilepsy as a brain disorder (around 400 BC) (Chaudhary *et al.*, 2011). The Hippocratic concept had, however, little influence on the prevailing supernatural view. A significant

paradigm shift occurred almost 150 years ago, when Hughlings-Jackson defined epilepsy as “a chronic disorder in which there are recurring, sudden, excessive and rapid discharges of the grey matter of some parts of the brain, the clinical manifestation of which are determined by the anatomical site in the brain of the discharge” (Hughlings-Jackson, 1876). Since then, our understanding of epilepsy has increased immensely, driven by a number of quantum leaps that have occurred mostly in the areas of diagnosis and treatment; e.g. the development and deployment of electroencephalography (EEG) as a useful tool in epilepsy (1924-1934), the systematisation of resective surgery for the treatment of epilepsy (1950s) and the application of MRI to epilepsy in the late 1980s (identifying a number of structural and functional changes associated with epilepsy) (Magiorkinis *et al.*, 2014). Despite these developments, the paradigm of epilepsy has not changed since Hughlings-Jackson’s time and variations of his definition of epilepsy are still used. The International League Against Epilepsy (ILAE) defines epilepsy as a collection of individual disorders that share an abnormal tendency to cause epileptic seizures, “the transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” (Fisher *et al.*, 2014).

Current epilepsy treatment is symptomatic: antiseizure medication (ASM) therapy, the mainstay of epilepsy treatment, serves to suppress seizures, while not affecting the underlying epileptogenic process. In up to 70% of people with newly diagnosed epilepsy, seizures are successfully controlled with ASM (Kwan and Sander, 2004; Thijs *et al.*, 2019). About 30% of people with epilepsy will continue to have seizures despite appropriate

pharmacological treatment (Brodie *et al.*, 2012). All the people with drug-resistant focal epilepsy should be screened for surgical treatment, as this is the most effective treatment (de Tisi *et al.*, 2011); seizure-freedom is achieved in 50 to 80% (Ryvlin *et al.*, 2014). Other non-pharmacological options for those refractory to ASM treatment include vagus nerve stimulation (VNS) and the ketogenic diet (Thijs *et al.*, 2019).

Disease burden in epilepsy populations is high (Murray *et al.*, 2012). Besides the paroxysmal and often unpredictable nature of seizures, people with epilepsy suffer from social stigma, psychosocial and economic (e.g. un(der)employment) problems and ASM side effects (Whiteford *et al.*, 2015). Co-existing conditions are present in the majority of people with epilepsy and form an important part of the overall burden (Forsgren, 1992; Gaitatzis *et al.*, 2012; Kadima N, 2013; Keezer *et al.*, 2016b; Yuen *et al.*, 2018).

People with epilepsy have a higher rate of somatic and psychiatric comorbidities compared to the general population; more than 50% of the people has one or several additional medical conditions (Keezer *et al.*, 2016b; Yuen *et al.*, 2018). Comorbidities affect quality of life, lead to frequent medical care visits and result in higher health-related costs (Keezer *et al.*, 2016b). Some comorbidities are up to eight times more common in epilepsy than in the general population, including migraine, dementia, depression, anxiety, autoimmune disease and heart disease (Keezer *et al.*, 2016b). The recent ILAE position paper highlighted the importance of comorbidities (Scheffer *et al.*, 2017). They advise to consider the presence of comorbidities for every person with epilepsy at every stage of

classification to enable early identification, diagnosis and appropriate management (Scheffer *et al.*, 2017).

1.2 Epilepsy and the heart

The brain and the heart are closely connected: the central autonomic nervous system signals the heart to pump and the heart, in turn, delivers oxygen-saturated blood to the whole body including the brain. Well over 100 years ago, the occurrence of asystole during an epileptic seizure was first described: “He uttered a cry and was seen to be rubbing his hands together. His pulse was immediately examined for but was not palpable” (Russell, 1906).

Since then, epilepsy has been associated with many cardiovascular conditions (Chapter 3). Cardiovascular comorbidities are common contributors to the morbidity and premature mortality in people with epilepsy (Keezer *et al.*, 2016b). Seizures can, for instance, affect the function of the autonomic nervous system and may cause cardiac arrhythmias. Epilepsy and cardiac conditions may also share a genetic underlying cause. Several ion channels are present in the brain and in the heart. Mutations in the genes encoding these ion channels, so called “cardiocerebral channelopathies”, may lead to seizures and cardiac arrhythmias.

Another connection between epilepsy and the heart is that both can lead to episodes of transient loss of consciousness (TLOC) with overlapping semiology. TLOC is a common clinical presentation, affecting up to half the population at some point in their lives (Moya *et al.*, 2009; National Institute for Health and Care Excellence, 2017). TLOC is defined as a spontaneous

loss of consciousness for a short period of time (minutes at most) with complete recovery (National Institute for Health and Care Excellence, 2017). Causes of TLOC span a range of clinical specialities and can be either traumatic (concussion) or non-traumatic. The most common causes of non-traumatic TLOC are convulsive seizures (CS), syncope, or psychogenic non-epileptic seizures (PNES) (Reuber *et al.*, 2016). Throughout this work I will use the term CS for focal to bilateral tonic-clonic and generalised tonic-clonic seizures. Vasovagal reflex syncope is by far the most common cause of non-traumatic TLOC, with an estimated 30-40% of people experiencing one or more episodes in their lifetime (Moya *et al.*, 2009). An obstacle when studying these events is that syncope is easily mistaken for epilepsy.

Misdiagnosis is a major problem in epilepsy (Xu *et al.*, 2016). Rates of misdiagnosis vary from 20 to 40% in most of the reported cohorts with well described diagnostic tools and availability of at least video and EEG (in epilepsy centres, tertiary hospitals and tilt-table test or implantable electrocardiography (ECG) centres) (Xu *et al.*, 2016). A misdiagnosis of epilepsy has severe consequences, including driving and employment restrictions, and side effects of unnecessary treatment. Accurately distinguishing the different causes of TLOC is vital to allow appropriate management and identification of patients at risk of morbidity and mortality from different underlying conditions (Moya *et al.*, 2009; National Institute for Health and Care Excellence, 2017; Reuber *et al.*, 2016).

Syncope is the commonest imitator (in 53% of the cases) (Xu *et al.*, 2016). Which is understandable, as various symptoms and signs are seen in both

conditions (Grubb *et al.*, 1991; Lempert *et al.*, 1994; van Dijk *et al.*, 2014; Zaidi *et al.*, 2000). Symptoms like jerks, tonic postures, roving eye movements and stertorous breathing are often interpreted as signs specific to epilepsy (van Dijk *et al.*, 2014). In Chapter 4, I compare motor phenomena in tilt-induced syncope and CS to aid the differential diagnosis of TLOC.

1.3 Premature mortality in epilepsy

Consistent and overwhelming evidence of premature mortality in people with epilepsy is accumulating, with up to a three-fold increase over the general population in high-income economies (Devinsky *et al.*, 2016; Fazel *et al.*, 2013; Hitiris *et al.*, 2007; Neligan *et al.*, 2011; Thurman *et al.*, 2017). The risk of sudden death in young people with epilepsy is 24 times as high when compared to the general population (Ficker *et al.*, 1998). Premature mortality is greatest in the young (20-40 years; standardised mortality ratio (SMR) 5-8) (Forsgren *et al.*, 2005; Thurman *et al.*, 2017) and even greater in low- and middle-income countries (Levira *et al.*, 2017) – in rural China the SMR even rises to over 20 (Mu *et al.*, 2011).

Risk of premature death appears to be lowest in people who attained seizure freedom (Nevalainen *et al.*, 2014). Premature death in those seizure-free, however, still remains significantly higher than in the general population (Bell *et al.*, 2016; Neligan *et al.*, 2011). This suggests that seizures cannot fully explain the risk of premature mortality but comorbidities may also play a role in this (Bell *et al.*, 2016).

1.3.1 Deaths indirectly related to epilepsy

Causes of indirect epilepsy-related premature mortality include suicide, aspiration pneumonia, the underlying epilepsy cause and comorbidities (Table 1). The risk of suicide was significantly elevated in people with epilepsy compared to the general population (Fazel *et al.*, 2013) and may account for about 5% of all deaths (Bell *et al.*, 2009). People with epilepsy and a comorbid psychiatric disease had the highest risk of suicide, even after adjusting for socioeconomic factors (Christensen *et al.*, 2007). Psychiatric conditions known to increase suicide risk in people with epilepsy include depression, impulsivity, psychosis and substance abuse (Fazel *et al.*, 2013; Granbichler *et al.*, 2015; Jones *et al.*, 2003; Singhal *et al.*, 2014). Incidence of psychiatric illness correlates with duration and severity of epilepsy (Devinsky *et al.*, 2016; Fazel *et al.*, 2013).

People with epilepsy also have increased risk of death due to pneumonia compared to control populations (Cockerell *et al.*, 1994; Granbichler *et al.*, 2015; Neligan *et al.*, 2011). Several possible explanations for this increased risk exist, including aspiration pneumonia resulting from seizures. If a seizure causes aspiration pneumonia and this leads to death it may be ignored that epilepsy initiated the fatal chain of events (Cockerell *et al.*, 1994; Granbichler *et al.*, 2015). People with epilepsy may also be prone to aspiration due to their underlying condition.

Three quarters of deaths within one year after epilepsy onset are a direct consequence of the underlying epilepsy cause in structural epilepsy (Keezer *et al.*, 2016a; Loiseau *et al.*, 1999). People with epilepsy aetiologies categorized as structural or metabolic, carry a higher risk of premature

mortality compared to those with genetic generalised or unknown aetiology (Thurman *et al.*, 2017). Specific causes within the structural or metabolic categories indicate an especially high risk, like brain tumours, stroke, and static or progressive acquired encephalopathies (Thurman *et al.*, 2017).

Comorbidities are important predictors of premature mortality in epilepsy and are the cause of the vast majority of deaths (Keezer *et al.*, 2016b). Cardiovascular comorbidities, together with neoplasm and cerebrovascular disease, are the most common causes of epilepsy-related deaths (Keezer *et al.*, 2016b).

1.3.2 Deaths directly related to epilepsy

Important causes of death directly attributable to epilepsy or seizures include SUDEP (Chapter 2.3), status epilepticus (SE), drowning and accidents (Table 1) (Devinsky *et al.*, 2016; Fazel *et al.*, 2013).

SE has a high mortality rate (10-20%) and accounts for up to 10% of epilepsy-related deaths (Neligan and Shorvon, 2010). Traditionally, SE was defined as a seizure lasting 30 minutes or more, but at this stage treatment may be too late to prevent serious consequences including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits (Lowenstein, 1999). That is why the ILAE altered the SE definition in 2015 by adding an operational time dimension (seizure duration of 5 minutes) at which time emergency treatment should be started (Trinka *et al.*, 2015). The most reliable clinical determinants for prediction of poor outcome include older age (>65 years), acute aetiologies (e.g. postanoxic SE), impairment

of consciousness, increased SE duration (more than one hour) and nonconvulsive SE (Sutter *et al.*, 2013).

Fatal accidents are a major cause of death in people with epilepsy (Fazel *et al.*, 2013; Forsgren *et al.*, 2005; Thurman *et al.*, 2017). Most accidents are likely to be seizure-related (van den Broek *et al.*, 2004). Especially high-risk estimates were found for drowning and falls (Thurman *et al.*, 2017). The risk of death by drowning is 15 to 19 times higher in people with epilepsy compared with the general population, most likely directly as a result of seizures (Bell *et al.*, 2008). A Canadian population-based study found that death rates of motor vehicle accidents are not significantly higher in people with epilepsy than that of the general population, which may be explained by strict driving restrictions (Kwon *et al.*, 2011).

Table 1. Direct and indirect epilepsy-related causes of premature mortality.

Deaths directly related to epilepsy	**References**
- Sudden unexpected death in epilepsy (Chapter 1.4)	Devinsky *et al.*, 2016; Harden *et al.*, 2017; Hesdorffer *et al.*, 2011; Massey *et al.*, 2014
- Status epilepticus	Neligan and Shorvon, 2010; Sutter *et al.*, 2013
- Drowning	Bell *et al.*, 2008; Thurman *et al.*, 2017
- Other accidents	Fazel *et al.*, 2013; Forsgren *et al.*, 2005; Thurman *et al.*, 2017; van den Broek *et al.*, 2004
Deaths indirectly related to epilepsy	
- Underlying epilepsy cause	Keezer *et al.*, 2016a; Loiseau *et al.*, 1999; Thurman *et al.*, 2017
- Comorbidities (for cardiac see Chapter 3)	Keezer *et al.*, 2016b
- Suicide	Fazel *et al.*, 2013; Bell *et al.*, 2009
- Aspiration pneumonia	Cockerell *et al.*, 1994; Granbichler *et al.*, 2015; Neligan *et al.*, 2011

1.4 SUDEP

SUDEP is the most common direct epilepsy-related premature death (Devinsky *et al.*, 2016; Massey *et al.*, 2014). In the UK at least 500 people die from SUDEP every year (Hanna *et al.*, 2002). Currently the cause of SUDEP is not known and no evidence-based preventative measures are available. SUDEP typically occurs in the aftermath of a CS and those with refractory epilepsy and high CS frequency are at highest risk (Harden *et al.*, 2017; Hesdorffer *et al.*, 2011). SUDEP is likely heterogeneous regarding underlying mechanisms and multiple factors that influence each other appear to play a role.

1.4.1 Definition

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in a person with epilepsy, with or without evidence for a seizure and excluding documented SE, and in whom post-mortem examination does not reveal a toxicological or anatomical cause of death (Nashef *et al.*, 2012). When all these criteria are met, death can be classified as ‘definite SUDEP’, whereas the term ‘probable SUDEP’ is used when there is sufficient evidence regarding the circumstances of the death, but post-mortem examination is lacking (Nashef *et al.*, 2012). If a concomitant condition other than epilepsy is identified that may have contributed to death this is described as ‘definite SUDEP plus’ or ‘probable SUDEP plus’ (Nashef *et al.*, 2012). In ‘possible SUDEP’ there a competing cause of death is identified, for example aspiration (Nashef *et al.*, 2012). ‘Near-SUDEP’ can be used when a person with epilepsy survives resuscitation for more than an hour after cardiorespiratory arrest and no structural cause can be identified (Nashef *et al.*, 2012).

1.4.2 Epidemiology

As previously mentioned, people with epilepsy are 24 times more at risk of dying suddenly compared to the general population (Ficker *et al.*, 1998). This is mainly attributed to SUDEP. A peak incidence of SUDEP between the age of 15 and 40 years has often been reported (Sillanpaa and Shinnar, 2010; Tellez-Zenteno *et al.*, 2005b). This age peak, however, was not demonstrated in two recent population-based studies (Keller *et al.*, 2018; Sveinsson *et al.*, 2017). Due to the young age at death it is the second leading neurological cause of total years of potential life lost after stroke

(Thurman *et al.*, 2014). In the UK at least 500 people die from SUDEP every year (Hanna *et al.*, 2002).

The American Academy of Neurology (AAN) published SUDEP guidelines, including a review of the incidence (Harden *et al.*, 2017). Based on the analysis of 12 Class I studies, risk of definite or probably SUDEP was estimated at 1.2 per 1,000 person-years in adults and 0.22 per 1,000 person-years in children (Harden *et al.*, 2017). The two previously mentioned population-based studies, however, have since reported SUDEP rates of 1.11 per 1,000 patients-years in children, comparable to those in adults (Keller *et al.*, 2018; Sveinsson *et al.*, 2017).

The incidence of SUDEP greatly depends on the population. Highest incidence rates of up to 9.3 per 1,000 person-years are reported in candidates for epilepsy surgery or those who continue to have seizures after surgery (Shorvon and Tomson, 2011). By contrast, lowest incidence, varying from 0.1 to 0.4 per 1,000 person-years, is reported from unselected cohorts or incident cases of epilepsy (Shorvon and Tomson, 2011). A study extrapolating from population-based and case-control studies suggested that people with frequent CS may suffer a risk of up to 18 per 1,000 person-years (Ryvlin *et al.*, 2013b). Incidence thus strongly correlates with epilepsy severity (Shorvon and Tomson, 2011; Sillanpaa and Shinnar, 2010; Surges *et al.*, 2009). As epilepsy is often a chronic disease, the risk can increase considerably: up to 12% in people with refractory epilepsy after 40 years follow-up (Sillanpaa and Shinnar, 2010).

The evidence for a difference in aetiology distribution in SUDEP cases is contradicting (Harden *et al.*, 2017). One study found no differences in aetiology distribution between SUDEP cases and controls (Lhatoo *et al.*, 2010). A second study found no differences in SUDEP rates when comparing unknown and genetic aetiologies with other types of epilepsy, and when comparing structural with other epilepsies (Aurlien 2012). Generalised genetic epilepsy (GGE) was associated was a lower SUDEP risk in a case-control study (Hesdorffer *et al.*, 2011). Another study contradicts these findings and reports that not having a localisation-related epilepsy is associated with an increased SUDEP risk (Sillanpaa and Shinnar, 2010). It is, therefore, yet unclear whether an epilepsy aetiology is associated with SUDEP (Harden *et al.*, 2017).

The rate of autopsy is a critical factor in determining the incidence of definite SUDEP. Studies based on death certificates are well known to underestimate death due to epilepsy, leading to a likely substantial underreporting of epilepsy deaths (Bell *et al.*, 2004; Devinsky *et al.*, 2017; Thurman *et al.*, 2014). When someone is found dead with signs of a seizure and no definite diagnosis can be made these deaths may have been classified as ‘epilepsy (not otherwise specified)’ or ‘status epilepticus’, even though the length of the seizure is not known. The most likely alternative, SUDEP (Thurman *et al.*, 2014), may not always be reported, as a post-mortem examination is often not performed. Results from death certificate studies should thus be interpreted with caution.

1.4.3 Dravet syndrome

One group with a particular high risk of SUDEP are people with Dravet syndrome (DS), a severe childhood-onset developmental epileptic encephalopathy (Chapter 5 and 6). In over 70% of people with DS heterozygous loss-of-function mutations are found in the *SCN1A* gene, encoding for the α-subunit of neuronal voltage-gated sodium channel Nav1.1 in the mammalian brain and heart (Depienne *et al.*, 2009; Djemie *et al.*, 2016; Marini *et al.*, 2007). Not only DS but also other so called 'cardiocerebral channelopathies' are known to have features related to both organs that may lead to sudden death – e.g. mutations in *SCN5A* have been linked to epilepsy and long QT (LQT) syndrome (Heron *et al.*, 2010; Parisi *et al.*, 2013). Mouse models support the strong association between DS and SUDEP (Auerbach *et al.*, 2013; Cheah *et al.*, 2012; Kalume *et al.*, 2013; Yu *et al.*, 2006) and also reported episodes of bradycardia progressing to asystole and death (Auerbach *et al.*, 2013; Kalume *et al.*, 2013; Kim *et al.*, 2018). These reports suggest that the mutation not only alters cortical excitability but may also increase the propensity to arrhythmias (Auerbach *et al.*, 2013; Cheah *et al.*, 2012; Kalume *et al.*, 2013; Yu *et al.*, 2006). Peri-ictal ECG recordings in people with of DS were subject of the study described in Chapter 6. Understanding mechanisms specific to DS could lead to better prediction of SUDEP risk and pave the way for the development of effective preventative measures.

1.4.4 Circumstances and risk factors

Most cases of SUDEP happen at night and are unwitnessed (>60%) (Ali *et al.*, 2017; Kloster and Engelskjon, 1999; Lamberts *et al.*, 2012; Langan *et*

al., 2000, 2005; Nashef *et al.*, 1998; Ryvlin *et al.*, 2013a). Victims are often found in a prone position in or beside their bed with signs of a recent seizure (e.g. tongue bite and urinary incontinence) (Liebenthal *et al.*, 2015; Nashef *et al.*, 1998). In Chapter 2, I will discuss the potential role of prone sleeping in SUDEP. Witness reports and recordings of SUDEP also indicate that most victims experienced a CS shortly before death (Langan *et al.*, 2000; Ryvlin *et al.*, 2013a). Witnesses typically also describe postictal breathing difficulties with cyanosis (Langan *et al.*, 2000). Recently, a large Swedish population-based series of 329 SUDEP cases confirmed all these typical circumstances (Sveinsson *et al.*, 2018). Of this cohort 71% of the people was living alone and only 14% shared a bedroom.

Case control studies have identified several risk factors for SUDEP (Harden *et al.*, 2017; Hesdorffer *et al.*, 2011). The most robust risk factor is a high frequency of CS (Harden *et al.*, 2017; Hesdorffer *et al.*, 2011; Hesdorffer *et al.*, 2012). Increasing frequencies of CS were associated with significant increased risk, when compared to people without CS: people with 1 to 2 CS per year have an OR of 3, 3 to 12 CS per year an OR of 8, those with 13 to 50 CS per year an OR of 9, and those with more than 50 CS per year an OR of 15 (Hesdorffer *et al.*, 2011).

Having nocturnal seizures appears to increase SUDEP risk further (Lamberts *et al.*, 2012). Additionally, the absence of nocturnal supervision is associated with an increased risk of SUDEP (Langan *et al.*, 2005; Nashef *et al.*, 1995; van der Lende *et al.*, 2018). It is likely that, conversely, nocturnal supervision is associated with decreased SUDEP risk. A case-control study of 154 cases and 530 controls showed that sleeping with a roommate (OR

0.4) or the presence of a baby monitor (OR 0.1) reduces SUDEP risk (Langan *et al.*, 2005). When comparing SUDEP incidence between two tertiary epilepsy centres that used different degrees of supervision the centre with lowest level of supervision had a significantly higher SUDEP rate (van der Lende *et al.*, 2018). These findings imply that early signalling of a nocturnal CS could potentially prevent SUDEP.

The increased nocturnal incidence of SUDEP is often attributed to an increased risk during sleep. Several studies found that most SUDEP cases were sleep related (Ali *et al.*, 2017; Lamberts *et al.*, 2012; Ryvlin *et al.*, 2013a). There are, however, several factors that may attribute to the occurrence of SUDEP at night (Purnell *et al.*, 2018). In addition to physiological changes related to the sleep-wake state and the circadian rhythm, seizures that occur during night are more likely unwitnessed and people are more likely to be in a prone position in bed after a CS (Purnell *et al.*, 2018).

SUDEP appeared more frequent amongst those with a higher number of ASM (Hesdorffer *et al.*, 2012). This association, however, was not significant when accounting for CS frequency (Hesdorffer *et al.*, 2012). This is underscored by a meta-analysis of 112 randomised controlled trials on ASM use in epilepsy, suggesting a sevenfold increased risk for SUDEP in those using a placebo (Ryvlin *et al.*, 2011). Thus, trying to achieve seizure freedom seems more important than limiting the number of ASM. An increased SUDEP risk due to lamotrigine use in women was suggested (Aurlien *et al.*, 2012; Hesdorffer *et al.*, 2011). I believe this is most likely an indirect effect of lamotrigine. This ASM is often chosen due to limited

teratogenicity, while it is not always the optimal treatment in the context of GGE. The association between lamotrigine and SUDEP, again, disappeared when taking CS frequency into account (Hesdorffer *et al.*, 2012).

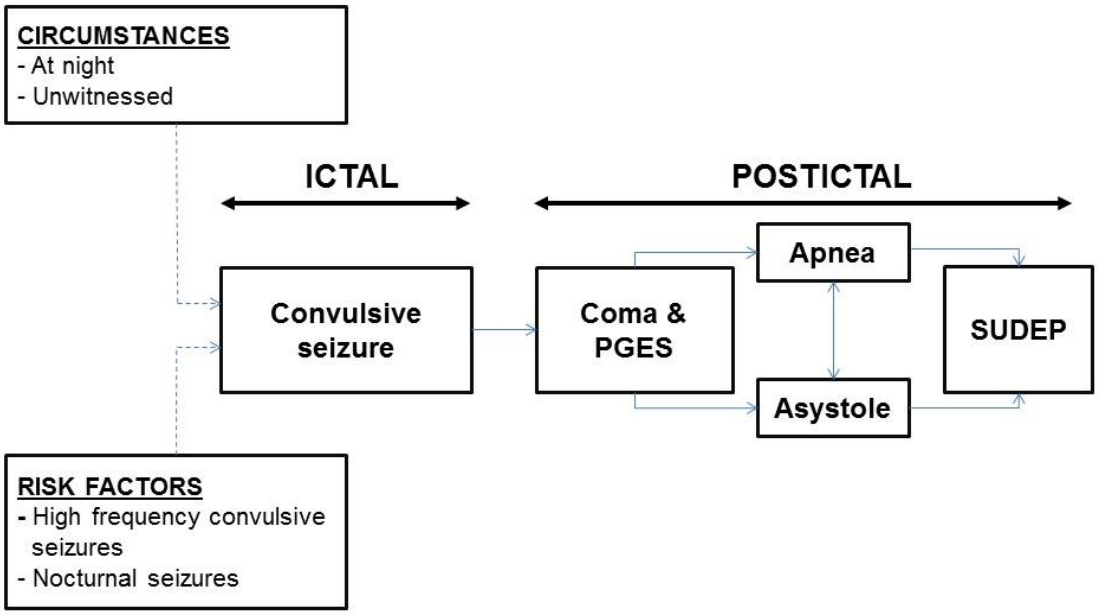
Other risk factors for which low evidence exists are intellectual disability, extratemporal epilepsy, anxiolytic drug use and the male sex (Harden *et al.*, 2017; Hesdorffer *et al.*, 2011). Insufficient evidence exists to determine whether an association exists between SUDEP risk and a long epilepsy duration and a young age at epilepsy onset (Harden *et al.*, 2017; Hesdorffer *et al.*, 2011).

1.4.5 Pathophysiology

Underlying pathology has not yet been completely elucidated but several interacting (pathological) mechanisms appear to play a role in the fatal cascade of events that lead to SUDEP (Figure 1). A few SUDEP cases were recorded during video-EEG registration, providing important insights into the underlying pathophysiology. The MORTEMUS study describes 11 recordings of SUDEP cases in epilepsy monitoring units (EMU) (Ryvlin *et al.*, 2013a). The low number of recordings seems contradictory to the high incidence of SUDEP in therapy resistant epilepsy. This finding, however, illustrates again that SUDEP mostly occurs in situations with little supervision: more often at home than in the hospital and mostly unwitnessed (Lamberts *et al.*, 2012; Sveinsson *et al.*, 2018). All 11 cases showed a comparable pattern of events: all had a CS and after seizure termination the EEG flattened completely, a phenomenon called postictal generalised EEG suppression (PGES) (Ryvlin *et al.*, 2013a). In all cases

PGES was followed a short period characterised by tachypnoea and tachycardia, and then a transient disruption of respiratory and cardiac activity. Apnoea always occurred within 3 minutes after the end of the seizure and terminal apnoea within 11 minutes, followed by cardiac arrest.

Figure 1. SUDEP model: circumstances, risk factors and underlying mechanisms.



PGES = postictal generalised EEG suppression; SUDEP = sudden unexpected death in epilepsy.

1.4.5.1 Genetic factors

Genetic drivers underlying SUDEP risk are largely unknown but evidence of genetic susceptibility in certain cases is growing. SUDEP rates seem higher in several genetic syndromes, including DS, than in those with non-genetic causes and similar epilepsy severity (Cooper *et al.*, 2016; Hindocha *et al.*, 2008; Kawamata *et al.*, 2010; Shmuely *et al.*, 2016a; Skluzacek *et al.*, 2011). A few families have also been described, with mutations in genes

encoding ion channels, in which SUDEP occurred in multiple members (Hindocha *et al.*, 2008; Kawamata *et al.*, 2010).

Several post-mortem genetic studies showed that SUDEP-victims appeared to have more mutations in genes encoding ion-channels that are expressed in the heart and the brain (Bagnall *et al.*, 2016; Leu *et al.*, 2015; Tu *et al.*, 2011a), as well as a higher overall burden of pathogenic genetic variants (Leu *et al.*, 2015). Finding theses mutations in post-mortem material of course does not prove involvement of the mutations in SUDEP. Post-mortem analysis of DNA can yield important novel hypotheses about and provide insight into potential underlying mechanisms.

1.4.5.2 Postictal generalised EEG suppression

PGES is the most frequently reported pathophysiological phenomenon in SUDEP recordings (Bateman *et al.*, 2010; Lhatoo *et al.*, 2010; Ryvlin *et al.*, 2013a; Tao *et al.*, 2010). PGES is defined as a generalised attenuation of EEG activity of more than one second, below 10µV, immediately or within the first 30s after the end of the ictal EEG pattern (Lhatoo *et al.*, 2010). PGES is commonly seen after non-fatal seizures, especially CS (Alexandre *et al.*, 2015; Asadollahi *et al.*, 2018; Bateman *et al.*, 2010; Lamberts *et al.*, 2013b; Lhatoo *et al.*, 2010; Surges *et al.*, 2011; Tao *et al.*, 2013). Postictal unresponsiveness or immobility (i.e. postictal coma) is strongly associated with PGES (94% of CS with PGES versus only 27% after seizures without PGES) (Asadollahi *et al.*, 2018; Tao *et al.*, 2013). PGES was more common in seizures arising from sleep (Lamberts *et al.*, 2012). Since sleep is associated with the activation of inhibitory networks, this may suggest that PGES is induced by excessive neuronal inhibition.

PGES following non-fatal seizures was originally associated with a higher SUDEP risk, which appeared to increase in tandem with PGES duration in a study of 10 SUDEP cases (Lhatoo *et al.*, 2010) This association was, however, not found in later studies (Odom and Bateman, 2018; Surges *et al.*, 2011). A fourth study even found that PGES after non-fatal CS was more common in controls compared to cases that later succumbed to SUDEP (47% versus 32%) and that controls had a longer duration of PGES (49s versus 24s) (Kang *et al.*, 2017). Several reasons might explain the discrepancy between the studies: small sample sizes, the retrospective designs, difficulties in the assessment of PGES and the fact that PGES may vary from seizure to seizure within the same person (Lamberts *et al.*, 2013a). Development of automated PGES detection tools may improve the assessment of PGES (Theeranaew *et al.*, 2018).

PGES was associated with more severe ictal respiratory hypoxaemia and hypercapnia (Alexandre *et al.*, 2015; Kuo *et al.*, 2016; Moseley *et al.*, 2012; Seyal *et al.*, 2013), suggesting that ictal respiratory depression may contribute to PGES. It seems unlikely that respiratory depression is the single contributing factor, since the respiratory changes were apparent during the ictal phase and returned to normal during PGES. Early administration of oxygen, however, was associated with a lower occurrence of PGES (Alexandre *et al.*, 2015). A case report showed significant postictal hypotension which closely correlated with PGES duration (Bozorgi *et al.*, 2013). This resembles findings in vasovagal syncope and raises the possibility that cerebral hypoperfusion may account for PGES in some cases. Postictal autonomic dysregulation in CS was associated with PGES

in some studies (i.e. increased duration of PGES was associated with increased sympathetically mediated electrodermal activity response and decreased parasympathetically modulated high frequency power) (Poh *et al.*, 2012; Sarkis *et al.*, 2015) but others found no associations between PGES and postictal heart rate variability (HRV) variables (Lamberts *et al.*, 2013b).

PGES was not related to seizure duration, which renders it unlikely that PGES results from 'neuronal exhaustion' (Lamberts *et al.*, 2013b; Lhatoo *et al.*, 2010; Semmelroch *et al.*, 2012; Seyal *et al.*, 2012; Surges *et al.*, 2011). CS with PGES did have a prolonged tonic phase compared to seizures without PGES and a longer tonic phase was associated with a longer duration of PGES (Asadollahi *et al.*, 2018; Tao *et al.*, 2013). This may be explained by a more severe respiratory dysfunction during the tonic phase. Additionally, the tonic phase is driven by brainstem mechanisms (Coffey *et al.*, 1996; Jobe and Browning, 2006), which may affect postictal brainstem function. Postictal dysfunction is shown to be more pronounced in the region from which the seizure arises (Devinsky *et al.*, 1994). A spreading depolarisation in the brainstem led to irreversible cardiorespiratory dysfunction in *KCNA1*-knock-out mice (Aiba and Noebels, 2015). It is thought that the neuronal networks that produce seizures, can cause excessive postictal inhibition and can thereby suppress vital brainstem function.

It seems likely that a complex interplay of various peri-ictal factors determines whether PGES will occur. Current evidence is insufficient to

support or refute that PGES in non-fatal seizures affects the risk of SUDEP or whether it can serve as a biomarker (Harden *et al.*, 2017).

1.4.5.3 Cardiac dysfunction

Postictal asystole is highly associated with SUDEP (7 of 13 were SUDEP cases) (van der Lende *et al.*, 2016b). Contrary to ictal bradyarrhythmias which are common and were always self-limiting in reported cases, postictal bradyarrhythmias appear rare (Ryvlin *et al.*, 2013a; van der Lende *et al.*, 2016b). Human (near) SUDEP recordings have shown, just as the previously mentioned mouse model study, that postictal bradycardia is always accompanied by decreased respiratory rate and terminal apnoea always seems to precede terminal asystole (Jin *et al.*, 2017; Kim *et al.*, 2018; Ryvlin *et al.*, 2013a). Although postictal bradyarrhythmias clearly play an important role in SUDEP, they seem strongly linked to respiratory dysfunction.

Dangerous seizure-related ventricular tachyarrhythmias (VT/VF), seem rare and have been described in two SUDEP and two near-SUDEP cases (Dasheiff and Dickinson, 1986; Espinosa *et al.*, 2009; Ferlisi *et al.*, 2013; Jeppesen *et al.*, 2014). The incidence may, however, be underestimated, as those with seizure-triggered VT/VF and cardiac lesions may not always be recognized as SUDEP and can easily be diagnosed as sudden cardiac death.

The mechanism of seizure-induced VT/VF is unclear. All occurred after a CS and it is possible that CS may exert proarrhythmogenic effects by triggering the sympathetic nervous system, as reflected by the peak in

catecholamines and electrodermal activity (Poh *et al.*, 2010; Simon *et al.*, 1984). At the same time, CS may increase cardiac oxygen deprivation by inducing sinus tachycardia (Eggleston *et al.*, 2014). It has also been found that ECG-markers of sudden cardiac death such as QTc-lengthening and/or shortening (Surges *et al.*, 2010a; Surges *et al.*, 2010b) and T-wave alternans (Strzelczyk et al., 2011) are more prevalent during and after CS. Prolongation of QTc can cause potentially lethal tachyarrhythmias (i.e. torsades de pointes) (Johnson and Ackerman, 2009). Whether these ECG markers relate to SUDEP is unclear.

1.4.5.4 Respiratory dysfunction

Respiratory dysfunction seems to play a crucial role in driving the sequence of events leading to SUDEP (Ryvlin *et al.*, 2013a). Peri-ictal respiratory dysfunction is common in non-fatal seizures and can be severe. Up to 33% of seizures have peri-ictal oxygen desaturations to less than 90% and this is more likely to occur in CS (Bateman *et al.*, 2008; Moseley *et al.*, 2010). In a series of 107 CS hypoxia was even reported in 86% of the seizures (Rheims *et al.*, 2019). Severe hypercapnia may last for a long time postictally (about 20 minutes) despite normalized breathing, indicating postictal depression of carbon dioxide chemoreception (Bateman *et al.*, 2008; Kim *et al.*, 2018; Massey *et al.*, 2014). Hypoxia might result from seizure-related hypoventilation as a consequence of (central or obstructive) apnoea. A study of 101 (focal and generalised) seizures that included airflow measurements found that central apnoea or hypopnoea occurred in 50%, whereas mixed or obstructive apnoea occurred in 9% (Bateman *et al.*, 2008).

Ictal central apnoea occurred in 37% of 312 focal seizures and was more common in temporal versus extratemporal epilepsies (Lacuey *et al.*, 2018). A study investigating the incidence of ictal and postictal central apnoea in CS found that ictal apnoea occurred during the focal phase prior to CS in 40% and postictally in 22% (Vilella *et al.*, 2019). Seizures can result in ictal central apnoea by activating (descending pathways to) the lower brainstem. Electrical stimulation of the human ventromedial prefrontal, insular and temporal pole cortices, the hippocampus and amygdala can each affect brainstem cardiorespiratory control and cause respiratory arrest (Chapman *et al.*, 1950; Kaada and Jasper, 1952; Lacuey *et al.*, 2017; Nobis *et al.*, 2018). Interestingly, the apnoea could be prevented by asking the person to inhale or to breathe through the mouth (Lacuey *et al.*, 2017; Nobis *et al.*, 2018).

Obstructive apnoea due to peri-ictal laryngospasm is suggested to play a role and this is based on evidence from animal models and human cases (Lacuey *et al.*, 2018; Nakase *et al.*, 2016; Stewart *et al.*, 2017; Tavee and Morris, 2008). Experimental data suggested that fatal laryngospasm may result from seizure-triggered acid reflux (Budde *et al.*, 2018).

Pulmonary oedema might aggravate ictal hypoxaemia and is thought to play a role in SUDEP (Devinsky *et al.*, 2016; Massey *et al.*, 2014; Swallow *et al.*, 2002). The majority of SUDEP cases show moderate to severe pulmonary oedema during autopsy (233 of 326 cases, 71%) (Nascimento *et al.*, 2017). Pulmonary oedema was, however, often mild and not severe enough to cause death by itself. Further, pulmonary oedema is a common finding in autopsies of many causes of death (Wang *et al.*, 2013). Post-mortem

studies of SUDEP cases did not always consider all factors that can contribute to pulmonary oedema: the post-mortem interval (Shiotani *et al.*, 2011), intravenous fluid administration, resuscitation with chest compression and premorbid cardiopulmonary diseases (Nascimento *et al.*, 2017).

In not-fatal CS postictal pulmonary oedema is also common. In 29% of cases pulmonary oedema was found on chest x-ray obtained immediately after the seizures (Kennedy *et al.*, 2015). Longer CS are more likely to lead to pulmonary oedema (Kennedy *et al.*, 2015). Postictal pulmonary oedema is a type of neurogenic pulmonary oedema which is likely related to sympathetic activation, leading to generalised vasoconstriction and increased systematic arterial and pulmonary vascular pressure (Nascimento *et al.*, 2017). In rare cases peri-ictal laryngospasm may lead to negative pressure pulmonary oedema as the inspiratory effort increases pulmonary capillary pressure (Umbrain and Camu, 1993). Pulmonary oedema alone is unlikely to cause SUDEP but it may be a contributing factor in some cases (Nascimento *et al.*, 2017; Rose *et al.*, 2015).

While changes in heart rate and breathing are common after CS and focal seizures, they usually do not lead to SUDEP. Postictal cardiorespiratory dysfunction might thus contribute but additional (interacting) pathophysiological mechanisms and environmental factors are required for SUDEP to occur.

1.4.5.5 Autonomic aspects

Seizures alter function of autonomic nervous system. During most seizures sympathetic activation dominates, which involves tachycardia, tachypnoea, increased blood pressure, pupillary dilatation, diaphoresis and facial flushing (Devinsky *et al.*, 2016). In CS sympathetic activation extends into the postictal phase, as elevated cerebrospinal and serum concentrations of adrenaline and noradrenaline have been reported to last more than 30 minutes (Simon, 2010). Ictal parasympathetic activation can also predominate with reduced heart and respiratory rates, increased salivation, miosis and decreased blood pressure (Devinsky, 2004). It is likely that combined sympathetic and parasympathetic activation and inhibition occur during and after individual seizures.

Decreased interictal HRV is more common in people with epilepsy compared to healthy controls (Ansakorpi *et al.*, 2000; Ferri *et al.*, 2002; Sevcencu and Struijk, 2010; Tomson *et al.*, 1998). HRV is an index of autonomic activity, with increased HRV reflecting dominance of parasympathetic over sympathetic activity, and decreased HRV reflecting a shift toward sympathetic dominance (Katona and Jih, 1975).

It has been established that decreased HRV is associated with increased risk of sudden cardiac death in general, post ischaemic stroke and post myocardial infarction populations (Dekker *et al.*, 1997; La Rovere *et al.*, 1998; Stein *et al.*, 2005; Tokgozoglu *et al.*, 1999) but the role of decreased HRV in SUDEP is unclear. Several studies of living people with epilepsy found a correlation between autonomic dysfunction and SUDEP risk factors (DeGiorgio *et al.*, 2010; Novak *et al.*, 2015), while another did not confirm

these findings (Baysal-Kirac *et al.*, 2017). Impaired HRV in epilepsy has been associated with brain stem atrophy particularly in those with severe atrophy of the periaqueductal grey and the medulla oblongata (Mueller *et al.*, 2018). A recent post-mortem study demonstrated alterations in medullary neuronal populations in SUDEP compared with material of non-epilepsy controls (Patodia *et al.*, 2018). A retrospective case-control study of SUDEP cases and controls living with refractory epilepsy found no differences in peri-ictal HRV (Surges *et al.*, 2010a). A recent study, however, did find more severe interictal autonomic dysregulation in SUDEP cases than epilepsy controls (lower awake HRV and either extremely high or extremely low ratios of sleep-to-awake HRV) (Myers *et al.*, 2018). It is plausible that underlying autonomic dysfunction may predispose individuals to sudden autonomic failure in the setting of a seizure but direct evidence linking HRV to SUDEP is lacking.

1.5 Aims and overview thesis

The research described in this thesis aims to increase understanding of cardiac comorbidities and SUDEP. Due to the heterogeneity of SUDEP, the relative low incidence and limited availability of recordings, it is challenging to study underlying mechanisms. To increase understanding of pathophysiological hallmarks I will focus on a subgroup of people with epilepsy with a marked increased risk of SUDEP, DS.

Chapter 1: This was the introductory chapter that laid the groundwork for the subsequent chapters.

Chapter 2: The potential role of prone sleeping in SUDEP will be discussed. I will report the findings of a retrospective study of body position dynamics during CS, to shed light on the discussion of whether people should be advised to sleep non-prone.

Chapter 3: This chapter provides an overview of all cardiovascular conditions associated with epilepsy, highlighting the important cardiac contribution to the morbidity and mortality in people with epilepsy.

Chapter 4: I will assess whether it is possible to distinguish epilepsy from its commonest imitator syncope by differences in motor phenomena, that can be assessed by eyewitnesses or from (home) video recordings.

Chapter 5: Premature mortality in DS will be discussed and I present the results of my scoping review on mortality in DS, with emphasis on SUDEP.

Chapter 6: Here, I explore the role of peri-ictal cardiac arrhythmias in SUDEP in DS. I will present the results of a prospective multicentre international observational study involving long-term ambulatory ECG measurements in people with DS.

Chapter 7: In the final chapter I discuss future perspectives of epilepsy and SUDEP and provide a conclusion of the overall thesis.

Chapter 2 Prone sleeping: a risk factor for sudden death?

2.1 Introduction

The majority (73%) of reported SUDEP cases was found in the prone position (Liebenthal *et al.*, 2015). In view of a possible association between this body position and SUDEP, it has been debated whether prone sleeping increases SUDEP risk (Dworetzky and Schuele, 2015; Sethi, 2015; Shankar *et al.*, 2013). Due to similarities with sudden infant death syndrome (SIDS) a 'back-to-sleep' campaign to prevent SUDEP has been promoted by some (Liebenthal *et al.*, 2015), while others argued that versive body turning rather than prone sleeping is a SUDEP risk factor (Lhatoo *et al.*, 2015).

I strongly felt it was too premature to advise people to sleep on their backs to reduce their risk of SUDEP. A few important steps were overlooked: 1) the body position might change during sleep, 2) the body position might change during a CS. I started thinking about how I could contribute to this discussion and realised I could solve one part of the puzzle. With the retrospective video-EEG data from the EMU I could find out how the body position changes during CS.

Previous studies of non-fatal focal seizures with impaired awareness and focal to bilateral tonic-clonic seizures found that body version is common: body turning (up to 90 degrees) was found in 22 of 263 (8%) (Mercan *et al.*, 2015) and whole body version (of at least 180 degrees) in 12 of 277 (4%) epilepsy surgery candidates (Dobesberger *et al.*, 2005). Of the seizures with whole body version 76% were bilateral tonic-clonic (13 of 17 seizures)

(Dobesberger *et al.*, 2005). Whole body version was more common in people with frontal (17%) than temporal lobe epilepsy (2%; p<0.001) (Dobesberger *et al.*, 2005). These studies did not specify the exact body positions (e.g. prone position).

I, therefore, conducted a study to explore body position dynamics in non-fatal CS and assess the occurrence of the prone position. I hypothesized that the body position is dynamic during CS and that people ending prone often do not start the CS in that position.

2.2 Methods

2.2.1 Subjects

I retrospectively reviewed the video-EEG database from two tertiary epilepsy referral centres, in Bonn, Germany and Heemstede, Netherlands. The databases were described previously (Lamberts *et al.*, 2013a; Lamberts *et al.*, 2013b). Pre-surgical video-EEG reports from between 2003 and 2011 of all people aged 15 years and older were reviewed and reports mentioning one or more recorded CS were selected (Lamberts *et al.*, 2013a; Lamberts *et al.*, 2013b). Those with whom the nursing staff had a physical interaction (such as touching) in the minute prior to seizure onset and those with video recordings that did not allow assessment of body positions were excluded.

2.2.2 Collection of variables

I collected the following clinical characteristics: sex, age, epilepsy aetiology (structural or other/unknown), age at onset, duration of epilepsy, CS frequency, learning disability (yes/no) and MRI lesion (yes/no). Of each

seizure I noted the state of wakefulness before seizure onset (awake/asleep), localisation of EEG seizure onset (temporal/extratemporal), duration of convulsive phase (s; i.e. tonic and clonic phase), PGES >20 s (yes/no) and the time between seizure onset and nursing intervention (s).

I scored all body positions from seizure onset to offset and related the timing to the CS phase. In case of uncertainty I consulted experienced neurologists (Roland Thijs and Rainer Surges) to reach consensus. I recorded body position data until a physical nursing intervention occurred. Body positions were categorized as: prone, supine, right or left lateral, sitting and standing (Table 2).

Table 2. Body position categories.

Prone	Lying on the front, upper body lifted less than 45° from horizontal plane and angle between shoulders and horizontal axis <45
Supine	Lying on the back, upper body lifted less than 45° from horizontal plane and angle between shoulders and horizontal axis <45°
Lateral	Right or left lateral; angle between shoulders and horizontal axis >45° and <135° and upper body lifted less than 45° from horizontal plane
Sitting	Angle between upper body and horizontal axis >45° and <135°
Standing	Standing or walking

2.2.3 EEG evaluation

Conventional scalp EEG recordings (International 10-20 System) (Stellate Harmonie, Stellate Systems, Montreal, QC, Canada) were performed at a sampling rate of 200 Hz. Two clinical neurophysiologists independently assessed the EEG and noted the times of seizure onset, onset tonic and clonic phase, seizure end and presence or absence of PGES >20 s

(Lamberts *et al.*, 2013a; Lamberts *et al.*, 2013b). The start of the seizure was defined as the moment of EEG onset. The onset of the tonic phase was defined as the occurrence of bilateral continuous muscle activity obscuring EEG background activity. The onset of the clonic phase was defined as a sustained pattern of bilateral and synchronous bursts of muscle artefact (with burst intervals of ≥150 ms), and absence of muscle activity between bursts. Seizure end was defined as the time of the last muscular jerk. PGES was defined as a generalised attenuation of EEG activity below 10μV of >20 s, with onset immediately or within the first 30s after the end of the ictal EEG pattern (Lhatoo *et al.*, 2010).

2.2.4 Statistical analysis

The association between prone position during the CS and other seizure characteristics was assessed with the Mann-Whitney U test for continuous and Chi-square test for categorical variables. Only those variables with $p < 0.05$ were considered significant. Correction for multiple testing was made using the Bonferroni method. Where significant associations occurred, I corrected for the correlation between seizures in the same individual using generalised estimating equations (GEE). Statistical analysis was performed with IBM SPSS Statistics 23 (IBM Corp. Armonk, NY).

2.3 Results

One-hundred and eighty-nine CS in 92 individuals were identified. Six CS were excluded as there was a physical interaction prior to seizure onset and three as the video did not allow assessment of body position. After

exclusions, 180 CS in 90 individuals remained. Most had a focal onset (n=171, 95%). Clinical and seizure characteristics are shown in Table 3.

Table 3. Clinical and seizure characteristics of the prone and non-prone group.

Seizure characteristics	**Prone (n = 16)[1]**	**Non-prone (n = 164)**	**All (n = 180)**	**P-value**
Arisen from sleep, n (%)	14 (88)	102 (62)	116 (64)	0.044
Ictal EEG onset, n (%) • Temporal • Extratemporal	 13 (81) 3 (19)	 83 (51) 81 (49)	 96 (53) 84 (47)	0.019
Duration seizure (s), median (range)	97 (68-149)	93 (25-720)	93 (25-720)	0.631
Duration convulsive phase (s), median (range)	70 (34-112)	59 (11-138)	61 (11-138)	0.229
PGES >20 s, n (%)	7 (44)	72 (44)	79 (44)	0.991
Nurse intervention time (s) after onset, median (range)	48 (5-127)	48 (1-640)	48 (1-640)	0.737
Body position changed, n (%)	13 (81)	68 (42)	81 (45)	0.002*
Clinical characteristics	**Prone (n = 13)[2]**	**Non-prone (n = 77)**	**All (n = 90)**	**Test**
Sex male, n (%)	9 (69)	40 (52)	49 (54)	NA
Age at onset of epilepsy (years), median (range)	15 (3-25)	13 (0-55)	13 (0-55)	NA
Age at time of EEG (years), median (range)	25 (16-32)	34 (15-63)	32 (15-63)	NA
Duration of epilepsy (years), median (range)	11 (0-27)	19 (1-53)	18 (0-53)	NA
Epilepsy classification, n (%) • Structural • Other/unknown	 9 (69) 4 (31)	 47 (61) 30 (39)	 56 (62.2) 34 (38)	NA
Lesion on MRI, n (%)	9 (69)	44 (58)	53 of 89 (59)	NA
Frequency of CS, n (%) • 1-2 CS/year • ≥ 3 CS/year	 9 (69) 4 (31)	 33 (43) 44 (57)	 42 (47) 48 (53)	NA
Learning disability, n (%)	2 of 11 (18)	3 of 47 (6.4)	5 of 58 (8.6)	NA
Epilepsy centre, n (%) • Bonn • Heemstede	 6 (46) 7 (53.8)	 33 (43) 44 (57.1)	 39 (43) 51 (56.7)	NA

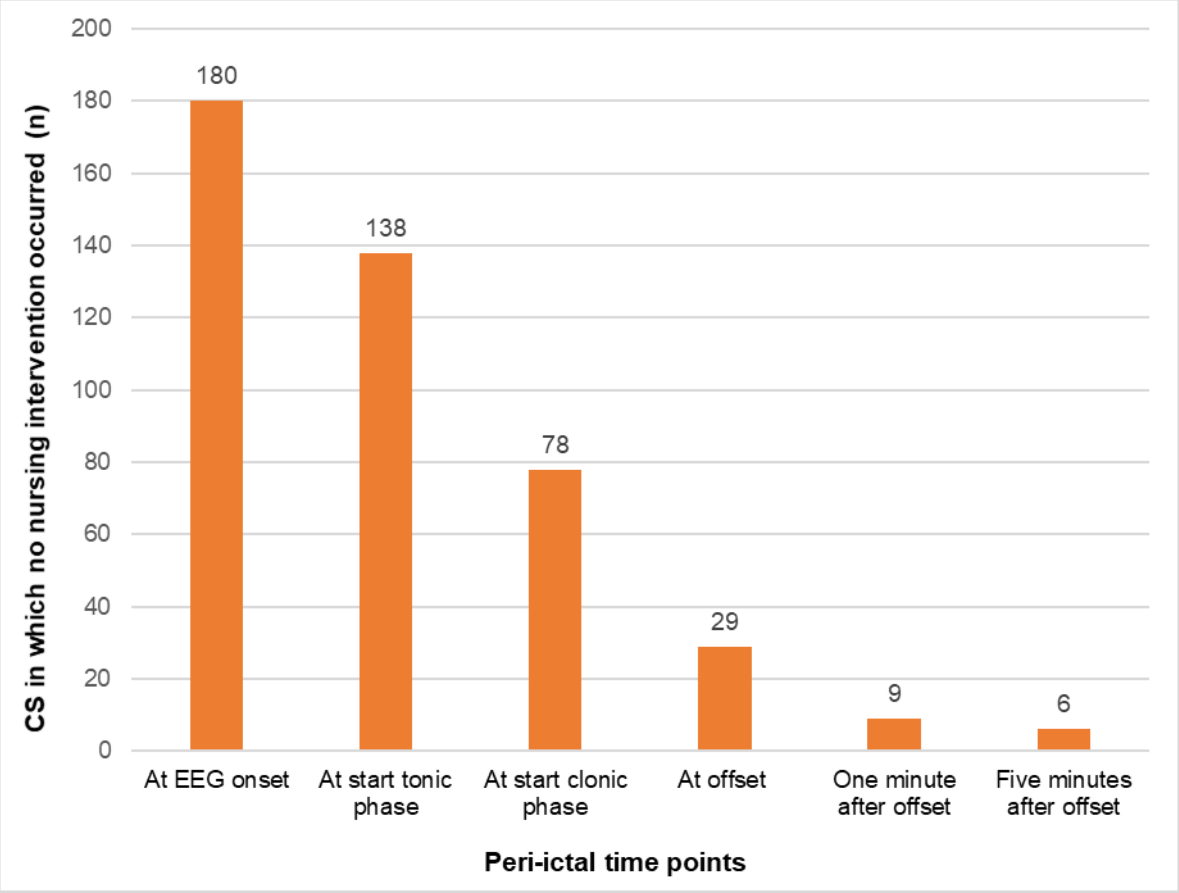
P-values based on univariate analysis. [1] Seizures in which the subjects were prone at some point; [2] Subjects who were prone at some point during at least one of the recorded seizures.

* Significance level after correction for multiple testing using the Bonferroni method p = 0.007. CS = convulsive seizure; NA = not applicable; PGES = postictal generalised EEG suppression.

2.3.1 Nursing intervention

Nearly all CS prompted the nursing staff to intervene (n=174, 97%): at the start of the clonic phase 43% (n=78) remained untouched and at offset only 16% (n=29). As a result of the nursing interventions most of the body position data are thus based on the first part of the CS (Figure 2).

Figure 2. Number of convulsive seizures in which no physical nursing intervention has occurred at six peri-ictal time points.



CS = convulsive seizure.

2.3.2 Body position change

In 45% of all 180 CS (n=81) the body position changed spontaneously during the seizure. The most common transition was from lateral to supine (n=37). Most position changes were observed during the tonic (n=35) and focal phase (n=32). In 53% of the seizures with onset in the temporal lobe the body position changed (51 of 96 CS) and in 36% of those with an extratemporal onset (30 of 84 CS).

2.3.3 Prone position

In 16 CS (9%), in 13 people, the prone occurred (Table 4). In seven CS the subject started in the prone position (4%) and in nine they turned prone during the CS (5%). Of the seven CS in which the subjects started in the prone position, three turned to a non-prone position. In 13 CS the prone position was the final position scored. Of the seven CS starting prone four ended prone (57%) while of the 173 CS starting non-prone, nine ended prone (5%). Of all CS ending prone (n=13), most started in a non-prone position (n=9, 69%).

In seizures with the prone position, an onset in the temporal lobe was more likely (n=13, 81%) than in the non-prone seizures (n=83, 51%; p=0.019). The three extratemporal prone seizures had EEG onset in the frontal lobe. Seizures with the prone position were also more likely to arise from sleep (14 of 16, 88%) than the non-prone seizures (102 of 116, 62%; p=0.044). The differences in EEG onset location and state of wakefulness, however, were not significant after correction for multiple testing (significance level p=0.007).

During the seizures in which the subject was prone at some point, a higher rate of spontaneous body position changes was seen compared to the non-prone seizures (p=0.002), while nursing intervention did not occur sooner (p=0.7). When correcting for within-subject correlation, the difference in spontaneous body position changes remained significant (adjusted p=0.001).

In the 13 subjects with 16 prone seizures, another 15 CS were recorded in which the prone position did not occur. The body positions in these 31 CS are shown in Table 4, to show the intra-individual variability.

Table 4. Body positions during the course of all convulsive seizures of the 13 subjects who were prone at some point during at least one of the recorded convulsive seizures.

Subject	Seizure	Peri-ictal phase				
		Pre-ictal	Focal	Tonic	Clonic	Postictal
1	**1**	**P**	**P**	**P**	**P, LR**	**LR, ***
1	2	Su	Su	Su	Su, *	
1	3	LR	LR	LR	LR, *	
2	**4**	**P**	**P**	**P, RL, P**	**P, ***	
2	5	Su	Su	Su	Su, *	
3	**6**	**P**	**P**	**P**	**P, ***	
3	7	Su	Su	Su, *		
3	8	Su	Su	Su	Su, *	
4	**9**	**P**	**LR**	**LR, ***		
4	10	Su	Su, *			
5	**11**	**P**	**P**	**P**	**P, ***	
5	12	Si	Si, *			
6	**13**	**P**	**P**	**P, ***		
6	**14**	**P**	**P**	**P, LL, ***		
6	15	Su	Su	Su	Su, *	
7	**16**	**LL**	**P, ***			
7	**17**	**Su**	**P, ***			
7	**18**	**LL**	**P, ***			
7	19	Su	Si, *			
8	**20**	**LR**	**P**	**P, ***		
8	21	Su, LL	LL	LL	LL	LL, *
9	**22**	**Su**	**P, ***			
9	23	Su	Si, *			
10	**24**	**LR**	**LR**	**P**	**P**	**P, ***
11	**25**	**LR**	**LR**	**P**	**P, ***	
11	26	Su	Su	Su	Su	Su
11	27	Si	Si	Si, *		
11	28	LL	LL	LL	LL, Su, *	
12	**29**	**LL**	**LL**	**P, ***		
13	**30**	**Su**	**P, ***			
13	31	Su	Si, *			

In seven seizures the subject was prone prior to seizure onset (1, 4, 6, 9, 11, 13, and 14) and in nine they turned prone during the course of the seizure (16, 17, 18, 20, 22, 24, 25, 29, and 30). * Nursing intervention. P = prone; Su = supine; LR = right lateral; LL = left lateral; Si = sitting.

2.4 Discussion

2.4.1 Main findings

By conducting this study, I have made an important contribution to the debate surrounding the role of the prone position in SUDEP. The results

suggest that the prone position is less common in closely supervised non-fatal CS compared to SUDEP victims, strengthening the association between the prone position and SUDEP. I found that body positions vary during nearly half of the CS, which clearly demonstrates that the pre-ictal position (e.g. during sleep) should not be confused with the postictal position. In most seizures in which the subject was prone at time of nursing intervention, the subject started in a non-prone position. A high intra-individual variability of body positions was seen in subjects with multiple CS.

Although the majority of SUDEP cases are found prone (73%), peri-ictal prone position in video-EEG recorded CS occurred in only 9% in this study and even in <5% of CS in two other recent studies (Oguz Akarsu *et al.*, 2018; Wang *et al.*, 2016). This contrast is partly explained by nursing interventions preventing the prone position. This intervention may be one of the reasons why SUDEP tends to be unwitnessed, as the prone position, along with the subjects' immobility, potentially compromises ventilation.

2.4.2 Prone sleeping and SUDEP

A major obstacle in this debate is the limited body position data of SUDEP cases prior to the terminal seizure. This will remain challenging since SUDEP is mostly unwitnessed and recordings are rare and often lack details on body positions. In only 12 of 253 published SUDEP cases body position prior to death was reported (Liebenthal *et al.*, 2015). Ten of these 12 cases were found prone and most of these (6 of 10) started in a non-prone position (Lhatoo, 2015; Purves *et al.*, 1992; Ryvlin *et al.*, 2013a).

In SIDS, sleeping in a non-prone position reduces mortality (Dwyer and Ponsonby, 2009). An important difference between SUDEP and SIDS is the cause of the immobility: new-born infants are not able to change body position during normal sleep. In people with epilepsy body movement is only beyond voluntary control during the seizure itself or postictally when unconsciousness prevents the subject arousing if hypoxia occurs (Semmelroch *et al.*, 2012). The effects of CS on body position and postictal recovery seem of greater importance than body position prior to the CS.

2.5 Limitations

A major, but inevitable, limitation of this study is that very little information is available on the positions at the end of the seizure, as all seizures are witnessed and there is nursing intervention before the end of the seizure in most. If CS without intervention could have been studied, the proportion of CS in which the subject turns to another position, including from and to the prone position, would have likely been higher.

It could be argued that the hospitalisation may have biased the results because of sleep disturbances or altered sleep behaviour. This effect seems to be minor as the proportion of cases sleeping prone prior to CS (4%) was quite similar to the figures obtained in a population and home-based study (9%) (Sahlin *et al.*, 2009).

I could not retrieve information about the exact seizure onset locations of all cases. This was due to privacy rules for the data from Bonn and because some of the older reports were not available anymore. I did find that all prone seizures with an extratemporal onset were frontal, but could not assess

whether frontal onset seizures were more likely to turn prone, as previously demonstrated (Dobesberger *et al.*, 2005). A recent study of 16 cases with ictal prone turning found no consistent single localising value and prone turning was seen in medial frontal, lateral frontal and lateral temporal onset seizures (Arain *et al.*, 2019). Location within the lobes thus also matters. Such precise localization is not always feasible with scalp EEG recordings.

2.6 Conclusion

The validity of a back-to-sleep campaign for people with epilepsy remains unproven. It is unknown whether an initial prone sleeping position could contribute to SUDEP risk. I believe the focus should lie on preventing a postictal prone position after a CS, when the people are immobile and have impaired arousal.

Chapter 3 Cardiac conditions associated with epilepsy

3.1 Introduction

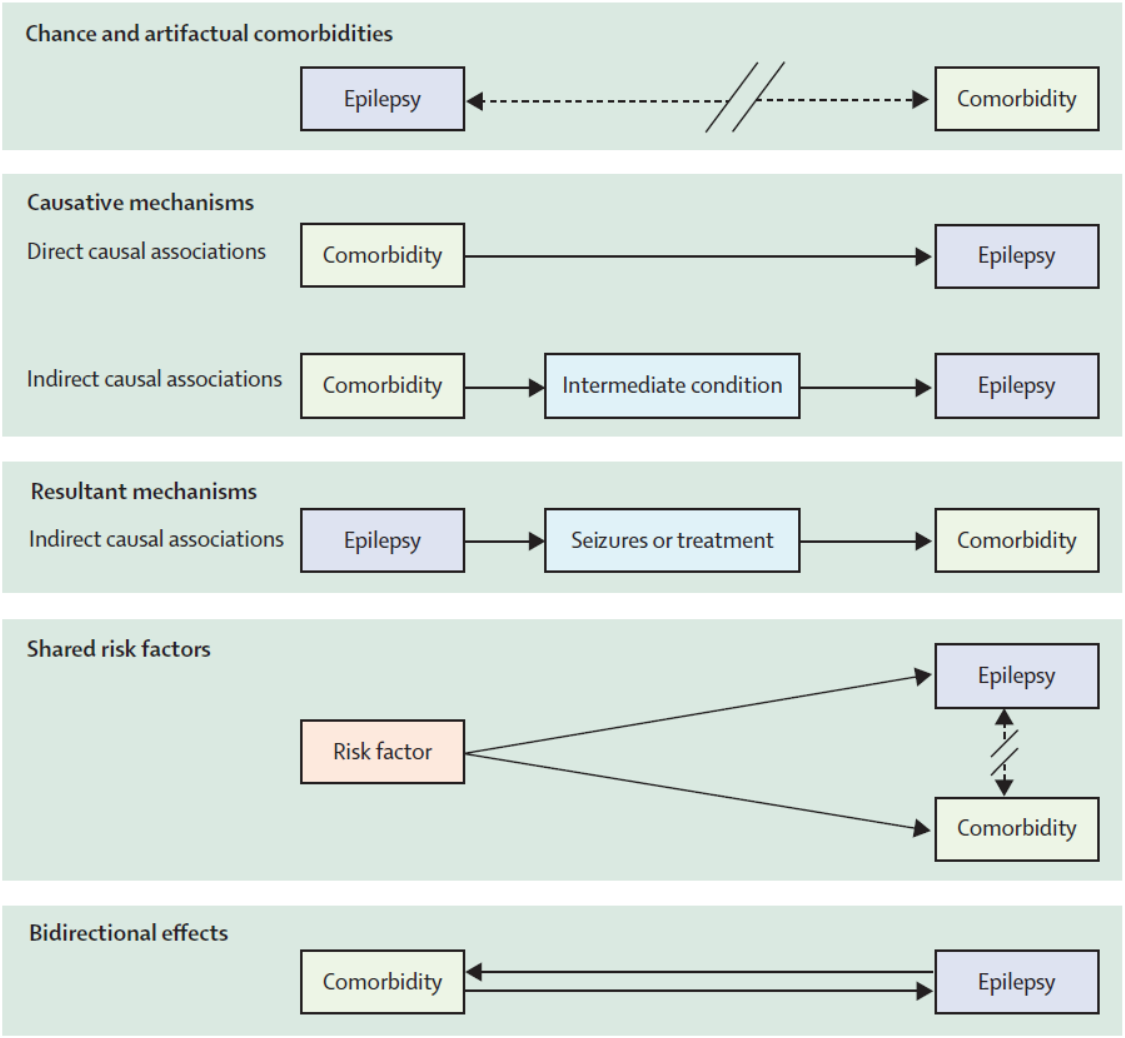
Since the first description of ictal asystole (Russell, 1906) numerous associations between epilepsy and cardiovascular conditions have been identified. Here, I discuss the intriguing borderland between epileptology and cardiology and focus on the major developments over the last 25 years.

3.2 Methods

I conducted an electronic literature searches using the PubMed database using a combination of Medical Subjects Headings (MeSH) terms and keywords to describe epilepsy and cardiac conditions. The searches were conducted in June 2016. A systematic search was performed for the search of peri-ictal cardiac arrhythmias in July 2013 (Appendix 2 and Table A1) (van der Lende et al., 2016b). All searches were updated in April 2019. Reference lists of relevant articles were screened for additional cases.

I used a comorbidity framework to review cardiac conditions known, and alleged, to be linked to epilepsy (Figure 3) (Gaitatzis *et al.*, 2012; Keezer *et al.*, 2016b). This framework describes several mechanisms of association between epilepsy and comorbid conditions: associations can be explained by cause or effect, a shared risk factor may cause both conditions, or the mechanism of the association is unknown or spurious (i.e. coincidental) (Gaitatzis *et al.*, 2012; Keezer *et al.*, 2016b). Associations with cardiac arrhythmias are discussed first, followed by an overview of structural cardiac conditions related to epilepsy.

Figure 3. Mechanisms of association between epilepsy and comorbid conditions.



Arrows with a solid line represent causal associations and arrows with dashed lines represent non-causal associations. Figure originates from (Keezer *et al.*, 2016b), permission to reproduce copyrighted material granted by Elsevier.

3.3 Results

3.3.1 Epilepsy and cardiac arrhythmias

Various arrhythmias have been described, occurring during (ictal) or after (postictal) seizures (Table 5). Sinus tachycardia is the most common ictal ECG pattern, seen in up to 80% of all seizures (Sevcencu and Struijk, 2010)

and in 82% of people with epilepsy (Eggleston *et al.*, 2014), but usually without symptoms. The most frequent clinically relevant arrhythmia is ictal asystole, occurring in 0.32% of people with refractory focal epilepsy admitted for video-EEG (van der Lende *et al.*, 2016b).

Clinically, ictal asystole (i.e. sinus arrest of ≥3s) is characterised by sudden loss of tone during a focal seizure with impaired awareness (Schuele *et al.*, 2007). The circulatory pattern resembles vasovagal syncope with a transient, progressive and self-limiting slowing of the heart rate, sinus arrest and a decrease of blood pressure (Schuele *et al.*, 2007; Tinuper *et al.*, 2001; van Dijk *et al.*, 2014).

Ictal asystole is assumed to be benign but may cause falls and injuries due to seizure-induced syncope (Moseley *et al.*, 2011a). A person with ictal asystole can get seriously injured in these falls as they will not be able to experience any of the classical syncopal prodromal signs (e.g. blurry vision and sweating). Proper trials are lacking but retrospective studies suggest that improving seizure control may prevent ictal asystole (Bestawros *et al.*, 2015; Kohno *et al.*, 2016; Strzelczyk *et al.*, 2011). It also seems advisable to withdraw negative inotropic drugs and to consider the implantation of a loop recorder to monitor possible future events in individuals in whom ictal asystole has been noted. If the asystolic episodes persist and if epilepsy is refractory to treatment, cardiac pacemaker implantation should be considered to reduce the risk of trauma (Bestawros *et al.*, 2015; Duplyakov *et al.*, 2014; Moseley *et al.*, 2011a; Strzelczyk *et al.*, 2011).

Table 5. Reported (post)ictal cardiac arrhythmias.

Seizure-related arrhythmia	Reported in n cases	Associated seizure types	Reported in n cases	EEG seizure onset	Reported in n cases	SUDEP association
Ictal asystole	103	99% FIAS 1% FAS	97	46% LT 31% RT 13% BT 10% Other	80	Unlikely
Postictal asystole	13	85% FBTCS 15% FIAS	13	20% LT 60% RT 20% Other	10	Likely, accompanied or preceded by PGES and apnoea (Ryvlin *et al.*, 2013a)
Ictal bradycardia	25	100% FIAS	8	52% LT 38% RT 10% Other	21	Unlikely
Ictal AV Block	11	90% FIAS 10% FAS	10	73% LT 18% BT 10% Other	11	Unlikely
Postictal AV Block	2	100% FBTCS	2	100% RT	1	Unlikely
Atrial Fibrillation	13	46% GTCS 46% FBTCS 8% FIAS	13	33% LT 33% Gen 33% Non loc	3	Unlikely
(Post)ictal ventricular fibrillation	4	100% GTCS	4	Insufficient data	0	Probable, but in a minority of cases

AV = atrioventricular; FIAS = focal impaired awareness seizure; FAS = focal autonomic seizure; FBTCS = focal to bilateral tonic-clonic seizure; GTCS = generalised tonic-clonic seizure; LT = left temporal; RT = right temporal; BT = bitemporal; Gen = generalised; Non loc = non-localising; PGES = postictal generalised EEG suppression. For more details see (van der Lende *et al.*, 2016b).

The precise mechanism of ictal asystole is unknown. It may result from epileptic activity directly stimulating the central autonomic networks (Leung *et al.*, 2006; Sevcencu and Struijk, 2010). For example, focal stimulation of parts of the limbic system (e.g. amygdala, cingulate gyrus and insular cortex) may provoke asystole (Altenmuller *et al.*, 2004; Oppenheimer *et al.*, 1992; Pool and Ransohoff, 1949; Sevcencu and Struijk, 2010). Ictal asystole and bradycardia are indeed predominantly described in people with temporal lobe epilepsy (Table 5) (van der Lende *et al.*, 2016b). These reports unfortunately do not distinguish different onset regions within the

temporal lobe, but it seems likely that central autonomic networks of the temporal lobe are involved. An alternative mechanism for ictal asystole is that seizure-induced fright and catecholamine release (Simon *et al.*, 1984) may evoke a vasovagal response causing cardio-inhibition and vasodilation (Nilsson *et al.*, 2016).

Two more rare and dangerous cardiac arrhythmias are postictal asystole and (post)ictal VT/VF (Chapter 1.4.5.3). In contrast to ictal asystole, postictal asystole is less common and is associated with convulsive rather than focal (temporal lobe) seizures. Out of 13 reported postictal asystole cases seven died from SUDEP (van der Lende *et al.*, 2016b). Postictal asystole appears to may play a crucial role in the pathophysiology of SUDEP and seem strongly linked to respiratory dysfunction (Ryvlin *et al.*, 2013a).

Seizure induced VT/VF have, as previously mentioned, been described in only four cases and all led to either near-SUDEP or SUDEP (Dasheiff and Dickinson, 1986; Espinosa *et al.*, 2009; Ferlisi *et al.*, 2013; Jeppesen *et al.*, 2014). All VT/VF occurred directly following a CS. No cardiac lesions were found in these cases except in one of the SUDEP cases who had a prior myocardial infarction and was having chest pain during the fatal cluster of seizures (Dasheiff and Dickinson, 1986). Potential causes of VT/VF and its role in SUDEP were discussed in Chapter 1.4.5.3.

Another mechanism explaining the association between arrhythmias and epilepsy is a shared genetic risk factor. A rapidly increasing number of genes potentially linking epilepsy to cardiac arrhythmias has been identified.

Here, I discuss some relevant examples of genes predominantly known for their cardiac functions and 'epilepsy genes'.

Various genetic ion-channel mutations are thought to be expressed in the brain as well as in the heart, the cardiocerebral channelopathies, and might thus cause seizures and cardiac arrhythmias. The first reported genetic link between epilepsy and cardiac arrhythmias was the discovery of the previously mentioned cardiac sodium channel gene *SCN5A* in the brain (Hartmann *et al.*, 1999). Subsequently, more pathogenic variants in LQT gene family (i.e. *KCNQ1*, *KCNH2* and *SCN5A*) were associated with epilepsy (Anderson *et al.*, 2014; Auerbach *et al.*, 2016; Aurlien *et al.*, 2012; Heron *et al.*, 2010; Parisi *et al.*, 2013; Partemi *et al.*, 2013; Zamorano-Leon *et al.*, 2012). Mice models indicated that other, non-LQT, cardiac channelopathy genes including *RYR2* (associated with catecholaminergic polymorphic ventricular tachycardia) (Lehnart *et al.*, 2008) and *HCN1-4* (Benarroch, 2013; Ludwig *et al.*, 2003) potentially predispose to epilepsy.

As mentioned in Chapter 1, several post-mortem studies suggested that mutations in LQT and non-LQT genes are seen more often in SUDEP victims (Bagnall *et al.*, 2016; Leu *et al.*, 2015; Tu *et al.*, 2011b). As ictal recordings are lacking, it remains questionable whether the fatal events were caused by arrhythmias. The same applies to the identification of 'epilepsy genes' in the post-mortem SUDEP cohorts, with *SCN1A* being the most recognised example (Chapter 5 and 6) (Bagnall *et al.*, 2016; Leu *et al.*, 2015).

Other less well-known examples of ‘epilepsy genes’ possibly mediating SUDEP risk include *KCNA1* and *SCN8A*. *KCNA1* is expressed in the vagal nerve as well as in the brain and is associated with seizures, cardiac arrhythmias, vagal hyperexcitability and premature death in *KCNA1* null mice (Glasscock *et al.*, 2010). Mutations in this gene were found in a SUDEP case with epileptic encephalopathy and suspected cardiac arrhythmias (Klassen *et al.*, 2014).

SCN8A-related developmental and epileptic encephalopathies appear to have a high mortality with SUDEP as the main culprit (Kong *et al.*, 2015; Veeramah *et al.*, 2012). The *SCN8A* gene encodes a sodium channel which is expressed in heart and brain of mice and rats and plays a role in excitation-contraction coupling, action potential propagation, and pacemaking (Du *et al.*, 2007; Noujaim *et al.*, 2012). In a recent systematic review of 190 published and unpublished cases with pathogenic *SCN8A* variants, three of 10 deaths were classified as SUDEP (Johannesen *et al.*, 2018). They concluded *SCN8A*-related epilepsies indeed seem associated with an increased SUDEP risk as compared to the whole paediatric population with epilepsy, although to a lesser extent than DS.

I previously discussed how seizures may cause arrhythmias. Whether the converse phenomenon exists is a subject of controversy. The major complication is the fact that syncopal events are easily mistaken for epilepsy. As mentioned earlier (Chapter 1.2) the rates of misdiagnosis in epilepsy are high and syncope is the commonest imitator (Xu *et al.*, 2016). If a proper investigation is performed (e.g. ictal recording with video, heart rate, blood pressure and EEG), however, most seemingly overlapping

presentations turn out to be an isolated phenomenon of either syncope or epilepsy. Two large scale surveys of up to 2000 tilt-table tests failed to identify any adult case with syncopal-induced seizures (Blad *et al.*, 2015; Mathias *et al.*, 2001).

In children, however, a few cases have been reported with a cardioinhibitory reflex syncope followed by video-EEG documented clonic seizures (Battaglia *et al.*, 1989; Horrocks *et al.*, 2005; Stephenson *et al.*, 2004). The reason why this phenomenon only appears to affect children is unknown. It may be that the seizure threshold is lower in children (paralleling febrile seizures that also peak in childhood). Alternatively, the depth of cerebral anoxia may be more profound in children as reflected by prolonged asystolic spells. For clinical management it is important to stress that syncope-induced seizures are extremely rare and probably only affect children. The diagnosis requires an ictal video-EEG recording. While syncope may rarely trigger epilepsy, it seems that the prevalence of syncope among people with epilepsy is higher than one would expect (Schuele, 2009). This would, however, require further studies.

Several ASM, particularly those with sodium blocking properties are known to trigger conduction abnormalities or arrhythmias (Schuele, 2009). Atrioventricular (AV) conduction block is the most frequent reported complication. ST changes, Brugada-like patterns, atrial fibrillation and QTc-prolongation have also been reported but the association with ASM treatment is less well established (Al Aloul *et al.*, 2007; DeGiorgio, 2010; El-Menyar *et al.*, 2011; Feldman and Gidal, 2013; Guldiken *et al.*, 2016; Ide and Kamijo, 2007; Ishizue *et al.*, 2016; Kasarskis *et al.*, 1992; Kaufman *et*

al., 2013; Krause *et al.*, 2011; Nizam *et al.*, 2011; Randazzo *et al.*, 1995; Strimel *et al.*, 2010; Swe *et al.*, 2016; Zoneraich *et al.*, 1976). Most clinically relevant arrhythmias were related to ASM overdose. Carbamazepine is, however, known to induce AV conduction blocks at low levels; this is almost exclusively reported in elderly women (Ide and Kamijo, 2007; Kasarskis *et al.*, 1992; Takayanagi *et al.*, 1998). Rapid administration of phenytoin may also trigger sinus arrest and hypotension; elderly people and those with pre-existing heart disease seem most vulnerable to these adverse effects. Intravenous administration should, therefore, be undertaken slowly, with continuous cardiac monitoring (DeToledo *et al.*, 2001; Guldiken *et al.*, 2016; Randazzo *et al.*, 1995; Zoneraich *et al.*, 1976). The above-mentioned ASM effects do not seem to play a role in ictal arrhythmias. Nevertheless, it is important to take these effects into consideration when selecting an ASM and to monitor adverse effects closely, especially in elderly people and those with cardiovascular comorbidities (Table 6).

Table 6. Putative mechanisms of associations between epilepsy and cardiac arrhythmias.

Mechanisms of association	Conditions	References
Causal	Arrhythmias → Seizures	Battaglia *et al.*, 1989; Horrocks *et al.*, 2005; Stephenson *et al.*, 2004
Shared risk factor	Genetics → Epilepsy and arrhythmias - Important 'heart genes': *HCN1-4*, *KCNQ1, KCNH2, SCN5A, RYR2* - Important 'epilepsy genes': *SCN1A, KCNA1, SCN8A*	Anderson *et al.*, 2014; Auerbach *et al.*, 2013; Auerbach *et al.*, 2016; Aurlien *et al.*, 2009; Heron *et al.*, 2010; Bagnall *et al.*, 2016; Benarroch, 2013; Delogu *et al.*, 2011; Du *et al*., 2007; Glasscock *et al.*, 2010; Goldman *et al*., 2016; Hartmann *et al*., 1999; Johnson *et al*., 2010; Kalume *et al.*, 2013; Keller *et al.*, 2009; Kong *et al.*, 2015; Lehnart *et al.*, 2008; Leu *et al.*, 2015; Ludwig *et al.*, 2003; Noujaim *et al.*, 2012; Papale *et al.*, 2009; Parisi *et al.*, 2013; Partemi *et al.*, 2013; Postma *et al.*, 2005; Tu *et al.*, 2011a; Veeramah *et al.*, 2012; Zamorano-Leon *et al.*, 2012
Resultant	ASM → Arrhythmias - Particularly carbamazepine, phenytoin and lacosamide	Al Aloul *et al.*, 2007; El-Menyar *et al.*, 2011; DeGiorgio, 2010; DeToledo *et al.*, 2001; Feldman and Gidal, 2013; Huang *et al.*, 2018; Guldiken *et al.*, 2016; Ide and Kamijo, 2007; Kasarskis *et al.*, 1992; Kaufman *et al.*, 2013; Krause *et al.*, 2011; Nizam *et al.*, 2011; Randazzo *et al.*, 1995; Takayanagi *et al.*, 1998;

		Strimel *et al.*, 2010; Swe *et al.*, 2016; Zoneraich *et al.*, 1976
	Seizures → Arrhythmias - Ictal: tachycardia, asystole, bradycardia and AV block. - Postictal: asystole, AV block, atrial flutter or fibrillation and ventricular fibrillation.	Bardai *et al.*, 2012; Chaila *et al.*, 2010; Eggleston *et al.*, 2014; Lanz *et al.*, 2011; van der Lende *et al.*, 2016b; Sevcencu and Struijk, 2010

HRV = heart rate variability; VT = ventricular tachycardia; VF = ventricular fibrillation; ASM = antiseizure medication.

3.3.2 Epilepsy and structural cardiac conditions

Epidemiological studies have consistently shown that people with epilepsy have a higher prevalence of structural cardiac disease than those without (Elliott *et al.*, 2009; Kadima N, 2013; Keezer *et al.*, 2016b; Kobau *et al.*, 2008; Strine *et al.*, 2005; Tellez-Zenteno *et al.*, 2005a). Cardiovascular disease seems to be a significant contributor to the increased mortality in people with epilepsy, compared with the general population (Ding *et al.*, 2006; Janszky *et al.*, 2009; Neligan *et al.*, 2011).

Shared cardiovascular risk factors can account for the relationship between epilepsy and heart disease, in addition to shared genetics and etiological factors. People with epilepsy are more likely to be obese, physically inactive and current smokers (Kobau *et al.*, 2008), and have a worse cardiovascular risk profile (i.e. hypertension, hypercholesterolemia, diabetes mellitus, stroke or transient ischaemic attack) than the general population (Centers for Disease Control and Prevention, 2013; Elliott *et al.*, 2008; Gaitatzis *et al.*, 2004; Kobau *et al.*, 2008). Unsurprisingly, people with epilepsy have higher rates of fatal and nonfatal cardio- and cerebrovascular disease than

controls (mortality ratios up to 5.3 and morbidity ratio up to 7) (Cockerell *et al.*, 1994; Gaitatzis *et al.*, 2004; Nilsson *et al.*, 1997). The presence of cardiovascular disease (e.g. congestive heart failure and cardiac arrhythmias) was also associated with higher mortality risk in people with epilepsy (St Germaine-Smith *et al.*, 2011).

Epilepsy treatment can also contribute to a poorer cardiovascular risk profile. Use of the enzyme-inducing ASMs phenytoin or carbamazepine may lead to elevated serological vascular risk markers (e.g. total cholesterol, LDL, homocysteine), and, thus, result in accelerated atherosclerosis (Brodie *et al.*, 2013; Katsiki *et al.*, 2014; Lopinto-Khoury and Mintzer, 2010; Mintzer *et al.*, 2009). Certain ASM (e.g. valproic acid, carbamazepine) are also known to cause weight gain and increase the risk of developing non-alcoholic fatty liver disease and metabolic syndrome, leading to further deterioration of the cardiovascular risk profile (Katsiki *et al.*, 2014).

The co-occurrence of epilepsy and (congenital) heart disease, often accompanied by intellectual disability, may result from a multiple malformation syndrome (Miller and Vogel, 1999). The causes of these syndromes include known or putative genetic defects that affect the development of heart and brain. Important examples include congenital anomalies in Down's syndrome (trisomy 21) (Antonarakis *et al.*, 2004), conotruncal defects in 22q11.2 deletion syndromes (Kobrynski and Sullivan, 2007) and cardiac rhabdomyoma in tuberous sclerosis (*TSC1* and *TSC2* mutations) (Curatolo *et al.*, 2008). Abnormal cardiovascular function in people with congenital heart disease may also lead to poor (intrauterine)

brain growth and, consequently, developmental and neurological (e.g. epilepsy) disorders (Miller and Vogel, 1999).

Cardiovascular disease can sometimes (indirectly) cause epilepsy through a predisposition to stroke (Attar *et al.*, 2016; Ferlazzo *et al.*, 2016). Stroke is a common risk factor for epilepsy and accounts for about a third of newly diagnosed seizures in people over the age of 60 years (Camilo and Goldstein, 2004; Ferlazzo *et al.*, 2016; Forsgren *et al.*, 1996; Hauser *et al.*, 1993). Particularly, those with ischaemic events with cortical involvement, cerebral haemorrhage (i.e. primary haemorrhage or haemorrhagic transformation of ischaemic stroke) and early post-stroke seizures, are at risk for post-stroke epilepsy (Ferlazzo *et al.*, 2016).

Seizure activity may not only induce arrhythmias but may also lead to structural cardiac changes (Natelson *et al.*, 1998; Nei *et al.*, 2012; Schuele, 2009; Tigaran *et al.*, 2003). Epileptic seizures have been reported to provoke cardiac ischaemia via acute and chronic effects on the heart (e.g. impaired HRV, cardiac fibrosis, ST-segment depression and increased heart rate) (Schuele, 2009; Tigaran *et al.*, 2003). Transient myocardial ischaemia as indicated by ST-segment depression, was reported in a small-scale study in 40% of 15 seizures (Tigaran *et al.*, 2003). Another study, however, failed to demonstrate troponin increases, suggesting that the reported ST changes do not usually cause myocardial damage (Woodruff *et al.*, 2003).

Seizures are the second most frequent central nervous system (CNS) condition known to induce the cardiomyopathy known as Takotsubo

syndrome (TTS) (Finsterer and Wahbi, 2014). TTS mimics myocardial infarction clinically, electrocardiographically and chemically (Finsterer and Bersano, 2015). It is characterized by acute onset of chest pain and dyspnoea, sometimes concomitant with palpitations, tiredness, oedema, fever, syncope, anxiety, nausea or vomiting (Finsterer and Wahbi, 2014). Seizure-induced TTS is mostly caused by CS (Le Ven *et al.*, 2011; Lemke *et al.*, 2008). Seizures most likely trigger TTS by stress-induced release of catecholamines (Szardien *et al.*, 2013). This abundant catecholamine release may be a contributing factor in fatal SE (Manno *et al.*, 2005). A relationship between TTS and SUDEP, however, does not appear likely (Finsterer and Wahbi, 2014) (Table 7).

Table 7. Putative mechanisms of associations between epilepsy and structural cardiac disease.

Mechanisms of association	Conditions	References
Causal	Cardiac conditions, e.g. embolism and congenital cardiac abnormalities → Stroke	Attar *et al.*, 2016; Ferlazzo *et al.*, 2016; Gaitatzis *et al.*, 2004
	Congenital cardiac abnormalities → poor (intrauterine) brain development	Miller and Vogel, 1999
Shared risk factor	Genetic → Malformation of cortical and cardiac development	Antonarakis *et al.*, 2004; Curatolo *et al.*, 2008; Kobrynski and Sullivan, 2007; Miller and Vogel, 1999
	Shared cardiovascular risk factors → Stroke	Centers for Disease Control and Prevention, 2013; Elliott *et al.*, 2008; Gaitatzis *et al.*, 2004; Kobau *et al.*, 2008
Resultant	ASM → Arteriosclerosis	Brodie *et al.*, 2013; Katsiki *et al.*, 2014; Lopinto-Khoury and Mintzer, 2010; Mintzer *et al.*, 2009
	ASM → Weight gain, non-alcoholic fatty liver disease and metabolic syndrome	
	Seizures → Transient myocardial ischaemia	Schuele, 2009; Tigaran *et al.*, 2003
	Seizures → Seizure-triggered Takotsubo syndrome	Finsterer and Bersano, 2015; Finsterer and Wahbi, 2014; Lemke *et al.*, 2008

ASM = antiseizure medication.

3.4 Discussion

I identified many associations between epilepsy and cardiac arrhythmias and structural cardiac conditions. Cardiovascular risk factors and conditions, such as embolism, can lead to stroke which in turn can cause

epilepsy. The conditions can share a shared genetic risk factor. ASM can increase propensity for arrhythmias and negatively affect cardiovascular risk (e.g. by weight gain and arteriosclerosis). Seizures can cause transient myocardial ischaemia and induce arrhythmias. Ictal arrhythmias are likely self-limiting, as no deaths were reported. In contrast, postictal arrhythmias including asystole and the less prevalent VT/VF usually occurred after a CS and were frequently associated with (near-)SUDEP. The differences in timing, associated seizure types and mortality risk suggests that seizures may trigger cardiac arrhythmias in various ways.

The commonest seizure-induced arrhythmia was ictal asystole. For many years, ictal asystole was thought to be a possible mechanism underlying SUDEP. This appears to be unlikely: all but one reported case so far of ictal asystole were self-limiting (van der Lende et al., 2016b). In this one case successful resuscitation was started after 44 seconds of asystole and the event was classified as near-SUDEP (Lanz et al., 2011). The longest ictal asystole reported so far, however, lasted 96 seconds and appeared self-limiting (Chaila et al., 2010). One case with ictal asystole fell victim to SUDEP despite a well-functioning pacemaker, suggesting ictal asystole was benign and did not cause death (Bank et al., 2018). This case also supports the hypothesis that terminal asystole is not primarily a cardiac mechanism (Bank et al., 2018). Whether an event is classified as near-SUDEP or not will depend on interventions of medical personnel: prompt resuscitation in response to ictal asystole will likely lead to more classified as near-SUDEP cases. While there are no reports of fatal ictal asystole, it remains debatable whether ictal asystole can cause SUDEP.

Seizure induced VT/VF seem rare, but there may be a publication bias, as cases with seizure-triggered VT/VF and cardiac lesions may not qualify as SUDEP and thus may be less likely to be reported. Though seizure-induced VT/VF appears to be rare. A prospective study of out-of-hospital cardiac arrests due to ECG-documented VT/VF showed, however, that VT/VF risk in those with epilepsy was three times as high as the general population (Bardai *et al.*, 2012; van der Lende *et al.*, 2016b). A further analysis of those cases with epilepsy and VT/VF showed that most were not seizure-related but rather occurred in the context of either pre-existing heart disease or as the immediate result of an acute myocardial infarction (Lamberts *et al.*, 2015b). Pre-existing heart disease was a stronger predictor for VT/VF in people with epilepsy than markers of epilepsy severity. In a minority of cases, however, VT/VF was unexplained and a diagnosis of (near) SUDEP was established. It thus appears that sudden cardiac arrest and SUDEP are partially overlapping disease entities.

The increased risk of non-seizure-related VF/VT episodes in people epilepsy may be explained by high cardiovascular comorbidity (Gaitatzis *et al.*, 2004; Gaitatzis *et al.*, 2012). People with epilepsy may have a propensity for sudden cardiac death as reduced HRV (i.e. measure of cardiac sympathovagal balance which is also a risk marker of sudden cardiac death) progressively worsens over time in people with refractory but not in those with well-controlled epilepsy (Suorsa *et al.*, 2011). Other interictal markers of sudden cardiac death, such as early repolarisation pattern and QTc-prolongation, are more frequently found in people with epilepsy than in those without (Lamberts *et al.*, 2015a).

3.5 Limitations

An important limitation of this chapter is that most of the electronic literature searches were not performed systematically and as a result relevant articles may have been missed. This may particularly concern articles describing new or rare associations between epilepsy and cardiac conditions that were not covered by my search terms. As three experienced epileptologists with special interest for cardiology (Ley Sander, Rainer Surges and Roland Thijs) were involved in this study, I trust the presented overview covers the majority of clinically relevant associations.

Selection bias may have played a role as many studies reporting structural cardiac conditions and peri-ictal cardiac arrhythmias were performed during video-EEG registration. Pre-surgical evaluation is the most common indication for video-EEG registration and therefore people with refractory and temporal lobe epilepsy may have been over-represented. This may have resulted in an overestimation of the association of temporal lobe epilepsy in those with ictal and postictal asystole.

Muscle artefacts, particularly those during CS, may have obscured the detection of ictal arrhythmias with a single lead ECG channel. This limitation may apply to all arrhythmias except for those causing (pre)syncope, as this will become apparent by a sudden diffuse slowing and flattening of the EEG (Schuele *et al.*, 2007). Nevertheless, it should be noted that the prevalence of ictal arrhythmias might have been underestimated.

3.6 Conclusion

Significant progress has been made since the publication of Russel's ictal asystole case (Russell, 1906) and the complex interrelationship between epilepsy and cardiac conditions has been explored widely. I aimed to capture all major discoveries made in this field. I showed that postictal arrhythmias, rather than ictal arrhythmias, seem of greater importance to the pathophysiology of SUDEP. Many discoveries of coexisting cardiac conditions were made by serendipity and underlying mechanisms are yet to be uncovered. Cardiovascular comorbidities, like channelopathies, can provide insight into common mechanisms for epilepsy and give a window into common genetic predispositions. Identification and adequate treatment of cardiovascular disorders in epilepsy should be an important part of epilepsy management.

Chapter 4 Differentiation syncope and epilepsy

4.1 Introduction

Motor phenomena, like myoclonic jerks, are common in vasovagal syncope (Gastaut and Fischer-Williams, 1957; Lempert *et al.*, 1994; Lin *et al.*, 1982; van Dijk *et al.*, 2014; Wieling *et al.*, 2009), and are often misinterpreted as signs of epilepsy. Accurately distinguishing these two common causes of TLOC is vital for appropriate management and identification of those at risk of morbidity and mortality (Moya *et al.*, 2009; National Institute for Health and Care Excellence, 2017; Reuber *et al.*, 2016).

The presence of motor phenomena cannot reliably distinguish syncope from CS. The characteristics of these motor phenomena may however help to differentiate, but a direct comparison is lacking. The advent of mobile devices provides new ways to document motor phenomena in TLOC, and guidance for the interpretation of such videos may help to improve differential diagnosis.

The pathophysiological mechanisms underlying syncopal motor phenomena are incompletely understood. Alterations in the autonomic nervous system lead to reduced cardiac output, vasodilatation and bradycardia, finally resulting in low blood pressure and cerebral hypoperfusion (van Dijk *et al.*, 2009). Various signs and symptoms are known to strongly correlate with the EEG pattern, suggesting a dependence on the level of cerebral hypoperfusion (van Dijk *et al.*, 2014). Two characteristic EEG patterns are distinguished: ‘slow’ (S) and ‘slow-flat-slow’

(SFS) (Gastaut and Fischer-Williams, 1957; Gastaut and Gastaut, 1958; van Dijk *et al.*, 2014). Flattening of the EEG in syncope was related to severe cerebral hypoperfusion (van Dijk *et al.*, 2014).

To aid the differential diagnosis of TLOC, I compared the motor phenomena in tilt-induced syncope and CS. My second aim was to understand the underlying pathophysiology of myoclonic jerks and tonic postures in syncope, by studying their association with the EEG patterns.

4.2 Methods

4.2.1 Subjects

I reviewed all tilt-table tests, performed at a tertiary referral centre for epilepsy and syncope in Heemstede, the Netherlands, between January 2009 and July 2016, of people aged ≥15 years in whom there was a clinical suspicion of vasovagal syncope. Tilt-table testing included 12-channel scalp EEG recording, 1-lead ECG, continuous non-invasive finger blood pressure measurements (Nexfin®, BMEye Amsterdam, the Netherlands) and video, recorded with a ceiling-mounted camera. Inclusion required tilt-induced syncope, defined as previously (van Dijk *et al.*, 2014): 1) video data compatible with loss of consciousness (i.e. loss of tone and unresponsiveness), 2) circulatory changes comprising an accelerating blood pressure decrease, with or without bradycardia or asystole, and 3) EEG changes with either a S or a SFS pattern. Exclusion criteria were: 1) lack of visibility of the arms, and 2) other conditions during the tilt test besides reflex syncope (e.g. psychogenic pseudosyncope).

CS recordings were selected from the video-EEG database of the same centre (January 2003 to December 2011), of people aged ≥15 years who underwent pre-surgical evaluation for epilepsy (Bauer *et al.*, 2017; Lamberts *et al.*, 2013a; Lamberts *et al.*, 2013b). The first recorded CS of each person was selected. Exclusion criteria were: 1) lack of visibility of the arms, 2) insufficient EEG quality, and 3) ≤1 minute postictal recording. The postictal recording is of interest as the EEG may become flat at this stage (Lhatoo *et al.*, 2010), allowing a comparison with the flat EEG during syncope.

4.2.2 Clinical tilt protocol and data collection

A modified 'Italian protocol' was used to provoke syncope (Bartoletti *et al.*, 2000). The test started in the supine position for 10 minutes, after which participants were tilted head-up to 70° for 20 minutes. If no relevant changes occurred 0.4 mg of sublingual nitroglycerin was given. Reasons to tilt back included 1) syncope, 2) prodromal complaints similar to spontaneous attacks, provided they coincided with a clear drop in blood pressure or heart rate, 3) occurrence of asystole, or 4) an S or SFS EEG pattern. Safety straps around the legs and abdomen were used to prevent falls.

4.2.3 Video analysis

Two types of arm movements were assessed: myoclonic jerks and tonic postures. Movements were occasionally incompletely visible on one side when a bystander moved in front of the camera. If this was the case, I noted a 'video limitation'. I inspected all syncope and seizure recordings together with two neurologists with a lot of experience with EEG and who are specialised in epilepsy and syncope. Recordings were examined repeatedly until consensus was achieved regarding the occurrence, timing and features

of the motor phenomena. Syncope and seizure videos were assessed in the same way.

Myoclonic jerks were noted as a quick change of joint position of the shoulder, elbow or wrist, with an estimated amplitude of at least 20 degrees. Myoclonus could consist of a sudden movement that ended in a sustained posture or of a movement against gravity after which the arm directly fell back. The timing of each jerk was taken from video recordings and noted in seconds rounded off to one decimal place (although I estimate the actual time resolution to lie around 200ms). When interclonic intervals were short, the video speed was reduced and movement artefacts in the EEG were used to accurately determine the exact timing of the jerks. Laterality (bilateral yes/no) and, when bilateral, synchrony (synchronous/asynchronous) were noted per movement but as an overall measure for each participant. Asynchronous jerks of both arms were counted as two separate jerks.

Tonic postures were noted if an arm moved into a position and stayed there, against gravity, for >1s, or when the arms moved slowly without reaching a stable position. For each posture the beginning and end time was noted. Occasionally, a posture lasted until the subject regained consciousness. In such cases, the end of the tonic movement was noted as the time at which EEG slowing ended, or the first conscious movement, whichever came first. I noted whether the posture involved flexion or extension of the elbow. Laterality and synchrony were noted as an overall measure for each participant. In case of asynchronous postures, left- and right-sided movements were counted as two separate postures.

I assessed whether a complete loss of tone, resulting in a change of body position (e.g. head dropping), was observed during the event.

4.2.4 EEG evaluation

Two experienced neurologists noted the beginning and end times of EEG slowing and flattening. The onset of EEG slowing was defined as the first delta wave of a consistent period of slowing, and the end of slowing as the last delta wave (van Dijk *et al.*, 2014). PGES in the CS group was analysed previously (Lamberts *et al.*, 2013a; Lamberts *et al.*, 2013b).

4.2.5 Statistical analysis

The following features were compared between the syncope and CS group: occurrence, laterality of jerks and the duration of the clonic period; tonic postures (yes/no); number, duration, synchrony and rhythmicity of jerks; type of posture (flexion/extension); and atonia (yes/no). Rhythmicity of jerks was quantified by calculating mean consecutive differences (MCD) (Ekstedt *et al.*, 1974) of successive interclonic intervals (i.e. the mean of absolute differences between consecutive intervals). Chi-Square, Fisher's Exact and Mann-Whitney U tests were used where appropriate.

To calculate diagnostic yield parameters (i.e. sensitivity, specificity, false positive (FPR) and negative (FNR) rate, positive (LR+) and negative (LR-) likelihood ratio), I assumed that most physicians associate movements more strongly with epileptic seizures than with syncope, and defined sensitivity as the occurrence rates of these features in the epilepsy group.

In syncope, I assessed whether jerks and tonic postures were more likely to occur in the SFS group compared to the S group. Within the SFS group I

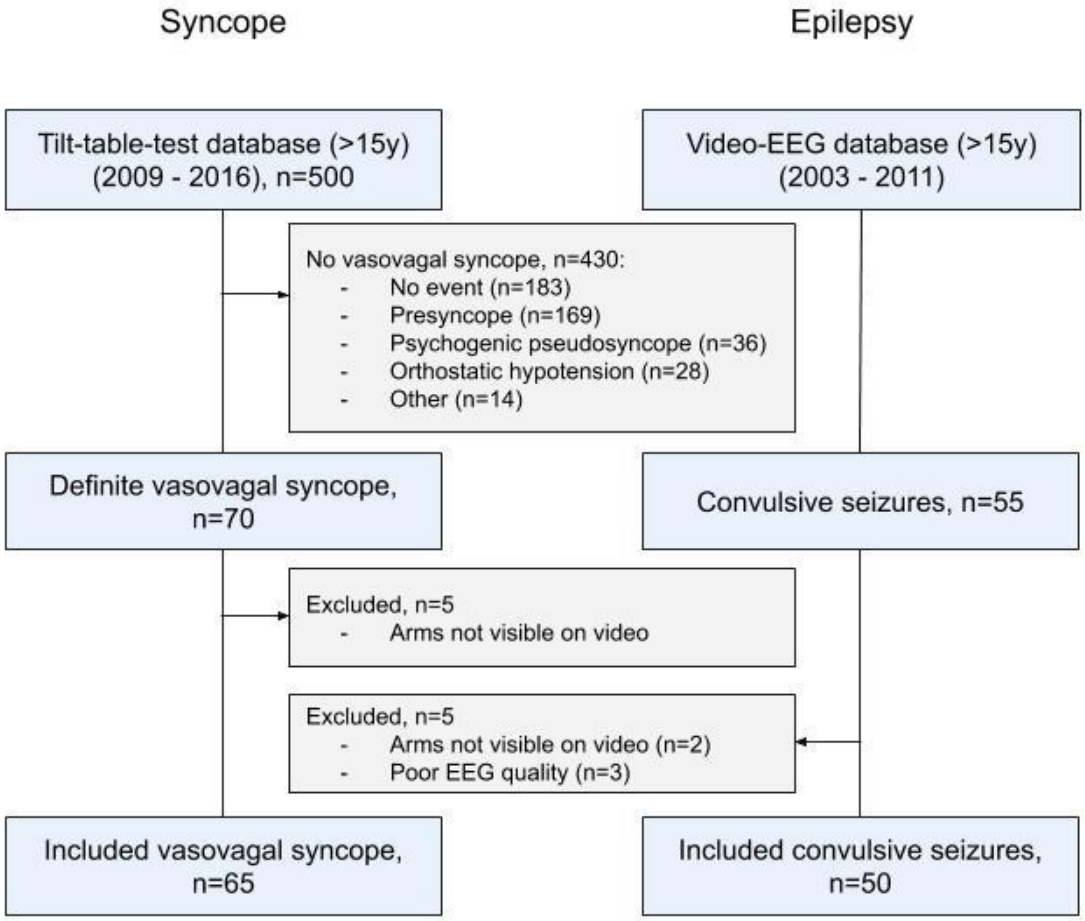
examined whether motor phenomena occurred at different rates during the slow and flat periods of the EEG. I performed a (one-sided) test to see if the overlap of the tonic postures with the flat EEG periods is greater than expected when compared with a random distribution of postures during TLOC. Similarly, I determined whether jerks occurred less often in flat EEG periods than expected when jerks are distributed randomly during TLOC. For these tests, I used a simulation approach with 100,000 replications. I corrected for multiple testing using the Bonferroni-Holm method; adjusted p-values are shown. P-values of <0.05 were considered statistically significant. Statistical analyses were done using IBM SPSS Statistics 23 (IBM Corp. Armonk, NY) and R version 3.3.

4.3 Results

4.3.1 Subjects

A total of 500 tilt-table tests were performed between January 2009 and July 2016. Clinical events occurred in 317 cases: presyncope in 169; psychogenic pseudosyncope in 36; orthostatic hypotension in 28; carotid sinus hypersensitivity in 4; and other events in 10. Syncope occurred in 70 cases. Five cases were excluded because of insufficient video quality, leaving 65 syncope recordings (Figure 4). Syncope occurred after administration of nitroglycerin in 40 of 65 cases (62%). Median age was 40 years (range 15-78), 41 were females (63%).

Figure 4. Flowchart of selection of syncope cases from the tilt-table database.



A total of 55 CS were identified from the video-EEG database. Two recordings were excluded due to insufficient EEG quality (e.g. disruption of EEG signal due to fall), one because of a postictal recording time of less than one minute, and two because the arms were not visible, leaving 50 seizures. Median age was 33 years (range 15-61), 32 were females (58%).

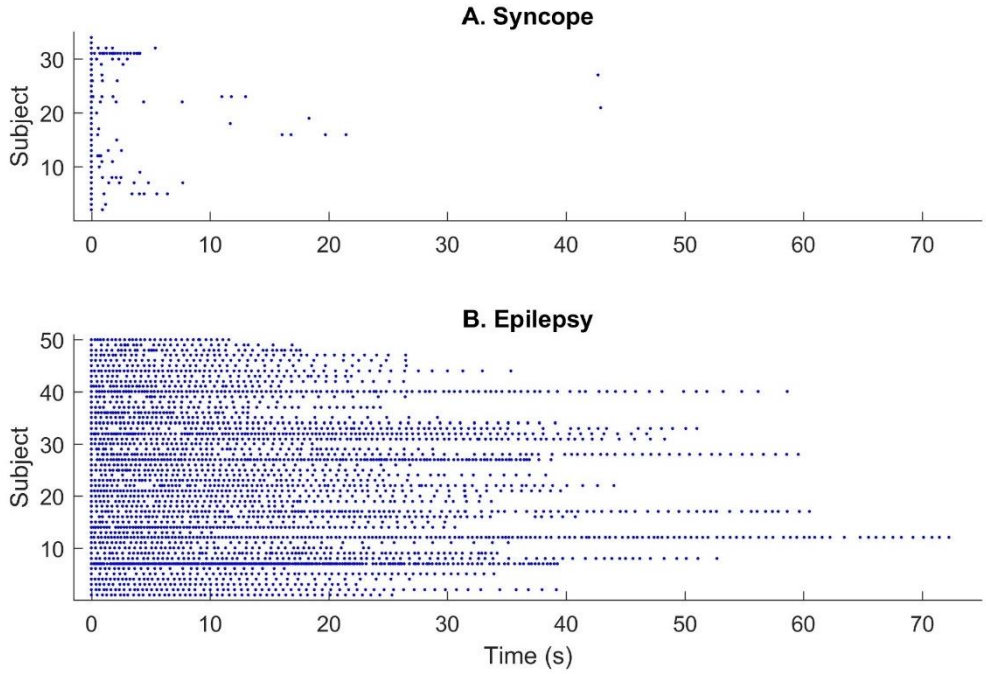
4.3.2 Motor phenomena

Video limitations occurred in 11 of 65 syncope cases, but most (n=9) did not hinder assessment of movements. In two cases one arm was not visible, precluding assessment of laterality of jerks in one, and of a posture in the other. Video limitations occurred in 10 of 50 CS. Due to the video limitations

in CS I could not assess the synchrony of jerks in one, and the laterality of a posture in two cases.

Myoclonic jerks occurred in 33 of 65 syncope cases (51%) and in all CS (Chi-Square p<0.001; Table 8 and Figure 5). Jerks occurred bilaterally in 25 (of 32) syncope cases (78%) and in all CS (p=0.002). The rate of synchrony was lower in the syncope group compared to the seizures (n=12 (48%) versus n=44 (90%); p<0.001). Fewer jerks were noted in participants with syncope (median 2, range 1-19) than in the seizures (median 48, range 20-191; p<0.001). In all CS there were more than 20 jerks, while in syncope all but one case exhibited fewer than 10 jerks. Accordingly, the clonic period was shorter in syncope (median 3.6s, range 0.4-43s) than in the seizures (median 29s, range 10-72s; p<0.001). The MCD of interclonic intervals could be calculated for 15 syncope cases as it requires at least three jerks. MCD was higher (i.e. less rhythmic) in the syncope cases (median 0.67s, range 0.07-41s) than in seizure cases (median 0.12s, range 0.04-0.25s; p<0.001).

Figure 5. Myoclonic jerks in syncope (A) and convulsive seizures (B).



Each horizontal line represents one person. Every dot represents one myoclonic jerk, plotted on its time of occurrence. The moment of the first jerk was taken as the zero point in time.

Tonic postures occurred in 42 syncope cases (65%) and in all CS ($p<0.001$). In syncope, 30 cases had one posture, eight had two and four had three postures. The rate of bilateral postures was lower in the syncope group compared to the seizures (n=31 (76%) versus n=48 (100%); $p<0.001$). In syncope, 23 of the bilateral postures were synchronous (74%).

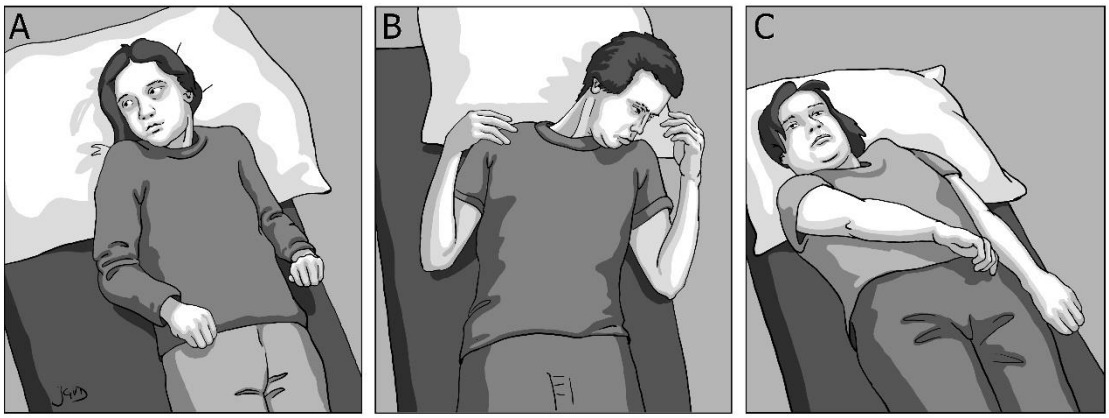
Table 8. Features of myoclonic jerks and tonic postures in the tilt-induced syncope and convulsive seizure group.

Motor phenomena	Syncope (n=65)	Convulsive seizures (n=50)	Test, p-value
Myoclonic jerks, n (%)	33 (51)	50 (100)	χ2, <0.001
• Number, median (range)	2 (1-19)	48 (20-191)	MW, <0.001
• Total duration of jerks (s), median (range)	3.6 (0.4-43)	29 (10-72)	MW, <0.001
• Bilateral, n (%)	25 out of 32 (78)	50 out of 50 (100)	FET, 0.002
• Synchronous, n (%)	12 out of 25 (48)	44 out of 49 (90)	χ2, <0.001
• Rhythmicity (s; MCD of ICI), median (range)	0.67 (0.07-41)	0.12 (0.04-0.25)	MW, <0.001
Tonic posture, n (%)	42 (65)	50 (100)	χ2, <0.001
• Bilateral, n (%)	31 out of 41 (76)	48 out of 48 (100)	FET, <0.001
• Synchronous, n (%)	23 out of 31 (74)	NA	NA
• Extension, n (%)[1]	3 out of 44 (7)	36 out of 62 (58)	χ2, <0.001
Evidence for loss of tone, n (%)[2]	65 (100)	0 (0)	χ2, <0.001

The Bonferroni-Holm method was used to correct for multiple testing; adjusted p-values are shown. P-values based on univariate analysis. [1] Some participants had both an extension and a flexion posture; [2] May be underreported in the convulsive seizures (see Results section).MCD = mean consecutive differences; ICI = interclonic intervals; χ2 = Chi-Square test; FET = Fisher's Exact test; MW = Mann-Whitney U test.

The commonest posture observed in syncope involved anteflexion of the shoulder, flexion of the elbow and simultaneous subtle exorotation of the shoulder and supination of the wrist (Figure 6). Extension was seen in three syncope cases (7%), of which two also had a flexion posture, and in 36 seizures (58%; p<0.001), of which 14 also had a flexion posture.

Figure 6. Illustration of flexion and extension postures in tilt-induced syncope.



These images were drawn from video frames during tilting back. Medical equipment such as straps, blood pressure devices and EEG electrodes were omitted. A and B show elbow flexion to various degrees, as well as head and eye turning (A) and head flexion (B). C shows arm extension and pronation; the head is pressed backwards against the pillow.

In all syncope cases loss of tone was seen, while this was not observed in any CS. It should be noted, however, that most CS (n=35, 70%) occurred in the supine position. In this position, atonia will not automatically result in an observable change of body position. Loss of tone in CS may therefore have been underreported.

4.3.3 Diagnostic value

Jerks and postures occurred in all CS, however, they were also often observed in syncope, resulting in a low LR+ (2 and 1.5 respectively; Table 9). Observing synchronous jerks does not make a CS more likely (LR+ 1.9), but asynchronous jerks do argue against this diagnosis (LR- 0.19). Tonic extension was 8.3 more likely to occur in a CS compared to syncope, but the absence of extension has limited diagnostic value (LR- 0.45). Fewer than 10 jerks occurred in 97% of the syncope group but in none of the

seizures, thus precluding diagnosis of a CS (LR+ 0), while a count of more than 20 jerks was highly specific to CS (LR+ ∞). Signs of atonia strongly argue against a CS (LR- 0).

Table 9. Diagnostic yield parameters of the occurrence and features of myoclonic jerks and tonic postures for diagnosis of epilepsy.

Clinical findings	Sensitivity (%)	Specificity (%)	FPR (%)	FNR (%)	LR+	LR-
Jerks occur	100	49	51	0	2	0
<10 jerks **>20 jerks**	0 100	3 100	97 0	100 0	0 ∞	33 0
Bilateral jerks	100	22	78	0	1.2	0
Synchronous jerks	90	52	48	10	1.9	0.19
Postures occur	100	35	65	0	1.5	0
Bilateral postures	100	24	76	0	1.3	0
Tonic extension	58	93	7	42	8.3	0.45
No loss of tone	100	100	0	0	∞	0

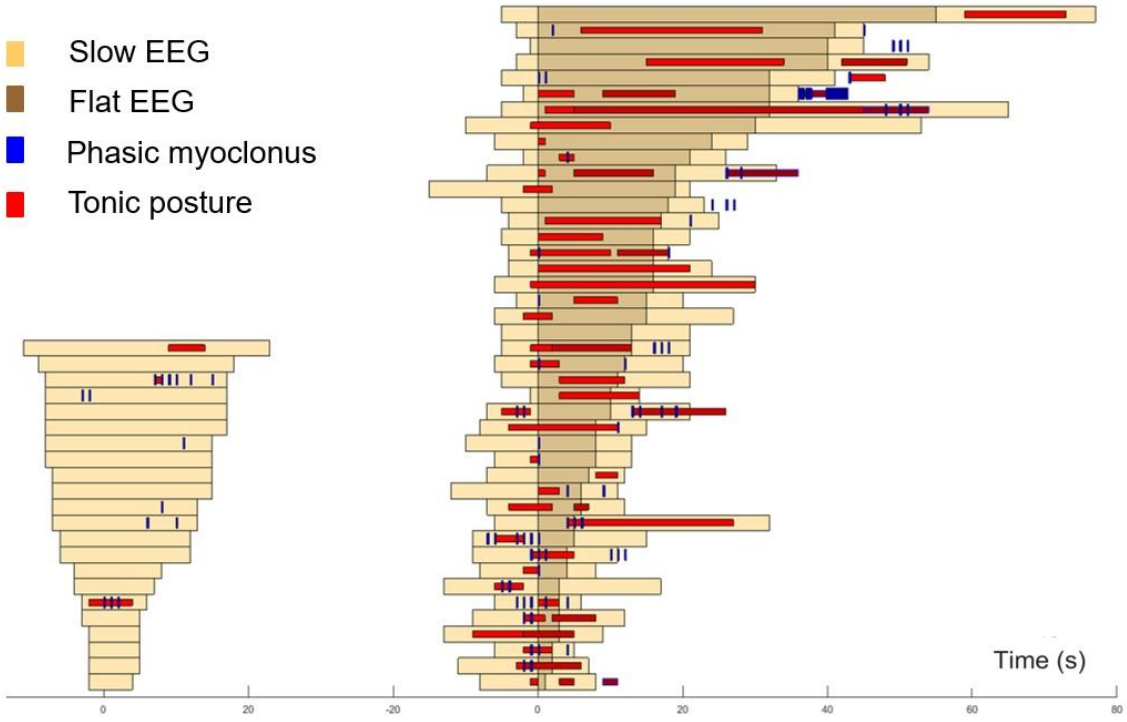
Sensitivity was defined as the occurrence of these clinical findings in the epilepsy group, and hence specificity concerns the syncope group. FNR = false negative rate; FPR = false positive rate; LR+ = positive likelihood ratio; LR- = negative likelihood ratio.

4.3.4 Relation between motor phenomena and EEG patterns

EEG slowing (S pattern) occurred in 22 syncope cases and an SFS pattern in 43 (Figure 7). Age did not differ between the S (median 43 years, range 16-74) and SFS group (median 36 years, range 15-78; p=0.94). SFS cases were more likely to have jerks (OR 4.5, 95% confidence interval (CI) 1.5-14) and postures (OR 62, 95% CI 13-304) than S cases. In those with SFS, jerks were not randomly distributed over the TLOC period, but more likely

to occur outside the flat EEG phase ($p<0.001$). This finding remained significant in a post-hoc analysis in which I excluded the case with 19 jerks, all occurring outside the flat EEG ($p=0.007$). Postures were more likely to overlap with the flat EEG than expected in a random distribution ($p=0.008$). All three cases with tonic extension of the arms had an SFS EEG and the postures occurred during flat EEG in two cases, and slow EEG in one (1s after the end of the flat phase).

Figure 7. Duration of EEG phases and timing of myoclonic jerks and tonic postures in syncope.



The groups with EEG slowing (S; left) and a slow-flat-flow (SFS; right) EEG pattern are shown separately. Each horizontal grey bar represents one person. Periods of EEG slowing are shown as light and periods of EEG flattening as dark brown bars. The blue marks represent the timing of each jerk, while the red horizontal bars correspond to periods of tonic postures. The onset of flattening was taken as the zero time point in the SFS group, and one-third of the EEG duration was taken as the zero point in the S group.

In the CS group, the median duration of the convulsive phase was 68s (range 32-118), during which epileptic discharges were seen on EEG. PGES occurred in 34 of 50 cases (duration ≥20s in 30 cases), and, contrary to syncope, no movements occurred during EEG flattening (PGES).

4.4 Discussion

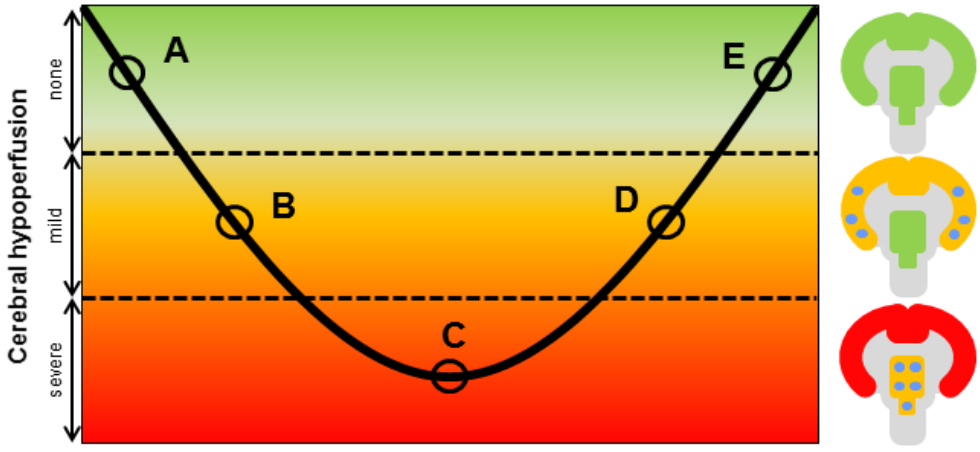
Myoclonic jerks and tonic postures occurred frequently in syncope and the mere presence of these motor phenomena can thus not distinguish syncope from CS. The semiology of jerks and postures, however, clearly differed between syncope and CS. Easily observable motor features on clinical or home videos may have important diagnostic consequences. The number of myoclonic jerks has the largest diagnostic potential. No overlap was seen in the number of jerks, suggesting that an event with fewer than 10 jerks indicates syncope and more than 20 a CS: the ‘10/20 rule’. Loss of tone during TLOC strongly favours syncope and argues against a CS. Characteristics that were more common in seizures but seem of lower diagnostic value as they often occurred in syncope, include bilateral movements, synchronous jerks and tonic extension.

4.4.1 Pathophysiology of motor phenomena in syncope

Jerks and postures in tilt-induced syncope correlated with the slow and flat EEG phases, providing hypotheses about their underlying pathophysiology. Animal studies have shown that electrical cortical activity ceases 15 to 30s after onset of sudden anoxia, during which time brainstem activity remains normal or increases (Noell and Dombrowski, 1947; Sugar and Gerard, 1938; Ward, 1947). Brainstem regions become inactive much longer after

circulatory arrest (>120s) (Sugar and Gerard, 1938). Motor phenomena in syncope are therefore likely related to cortical ischaemia, with slow EEG periods reflecting a reduced cortical function, and flat EEG periods a nearly complete loss of cortical activity (Figure 8).

Figure 8. Schematic illustration of the relation between cerebral hypoperfusion, functions and motor phenomena and other clinical signs in syncope.



	A & E	B & D	C	
Functions				
• EEG	Normal	Slow	Flat	
• Cortex	Normal	Reduced & disinhibition	Loss	
• Brainstem	Normal	Normal	Reduced & disinhibition	
Clinical signs	Sweating[1]	LOC		Frequent
	Pallor[1]	Eyes open		
	Yawning[1]	Dilated pupils		
	Dozing[2]	Making sounds		
	Crying[2]	**Jerks (<10)[3]**	Jerks (<10)[3]	
		Tonic posture (flexion>extension)[4]	**Tonic posture (flexion>extension)[4]**	
		Eyes upwards		
		Oral automatisms		
		Head turning		
		Jaw dropping		
		Head dropping		
		Roving eye movements[4]	**Roving eye movements[4]**	
		Snoring		Infrequent
		Stertorous breathing[4]	**Stertorous breathing[4]**	
		Nonsensical talking		
		Nystagmus		

The top graph shows a hypothetical time course of cerebral hypoperfusion (bold line) and the corresponding EEG phases. Three situations are distinguished in the schematic graphs of the brain: (A and E) during normal cerebral perfusion: the EEG and function of the cortex and brain stem are normal; (B and D) during mild hypoperfusion: the EEG slows and some cortical functions are impaired while cortical disinhibition also occurs, brainstem function is normal, and jerks may be observed; (C) during deeper hypoperfusion: the EEG flattens, cortical function is nearly completely lost, disinhibition occurs in the brainstem, and tonic postures may be observed. [1] More frequent prior (A) than after (E) syncope; [2] More frequent after (E) than before (A) syncope; [3] More frequent during B and D than during C; [4] More frequent during C than during B and D. Colour legend: green = normal function; yellow =

reduced function with EEG slowing; blue = disinhibition; red = loss of function with flattening of the EEG. LOC = loss of consciousness.

In line with previous observations, myoclonic jerks in syncope were more likely to occur during the slow EEG phase (Gastaut and Fischer-Williams, 1957; van Dijk *et al.*, 2014; Wieling *et al.*, 2009). Myoclonic jerks in syncope are likely of cortical origin (van Dijk *et al.*, 2014) and may result from cortical hyperexcitability due to impaired cortical function and cortical disinhibition (Figure 8). A cortical origin of myoclonus has been demonstrated in a case of limb-shaking transient ischaemic attack a condition that parallels syncope, as myoclonus also coincides with transient cerebral hypoperfusion, causing reversible cortical ischaemia with EEG slowing (Muraga *et al.*, 2016; Persoon *et al.*, 2010; Yanagihara *et al.*, 1985).

Tonic postures were frequently seen during the flat EEG, which corresponds to previous clinical observations (Gastaut and Fischer-Williams, 1957; Gastaut and Gastaut, 1958; Luft and Noell, 1956; Noell and Dombrowski, 1947; Sugar and Gerard, 1938; Ward, 1947). These postures likely result from brainstem disinhibition due to a nearly complete loss of cortical function (Figure 8) (Gastaut and Fischer-Williams, 1957; Gastaut and Gastaut, 1958; Ward, 1947). Accordingly, tonic spasms provoked by cerebral hypoxia in monkeys ceased to occur after destruction of the brainstem reticular formation (Ward, 1947). Other symptoms that coincide with flattening of the EEG, like stertorous breathing and roving eye movements, also fit brainstem activity (van Dijk *et al.*, 2014). Cerebral hypoxia may also lead to reduced brainstem function: e.g. the corneal reflex may disappear in severe syncope (Rossen *et al.*, 1943).

4.4.2 Pathophysiology of motor phenomena: syncope versus convulsive seizures

The pathophysiological mechanisms underlying the motor phenomena in CS differ from those in syncope. In CS, movements occur during epileptic EEG discharges and are hence probably occur due to excessive cortical activity, as opposed to ischaemic impaired cortical activity and brainstem inhibition in syncope.

The differences extend to EEG flattening: I observed no tonic posturing during PGES, and the return of EEG activity after PGES was not accompanied by myoclonic jerks. The differences in semiology fit the two distinct mechanisms underlying the apparently similar EEG flattening. While in syncope flattening is likely due to a complete inability of cortical neurons to discharge due to severe cerebral hypoperfusion (van Dijk *et al.*, 2014), PGES is thought to result from active suppression of neurons that are otherwise capable of discharging (Bauer *et al.*, 2017).

4.5 Limitations

The study has several limitations. Electromyographical recordings of the myoclonic jerks would have increased precision. Yet the aim was to translate the results to clinical practice where videos and eyewitness reports are crucial. Hence, while assessing the videos there was continuous awareness of the fact that an eyewitness should have been able to observe the movement.

The video assessment does, however, not equal eyewitness accounts. Eyewitnesses observe an event only once, often in emotionally charged

circumstances, and the episode is narrated weeks or longer hereafter. Eyewitnesses may overlook salient observable features (Thijs *et al.*, 2008). Whether the '10/20 rule' is applicable in eyewitness accounts requires future validation.

It could be argued that the semiology of tilt-induced syncope and CS recorded at the epilepsy monitoring unit may differ from spontaneous events. Major differences in semiology are, however, not expected. In syncope, loss of consciousness will coincide with loss of postural control causing the person to fall. Once supine, fluid shifts will initiate haemodynamic recovery and thereby terminate loss of consciousness. If there is any difference with the tilt situation, tilting back may have caused TLOC to last slightly longer than syncope in real life, possibly resulting in more jerks. If this is true, the number of jerks (and postures) may be an overestimation, which makes the '10/20 rule' even stronger. In the epilepsy group, only people with focal epilepsy were included and no generalised epilepsies. As no differences were found in the duration of the convulsive phase in those with genetic generalised (mean 65s) and focal epilepsy (mean 65s) (Dobesberger *et al.*, 2015), similar numbers of jerks are expected. As the analysis was of CS only and the full spectrum of epileptic seizures were not studied, the '10/20 rule' is only of help in the differential diagnosis of TLOC and not in the broad differential diagnosis of paroxysmal events.

Most CS (n=35, 70%) occurred while supine, while all syncopal events started in the upright position. As atonia in the supine position will not

automatically result in an observable body position change, it may have been underestimated in the seizure group.

Lastly, only arm movements were assessed. Leg movements were limited by straps at knee level during the tilt-table test and the camera position did not provide a view of the whole body in some cases. This may have led to an underestimation of the number of movements.

4.6 Conclusion

This study underscores the diagnostic value of motor phenomena in syncope and epilepsy, and provides guidance for the interpretation of clinical and home videos. The diagnosis underlying TLOC should never be based in a single detail, but can only be obtained by combining multiple details from the clinical history (van Dijk *et al.*, 2009). In case of uncertainty, it is recommended to obtain a video or detailed recording of a typical event (e.g. tilt-table test, preferably with video-EEG, long-term video-EEG or an implantable loop recorder, depending on the most likely diagnosis).

Chapter 5 Premature mortality in Dravet syndrome

5.1 Introduction

People with DS face a substantial risk of premature mortality, estimated to affect up to 15% by the age of 20 years (Dravet, 2011b; Genton *et al.*, 2011). Majority of deaths appear to result from direct epilepsy-related causes as SUDEP and SE (Dravet, 2011b; Genton *et al.*, 2011). Typically, seizure onset is in the first year of life, with prolonged fever- or temperature-sensitive CS and unilateral clonic seizures (Dravet, 2011a). Other seizure types, including myoclonus, absences, and focal seizures with impaired awareness may follow in the following years (Dravet, 1978; Dravet, 2011b; Dravet *et al.*, 2005). Predominant seizure types may vary during the course of the disease and differ between children and adults. The majority of subjects experiences SE during childhood (Brunklaus *et al.*, 2012) but this is less common in adults (Akiyama *et al.*, 2010; Dravet, 2011a). Seizures are often refractory to ASM (Dravet *et al.*, 2005; Genton *et al.*, 2011). Therapy focusses on reduction of seizure frequency and prevention of SE.

A slowing of psychomotor development becomes apparent after the first year of life, resulting in mild to severe intellectual disability (Brunklaus *et al.*, 2012). Behavioural problems are reported in the majority of cases and consist mostly of a lack of attention and hyperactivity (Dravet, 2011a). Motor disorders often develop before the end of puberty which, combined with common skeletal misalignment due to joint deformities, can result in a typical crouch gait (Dravet, 2011a; Gitiaux *et al.*, 2016).

Incidence numbers of premature death in DS predominantly rely on small cohort studies or case reports. To improve understanding of premature mortality in DS, I conducted a comprehensive literature search with an emphasis on SUDEP.

5.2 Methods

5.2.1 Scoping review

The scoping review method was used (Levac *et al.*, 2010; Tricco *et al.*, 2018) to identify and summarize all relevant literature on DS mortality, regardless of quality or study design of included studies. Scoping reviews follow a systematic approach and are useful for answering broad questions. They serve a different purpose than systematic reviews, which are useful for answering clearly defined questions and include a risk-of-bias assessment with or without a meta-analysis. Traditional, or narrative, reviews may provide a broad overview of a research topic, without a specific question and with no clear methodological approach. The scoping method was thus the most appropriate for my research question.

5.2.2 Database search

I conducted a full literature search of PubMed, EMBASE, Web of Science, Cochrane, CENTRAL, CINAHL, PsycINFO, Academic Search Premier, and ScienceDirect, with the following keywords: “Dravet syndrome”, “severe myoclonic epilepsy”, “SMEI” (severe myoclonic epilepsy of infancy), “mortality”, “survivors”, “prognosis”, and “death”. All available publications up to 12 February 2016 were searched. The detailed search strategy is shown in Table A2. The EMBASE database was included as some results

of the meeting abstracts are not published yet published as full papers but may still present useful extractable data. I developed the search strategy together with Dr Roland Thijs and a librarian.

5.2.3 Inclusion and exclusion criteria

Inclusion criteria were: 1) title and abstract available in English, 2) human DS case(s) (SMEI or severe myoclonic epilepsy of infancy borderline (SMEB)), and 3) mortality data available for these case(s). Articles describing previously published mortality data were excluded. References of all included articles were screened for additional eligible papers.

5.2.4 Data collection

I collected the following data: cause of death, age at death, *SCN1A* testing (yes or no), and *SCN1A* mutation identified (yes or no). Cause of death was categorized as 1) SUDEP, 2) SE, 3) accidental (including drowning), 4) infective, 5) other, and 6) unknown (i.e. not known or not reported). Cases of SUDEP were classified as definite, probable, or possible (Nashef *et al.*, 2012). The following SUDEP characteristics were collected: witnessed or unwitnessed, from sleep or wakefulness, body position they were found in, and signs of a recent seizure (yes or no). The standardised data extraction form that was used to collect the data is provided in Table A3.

5.2.5 Data analysis

Descriptive statistics were used to present the results. When the mean was calculated, standard deviation was added as a measure of variability.

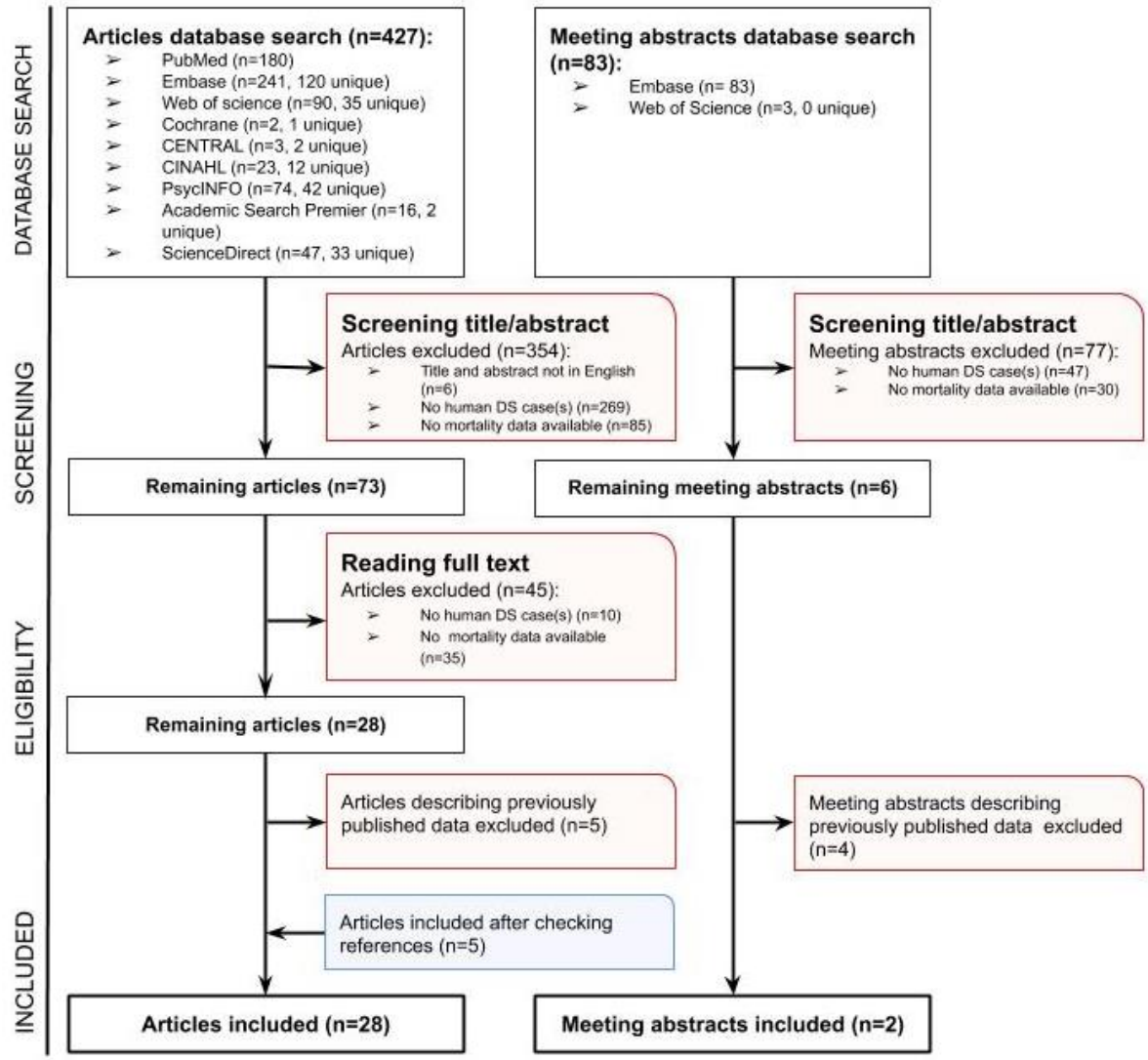
5.3 Results

5.3.1 Database search

The search yielded 676 articles and 86 meeting abstracts. Duplicate titles were removed, leaving 427 articles and 83 meeting abstracts. After screening titles and abstracts, 354 articles and 77 meeting abstracts did not meet inclusion criteria (reasons detailed in Figure 9).

Full texts of 73 articles and six meeting abstracts were obtained. After reading full texts, 45 articles were excluded, yielding 28 articles and six meeting abstracts that met the inclusion criteria. Five articles and four meeting abstracts were excluded, as the case(s) were also described elsewhere. After checking the references of all included articles, five additional studies were added resulting in a total of 30 included publications (23 cohorts and seven case reports; Table A4) (Akiyama *et al.*, 2010; Barba *et al.*, 2014; Brunklaus *et al.*, 2013; Brunklaus *et al.*, 2012; Caraballo and Fejerman, 2006; Castro-Gago *et al.*, 1997; Catarino *et al.*, 2011; Ceulemans *et al.*, 2004a; Dede *et al.*, 2015; Donner *et al.*, 2015; Dooley *et al.*, 1995; Dravet *et al.*, 1992; Friedman *et al.*, 2013; Genton *et al.*, 2011; Jansen *et al.*, 2006; Klassen *et al.*, 2014; Kolikonda *et al.*, 2015; Le Gal *et al.*, 2010; Miyake *et al.*, 1991; Nabbout *et al.*, 2013; Ogino *et al.*, 1989; Oguni *et al.*, 2001; Okumura *et al.*, 2012; Perez *et al.*, 1999; Renier and Renkawek, 1990; Sakauchi *et al.*, 2011; Skluzacek *et al.*, 2011; Takayama *et al.*, 2014; Verbeek *et al.*, 2015; Wirrell *et al.*, 2013). A total of 177 unique fatal DS cases were described (Table 10); of these, only 30 were known to have been tested for an *SCN1A* mutation, found in 28/30.

Figure 9. Flow diagram of database search on February 12th, 2016.



Included references are listed in Table A4.

Table 10. Data collected from the 30 included articles presenting unique Dravet syndrome mortality cases.

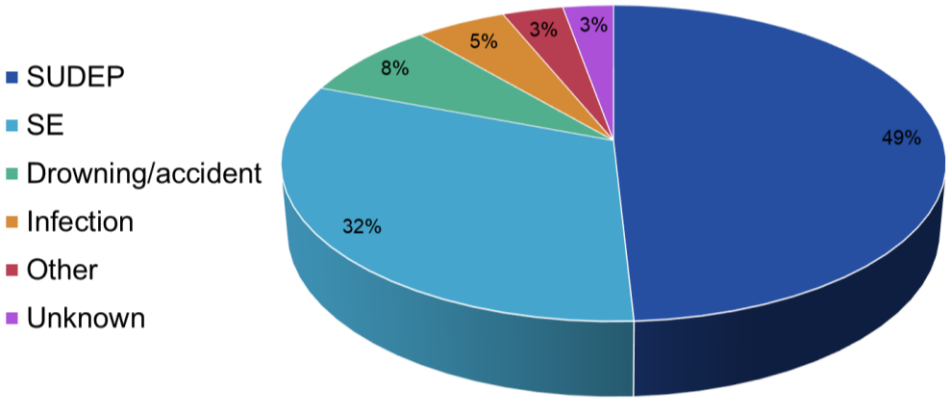
Study	Year	Deaths	Age known	*SCN1A* tested	*SCN1A*+	Cause of death					Comments
						SUDEP	SE	Accident	Infection	Other	Unknown	
1	1989	1	1	0	0	1	0	0	0	0	0	DS cohort children (n=10)
2	1990	1	1	0	0	1	0	0	0	0	0	Case report
3	1991	4	0	0	0	0	3	0	0	0	1	Children died at neurology department (n=237)
4	1992	10	9	0	0	2	2	4	1	0	1	DS cohort all ages (n=63)
5	1995	1	1	0	0	0	0	1	0	0	0	DS cohort children (n=7)
6	1997	1	1	0	0	0	0	0	0	1	0	Case report
7	1999	1	0	0	0	1	0	0	0	0	0	Refractory epilepsy children (n=104, of which 21 DS)
8	2001	12	6	0	0	3	7	1	1	0	0	DS cohort children (n=84)
9	2004	1	1	1	1	0	1	0	0	0	0	DS (*SCN1A*+) cohort all ages (n=12)
10	2006	2	0	NR	NR	0	0	0	1	0	1	DS cohort children (n=53)
11	2006	1	1	0	0	0	0	0	0	0	1	DS cohort adults (n=14)
12	2010	6	0	NR	NR	1	3	0	2	0	0	DS cohort all ages (n=37)
13	2010	1	1	1	1	1	0	0	0	0	0	Case report
14	2011	8	8	6	4	4	0	0	3	1	0	DS cohort all ages (3 post-mortem diagnosis; n=22)
15	2011	5	5	NR	NR	3	1	0	0	0	1	DS cohort adults (n=24)
16	2011	59	58	NR	NR	31	21	6	1	0	0	Questionnaire paediatricians, ≤24 years of age (n=623)
17	2011	31	31	NR	NR	19	10	1	0	1	0	DS cohort all ages (n=833)
18	2012	5	0	5	5	3	2	0	0	0	0	DS (*SCN1A*+) cohort children (n=88)
19	2012	4	4	2	2	0	4	0	0	0	0	DS cohort children with SE (n=15)
20[1]	2013	3	0	3	3	2	1	0	0	0	0	DS cohort all ages (n=207); meeting abstract
21	2013	1	1	1	1	1	0	0	0	0	0	Case report
22	2013	2	2	NR	NR	1	0	0	0	1	0	DS cohort ≤24 years of age (n=67)
23	2013	2	2	NR	NR	1	0	0	0	1	0	DS cohort children (n=82)
24[2]	2014	1	1	1	1	0	0	0	0	1	0	DS (*SCN1A*+) cohort children (n=6)
25	2014	1	1	1	1	1	0	0	0	0	0	Case report
26	2014	2	2	0	0	1	0	1	0	0	0	DS cohort adults (n=64)
27	2015	1	1	1	1	1	0	0	0	0	0	Case report
28	2015	6	0	5	5	6	0	0	0	0	0	DS cohort all ages (n=34); meeting abstract
29	2015	1	1	NR	NR	1	0	0	0	0	0	Case report
30	2015	3	3	3	3	2	1	0	0	0	0	DS (*SCN1A*+) cohort ≤20 years of age (n=77)
Totals		**177**	**142**	**30**	**28**	**87**	**56**	**14**	**9**	**6**	**5**	

References are listed in Table A4. The cause of death category ‘accidents’ includes cases of drowning, and ‘other’ included (from top to bottom) the following: respiratory insufficiency and generalised hypoxaemia secondary to acute respiratory distress syndrome, ketoacidosis, global ischaemic brain injury, brainstem tumour, found dead day after tonsillectomy, and postoperative multiple organ failure. [1] Five of eight reported deaths were previously described (in study #18 (Brunklaus *et al.*, 2012)) and therefore not included; [2] One of two mortality cases was previously described (in study #13 (Le Gal *et al.*, 2010)) and therefore not included. DS = Dravet syndrome; NR = not reported; SE = status epilepticus; SUDEP = sudden unexpected death in epilepsy.

5.3.2 Cause of death

Causes of death for the 177 cases are shown in Figure 10. SUDEP was the leading cause of death (n=87, 49%) followed by SE (n=56, 32%). Fatal drowning and accidents were described in 14 cases (8%) and fatal infections in nine (5%). Other causes (n=6, 3%) included (one case each): respiratory insufficiency and generalised hypoxaemia secondary to acute respiratory distress syndrome, ketoacidosis, global ischaemic brain injury, brainstem tumour, found dead shortly after tonsillectomy, and postoperative multiple organ failure. In five cases, the cause of death was unknown or not reported (3%). To test whether publication bias may have increased the proportion of SUDEP, I performed a separate analysis of cause of death in the 23 cohorts. After exclusion of all fatal case reports, the distribution of causes of death was 47% SUDEP (n=81), 34% SE (n=56), 8% drowning or accident (n=14), 5% fatal infection (n=9), 2% other cause (n=5), and 3% unknown (n=5). One cohort study reported only SE cases.(Okumura *et al.*, 2012) When also excluding these four deaths, the distribution was the following: total n=166; 49% SUDEP (n=81), 31% SE (n=52), 8% drowning or accident (n=14), 5% fatal infection (n=9), 3% other cause (n=5), and 3% unknown (n=5).

Figure 10. Six categories of cause of death in 177 Dravet syndrome cases and percentage of cases in each category.

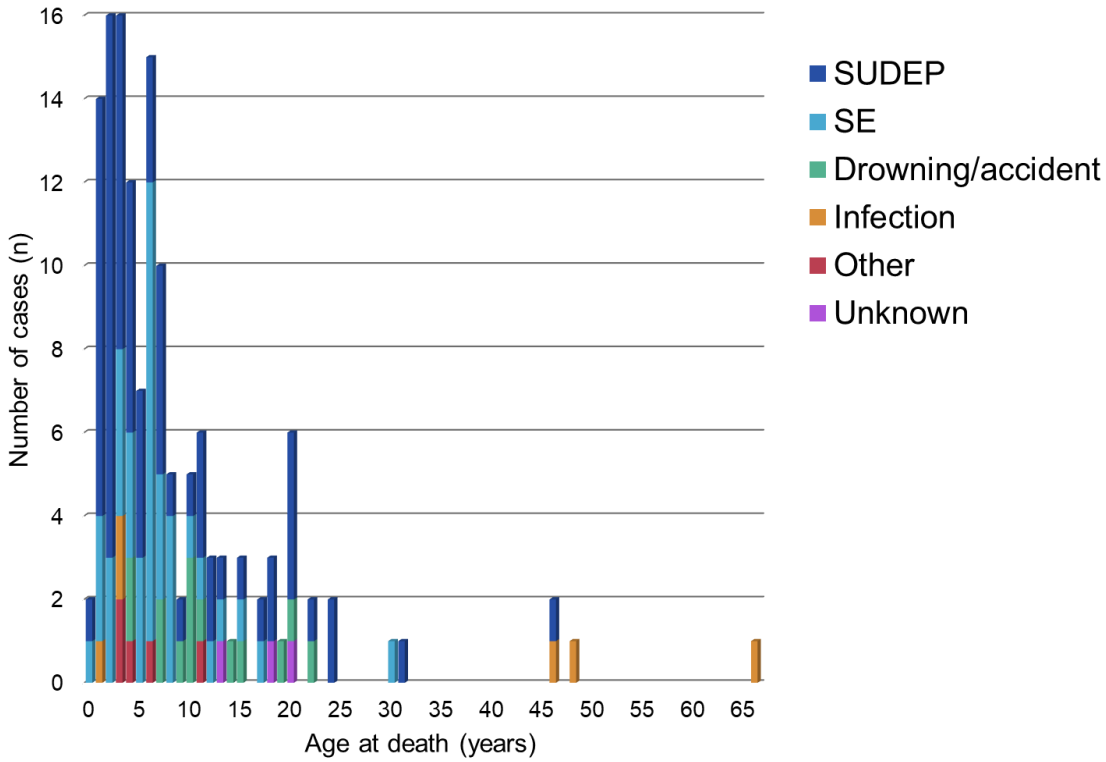


DS = Dravet syndrome; SUDEP = sudden unexpected death in epilepsy; SE = status epilepticus.

5.3.3 Age at death

Age at death was reported for 142 of the 177 cases (80%). The mean age at death was 8.7 ± 9.8 years; 73% occurred before the age of 10 years, and 93% occurred before the age of 20. The age distribution for all causes of death is shown in Figure 11. Six cases (four SUDEP and two drowning) were grouped into an '18+ category' with a maximum age of 24 years (Sakauchi *et al.*, 2011). These cases were divided evenly over this age category (SUDEP 18, 20, 22, and 24 years; drowning 20 and 22 years).

Figure 11. Age distribution for all causes of death in 142 Dravet syndrome cases.



DS = Dravet syndrome; SUDEP = sudden unexpected death in epilepsy; SE = status epilepticus.

5.3.4 Characteristics of SUDEP cases

Post-mortem examination was reported in 12 of 87 SUDEP cases and autopsy was not performed in 37 cases; thus, 12 cases (14%) could be classified as definite SUDEP, 37 (43%) as probable SUDEP, and 38 cases (44%) could not be classified. The following SUDEP characteristics were present when reported: six out of seven were unwitnessed, 26 of 34 occurred from sleep (76%), two of three were found prone, and seven of eight cases had signs of a recent seizure.

5.4 Discussion

DS is characterized by high epilepsy-related premature mortality and a marked young mean age at death. Direct epilepsy-related deaths (SUDEP and SE) comprise the vast majority of premature mortality in DS (up to 81%). This contrasts with previous cohorts of new-onset epilepsies (up to 3%) (Hauser *et al.*, 1980; Neligan *et al.*, 2011). In chronic epilepsy cohorts, the proportion of epilepsy-related deaths is higher, varying from 46 to 73% of all cases of premature mortality (Tomson *et al.*, 2004). Even compared with those cohorts, DS stands out with remarkably high epilepsy-related premature mortality.

The leading cause of death in DS, SUDEP, accounts for nearly half of overall mortality (49%). This figure contrasts with population-based cohorts of people with epilepsy (2-4%) (Ficker *et al.*, 1998; Kaiboriboon *et al.*, 2014) and some cohorts of people with therapy-resistant epilepsy (20-25%) (Jick *et al.*, 1992; Walczak *et al.*, 2001). Other studies of chronic epilepsy cohorts show similar SUDEP proportions of overall mortality (42-44%) (Leestma *et al.*, 1997; Racoosin *et al.*, 2001), up to 50% in cohorts with chronic intractable epilepsy and learning difficulties (Nashef *et al.*, 1995).

SUDEP in DS tends to occur at a younger age (73% before the age of 11) than in other epilepsy cohorts (3-9% ≤10 years) (Clark and Riney, 2016; Nashef *et al.*, 1995; Tellez-Zenteno *et al.*, 2005b; Thurman *et al.*, 2014). In these cohorts, SUDEP risk peaks in early adulthood (45-56% 20-40 years versus 6% 20-40 years in DS) (Clark and Riney, 2016; Mohanraj *et al.*, 2006; Thurman *et al.*, 2014).

Circumstances of SUDEP in the studied cases was rarely reported. This can partly be explained by that some of the studies were done in a time where there was little awareness for SUDEP and its characteristics. The characteristics that were reported seem quite similar to those previously reported in other epilepsies (e.g. most unwitnessed and at night) (Hesdorffer *et al.*, 2011; Lamberts *et al.*, 2012; Langan *et al.*, 2000; Liebenthal *et al.*, 2015).

High SUDEP rates in DS may partly be explained by epilepsy severity. The main SUDEP risk factors, including high frequency of convulsions and ASM polytherapy (Devinsky *et al.*, 2016; Hesdorffer *et al.*, 2011; Lamberts *et al.*, 2012; Langan *et al.*, 2000; Surges and Sander, 2012), relate to epilepsy severity and these factors are common in DS. Young age at death may also, at least partly, be explained by epilepsy severity, as high frequency of CS peaks in childhood and decreases over time (Akiyama *et al.*, 2010; Takayama *et al.*, 2014).

Up to a third of all deaths in DS are the results of episodes of SE. In other epilepsy cohorts, the proportion of fatal SE is much lower; 0.2-1% in population-based cohorts (Kaiboriboon *et al.*, 2014; Neligan *et al.*, 2011) and up to 14% in chronic cohorts (Leestma *et al.*, 1997; Nashef *et al.*, 1995; Racoosin *et al.*, 2001). The age at death for SE in DS (86% ≤10 years; 98% ≤20 years) was remarkably lower than seen in other epilepsies; 4% ≤10 years (Koubeissi and Alshekhlee, 2007) and 3% <20 years (Wu *et al.*, 2002).

The occurrence of SE in DS peaks in childhood and is rare after the age of 10 (Akiyama *et al.*, 2010; Takayama *et al.*, 2014). In other epilepsies, SE occurs in 15-20% of the people and appears to have a bimodal age distribution, with the highest frequency in children and the elderly (Hesdorffer *et al.*, 1998; Wu *et al.*, 2002). This does not apply, however, to the mortality figures. The mortality of SE in non-DS children is low, whereas in the elderly, a high incidence and mortality rate of SE have been reported (Koubeissi and Alshekhlee, 2007; Wu *et al.*, 2002). The fatal SE cases in children with DS may be largely explained by the high occurrence of, often repetitive and febrile, SE in this population (80%) (Brunklaus *et al.*, 2012). Another possible contributing factor may be that people with DS seem to be more likely to develop acute encephalopathy after SE (Myers *et al.*, 2017; Okumura *et al.*, 2012; Sakauchi *et al.*, 2011; Tian *et al.*, 2018). Acute encephalopathy after SE occurs in 6-8% of DS cases and is fatal in about one of four cases (Okumura *et al.*, 2012; Tian *et al.*, 2018). Possible predicting factors include high fever and genetic predisposition (Tian *et al.*, 2018).

5.5 Limitations

This scoping review has some limitations. The findings of this review may have been affected by differences in methods and reporting. Publication bias on epilepsy-related mortality reporting, especially SUDEP, may have played a role. SUDEP, however, remained the major cause of death even after exclusion of case reports. It is likely that more severe DS phenotypes were included, as most cases were seen at tertiary centres. This referral

bias may have led to an overestimation of epilepsy-related mortality. This may also apply to the time frame: most cases were identified in a period when DS was still diagnosed by strict clinical criteria (Dravet, 2011b).

Several factors may have influenced the age distribution. The reported DS population is likely biased toward younger cases. Underdiagnoses is a recognized problem in DS. In the last 10 to 15 years, genetic testing for DS has been widely implemented, and this has likely led to increased diagnosis in children rather than adults, as DS is seen as a paediatric syndrome. Awareness of DS is also recent, as it was first described only four decades ago (Dravet, 1978). Adults may have thus missed out on a diagnosis (Catarino *et al.*, 2011; Verbeek *et al.*, 2011). Most studies described here are indeed paediatric cohorts, which may have affected the results. The peak of deaths at young age in DS, however, seems consistent and is also seen in cohorts with long follow-up into adulthood (Akiyama *et al.*, 2010; Dravet *et al.*, 1992). Additionally, it is plausible that very young cases below the age of two years may have died undiagnosed.

Another limitation involves the diagnostic accuracy of DS and SUDEP. Clinical features of most DS cases were poorly described and in the majority of cases no information was provided on whether they had been tested for an *SCN1A* mutation. In nearly half of the SUDEP cases could not be classified due to a lack of information (e.g. about whether autopsy was done).

Although inclusion of yet unpublished meeting abstracts is common in scoping reviews (Levac *et al.*, 2010; Tricco *et al.*, 2018) this may carry a risk

of lower study quality leading to bias. More than half of results from abstracts, however, fail to ever get published in full (Scherer *et al.*, 2018). An important reason for this is seems to be the issue of publication bias, where factors like native English-speaking countries and ‘positive’ results, in addition to the quality play an important role (ref). Only two abstracts were included but they did provide valuable extractable data about eight mortality cases.

5.6 Conclusion

These factors all underscore the need for further studies. Reliable figures are crucial to inform health care professionals, individuals with the condition, and their carers. Future studies are warranted to confirm and update these findings and should involve long-term follow-up of large, properly genetically detailed, DS cohorts. Preferably, nationwide genetic databases should be used for recruitment to avoid referral bias (Verbeek *et al.*, 2015) and should include complete documentation of the full clinical DS spectrum, as well as detailed reporting of the circumstances of death, including autopsy reports. These studies would provide better estimates of mortality and SUDEP frequency in people with DS.

Chapter 6 Cardiac arrhythmias in Dravet syndrome

6.1 Introduction

In the previous chapter I showed that SUDEP is the most common cause of premature death in DS and affects mostly young children. I hypothesised, based on CS frequency and disease progression, the increased SUDEP rates can be partly, but not completely, explained by epilepsy severity. The mutation in the *SCN1A* gene, expressed in brain and heart, may result in a vulnerability for cardiac arrhythmias and thereby further increase risk of SUDEP. *SCN1A* has been suggested as a possible candidate SUDEP gene (Bagnall *et al.*, 2016; Goldman *et al.*, 2016; Hindocha *et al.*, 2008; Leu *et al.*, 2015). This hypothesis predominantly relies on the previously mentioned mouse model studies (reporting episodes of bradycardia, asystole and sudden death following CS) and post-mortem genetic analyses of SUDEP cases (Bagnall *et al.*, 2016; Leu *et al.*, 2015; Tu *et al.*, 2011a). Potentially deleterious variants in the *SCN1A* gene have been found in SUDEP cases without a clinical diagnosis of DS (Bagnall *et al.*, 2016; Hindocha *et al.*, 2008; Leu *et al.*, 2015). Whether *SCN1A* is a true 'SUDEP gene' is not clear yet, as this would require a proof that *SCN1A* independently confers SUDEP risk beyond epilepsy severity.

Interictal data in people with DS showed increased QT and P wave dispersion and decreased HRV compared to healthy and epilepsy controls (Delogu *et al.*, 2011; Ergul *et al.*, 2013; Lyu *et al.*, 2019; Myers *et al.*, 2018). A decreased HRV (Chapter 1.4.5.5) strongly correlates with increased risk of sudden cardiac death in non-epilepsy cases, presumably due to lethal

tachyarrhythmias (Dekker *et al.*, 1997; La Rovere *et al.*, 1998; Stein *et al.*, 2005; Tokgozoglu *et al.*, 1999). In DS, decreased HRV may reflect underlying autonomic dysfunction, possibly contributing to mechanisms of SUDEP (Myers et al., 2018). To date, apart from one case of SE (Daverio et al., 2016), little has been reported on cardiac and autonomic function during fatal or non-fatal seizures in human DS cases.

I prospectively conducted long-term ambulatory ECG recordings in people with DS and compared them to historical controls to find an explanation for the high SUDEP rate. I assessed seizure-induced arrhythmias, repolarisation and conduction abnormalities, and peri-ictal heart rates and HRV.

6.2 Methods

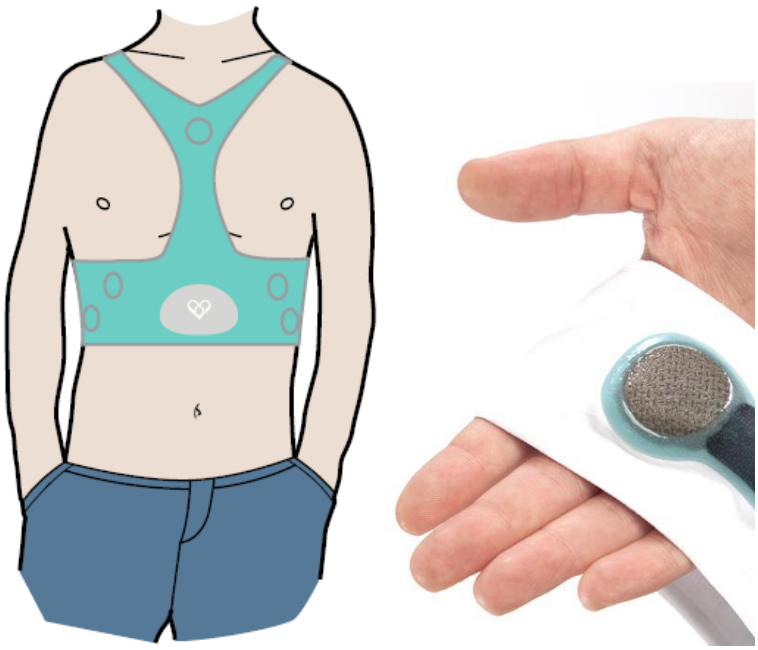
6.2.1 Subject and seizure selection

I selected individuals with DS from local diagnostic registries of four centres: Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede and Zwolle, the Netherlands; Kempenhaeghe, Heeze, the Netherlands; Department of Epileptology, University Hospital of Bonn, Bonn, Germany; Great Ormond Street Hospital for Children (GOSH), London, United Kingdom. Inclusion criteria were:

1) clinical DS with a confirmed pathogenic *SCN1A* mutation,
2) ≥6 years of age,
3) ≥1 seizure per week averaged over the previous year (all seizure types except absences or myoclonic seizures), and
4) no history of self-harm.

All cases had two baseline 12-lead ECGs (standard and Brugada (Meregalli et al., 2005) lead placement). During the ambulatory recording, subjects wore a 3-lead ECG device continuously for 20 days (nECG MINDER, Nuubo®, Madrid, Spain; sampling frequency 250 Hz and including a tri-axial accelerometer. The continuous data was stored on a microSD card with enough space for about 40 days of continuous measurements (8GB). A new file was created every time the sensor was being charged, which had to be done daily. Data was never overwritten. The device was attached to a comfortable vest with textile electrodes, allowing for all normal daily activities (Figure 12). Carers received a user manual with a detailed explanation of all proceedings (Appendix 3). I discussed all seizure types, their semiology, typical time of occurrence and frequency with the carers. The seizure types were coded and written on the diaries so that when other caregivers were with the subject, they would know how to fill in the diary. Carers and subjects were asked to record all seizure details (e.g. seizure time, duration and type), except for absences and myoclonic jerks. A daily note was also made of the time the subject got out and into bed. Gel had to be applied daily to improve the contact between the electrodes and the skin.

Figure 12. The 3-lead ECG vest and a textile electrode.



During the first week I evaluated the home-based recordings to check the quality of the ECG. To this end, the carers were asked to send the first files after one day. In case the recording was not going well, I would discuss it with the carers and provide possible solutions (e.g. more gel on the electrodes or tightening of the vest). In case of technical issues, the materials were immediately replaced.

The complete 20-day recordings of the DS cases were visually inspected and reported seizures were identified. The timing of seizure onset and end were based on diary notes, movement artefacts and heart rate profile. A heart rate increase of at least 10% was required to recognize seizures. I additionally looked for heart rate patterns suspicious for seizures that were not reported in the diary. I made a note of these possible seizures when the heart rate patterns resembled that of a reported CS of that subject. I specifically looked at a similar slope of the heart rate increase at seizure

onset, maximum heart rate and heart rate recovery postictally. I included these seizures for further analysis as ‘unreported seizures’ if: 1) the heart rate changes did not coincide with a sudden change in body position (as indicated by the tri-axial accelerometer) and 2) seizures in this subject were known to be missed sometimes (e.g. found in a postictal state or with incontinence). Cases with no recorded seizures were excluded from analysis.

Historical controls were selected from a video-EEG database. A 1-lead ECG was measured during EEG recording. Two controls were selected for each case, as the number of recorded seizures were expected to be lower in controls due to shorter recordings. Inclusion criteria were:

1) ≥6 years of age,
2) definite diagnosis of epilepsy,
3) no clinical suspicion of DS,
4) ≥1 major motor seizure (i.e. CS, generalised or focal motor seizures) and
5) seizure should have had at least 5 minutes of postictal recording.

Controls were frequency matched to mean age and sex ratio of the DS group, as these variables are known to affect cardiac function. For controls, I included all clinical seizures, except absences and myoclonic jerks, which resulted in a heart rate increase of at least 10%.

The following data for cases and controls were obtained from the medical records: sex, age, epilepsy duration, seizure frequency, seizure cluster (yes/no), seizures nocturnal, diurnal or both, ASM, vagal nerve stimulation

(yes/no), and aetiology. Additionally, for the DS group I recorded: *SCN1A* mutation type, including test results of the parents, seizure triggers, autistic features (yes/no), behavioural problems (yes/no), type of motor disorders, age at which developmental delay was first noticed, age of first abnormal EEG, family history of febrile seizures, epilepsy and sudden cardiac death.

The study protocol was independently approved by the local Medical Ethics Committee of each of the participating centres. Written informed consent was obtained from the participants or assent from parents or legal guardians in case of minors or those with learning disability. The study was registered at the ClinicalTrials.gov registry (NCT02415686).

6.2.2 Electrocardiographic analysis

Baseline 12-lead ECG recordings were evaluated by one experienced cardiologist (Dr Hanno Tan).

I assessed the ictal ECG data of cases and controls manually for abnormalities from 1 minute before onset to 5 minutes after end of seizure. As data sources of the groups differed, the ECG data was imported into MATLAB to enable assessment in the same viewer, with the same measuring tools. For both groups the exact timing of seizure onset and seizure end was determined based on ECG data in this viewer. The EEG of the control group was not imported and was not used to determine these timepoints.

I noted peri-ictal times: T1 just before seizure onset, T2 immediately after seizure end, T3 2 minutes and T4 5 minutes after seizure end.

When an ECG abnormality was identified, or in case of uncertainty, the cardiologist was consulted and if deemed necessary referral for further cardiac evaluation was arranged.

6.2.2.1 Analysis part 1: Brady-arrhythmias and QTc-intervals

Main study variables were postictal asystole (sinus arrest of ≥3s) and bradycardia (<2nd heart rate percentile for age, average of three consecutive RR intervals (female 6-8 years 68 bpm, 8-12 years 58 bpm, 12-16 years 54 bpm; male 6-8 years 62 bpm, 8-12 years 55 bpm, 12-16 years 48 bpm; >16 years 50 bpm) (Rijnbeek *et al*., 2001)). Bradycardia and asystole detection were carried out manually.

I measured QT intervals manually at time points T1-4. The RR intervals were measured at the same time points. QT intervals and RR intervals were averaged from three successive ECG complexes. Four correction formulas (Bazett, Fridericia, Hodges and Framingham) were used to calculate QTc intervals. All formulas are known to lead to over- or undercorrection of QTc (Aytemir *et al*., 1999; Batchvarov and Malik, 2002). To reduce bias error of putatively pathologic intervals I considered only those on which Bazett and at least one other formula was abnormal. Table 11 shows the QTc variables that were determined for each seizure. QTc-lengthening and -shortening of ≥60 ms was determined by subtracting QTc at T2-4 from the pre-ictal value (T1). I noted the occurrence of clinically significant prolonged QTc (defined as: ≤13 years ≥460 ms, males >13 years ≥470 ms and females >13 years ≥480 ms), shortened QTc (≤340 ms) and marked prolongation (≥500 ms) and shortening (≤300 ms) at every time point (Johnson and Ackerman, 2009; Moseley *et al.*, 2011b).

Table 11. Overview of QTc variables that were determined for each seizure.

QTc variables	
Marked prolongation - ≥500 ms	**Marked shortening** - ≤300 ms
Clinically significant prolonged - ≥460 ms ≤13 years - ≥470 ms >13 years male - ≥480 ms >13 years female	**Clinically significant shortened** - ≤340 ms
Lengthening of ≥60 ms - T2 versus T1 - T3 versus T1 - T4 versus T1	**Shortening of ≥60 ms** - T2 versus T1 - T3 versus T1 - T4 versus T1

T1 = time of seizure onset; T2 = seizure end; T3 = two minutes after seizure end; T4 = five minutes after seizure end.

6.2.2.2 Analysis part 2: Peri-ictal heart rates, heart rate variability, QRS-width and PR-interval in convulsive seizures

This part of the analysis was only done in CS. For most cases one of three leads had good recording quality and could be used for all subsequent analyses. In case of prominent ECG artefacts, all leads were visually inspected and compared to determine the least affected lead, which could vary between and within seizures.

Consecutive RR intervals were automatically determined by one of two peak detection methods. First, the Pan-Tompkins QRS detection algorithm was used and the results were visually inspected (Pan and Tompkins, 1985). If there were quality concerns a second beat detection method based on the Hilbert-Huang transform was applied (Tavares *et al.*, 2011). Additional filtering was applied in individual cases depending on signal quality (e.g. removal of low frequencies as only R peaks are needed).

Peri-ictal heart rates were determined automatically in all CS at T1-T4 by averaging 10 RR intervals. In case a heart rate was aberrant it was checked and measured manually (e.g. all extreme values <50 bpm or >180 bpm or inexplicable values like when the heart rate at T2 is lower than at T1).

I estimated HRV from 1-minute windows during three periods: pre-ictal, postictal, and in resting state. The windows were first visually inspected and those in which the ECG was of insufficient quality were excluded from further analysis. The windows were selected as follows:

- The pre-ictal minute was the minute immediately before T1.
- The post-ictal minute was selected between T3 and T4, depending on the quality of the ECG. In this epoch RR intervals >3 SD from the average were considered artefacts and were removed. A 1-minute sliding window was then moved along the postictal ECG with steps of 1s (starting from T3) until a window was reached in which the summed duration of the valid RR intervals was above 50s.
- The resting state minute required an awake state in a lying position and that no seizure had occurred in the previous hour and no CS in the previous six hours (Toth *et al.*, 2010). I preferably selected the period five minutes after the subject went to bed. To select this minute, I used movement and body position data (from the tri-axial accelerometer in ECG sensor) and the time the subject went to bed (from diary) for the DS cases and the video-EEG recordings for the controls.

The following HRV measures were estimated: average RR interval, root mean square of successive differences of RR intervals (RMSSD), the

standard deviation of RR intervals (SDNN) and the percentage of consecutive RR intervals differing by ≥50 ms (pNN50).

QRS-widths and PR-intervals were measured manually at T1 and T4. I noted whether these values were pathologically prolonged (>98th percentile for age: QRS-width female 6-8 years 95 ms, 8-12 years 99 ms, 12-16 years 106 ms; male 6-8 years 98 ms, 8-12 years 103 ms, 12-16 years 111 ms; all >16 years 120 ms; PR-interval female 6-8 years 156 ms, 8-12 years 163 ms, 12-16 years 176 ms; male 6-8 years 160 ms, 8-12 years 174 ms, 12-16 years 178 ms; all >16 years 200 ms) (Rijnbeek *et al.*, 2001).

6.2.3 Statistical analysis

Clinical characteristics were described with means, SDs, medians, (interquartile) ranges, frequencies and percentages, and compared between the groups using the two-sided unpaired *t*-test or Mann-Whitney U test for continuous variables and Chi-square for categorical data. To determine whether DS was independently associated with the occurrence of bradycardia, asystole and QTc variables, I compared these to the controls using GEE logistic models (analysis part 1). Pre-ictal and postictal HRV variables and heart rates at T1-T4 of CS in DS were compared to controls using GEE linear models (analysis part 2). I used GEE to correct for within-subject correlation, seizure onset from sleep or wakefulness and (in analysis part 1 only) for seizure type (CS yes or no). Resting HRV variables were compared using two-sided unpaired *t*-tests or Mann-Whitney U test. For visual comparison, boxplots were constructed for heart rates at T1-4 of CS for both groups. Normality tests were performed and logarithmic transformation was applied to right skewed dependant variables. Outliers

were defined as values that lie more than three SD from the mean. The Holm-Bonferroni method was used to correct for multiple comparisons within the different data sets; adjusted p-values are shown. All tests were two-tailed and a p-value of <0.05 was considered significant. Statistical analyses performed with IBM SPSS Statistics 24 (IBM Corp. Armonk, NY).

6.3 Results

6.3.1 Subjects

I included 59 people from June 2015 to January 2018 (48 in the Netherlands, nine in Germany and two in the UK; Figure 13). No seizures were recorded in eight cases and in six the study was terminated prematurely prior to any seizure thus leaving 45 cases with ictal ECG recordings. Mean age was 19 years (± 10 years) and 23 were female (51%; Table 12). A total of 22 different ASM were used between the groups and most were using more than one ASM (DS n=41 (91%) and controls n=57 (63%)). In 90 controls the mean age was 20 years (±9 years) and 46 were female (51%). Most controls were refractory to treatment (n=82, 91%) and 25 controls had a learning disability (28%). Table A5 shows the *SCN1A* variants.

Figure 13. Study flow chart.

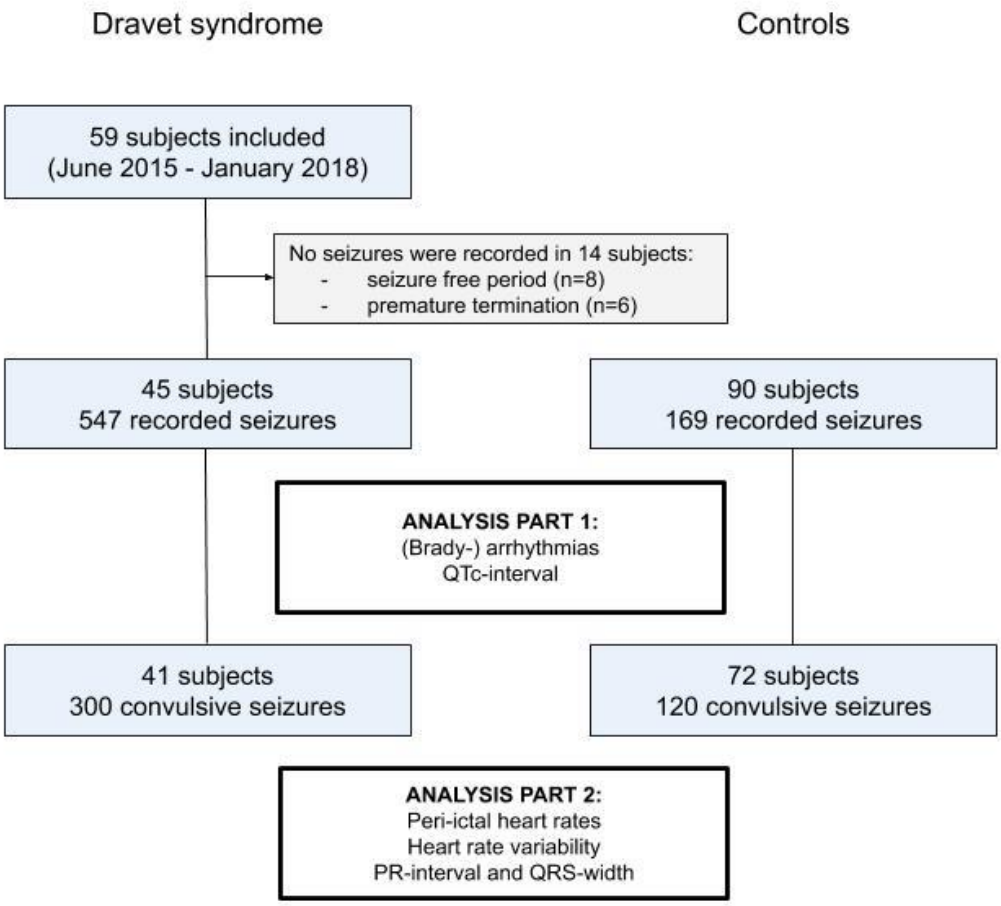


Table 12. Clinical characteristics Dravet syndrome cases and historical epilepsy controls.

Characteristics	Dravet syndrome (n = 45)	Controls (n = 90)	P-value
Sex, n (%) female	23 (51)	46 (51)	1
Age, years mean (SD)	19 (10)	20 (9.4)	0.54
Epilepsy duration, years mean (SD)	19 (12)	9 (6.5)	<0.001
Seizure frequency per month, median (IQR)	12 (8-25)	8 (3-30)	0.09
Seizures predominantly, n (%)[1]			0.001
• **Nocturnal**	• 26 (58)	• 26 (29)	
• **Diurnal**	• 4 (9)	• 31 (34)	
• **Both**	• 15 (33)	• 33 (37)	
Number of ASM, median (range)	3 (0-4)	2 (0-4)	<0.001
ASM differences[2]			
• **Valproic acid**	35 (78)	27 (30)	<0.001
• **Clobazam**	28 (62)	19 (21)	<0.001
• **Stiripentol**	19 (42)	1 (1)	<0.001
• **Topiramate**	14 (31)	3 (3)	<0.001
• **Lamotrigine**	3 (7)	28 (31)	0.001
• **Carbamazepine**	2 (4)	24 (27)	0.002
• **Oxcarbazepine**	2 (4)	21 (23)	0.006
• **Lacosamide**	0	8 (9)	0.039
VNS, n (%)	8 (18)	3 (3.3)	0.012
MRI abnormalities, n (%)	8 (18)	39 (43)	0.001
History cardiac illness, n (%)[3]	0 (0)	2 (2.2)	NA
Epilepsy aetiology, n			NA
• **Structural**	• 0	• 50	
• **Genetic**	• 45	• 13[4]	
• **Infectious**	• 0	• 1	
• **Metabolic**	• 0	• 0	
• **Immune**	• 0	• 1	
• **Unknown**	• 0	• 25[5]	
Seizure triggers, n (%)	41 (91)	Not assessed	NA
• **Fever/illness**	• 29 (64)		
• **Excitement or stress**	• 22 (49)		
• **Fatigue or lack of sleep**	• 13 (29)		
• **Exercise**	• 5 (11)		
• **Heat**	• 16 (36)		
• **Temperature changes**	• 4 (8.9)		
• **Vaccination**	• 20 (44)		
• **Photosensitivity[6]**	• 5 (11)		

• **Menstruation**	• 2 (4.4)		
Behaviour problems, n (%)	19 (42)	Not assessed	NA
Motor disorder, n (%) • **Crouched gait** • **Wide based gait** • **Spaghetti legs** • **No walking/wheelchair** • **No disorder**	 • 27 (60) • 7 (16) • 2 (4.4) • 4 (8.9) • 5 (11)	Not assessed	NA
Age developmental delay first noticed, years mean (SD)	2.4 (1.7)	Not assessed	NA
***SCN1A* variant type, n[7]** • **Missense** • **Splice site** • **Nonsense** • **Small frameshift deletions** • **Small frameshift duplications** • **Gross deletions** • **Gross duplications** • **Unknown** **Parents tested, n** • **Negative** • **Positive[8]** • **Not tested**	 • 15 • 2 • 12 • 11 • 3 • 2 • 1 • 2 • 35 • 1 • 9	Not assessed	NA
Family history, n • **Febrile seizures** • **Epilepsy** • **Sudden cardiac death**	 12 (8 first-degree) 11 (4 first-degree) 6 (1 first-degree)	Not assessed	NA

[1] As reported by cases/caregivers; [2] Antiseizure medication types per subject are provided in Table A6; [3] One control with an atrial septum defect type II and one with bigeminy/trigeminy; [4] Six controls had a generalised epilepsy syndrome with a presumed genetic aetiology (e.g. juvenile myoclonic epilepsy), five a genetic cause of a focal epilepsy/encephalopathy (DEPDC5, GRIN1, SLC6A5 and PCDH19, and trisomy 13), one Doose syndrome and one blepharophimosis-mental retardation syndrome (BMRS); [5] 10 of these 25 underwent genetic testing without any findings; [6] As reported by cases/caregivers; [7] One case had a missense variant type and a small frame shift deletion, and two cases had a small frameshift deletion and insertion; all *SCN1A* variants are shown in Table A5; [8] One case has a mother with low-graded mosaicism. ASM = antiseizure medication; IQR = interquartile range; NA = not applicable; VNS = vagal nerve stimulator.

6.3.2 Seizures

Continuous ECG during a total of 19,174 hours was recorded in the 45 cases (mean 426 hours per case; Figure 14). A total of 547 seizures were

captured, resulting in a median of 7 seizures per person (range 1-69). Seizure types recorded in cases were: 300 CS (55%), 33 tonic (6%), 12 focal seizures with impaired awareness (2.2%), nine focal motor seizures (1.6%), seven hemiclonic (1.3%), one clonic (0.2%), 41 unknown type (7.5%) and 144 unreported seizures (26%) (Table 13). Of all 547 seizures, 77 arisen from wakefulness (14%) and 470 from sleep (86%). Nearly all unreported seizures were from sleep (135, 94%). Examples of how the unreported seizures were identified are shown in Figure 15. None of the recorded seizures in cases occurred during a period of illness or fever.

Figure 14. Hours of ECG recording, total number of seizures and the proportion of unreported seizures for each subject of the Dravet syndrome group.

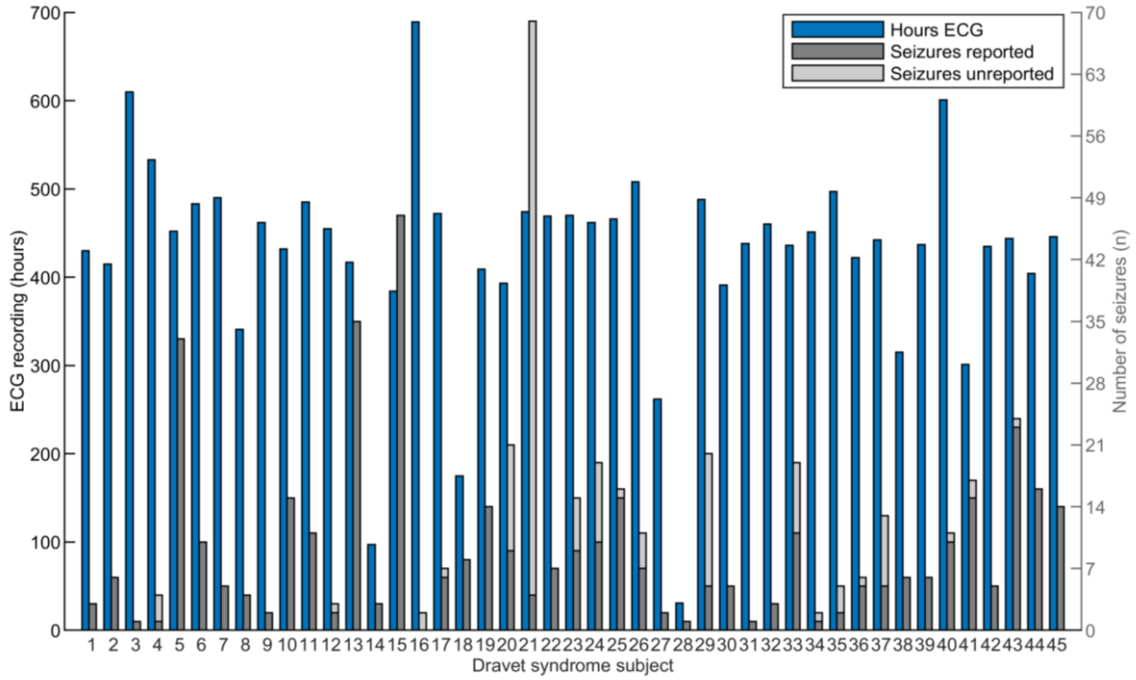
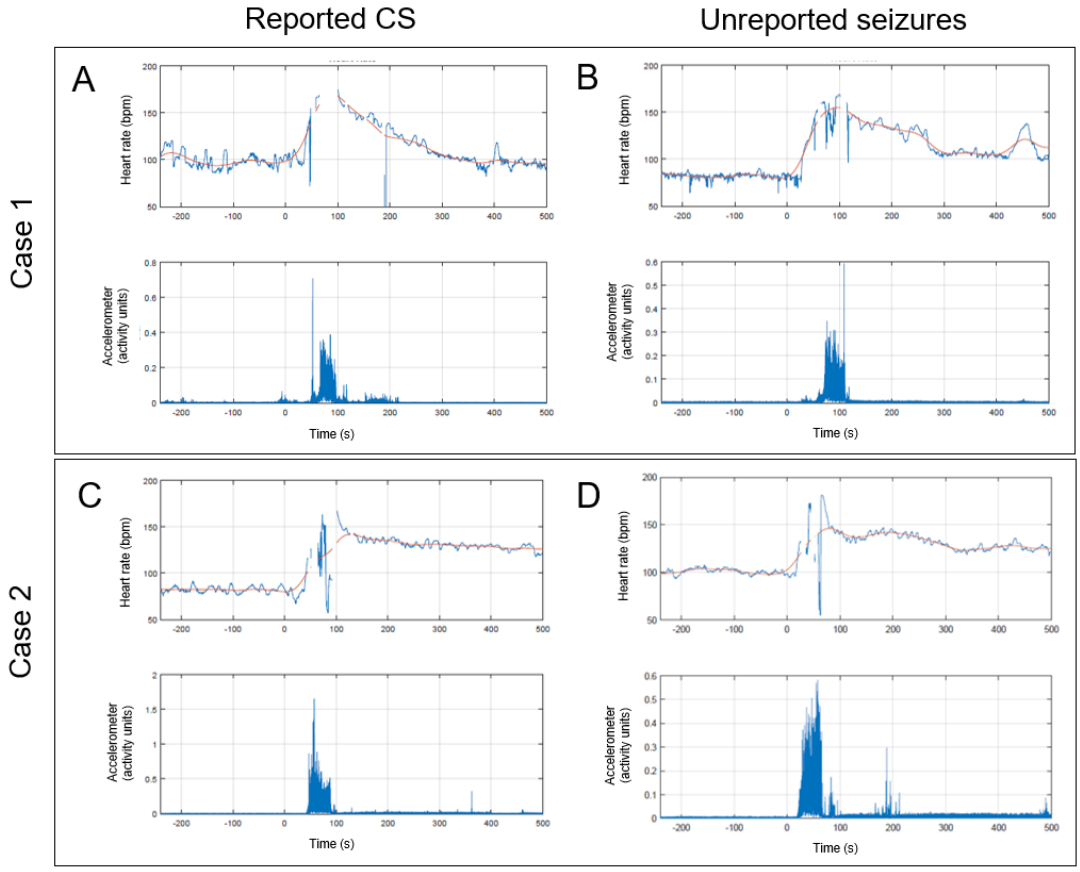


Figure 15. Example of how unreported seizures were detected based on the resemblance to heart rate patterns and accelerometery of reported convulsive seizures in two Dravet syndrome cases.



Seizures A and C were reported convulsive seizures and B and D were unreported seizures. For each seizure the heart rate curve is shown in the top graph and the accelerometer activity in the graph below. A and D occurred from wakefulness and B and C from sleep. Unreported seizures were only included in the study if: 1) the heart rate pattern resembles a reported CS, as illustrated in this figure; 2) heart rate changes did not coincide with a sudden body position change (as indicated by the tri-axial accelerometer) and 2) seizures in this person were known to be sometimes missed (e.g. found in a postictal state or with incontinence). CS = Convulsive seizure.

In the 90 controls, 169 seizures were recorded with a median of 1 seizure per person (range 1-8). Seizure types recorded were: 120 CS (71%), 29

tonic seizures (17%), 18 focal seizures with impaired awareness (11%) and two hemiclonic seizures (1.2%). Of the 169 seizures, 67 were from wakefulness (40%) and 102 from sleep (60%).

6.3.3 Electrocardiographic findings

6.3.3.1 Baseline 12-lead ECG

In five people with DS, abnormalities were found in the baseline ECG: atrial rhythm (n=2), right axis deviation (n=1), ST-segment abnormalities in all leads (n=1) and negative T-waves in V1-4 (n=1) leading to two referrals for further cardiac evaluation (ST-segment abnormalities and negative T-waves). No signs of cardiomyopathy were found in the case with negative T-waves.

6.3.3.2 Analysis part 1: Brady-arrhythmias and QTC-intervals

Post-ictal asystole was not seen in either group. Postictal bradycardia was more common in seizures of controls (n=11 (6.5%), in eight subjects) compared to cases (n=4 (0.7%), in two subjects; p=0.002; corrected for within-subject correlation, onset sleep/wakefulness and seizure type; Table 13). In the controls five of these 11 seizures were CS and six were tonic, and eight seizures occurred from sleep. In the cases all four were tonic seizures occurring from sleep. The only ASM used by these controls known to cause bradycardia sometimes, carbamazepine, was not used more often in those with bradycardia (n=3 (38%)) versus without (n=21 (26%); p=0.48).

Peri-ictal QTc-lengthening of ≥60 ms was more common in cases (n=64 (12%), in 23 subjects) than controls (n=8 (4.7%), in eight subjects; p=0.048; corrected for within-subject correlation, onset sleep/wakefulness and

seizure type). Within the Dravet group the median age did not differ between those with QTc-lengthening (n=23; median age 14 years, interquartile range (IQR) 12-21 years) and those without (n=22; median age 18 years, IQR 14-25; p=0.119). The use of drugs which may prolong QTc-interval did also not differ between cases with QTc-lengthening (n=3, 13%) and those without (n=1, 5%; p=0.32). This concerned antipsychotic drugs in all four cases. Types of ASM per person and the presence of ictal QTc-lengthening of ≥60 ms or bradycardia are provided in Table A6.

No difference was found in the number of seizures with ictal QTc-shortening of ≥60 ms between cases (n=15 (2.7%), in seven subjects) and controls (n=13 seizures (9.5%), in 11 subjects; p=0.39). The occurrence of prolonged (cases n=1 (0.2%) versus controls n=1 (0.6%); p=0.7) and shortened QTc (cases n=31 (5.7%) versus controls n=12 (7.1%); p=0.82) also did not differ between the groups. Marked prolongation and shortening did not occur in either group.

Table 13. Seizure types and ictal electrocardiographic findings in the Dravet syndrome and historical epilepsy control group.

	Dravet syndrome n = 45	**Controls n = 90**	**P-value**	**95% CI of OR**
Seizure types, n (%)				
Total	547	169	NA	NA
Convulsive	300 (55)	120 (71)	NA	NA
Tonic	33 (6)	29 (17)	NA	NA
Focal impaired awareness	12 (2.2)	18 (11)	NA	NA
Focal motor	9 (1.6)	0	NA	NA
Hemiclonic	7 (1.3)	2 (1.2)	NA	NA
Clonic	1 (0.2)	0	NA	NA
Unknown type reported	41 (7.5)	0	NA	NA
Unreported	144 (26)	0	NA	NA
Electrocardiographic findings, n seizures (n subjects; %)				
Bradycardia	4 (2; 0.7)	11 (8; 6.5)	0.002	1.2-5.3
Prolonged QTc • **T1** • **T2** • **T3** • **T4**	1 (1; 0.2) • 0 • 0 • 1 • 1	1 (1; 0.6) • 0 • 1 • 0 • 0	0.7	-1-2.8
Shortened QTc • **T1** • **T2** • **T3** • **T4**	31 (12; 5.7) • 17 • 5 • 10 • 5	12 (12; 7.1) • 5 • 4 • 3 • 2	0.82	-0.72-0.92
Ictal QTc-lengthening of ≥60 ms versus T1 • **T2** • **T3** • **T4**	64 (23; 12) • 53 • 4 • 9	8 (8; 4.7) • 4 • 1 • 3	0.048	-1.7--0.21
Ictal QTc-shortening of ≥60ms versus T1 • **T2** • **T3** • **T4**	15 (7; 2.7) • 12 • 3 • 2	13 (11; 7.7) • 10 • 5 • 4	0.39	-0.26-2

The Holm-Bonferroni method was used to correct for the multiple comparisons of the QTc-interval. Corrected p-values and original CIs are shown. Generalised estimating equations were used to correct for within-subject correlation, seizure onset from sleep or wakefulness and seizure type (convulsive seizure yes/no). QTc changes can occur at multiple time

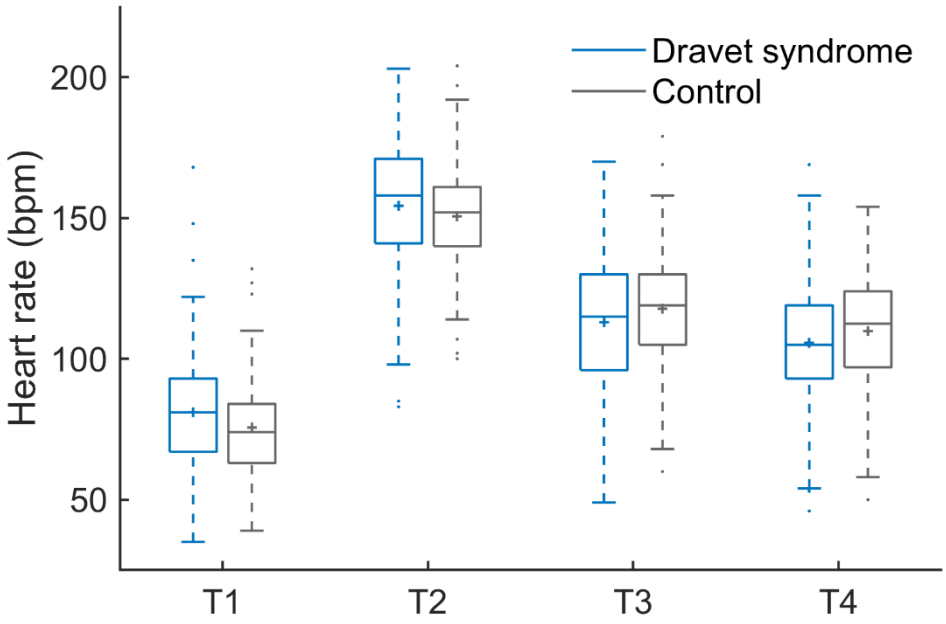
points within seizures. CI = confidence interval; NA = not applicable; OR = odds ratio; T1 = time of seizure onset; T2 = seizure end; T3 = two minutes after seizure end; T4 = five minutes after seizure end.

6.3.3.3 Analysis part 2: Peri-ictal heart rates, heart rate variability, QRS-width and PR-interval in convulsive seizures

In 41 cases, 300 CS and in the 72 controls, 120 CS were analysed. In cases 56 CS (19%) were from wakefulness and 244 (81%) from sleep and in the controls 49 CS (42%) from wakefulness and 71 from sleep (59%). Mean age in this selection of the DS group was 19 years (±11 years) and 20 were female (49%). In controls the mean age was 21 years (±9.3 years) and 35 were female (49%).

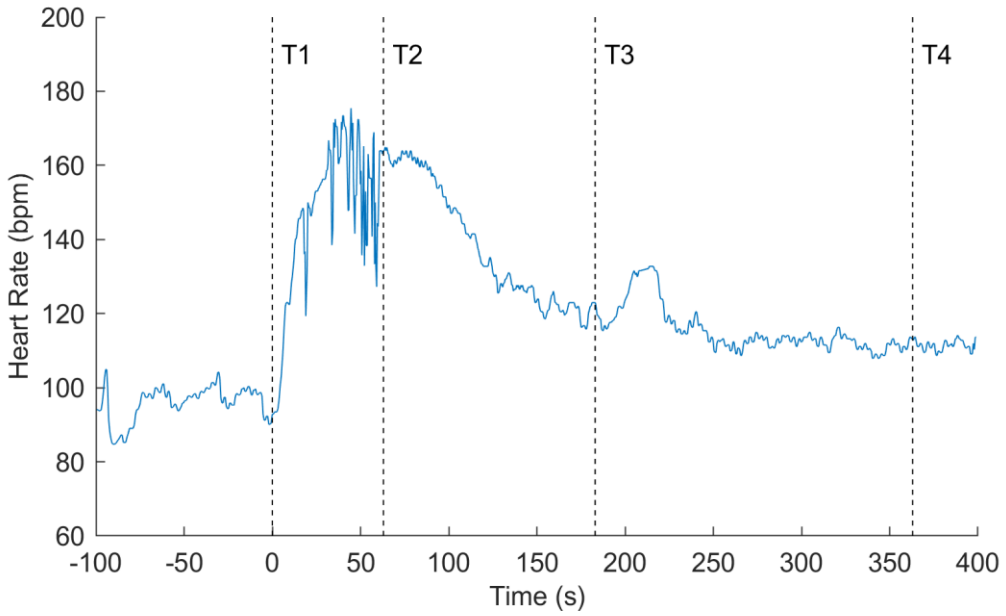
Heart rates did not differ between cases and controls (Figure 16). At T1 mean heart rate in DS was 81 bpm (±19) versus 76 bpm (±17) in controls (p=0.092); at T2 154 bpm (±23) versus 151 bpm (±20; p=0.75); T3 113 bpm (±24) versus 118 bpm (±22; p=0.92); T4 106 bpm (±22) versus 110 bpm (±21; p=0.39). Figure 17 is an example of a continuous heart rate curve during a CS in a DS case, with the timing of the four peri-ictal timepoints.

Figure 16. Box plots of peri-ictal heart rates in convulsive seizures of the Dravet syndrome (blue) and historical epilepsy control group (grey).



Median (solid line), mean (plus sign), interquartile interval (box), minimum, maximum (whiskers, 1.5 interquartile range) and suspected outliers (dots) are shown. Generalised estimating equation linear models were used to compare heart rates between the groups, correcting for within-subject correlation and seizure onset from sleep or wakefulness. T1 = time of seizure onset; T2 = seizure end; T3 = two minutes after T2; T4 = five minutes after T2.

Figure 17. Heart rate curve during a convulsive seizure of a 14-year-old girl with Dravet syndrome from one minute prior to seizure onset to five minutes after seizure end.



This seizure occurred from wakefulness. T1 = time of seizure onset; T2 = seizure end; T3 = two minutes after T2; T4 = five minutes after T2.

The median resting state HRV variable RMSSD was lower in Dravet (37ms) than in controls (51ms; p=0.029; corrected for within-person correlation and onset sleep/wakefulness; Table 14). Other resting state HRV variables were not significantly lower in DS: SDNN was 40ms in Dravet and 55ms in controls (p=0.052) and pNN50 was 16ms in Dravet and 32ms in controls (p=0.06). During the resting state minute, mean heart rate was higher in cases (RR 740ms) than in controls (RR 884ms; p<0.001). Mean heart rate and HRV variables of the pre- and post-ictal minute did not differ between the groups.

Table 14. Heart rate variability in rest and before and after convulsive seizures in Dravet syndrome and historical epilepsy controls.

HRV variables (ms)	Dravet syndrome n = 300 in 41 subjects	Controls n = 120 in 72 subjects	P-value	95% CI
Awake rest, n subjects				*CI of difference*
Number of people	41	66	NA	NA
RR interval, mean (SD)	740 (140)	884 (175)	<0.001	80-208
RMSSD, median (IQR)[1]	37 (20-58)	51 (33-76)	0.029	-15-26
SDNN, median (IQR)[1]	40 (23-60)	55 (37-68)	0.052	-9.6-22
pNN50, median (IQR)	16 (1.2-42)	32 (12-52)	0.06	0.14-19
Pre-ictal				*CI of OR*
Number of seizures	285	100	NA	NA
RR interval, mean (SD)	769 (201)	821 (202)	0.18	1.8-168
RMSSD, median (IQR)[1]	46 (21-107)	44 (26-81)	1	-0.1-0.09
SDNN, median (IQR)[1]	46 (26-99)	51 (31-73)	1	-0.07-0.08
pNN50, median (IQR)[2]	22 (2.4-58)	20 (4.9-51)	0.99	-11-11
Postictal				
Number of seizures	288	117	NA	NA
RR interval, mean (SD)	582 (151)	530 (105)	0.34	-98-6.1
RMSSD, median (IQR)[1]	21 (8.8-66)	17 (6.3-52)	0.8	-0.24-0.07
SDNN, median (IQR)[1]	29 (15-59)	27 (14-50)	0.68	-0.13-0.09
pNN50, median (IQR)[2]	3.2 (0-31)	1.7 (0-16)	0.72	-12-4.5

The Holm-Bonferroni method was used to correct for multiple comparisons within each epoch. Corrected p-values and original CIs are shown. Resting HRV variables were compared using two-sided unpaired t-tests or Mann-Whitney U test. Peri-ictal HRV variables were compared using generalised estimating equation linear models, correcting for within-person correlation and seizure onset from sleep or wakefulness. [1] Logarithmic transformation was applied to RMSSD and SDNN; [2] pNN50 variable was treated as normal distribution in the model as no distribution type fitted original or transformed data. CI = confidence interval; OR = odds ratio; HRV = heart rate variability; IQR = interquartile range; pNN50 = proportion of pairs of successive RR intervals that differ ≥50 ms; RMSSD = root mean square of successive differences of RR intervals; SDNN = standard deviation of RR intervals.

There were no differences between the groups in the occurrence of peri-ictal prolonged QRS-widths and PR-intervals. Prolonged QRS did not occur in cases while in the control group one mild prolongation was seen (at T1, 2ms above normal limit). Prolonged PR was rare in controls (n=3) and DS (n=1). The first control had prolonged PR in one CS at T4 (3ms above

normal limit), the second subject in one of six CS at T1 and T4 (by 17ms and 6ms) and the third control in one CS at T1 and T4 (by 3ms and 7ms). The DS case had a mildly prolonged PR interval in one CS at T1 (1ms above normal limit).

6.4 Discussion

I prospectively recorded a total of 19,174 hours of ECG and captured 547 seizures in 45 people with DS. I did not identify actionable major arrhythmias. Peri-ictal QTc-lengthening of ≥60 ms was, however, more prevalent in DS compared to controls. In line with previous reports, interictal HRV was lower in DS compared to controls.

6.4.1 Main findings

Peri-ictal QTc-lengthening of ≥60 ms in cases was more common than in controls and up to four times more common than in other epilepsy syndromes (Brotherstone *et al.*, 2010; Moseley and Britton, 2014; Moseley *et al.*, 2011b). The prolongation of QTc may be the result of a less stable cardiac repolarisation in DS that increases the propensity for malignant tachyarrhythmias (Johnson and Ackerman, 2009). Peri-ictal prolongation of ≥60 ms in DS rarely resulted in pathologically prolonged QTc. It was brief in most seizures and often resolved right after seizure end.

Peri-ictal respiratory dysfunction is common in people with DS (Kim *et al.*, 2018). Studies in healthy subjects showed that hypoxia and hypercapnia can prolong QTc (Kiely *et al.*, 1996; Roche *et al.*, 2003). Results of studies comparing QTc changes in seizures with and without an SpO2 drop of <90% were conflicting: one found more QTc-shortening and lengthening in the

desaturation group (Seyal *et al.*, 2011), while the other found no differences (Moseley and Britton, 2014). A recent larger study, using a mixed-effect model, that, unlike previous studies, included SpO2 as a continuous variable, and heart rate and peri-ictal phase as essential covariates, found that peri-ictal QTc changes strongly correlate with SpO2 (Goldenholz *et al.*, 2017). The QTc-prolongation found in this cohort may thus result from ictal hypoxaemia rather than unstable repolarisation caused by the *SCN1A* mutation.

The lower interict al resting HRV in DS compared to controls confirms previous findings (Delogu *et al.*, 2011; Ergul *et al.*, 2013; Lyu *et al.*, 2019; Myers *et al.*, 2018). This may predispose individuals to sudden autonomic dysfunction in the setting of a seizure, although direct evidence linking HRV to SUDEP is lacking. Increases in heart rate are correlated with decreases in HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Toth *et al.*, 2010). Decreased interictal HRV in Dravet may thus particularly cohere with a higher resting heart rate. No excessive peri-ictal heart rate changes occurred in DS, as peri-ictal heart rates and HRV did not differ from those in the control group.

Postictal bradycardia was unexpectedly more common in controls than in DS. Mouse model studies have reported episodes of bradycardia postictally prior to death but also during non-fatal seizures (Auerbach *et al.*, 2013; Kalume *et al.*, 2013; Kim *et al.*, 2018). Breathing measurements showed that ictal bradycardia only occurred if there was apnoea or severely decreased breath amplitude in seizures of *Scn1a*$^{R1407X/+}$ mice (Kim *et al.*,

2018). Postictal abnormal breathing may thus explain the occurrence of postictal bradycardia in these controls. Alternatively, comedications or ASM may have played a role. The only ASM used in these controls, however, that is known to sometimes cause bradycardia (i.e. carbamazepine) was not used more in controls with bradycardia versus without.

6.4.2 Cardiac function in Dravet syndrome

The role of cardiac dysfunction in SUDEP in people with DS may not be as prominent as previous evidence suggested and may only occur in response to respiratory dysfunction. Mice with selective knockout of *SCN1A* in brain interneurons only, and not in cardiac myocytes only, can also experience seizures and die spontaneously (Cheah *et al.*, 2012). Single cell electrophysiology experiments of human- and mice-derived cardiac myocytes did find increased sodium currents and spontaneous contraction rates in DS compared to control cells (Auerbach *et al.*, 2013; Frasier *et al.*, 2018). It may seem counterintuitive that reduced sodium channels (due to *SCN1A* haploinsufficiency) leads to these findings. This may, however, reflect compensatory overexpression of other sodium channels (i.e. Nav1.5 encoded by *SCN5A*) (Auerbach *et al.*, 2013; Frasier *et al.*, 2018), which would be in line with the observed QTc-lengthening. It is not clear, however, how these electrophysiological studies of mice and single mutated cells translate to whole-organ, innervated, human cardiac function. Human phenotypes caused by pathogenic de novo *SCN1A* variants are highly variable with regards to developmental outcome and epilepsy severity (Ceulemans *et al.*, 2004b; Meng *et al.*, 2015; Zuberi *et al.*, 2011). Major determinants of disease severity are type and location of variants.

Mosaicism is another important modifier that is common in DS (de Lange *et al.*, 2018; Depienne *et al.*, 2009; Meng *et al.*, 2015). Overall, cases with mosaicism show milder phenotypes (Depienne *et al.*, 2009; Meng *et al.*, 2015) but severely affected (i.e. profound learning disability and high seizure frequency) and SUDEP cases have been described (de Lange *et al.*, 2018). Modifiers other than the presence mosaicism must have a large influence, like the degree of mosaicism (i.e. percentage of mutated allele in blood) and variants in other genes (de Lange *et al.*, 2018). Phenotype variability likely also applies to cardiac function but the severity of channel disruption in the heart by the different variants (i.e. types, locations, and presence and degrees of mosaicism) remains to be discovered.

6.5 Limitations

The Dravet cohort, of people six years and older, might be an enriched selection, as SUDEP in this syndrome mostly affects young children. The reported SUDEP cases in DS are, however, likely to be biased towards the young, as improved genetic testing and awareness over the last two decades has enabled increased early diagnosis. A younger cohort might have exhibited a higher SUDEP risk but the high frequency of CS alone places them at high risk for SUDEP (Harden *et al.*, 2017; Hesdorffer *et al.*, 2011). The age of cases with and without QTc-lengthening did not differ. The age factor therefore does not appear to influence conclusions of this study.

Seizure frequencies reported by carers in diary notes are known to be underestimated (Elger and Hoppe, 2018). Some seizures, and thus

potential ictal arrhythmias, within this cohort may therefore have been missed. To overcome this, the complete recordings were meticulously inspected for (likely convulsive) seizures, and many unreported seizures were identified and assessed for arrhythmias. These unreported seizures were not included in the peri-ictal heart rate analysis as to ensure only definite CS were involved.

A second issue with the seizure diaries is the accuracy of the data (Elger and Hoppe, 2018). I compared diary reported seizures to video-EEG reported seizures, the gold-standard for detection and diagnostic evaluation (Hamandi *et al.*, 2017). Although the identification of seizures in controls were based on video-EEG, the timing of seizure onset and end was determined from ECG data only. To minimise potential error of data on seizure type, I extensively discussed and coded all seizure types with the carers before the measurements started. I could validate the occurrence and timing of seizures with ECG and tri-axial accelerometer. Additionally, I included only those seizures with a clear heart rate increase of at least 10%. Nevertheless, without EEG correlation it is not certain that all reported events are truly epileptic.

Ideally, controls should consist of people resembling the DS phenotype, with refractory epilepsy and learning disabilities, and be recorded prospectively. Equal recording methods would also enable blinding for the analysis, which was not possible due to different data sources (i.e. one versus three ECG channels and fragmented data from the video-EEG database versus continuous data of cases). The study burden would, however, be of concern in view of the young age and behavioural problems. The burden would not

be outweighed by evidence for increased propensity for arrhythmias, as in DS. The controls here, however, were predominantly people with refractory epilepsy, and learning disabilities were present in a considerable proportion – strengthening the power of the study population and supporting the validity of the results and conclusions.

Controls had more MRI abnormalities causing predominantly focal epilepsy than cases, who have a combined generalised and focal epilepsy (Scheffer *et al.*, 2017). Ictal asystole is more prevalent in those with temporal lobe epilepsy (van der Lende *et al.*, 2016b). No cases or controls with ictal asystole were identified in our cohort, so this bias did not seem to affect this study. For all other peri-ictal ECG changes (e.g. post-ictal asystole) no reliable studies are available that compare their prevalence in focal versus generalised epilepsies.

Some people in the control group with a genetic or unknown aetiology may have undiscovered cardiocerebral channelopathies. In the control group 15 of the 25 cases with an unknown aetiology were likely not tested for genetic mutations. I can, thus, not rule out that they have a mutation that puts them at risk for arrhythmias. Of the cases with a genetic aetiology only one had a mutation in an ion-channel (i.e. GRIN1) but this channel is not expressed in the heart. None of these controls had any clinical suspicion for DS (this was an inclusion criteria) or a history of cardiac illness.

Another limitation concerns the differences in ASM profiles. Stiripentol and valproic acid were more common in DS and can both increase levels of other medications (by enzyme inhibition) that can prolong the QT-interval

(e.g. antipsychotics and antidepressants). The dosages were not recorded. Of the DS cases only three of 23 QTc-lengthening were using comedications that may prolong the QT-interval and all were using either stiripentol or valproic. Of the controls, I could unfortunately not retrieve information about comedication. With this cohort size and high rates and heterogeneity of ASM polytherapy, however, I am insufficiently powered to assess the effect of separate ASM types on the study outcomes.

6.6 Conclusion

The analysis did not suggest any major peri-ictal cardiac arrhythmias which directly explain high SUDEP rates in DS. The QTc-lengthening measured in the immediate postictal period in the DS cohort may reflect unstable repolarisation due to the *SCN1A* mutation but can also be explained by ictal hypoxia. I believe important factors underlying SUDEP risk in DS are epilepsy severity, particularly the frequency of CS, and possibly ictal respiratory dysfunction.

Chapter 7 Future perspectives and conclusion

7.1 Future vision for epilepsy

7.1.1 Paradigm shift

An important conceptual breakthrough is currently happening. Epilepsy is increasingly seen as a symptom-complex which probably has multiple risk factors and a genetic predisposition rather than a condition with a single cause (Shmuely *et al.*, 2016b). The common comorbidities seem to suggest that epilepsy is a systemic problem and not a problem limited to the brain (Keezer *et al.*, 2016b). This evolving conceptualisation of epilepsy will have a major impact on the clinical interpretation, diagnosis and treatment.

7.1.2 Genetics

A ‘genetic contribution’ does not necessarily imply that a condition is inherited. As well as inherited mutations in a gene, epigenetic changes (switches in gene function that are not related to changes in underlying DNA sequence, e.g. environmental interactions explaining the variable risk of developing seizures in the aftermath of a head trauma or brain infection) and localised or organ-specific gene miscopying (deletions and duplications) also play a role (Thijs *et al.*, 2019). Accordingly, in the recent ILAE position paper on aetiology classification the term ‘idiopathic’, implying inheritance, is replaced by ‘genetic’ (Scheffer *et al.*, 2017). Genetic aetiologies are diverse, mutations can be either inherited or de novo, and, in most cases, the underlying genes are not (yet) known (Scheffer *et al.*, 2017).

Genome wide scanning in which the whole genomic code is available for assessment will soon be widely available. Genomic data of people with epilepsy can provide information on the cause, susceptibility, diagnosis and prognosis. Gene variations that contribute to refractoriness to ASM and associate with certain side effects may be identified. It will then not be long before developments in the area of pharmacogenomics will allow for tailored treatment, leading to a change from the current treatment model. To succeed in this, genomic assessment should be included as part of the clinical phenotyping of people with epilepsy at an early stage. It should be used as a tool, grounded in the whole clinical context, as we currently use EEG and MRI.

7.1.3 Comorbidities

All comorbidities, even the most inconspicuous, should be considered as part of the stratification and phenotyping in people with epilepsy. Physicians need to become better at noticing these symptom patterns. Pattern recognition can be fostered by incorporating validated screening instruments and guidelines, aiding the early identification and treatment of comorbid conditions. The presence of comorbidities should not deter treatment but requires a holistic approach. Insights into common mechanisms of epilepsy and comorbid conditions can lead to the ascertainment of common predispositions.

I believe epileptologists and cardiologists should work more closely together as more and more overlapping syndromes are recognised. The incorporation of ‘neurocardiology’ will require a critical review of current epilepsy services. Epileptologists may need to improve their cardiac skills.

Every person with epilepsy should have at least one baseline 12-lead ECG recording, as was recently included in the 2018 guideline of the National Institute of Health and Care Excellence (NICE) (National Institute for Health and Care Excellence, 2018). This guideline, however, does not clarify who should look at the recording and who is responsible for the assessment. I believe epileptologists can be trained to assess the 12-lead ECG and they should have regular consultations with a cardiologist to discuss any uncertainties or abnormalities. In cases with abnormal ECG findings or a relevant family history, a specialist cardiac assessment should be done. Modern non-invasive long-term ECG devices ought to be accessible for selected individuals to further screen for cardiac conditions.

I found that some overlapping symptoms in CS and syncope, a major cause for misdiagnosis in epilepsy, can be easily distinguished by the differences in motor phenomena characteristics. The '10/20 rule' for jerks (<10 syncope and >20 CS) should be validated on other datasets of syncope and CS. It would also be valuable to see whether the motor features in cardiac syncope are similar to those found in the vasovagal syncope. In cardiac syncope, misinterpretation of the myoclonic jerks for signs of epilepsy can cause people to wait a few minutes and may lead to life-threatening situations (Moya *et al.*, 2009; National Institute for Health and Care Excellence, 2017).

7.1.4 Premature mortality

Many premature deaths in epilepsy are potentially preventable *(*Thurman *et al.,* 2017*)*. Specific precautions can reduce mortality in some cases, as with

driving restrictions – e.g. people could be advised to shower instead of bathe, or only bathe supervised to prevent drowning (Bell *et al.*, 2009).

Abovementioned timely identification and treatment of comorbid conditions will reduce future premature mortality rates. Epileptologists should screen for potentially modifiable risk factors in all people with epilepsy, as smoking, obesity, sedentary lifestyle, and hypertension. In case any of these factors are present, general health information and appropriate guidance should be provided.

7.2 Future vision for SUDEP

I believe there are three important pillars in future SUDEP research and developments: 1) increasing awareness, 2) improving individual risk determination and 3) development of prevention strategies.

7.2.1 Increasing awareness

Awareness of SUDEP remains poor among people with epilepsy, carers, medical students and physicians (Friedman *et al.*, 2014; Miller *et al.*, 2014). Studies have shown that the incidence of SUDEP is still likely underestimated due to insufficient recognition and misclassification of cause of death by physicians, medical examiners and coroners (Atherton *et al.*, 2017; Devinsky *et al.*, 2017; Kim *et al.*, 2016; Schraeder *et al.*, 2006). Accurate identification of SUDEP cases is essential to define public health burden, the full (heterogeneous) spectrum of cases, risk factors and potential preventative strategies.

In the UK, awareness did increase significantly after the National Sentinel Audit in 2002 (Hanna *et al.*, 2002). In 2005, SUDEP was included as an epilepsy-related death in the 'guidelines on autopsy practice' (Royal College of Pathologists, 2005). This led to a considerable increase in records of SUDEP as cause of death and helped to improve awareness substantially (Thom *et al.*, 2015). Deaths now classified as SUDEP, might have been classified as another epilepsy-related cause of death before 2005 (Shankar *et al.*, 2014). It is essential to be aware of these factors that greatly influence incidence numbers, especially when interpreting and comparing studies that report on incidences at different moments in time.

There is a big difference between what neurologists tell people with epilepsy about SUDEP and what the people would like to know. In North-America only 7% of neurologists discusses SUDEP with more than 90% of their patients and 12% of neurologists did not discuss it at all (Kroner *et al.*, 2014). Neurologists who did discuss SUDEP, more often experienced a SUDEP-case in the last two years or saw many people with epilepsy. This contrasts with polls among people with epilepsy, which shows that 71% would like to be informed about SUDEP irrespective of their own risk, 27% only if they have increased risk and only 2% would not like to be informed (Kroner *et al.*, 2014).

It is important that people with epilepsy and their families are well informed about the possibility of SUDEP and the known risk factors. It has not been assessed but it seems likely that increased awareness may help prevent deaths. Knowing about the risk can improve therapy compliance and may stimulate adherence to lifestyle measures (e.g. sufficient sleep). A person

may, for example, choose to live with a roommate instead of alone. It may also trigger people to quickly inform the neurologist when seizure frequency increases. Knowing about risk factors could increase a person's sense of control and reduce some of the suspense that may come from awareness of the risk. In my opinion, it makes sense to check whether any risk exists in this individual. In certain epilepsy syndromes, like childhood absence epilepsy, SUDEP risk is negligible and informing them could lead to unnecessary anxiety. A way to achieve this goal is to clearly instruct physicians about when and how to inform their patients through guidelines, like recently done in the SUDEP guideline of the AAN (Harden *et al.*, 2017).

Despite significant improvements in SUDEP awareness over the last two decades insufficient recognition and misclassification of death is still a concern. Increasing autopsy rates will yield more accurate estimates of epilepsy-related mortality. Post-mortem investigations of people with epilepsy should ideally be carried out in specialised centres, using epilepsy-specific protocols (e.g. thorough macro- and microscopic inspection of brain tissue) (Royal College of Pathologists, 2005). This will not only benefit recognition of epilepsy-related mortality but can also lead to discovery of previously unknown underlying causes of epilepsy.

There will always remain cases in which no autopsy is done that will be classified as probable SUDEP. As a result, risk factor studies often combine definite and probable cases. Standards for clinical evaluation of sudden death are lacking. This evaluation is particularly challenging in the elderly, as competing causes of death are more likely but not always evident. A retrospective review of sudden unexplained deaths with autopsy in a

population-based epilepsy cohort could be done to develop an algorithm for verbal autopsy. Clinical characteristics and circumstances of death, collected while blinded for autopsy findings, can be included in the model. This algorithm should be able to distinguish between SUDEP and non-SUDEP sudden deaths. After development it can be tested on a different cohort for validation.

7.2.2 Improving individual risk determination

Reliable interictal or ictal biomarkers, that can identify those at highest risk, would be extremely valuable. It will improve counselling and treatment of the individual, provide new means to search for risk factors, and may thereby lead to improved understanding of the underlying pathophysiology.

Numerous biomarkers (e.g. cardiac, autonomic, respiratory) have been and are being investigated in relation to SUDEP but all still lack evidence of being effective in predicting its occurrence. Many studies have used the (revised) SUDEP-7 inventory to search for risk factors or biomarkers (DeGiorgio *et al.*, 2010; Novak *et al.*, 2015). This inventory was developed as a surrogate marker for overall SUDEP risk but does not appear to be a reliable instrument (Odom and Bateman, 2018). Using this inventory carries the risk to identify markers that relate to CS rather than SUDEP. A trustworthy biomarker should, contrary to fluctuating clinical variables, always be present either in an interictal or ictal state.

Prospective studies of large cohorts with assessment of multiple potential biomarkers, full clinical phenotyping, and long-term follow-up can improve future risk profiling. My study on arrhythmias in DS stresses the need for

further studies on whether peri-ictal cardiac variables as QTc-lengthening, bradycardia, and decreased HRV can predict SUDEP risk. A 10-year follow-up of the studied DS cohort will be done and, in case some people have succumbed to SUDEP, additional analyses will be carried out. Future prospective studies should include EEG, breathing and oxygen saturation measurements in addition to ECG to reliably detect seizures and understand how the different mechanisms influence each other. I would specifically want to find out whether peri-ictal QTc-lengthening in Dravet syndrome occurs only in case of ictal oxygen desaturations or also without.

Certain genes may be identified as contributing to the risk of SUDEP as genome wide scanning is becoming more widely available. These genetic factors can provide insight into possible underlying pathomechanisms and benefit the development of individualised risk assessment (Leu *et al.*, 2015). For instance, in DS, the potential role of the variety of *SCN1A* mutations and mosaicism (de Lange *et al.*, 2018) in relation to sudden death is still understudied and may provide novel risk markers. A national repository of genetic material from a group of well-phenotyped SUDEP cases can enable future case-control association studies for detection of genetic risk factors. Genetic material can originate from various sources: 1) existing genetic repositories, 2) post-mortem collection during autopsy and 3) post-mortem collection in case no autopsy is performed (e.g. hair or nail). I have helped to plan the structure of such a database in the Netherlands and it has recently been put into use.

Search for novel biomarkers will likely be more successful when based on an improved understanding of the mechanisms underlying SUDEP. It is,

however, extremely challenging to assess underlying mechanisms as SUDEP is heterogeneous, unpredictable, rare, and mostly unwitnessed. Most of what is known about the pathomechanisms, originates from just a few SUDEP recordings in epilepsy monitoring units (Ryvlin *et al.*, 2013a). Efforts like MORTEMUS will continue but will inevitably consist of small groups. Large international retrospective case-control studies of peri-ictal data of non-fatal seizures of SUDEP victims in EMU seems a promising way to unveil relevant biomarkers.

7.2.3 Development of prevention strategies

Currently no evidence-based interventions for prevention of SUDEP are available. Some anti-SUDEP interventions currently practised, include rapid seizure identification and basic life support measures like repositioning from prone to lateral body position and tactile or auditory stimulation (Rugg-Gunn *et al.*, 2016). As the risk of SUDEP is strongly linked to seizures, especially CS, optimal treatment is the best way to minimize the risk (Ryvlin *et al.*, 2011).

When optimising the treatment, it is crucial to first reconsider whether this person truly has epileptic seizures. Often people with seemingly refractory epilepsy do not have epilepsy but PNES or syncope (Xu *et al.*, 2015). When the diagnosis of epilepsy is definite, epilepsy classification should be checked. A generalised epilepsy treated as a focal epilepsy can also result in refractory seizures. The next step is to make sure the person is taking the ASM.

It was found that 39% of people with epilepsy do not or irregularly take their ASM (Davis *et al.*, 2008). Breakthrough seizures most often result from non-adherence to ASM (Montouris and Jagoda, 2007). Non-adherence in people with epilepsy appears to be associated with increased health care costs (Davis *et al.*, 2008) and increased mortality (Faught *et al.*, 2008). Investigation and improvement of the adherence may have a far greater impact than any improvement in specific antiseizure treatments (Al-Aqeel and Al-Sabhan, 2011). Besides non-adherence, lifestyle factors such as sleep deprivation and excessive alcohol- or drug-use can negatively influence seizure frequency.

In case these measures are unsuccessful and seizures continue to occur, seizure detection could enable early signalling of CS, which may prevent SUDEP in some cases (van der Lende *et al.*, 2018). Evidence, including my own work, suggests that nocturnal CS are often missed (van der Lende *et al.*, 2016a), underscoring the need for improved detection. Timely detection of seizures, however, does not guarantee a successful outcome: there are reported cases in which, despite early resuscitation by medical staff, the person died (Langan *et al.*, 2000; Swinghamer *et al.*, 2012).

Promising developments in seizure detection are the miniaturised multimodal wearable detection devices, combining heart rate with other modalities, including accelerometery and electrodermal activity. These devices will likely improve detection accuracy and facilitate widespread use (Ulate-Campos *et al.*, 2016; van Andel *et al.*, 2016).

A bracelet measuring heart rate and accelerometery was found to reliably detect major nocturnal motor seizures (median sensitivity of 86%) in adults with intellectual disability in residential care (Arends *et al.*, 2018). The downside of a high sensitivity is the occurrence of false alarms. False alarms tend to be clustered in selective cases for yet unknown reasons (Arends *et al.*, 2018). I noticed, in the DS group, that within-subject interictal heart rate patterns of CS showed high similarity. I expect that personalised detection algorithms may provide a solution for these individuals with high false alarm rates. Further prospective home-based studies are needed to assess performance and tolerability of this device in children. The impact on the quality of life in these families should also be addressed in these studies, like the burden of false alarms. I would be wary of the involved sense of responsibility a carer may feel to attend every seizure and, consequently, the guilt one may experience in case of SUDEP.

7.3 Concluding remarks

Premature mortality in epilepsy is a major health problem. Cardiac comorbidities are common in people with epilepsy and are important contributors to the premature mortality. Cardiac comorbidities and epilepsy can have common genetic predispositions, like channelopathies, which can provide insight into common mechanisms for epilepsy. When cardiovascular conditions have events with similar semiology to seizures this can complicate the diagnostic process and lead to misdiagnosis. I found that easily observable motor features can distinguish syncope from epilepsy and I provide a guidance for the interpretation of clinical and home videos.

SUDEP is the most common cause of direct epilepsy-related mortality and despite efforts a substantial knowledge gaps still exist. A complex interplay of several pathomechanisms together with environmental factors likely underlies SUDEP. Effective preventative measures are lacking and the only known ways to potentially reduce SUDEP risk are optimal treatment of CS and nocturnal supervision. By conducting a literature review, I found that SUDEP is the most common cause of death in DS and that it mostly affects young children. High frequencies of CS are described particularly in young children with DS. In a prospective study, I found no major peri-ictal cardiac arrhythmias in people with DS that may directly explain high SUDEP rates. Peri-ictal QTc-lengthening, however, was more common in DS than in controls. This may reflect unstable repolarisation due to the *SCN1A* mutation but may also be explained by ictal hypoxia. I believe important factors underlying high SUDEP risk in DS include epilepsy severity and possibly respiratory dysfunction. Hopefully through continued high-quality research and increased awareness the incidence of SUDEP will reduce, and ultimately effective preventative measures can be developed.

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Appendix

Appendix 1: Tables

Table A1. Search strategy peri-ictal cardiac arrhythmias 2 July 2013.

Database	Search
PubMed	("Arrhythmias, Cardiac"[majr] OR "Death, Sudden, Cardiac"[Majr] OR "Heart Arrest"[majr] OR "Dysrhythmia"[ti] OR "Dysrhythmias"[ti] OR "Arrhythmia"[ti] OR "Arrhythmias"[ti] OR "Arrythmia"[ti] OR "Arrythmias"[ti] OR "Sick Sinus Syndrome"[ti] OR "Cardiac Sinus Arrest"[ti] OR "Atrial Fibrillation"[ti] OR "Atrial Flutter"[ti] OR "Bradycardia"[ti] OR "Brugada Syndrome"[ti] OR "Premature Cardiac Complexes"[ti] OR "Atrial Premature Complexes"[ti] OR "Ventricular Premature Complexes"[ti] OR "Commotio Cordis"[ti] OR "Heart Block"[ti] OR "Adams-Stokes Syndrome"[ti] OR "Atrioventricular Block"[ti] OR "Bundle-Branch Block"[ti] OR "Sinoatrial Block"[ti] OR "Long QT Syndrome"[ti] OR "Andersen Syndrome"[ti] OR "Jervell-Lange Nielsen Syndrome"[ti] OR "Romano-Ward Syndrome"[ti] OR "Parasystole"[ti] OR "Pre-Excitation Syndromes"[ti] OR "Lown-Ganong-Levine Syndrome"[ti] OR "Mahaim-type Pre-Excitation"[ti] OR "Wolff-Parkinson-White Syndrome"[ti] OR "Tachycardia"[ti] OR "Tachycardias"[ti] OR "Ventricular Fibrillation"[ti] OR "Ventricular Flutter"[ti] OR "heart rate variability"[ti] OR "Sudden Cardiac Death"[ti] OR "Sudden Cardiac Arrest"[ti] OR "asystole"[all fields] OR asystol*[all fields] OR "heart arrest"[ti] OR "cardiac arrest"[ti]) AND ("Epilepsy"[majr] OR "epilepsy"[ti] OR "epileptic"[ti] OR "Epilepsies"[ti] OR "Landau-Kleffner Syndrome"[ti] OR "Epilepticus"[ti] OR "Epilepsia"[ti] OR epileps*[ti] OR epilept*[ti] OR "sudep"[all fields] OR sudden unexpected death in epilepsy OR sudden unexplained death in epilepsy) ("Arrhythmias, Cardiac"[mesh] OR "Dysrhythmia"[ti] OR "Dysrhythmias"[ti] OR "Arrhythmia"[ti] OR "Arrhythmias"[ti] OR "Arrythmia"[ti] OR "Arrythmias"[ti] OR "Sick Sinus Syndrome"[ti] OR "Cardiac Sinus Arrest"[ti] OR "Atrial Fibrillation"[ti] OR "Atrial Flutter"[ti] OR "Bradycardia"[ti] OR "Brugada Syndrome"[ti] OR "Premature Cardiac Complexes"[ti] OR "Atrial Premature Complexes"[ti] OR "Ventricular Premature Complexes"[ti] OR "Commotio Cordis"[ti] OR "Heart Block"[ti] OR "Adams-Stokes Syndrome"[ti] OR "Atrioventricular Block"[ti] OR "Bundle-Branch Block"[ti] OR "Sinoatrial Block"[ti] OR "Long QT Syndrome"[ti] OR "Andersen Syndrome"[ti] OR "Jervell-Lange Nielsen Syndrome"[ti] OR "Romano-Ward Syndrome"[ti] OR "Parasystole"[ti] OR "Pre-Excitation Syndromes"[ti] OR "Lown-Ganong-Levine Syndrome"[ti] OR "Mahaim-type Pre-Excitation"[ti] OR "Wolff-Parkinson-White Syndrome"[ti] OR "Tachycardia"[ti] OR "Tachycardias"[ti] OR "Ventricular Fibrillation"[ti] OR "Ventricular Flutter"[ti] OR "heart rate variability"[ti] OR "asystole"[all fields] OR asystol*[all fields]) AND ("Epilepsy"[mesh] OR "epilepsy"[ti] OR "epileptic"[ti] OR "Epilepsies"[ti] OR "Landau-Kleffner Syndrome"[ti] OR "Epilepticus"[ti] OR "Epilepsia"[ti] OR epileps*[ti] OR epilept*[ti] OR "sudep"[all fields])
Embase	(exp *heart arrhythmia / OR exp *Heart arrest/ OR "Dysrhythmia".ti OR "Dysrhythmias".ti OR "Arrhythmia".ti OR "Arrhythmias".ti OR "Arrythmia".ti OR "Arrythmias".ti OR "Sick Sinus Syndrome".ti OR "Cardiac Sinus Arrest".ti OR "Atrial Fibrillation".ti OR "Atrial Flutter".ti OR "Bradycardia".ti OR "Brugada Syndrome".ti OR "Premature Cardiac Complexes".ti OR "Atrial Premature Complexes".ti OR "Ventricular Premature Complexes".ti OR "Commotio Cordis".ti OR "Heart Block".ti OR "Adams-Stokes Syndrome".ti OR "Atrioventricular Block".ti OR "Bundle-Branch Block".ti OR "Sinoatrial Block".ti OR "Long QT Syndrome".ti OR "Andersen Syndrome".ti OR "Jervell-Lange Nielsen Syndrome".ti OR "Romano-Ward Syndrome".ti OR "Parasystole".ti OR "Pre-Excitation Syndromes".ti OR "Lown-Ganong-Levine Syndrome".ti OR "Mahaimtype Pre-Excitation".ti OR "Wolff-Parkinson-White Syndrome".ti OR "Tachycardia".ti OR "Tachycardias".ti OR "Ventricular Fibrillation".ti OR "Ventricular Flutter".ti OR "heart rate variability".ti OR "Sudden Cardiac Death".ti OR "Sudden Cardiac Arrest".ti OR "asystole".mp OR asystol*.mp OR "heart

	arrest".ti OR "cardiac arrest".ti) AND (exp *Epilepsy/ OR "epilepsy".ti OR "epileptic".ti OR "Epilepsies".ti OR "Landau-Kleffner Syndrome".ti OR "Epilepticus".ti OR "Epilepsia".ti OR epileps*.ti OR epilept*.ti OR "sudep".mp OR sudden unexpected death in epilepsy.mp OR sudden unexplained death in epilepsy.mp)
Web of Science	(TI=((heart arrhythmia OR Heart arrest OR Dysrhythmia OR Dysrhythmias OR Arrhythmia OR Arrhythmias OR Arrythmia OR Arrythmias OR Sick Sinus Syndrome OR Cardiac Sinus Arrest OR Atrial Fibrillation OR Atrial Flutter OR Bradycardia OR Brugada Syndrome OR Premature Cardiac Complexes OR Atrial Premature Complexes OR Ventricular Premature Complexes OR Commotio Cordis OR Heart Block OR Adams-Stokes Syndrome OR Atrioventricular Block OR Bundle-Branch Block OR Sinoatrial Block OR Long QTSyndrome OR Andersen Syndrome OR Jervell-Lange Nielsen Syndrome OR Romano-Ward Syndrome OR Parasystole OR Pre-Excitation Syndromes OR Lown-Ganong-Levine Syndrome OR Mahaim-type Pre-Excitation OR Wolff-Parkinson-White Syndrome OR Tachycardia OR Tachycardias OR Ventricular Fibrillation OR Ventricular Flutter OR heart rate variability OR Sudden Cardiac Death OR Sudden Cardiac Arrest OR asystole OR asystol* OR cardiac arrest) AND (Epilepsy OR epilepsy OR epileptic OR Epilepsies OR Landau-Kleffner Syndrome OR Epilepticus OR Epilepsia OR epileps* OR epilept* OR sudep OR sudden unexpected death in epilepsy OR sudden unexplained death in epilepsy))) OR (TI=("heart arrhythmia" OR "Heart arrest" OR "Dysrhythmia" OR "Dysrhythmias" OR "Arrhythmia" OR "Arrhythmias" OR "Arrythmia" OR "Arrythmias" OR "Sick Sinus Syndrome" OR "Cardiac Sinus Arrest" OR "Atrial Fibrillation" OR "Atrial Flutter" OR "Bradycardia" OR "Brugada Syndrome" OR "Premature Cardiac Complexes" OR "Atrial Premature Complexes" OR "Ventricular Premature Complexes" OR "Commotio Cordis" OR "Heart Block" OR "Adams-Stokes Syndrome" OR "Atrioventricular Block" OR "Bundle-Branch Block" OR "Sinoatrial Block" OR "Long QT Syndrome" OR "Andersen Syndrome" OR "Jervell-Lange Nielsen Syndrome" OR "Romano-Ward Syndrome" OR "Parasystole" OR "Pre-Excitation Syndromes" OR "Lown-Ganong-Levine Syndrome" OR "Mahaim-type Pre-Excitation" OR "Wolff-Parkinson-White Syndrome" OR "Tachycardia" OR "Tachycardias" OR "Ventricular Fibrillation" OR "Ventricular Flutter" OR "heart rate variability" OR "Sudden Cardiac Death" OR "Sudden Cardiac Arrest" OR "asystole" OR asystol* OR "cardiac arrest") AND TS=("sudep" OR "sudden unexpected death in epilepsy" OR "sudden unexplained death in epilepsy"))
Cochrane	(heart arrhythmia OR Heart arrest OR Dysrhythmia OR Dysrhythmias OR Arrhythmia OR Arrhythmias OR Arrythmia OR Arrythmias OR Sick Sinus Syndrome OR Cardiac Sinus Arrest OR Atrial Fibrillation OR Atrial Flutter OR Bradycardia OR Brugada Syndrome OR Premature Cardiac Complexes OR Atrial Premature Complexes OR Ventricular Premature Complexes OR Commotio Cordis OR Heart Block OR Adams-Stokes Syndrome OR Atrioventricular Block OR Bundle-Branch Block OR Sinoatrial Block OR Long QT Syndrome OR Andersen Syndrome OR Jervell-Lange Nielsen Syndrome OR Romano-Ward Syndrome OR Parasystole OR Pre-Excitation Syndromes OR Lown-Ganong-Levine Syndrome OR Mahaim-type Pre-Excitation OR Wolff-Parkinson-White Syndrome OR Tachycardia OR Tachycardias OR Ventricular Fibrillation OR Ventricular Flutter OR heart rate variability OR Sudden Cardiac Death OR Sudden Cardiac Arrest OR asystole OR asystol* OR cardiac arrest) AND (Epilepsy OR epilepsy OR epileptic OR Epilepsies OR Landau-Kleffner Syndrome OR Epilepticus OR Epilepsia OR epileps* OR epilept* OR sudep OR sudden unexpected death in epilepsy OR sudden unexplained death in epilepsy)

For more information see (van der Lende et al., 2016b).

Table A2. Search strategy scope review 12 February 2016.

Database	Search
PubMed	(("Dravet syndrome"[tw] OR dravet*[tw] OR "severe myoclonic epilepsy"[tw] OR "severe myoclonic"[tw] OR severe myoclon*[tw] OR "SMEI"[tw] OR "smeb"[tw] OR "severe action"[tw] OR ("severe"[ti] AND myoclon*[ti] AND epilep*[ti])) AND ("Mortality"[Mesh] OR "mortality"[Subheading] OR "mortality"[tw] OR "Survivors"[Mesh] OR "Survivors"[tw] OR surviv*[tw] OR "Prognosis"[Mesh] OR "Prognosis"[tw] OR prognos*[tw] OR "death"[Mesh] OR "death"[tw] OR death*[tw]))
Embase	(("severe myoclonic epilepsy in infancy"/ OR "Dravet syndrome".mp OR dravet*.mp OR "severe myoclonic epilepsy".mp OR "severe myoclonic".mp OR severe myoclon*.mp OR "SMEI".mp OR "smeb".mp OR "severe action".mp OR ("severe".ti AND myoclon*.ti AND epilep*.ti) OR ("severe" ADJ3 myoclon* ADJ3 epilep*).mp) AND (exp "Mortality"/ OR "mortality".mp OR exp "Survivor"/ OR "Survivors".mp OR surviv*.mp OR "Prognosis"/ OR "Prognosis".mp OR prognos*.mp OR exp "death"/ OR "death".mp OR death*.mp)) NOT conference review.pt
Web of Science	(ts=("severe myoclonic epilepsy in infancy" OR "Dravet syndrome" OR dravet* OR "severe myoclonic epilepsy" OR "severe myoclonic" OR severe myoclon*) AND ti=("Mortality" OR "mortality" OR "Survivor" OR "Survivors" OR surviv* OR "Prognosis" OR "Prognosis" OR prognos* OR "death" OR "death" OR death*)) OR (TI=("severe myoclonic epilepsy in infancy" OR "Dravet syndrome" OR dravet* OR "severe myoclonic epilepsy" OR "severe myoclonic" OR severe myoclon*) AND TS=("Mortality" OR "mortality" OR "Survivor" OR "Survivors" OR surviv* OR "Prognosis" OR "Prognosis" OR prognos* OR "death" OR "death" OR death*))
Cochrane	ti/ab/kw (("severe myoclonic epilepsy in infancy" OR "Dravet syndrome" OR dravet* OR "severe myoclonic epilepsy" OR "severe myoclonic" OR severe myoclon*) AND ("Mortality" OR "mortality" OR "Survivor" OR "Survivors" OR surviv* OR "Prognosis" OR "Prognosis" OR prognos* OR "death" OR "death" OR death*))
CENTRAL	all text (("severe myoclonic epilepsy in infancy" OR "Dravet syndrome" OR dravet* OR "severe myoclonic epilepsy" OR "severe myoclonic" OR severe myoclon*) AND ("Mortality" OR "mortality" OR "Survivor" OR "Survivors" OR surviv* OR "Prognosis" OR "Prognosis" OR prognos* OR "death" OR "death" OR death*))
CINAHL	ti/ab/mw/su (("severe myoclonic epilepsy in infancy" OR "Dravet syndrome" OR dravet* OR "severe myoclonic epilepsy" OR "severe myoclonic" OR severe myoclon*) AND ("Mortality" OR "mortality" OR "Survivor" OR "Survivors" OR surviv* OR "Prognosis" OR "Prognosis" OR prognos* OR "death" OR "death" OR death*))
PsycINFO	ti/ab/mj/su (("severe myoclonic epilepsy in infancy" OR "Dravet syndrome" OR dravet* OR "severe myoclonic epilepsy" OR "severe myoclonic" OR severe myoclon*) AND ("Mortality" OR "mortality" OR "Survivor" OR "Survivors" OR surviv* OR "Prognosis" OR "Prognosis" OR prognos* OR "death" OR "death" OR death*))
Academic Search Premier	ti/su/kw (("severe myoclonic epilepsy in infancy" OR "Dravet syndrome" OR dravet* OR "severe myoclonic epilepsy" OR "severe myoclonic" OR severe myoclon*) AND ("Mortality" OR "mortality" OR "Survivor" OR "Survivors" OR surviv* OR "Prognosis" OR "Prognosis" OR prognos* OR "death" OR "death" OR death*))
ScienceDirect	TITLE("severe myoclonic epilepsy in infancy" OR "Dravet syndrome" OR dravet* OR "severe myoclonic epilepsy" OR "severe myoclonic" OR severe myoclon*) AND ("Mortality" OR "mortality" OR "Survivor" OR "Survivors" OR surviv* OR "Prognosis" OR "Prognosis" OR prognos* OR "death" OR "death" OR death*) KEY("severe myoclonic epilepsy in infancy" OR "Dravet syndrome" OR dravet* OR "severe myoclonic epilepsy" OR "severe myoclonic" OR severe myoclon*) AND ("Mortality" OR "mortality" OR "Survivor" OR "Survivors" OR surviv* OR "Prognosis" OR "Prognosis" OR prognos* OR "death" OR "death" OR death*)

Table A3. Standardised data extraction form scope review on premature mortality in Dravet syndrome.

Premature mortality in Dravet syndrome scope review	
Study details	
• Title	
• First author	
• Year	
• Country	
• Design	
• Study aims	
• Sampling approach	
• Case characteristics	
• Data collection methods	
Dravet syndrome cases	
• Cohort size (n)	
• Genetic testing performed (n)	
• Genetic test positive (n)	
• Age (y)	
• Follow-up (duration (y) and during what ages)	
Dravet syndrome mortality cases	
• Number of cases (n)	
• Age at death known (n)	
• Ages (list all ages)	
• Cause of death known (n)	
○ SUDEP (n, ages)	
○ SE (n, ages)	
○ Accident (n, ages)	
○ Infection (n, ages)	
○ Other (n, ages, description)	
○ Unknown (n, ages, description)	
Dravet syndrome SUDEP cases	
• Autopsy (n, n reported)	
• SUDEP classification	
• Signs of recent seizures (n, n reported)	
• Witnessed (n, n reported)	
• From sleep (n, n reported)	
• Found in prone position (n, n reported)	
Comments	

Table A4. Reference list of the 30 included publications on premature mortality in Dravet syndrome.

1	Ogino T, Ohtsuka Y, Yamatogi Y, Oka E, Ohtahara S. The epilectic syndrome sharing common characteristics during early childhood with severe myoclonic epilepsy in infancy. *Jpn J Psychiatry Neurol* 1989; 43: 479-81.
2	Renier WO, Renkawek K. Clinical and neuropathologic findings in a case of severe myoclonic epilepsy of infancy. *Epilepsia* 1990; 31: 287-91.
3	Miyake S, Tanaka M, Matsui K, Miyagawa T, Yamashita S, Yamada M, et al. Mortality patterns of children with epilepsies in a children's medical center. *No To Hattatsu* 1991; 23: 329-35.
4	Dravet C, Bureau M, Guerrini R, Giraud N, Roger J. Severe myoclonic epilepsy in infants. In Roger J, Bureau M, Dravet C, Dreifuss FE, Perret A, Wolf P (Eds) *Epileptic Syndromes in Infancy, Childhood and Adolescence*. 2nd edn. London: John Libbey & Company Ltd, 1992; 75–88.
5	Dooley J, Camfield P, Gordon K. Severe polymorphic epilepsy of infancy. *J Child Neurol* 1995; 10: 339-40.
6	Castro-Gago M, Sánchez JSM, Rodrígues-Nunez A, Fernández JLH, Eirís-Punal J. Severe myoclonic epilepsy and mitochondrial cytopathy. *Childs Nerv Syst* 1997; 13: 570-1.
7	Perez J, Chiron C, Musial C, Rey E, Blehaut H, d'Athis P, et al. Stiripentol: Efficacy and tolerability in children with epilepsy. *Epilepsia* 1999; 40: 1618-26.
8	Oguni H, Hayashi K, Awaya Y, Fukuyama Y, Osawa M. Severe myoclonic epilepsy in infants--a review based on the Tokyo women's medical university series of 84 cases. *Brain and Development* 2001; 23: 736-48.
9	Ceulemans B, Boel M, Claes L, Dom L, Willekens H, Thiry P, et al. Severe myoclonic epilepsy in infancy: toward an optimal treatment. *J Child Neurol* 2004; 19: 516-21.
10	Caraballo RH, Fejerman N. Dravet syndrome: a study of 53 patients. *Epilepsy Research* 2006; 70: 231-8.
11	Jansen FE, Sadleir LG, Harkin LA, Vadlamudi L, McMahon JM, Mulley JC, et al. Severe myoclonic epilepsy of infancy (Dravet syndrome): Recognition and diagnosis in adults. *Neurology* 2006; 67: 2224-6.
12	Akiyama M, Kobayashi K, Yoshinaga H, Ohtsuka Y. A long-term follow-up study of Dravet syndrome up to adulthood. *Epilepsia* 2010; 51: 1043-52.
13	Le Gal F, Korff CM, Monso-Hinard C, Mund MT, Morris M, Malafosse A, et al. A case of SUDEP in a patient with Dravet syndrome with *SCN1A* mutation. *Epilepsia* 2014; 51: 1915-8.
14	Catarino CB, Liu JY, Liagkouras I, Gibbons VS, Labrum RW, Ellis R, et al. Dravet syndrome as epileptic encephalopathy: Evidence from long-term course and neuropathology. *Brain* 2011; 134: 2982-3010.
15	Genton P, Velizarova R, Dravet C. Dravet syndrome: The long-term outcome. *Epilepsia* 2011; 52: 44-9.
16	Sakauchi M, Oguni H, Kato I, Osawa M, Hirose S, Kaneko S, et al. Retrospective multi-institutional study of the prevalence of early death in Dravet syndrome. *Epilepsia* 2011; 52: 1144-9.
17	Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations. *Epilepsia* 2011; 52: 95-101.
18	Brunklaus A, Ellis R, Reavy E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in *SCN1A* mutation-positive Dravet syndrome. *Brain* 2012; 135: 2329-36.
19	Okumura A, Uematsu M, Imataka G, Tanaka M, Okanishi T, Kubota T, et al. Acute encephalopathy in children with Dravet syndrome. *Epilepsia* 2012; 53: 79-86.
20	Brunklaus A, Ellis R, Reavey E, Forbes G, Zuberi SM. Epilepsy related death in *SCN1A* mutation positive Dravet syndrome. *Epilepsy Currents* 2013; Conference: 231.
21	Friedman D, Chyou J, Devinsky O. Sudden death in epilepsy: of mice and men. *J Clin Invest* 2013; 123: 1415-6.
22	Nabbout R, Chemaly N, Chipaux M, Barcia G, Bouis C, Dubouch C, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. *Orphanet J Rare Dis* 2013; 8: 176.
23	Wirrell EC, Laux L, Franz DN, Sullivan J, Saneto RP, Morse RP, et al. Stiripentol in Dravet syndrome: Results of a retrospective U.S. study. *Epilepsia* 2013; 54: 1595-1604.
24	Barba C, Parrini E, Coras R, Galuppi A, Craiu D, Kluger G, et al. Co-occuring malformations of cortical development and *SCN1A* gene mutations. *Epilepsia* 2014; 55: 1009-19.

25	Klassen TL, Bomben VC, Patel A, Drabek J, Chen TT, Gu W, et al. High-resolution molecular genomic autopsy reveals complex sudden unexpected death in epilepsy risk profile. *Epilepsia* 2014; 55: 6-12.
26	Takayama R, Fujiwara T, Shigematsu H, Imai K, Takahashi Y, Yamakawa K, et al. Long-term course of Dravet syndrome: A study from an epilepsy center in Japan. *Epilepsia* 2014; 55: 528-38.
27	Dede HÖ, GelİşİN Ö, Baykan B, GökyİğİT A. Definite SUDEP in Dravet Syndrome: An Adult Case Report. *J Neurol Sci* 2015; 7: 610-6.
28	Donner E, Friedman D, Kaufman B, et al. Sudden unexpected death in Dravet syndrome: A case-control study. *Epilepsy Currents*. 2015;Conference:450.
29	Kolikonda MK, Cherlopalle S, Shah VC, Lippmann S. Prevention of sudden death in patients with epilepsy. *Primary Care Companion for CNS Disorders*. 2015;17.
30	Verbeek NE, van der Maas NAT, Sonsma ACM, et al. Effect of vaccinations on seizure risk and disease course in Dravet syndrome. *Neurology.* 2015; 85:596-603.

Table A5. *SCN1A* variants of the 45 subjects in the Dravet syndrome group.

Subject #	***SCN1A* variant**	**Variant type** 1 missense 2 splice site 3 nonsense 4 small frameshift deletions 5 small duplications 6 gross deletions 7 gross duplications	**Parents tested negative**
1	c.1738C>T (p.Arg580Stop)	3	Yes
2	c.812G>A (p.Gly271Asp)	1	Yes
3	c.2837G>A (p.Arg946His)	1	Yes
4	c.4573C>T (p.Arg1525Stop)	3	Not tested
5	c.[4289C>A (+) 4551A>G] (p.[Thr1430Lys (+) Lys1517Lys]) (UV)	1; and a synonymous variant	Yes
6	c.3430-?_4002+?dup (dup exon17_exon20)	7	Yes
7	c.4841delT (p.Leu1614ProfsX4)	4	Yes
8	c.3790delA (p.Ile1264fs)	4	Yes
9	c.1510_1514delGAAAA (p.Arg504fs)	4	Yes
10	c.4298:G>A (p. Gly1433Glu)	1	Yes
11	c.5536_5539delAAAC (p.Lys1846fs)	4	Yes
12	c.2343T>A (p.Asn781Lys)	1	Yes
13	c.5734C>T (p.Arg1912Stop)	3	Not tested
14	c.5266T>C (p.Cys1756Arg)	1	Yes
15	c.[2113G>T];[=] (p.[(Glu705*)];[(=)] Chr2(GRCh37):g.[166898865C>A;=])	3	Yes
16	c.2791C>T (p.Arg931Cys)	1	Yes
17	c.[5536_5539del];[=] (p.[(Lys1846fs)]; [(=)])	4	Yes
18	c.2584C>T (p.Arg862Stop)	3	Yes
19	c.2814C>T (p.Arg1407Stop)	3	Yes
20	del SCN1A exon 2-23	6	Yes
21	c.[140delA (+) 2770G>A] (p.[Asn47fs (+) Ala924Thr])	4 and 1	Yes
22	c.4331C>A (p.Ser1444Tyr)	1	Yes
23	c.3542 del T (p. Phe 1181 fs X 1208)	4	Yes
24	c.[383+6delC];[=] (p.[(?)](VUS);[(=)])	2	Yes
25	c.5013delT (p.Phe1671fs)	4	Yes
26	c.2836G>A (p.Arg946His)	1	Not tested
27	c.1360C>T (p.Gln454X)	3	Yes
28	c.4757G>A (p.Gly1586Glu)	1	Not tested
29	c.[1285C>T];[=] p.[(Gln429*)];[(=)] (Chr2(GRCh37):g.[166903372G>A];[=])	3	Not tested
30	c.4633A>G (p.Ile1545Val) (UV)	1	Yes
31	c.4904_4905insT (p.Phe1635fsX1641)	5	Yes
32	c.4219C>T (p.Arg1407Stop)	3	Yes
33	c.1178G>A (p.Arg393His)	1	Yes
34	c.987_988delinsC (p.Leu331fs)	4 and 5	No, mother low graded mosaicism
35	c.2837G>A (p.Arg946His)	1	Not tested
36	c.5674C>T (p.Arg1892Stop)	3	Yes
37	c.3762T>A (p.Tyr1254Stop)	3	Not tested
38	C.383+5C>T	2	Yes
39	2q24.3-q31.1	6	Yes
40	c.1837C>T (p.Arg613Stop), Exon 11	3	Not tested
41	c.1177C>T (p.Arg393Cys), Exon 9	1	Yes
42	c.5536-5539 delAAAA (pLys 1846fsX.1858)	4	Yes
43	c.3458-3459delAAins CTACTGT	4 and 5	Yes
44	Unknown	Unknown	Yes
45	Unknown	Unknown	Yes

Table A6. Antiseizure medication types and presence of peri-ictal QTc prolongation ≥60ms and postictal bradycardia in ≥1 of the recorded seizures, of Dravet syndrome cases and historical epilepsy controls.

Case#	Age	ASM	QTc↑	Brady	Control#	Age	ASM	QTc↑	Brady
1	22	CLB, TPM, VPA	Yes		**1**	18	LCM, OCB		
2	15	-			**2**	22	CLB, LTG, OCB		
3	32	CLB, VPA			**3**	35	LTG, VPA	Yes	
4	66	CLP, VPA			**4**	63	CBZ, LTG		
5	14	CLB, STI, TPM, VPA	Yes		**5**	61	VPA		
6	13	PHN, TPM, VPA			**6**	39	CBZ, LEV, VPA		
7	7	CLB, LEV, STI, VPA			**7**	34	CBZ, LEV, LTG		
8	20	CLB, LEV			**8**	33	VPA		
9	18	LEV, TPM, VPA			**9**	34	CBZ, LCM		
10	17	CBD, STI, TPM	Yes		**10**	30	LTG, LEV, OCB, VPA		
11	11	CBD, CLB, LEV, STI, VPA	Yes		**11**	30	LEV	Yes	Yes
12	25	CLB, FLB, VPA			**12**	29	CLB, LCM		
13	13	CLB, TPM, VPA	Yes		**13**	27	CLB, VPA	Yes	Yes
14	7	CBD, CLB, LEV, ZNS	Yes		**14**	25	-		Yes
15	12	CLB, VPA	Yes		**15**	25	CBZ, LEV, LTG		
16	23	CLB, VPA			**16**	30	CBZ, CLB, VPA		
17	39	CBZ, PRI, TPM, VPA	Yes		**17**	27	CLB, LTG		
18	8	CLB, STI, VPA	Yes	Yes	**18**	25	LTG		
19	21	CLB, STI, VPA	Yes		**19**	23	CBZ, LTG		
20	25	CLB, OCB, TPM			**20**	23	LCM		
21	20	VPA, ZNS	Yes		**21**	27	LEV, OCB		
22	30	CLB, LEV, TPM, VPA		Yes	**22**	22	CBZ, VPA		
23	15	CBD, LEV, TPM, VPA	Yes		**23**	22	CLB, LEV, TPM		
24	23	CBZ, LTG, VPA	Yes		**24***	22	CLB, LTG, VPA		
25	29	LTG, TPM, VPA	Yes		**25**	23	OXZ	Yes	
26	14	CBD, LEV, STI, VPA	Yes		**26**	23	CBZ, VPA		
27	16	CLB, LTG, STI, TPM			**27**	22	LEV		
28	32	OCB, VPA			**28**	21	CLB, LEV, VPA		
29	22	VPA	Yes		**29**	22	LEV		Yes
30	12	CLB, STI, VPA	Yes		**30**	20	CBZ, CLP, VPA	Yes	Yes
31	14	CLB, STI, VPA			**31**	20	LEV, LTG		
32	10	STI, VPA			**32***	21	CBZ, LCM		
33	13	CLB, STI, VPA			**33**	22	LTG		
34	18	CLB, PGB, STI, VPA			**34**	21	LEV		
35	10	CLB, LEV, STI, VPA	Yes		**35**	20	LTG		
36	16	CLB, TPM, VPA	Yes		**36***	23	LTG, OCB, VPA		

37	21	CLB, STI, TPM, VPA	Yes		**37**	21	VPA		
38	25	BRI, CLB, PHB, VPA			**38***	21	OCB, STI, ZNS		
39	6	STI, VPA	Yes		**39**	21	LZP, VPA	Yes	
40	12	VPA	Yes		**40***	19	CLB, LTG, TPM		
41	26	CLB, STI			**41***	19	CBZ, CLB, LTG		
42	11	CLB, STI			**42**	19	GBP, OCB, ZNS		
43	10	CBD, CLB, STI			**43**	18	CBZ, CLB, VPA		
44	14	-			**44***	19	CLB, OCB		
45	15	CLB, STI, VPA			**45**	19	CBZ, SLT	Yes	
					46	25	OCB		
					47	23	CBZ, LTG		Yes
					48	19	CBZ		
					49*	16	-		
					50*	15	OCB, VPA		
					51	13	CBZ, LEV		
					52	14	OCB, VPA		
					53	15	LTG		
					54	14	LCM, LEV, GBP, VPA		
					55*	15	CBZ, LCM, LEV		
					56*	17	ETH, LTG, OCB		
					57	16	LEV		
					58*	12	LTG, TPM		
					59*	17	CBZ		
					60	18	CBZ, CLB		
					61	14	-		
					62	15	LEV		
					63	13	LTG		
					64*	11	LTG, VPA, ZNS		
					65*	12	CLP, FLB, LTG, VPA		
					66*	11	CBZ		
					67	11	LTG, OCB		
					68*	15	CBZ, LTG		
					69	17	OCB, ZNS		
					70	16	CLB, LCM, OCB, SLT		
					71	21	LEV		
					72*	10	-		Yes
					73	9	VPA		
					74*	9	OCB, VPA		
					75*	9	LEV, VPA		
					76	17	OCB, LTG		
					77	18	OCB		
					78	10	OCB		
					79	7	CLB, LTG		
					80	12	-		
					81	14	-		
					82*	12	LTG, VPA		
					83	6	CLB, LEV, VPA		
					84*	12	LEV, VPA	Yes	
					85*	9	CLB, OCB		
					86	8	CBZ, CLB		Yes
					87	14	OCB		
					88	8	LEV		
					89	18	CLB, LEV		
					90*	16	CBZ, LEV		

AED, n (%)	Dravet syndrome (n = 45)	Controls (n = 90)
BRI	1 (2)	0 (0)
CBD	6 (13)	0 (0)
CBZ	2 (4)	24 (27)
CLB	28 (62)	19 (21)
CLP	1 (2)	2 (2)
ETH	0 (0)	1 (1)
FLB	1 (2)	1 (1)
GBP	0 (0)	2 (2)
PHB	1 (2)	0 (0)
PHN	1 (2)	0 (0)
LCM	0 (0)	8 (9)
LEV	9 (20)	24 (27)
LTG	3 (7)	28 (31)
LZP	0 (0)	1 (1)
OCB	2 (4)	21 (23)
OXZ	0 (0)	1 (1)
PGB	1 (2)	0 (0)
PRI	1 (2)	0 (0)
SLT	0 (0)	2 (2)
STI	19 (42)	1 (1)
TPM	14 (31)	3 (3)
VPA	35 (78)	27 (30)
ZNS	2 (4)	4 (4)

A “yes” indicates QTc-lengthening or bradycardia is present in one or more seizures of this subject. * Epilepsy control has a learning disability. ASM = antiseizure medication; Brady = bradycardia; QTc ↑ = peri-ictal QTc prolongation of ≥60ms; BRI = brivaracetam; CBD = cannabidiol; CBZ = carbamazepine; CLB = clobazam; CLP = clonazepam; ETH = ethosuxamide; FLB = felbamate; GBP = gabapentin; LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; LZP = lorazepam; OCB = oxcarbazepine; PGB = pregabalin; PHB = phenobarbital; PHN = phenytoin; PRI = primidone; SLT = sulthiame; STI = stiripentol; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide.

Appendix 2: Search strategy and results peri-ictal cardiac arrhythmias

A systematic review was performed in the search for cardiac arrhythmias occurring during or after a seizure (van der Lende et al., 2016b). The search was done from first date available to July 2013 in databases PubMed, EMBASE, Web of Science and COCHRANE. Queries consisted of the combination of (various synonyms of) ‘cardiac arrhythmias’ and ‘epilepsy’ (Table A1). Titles and abstracts were screened, and articles were excluded when they related to cardiac arrhythmias mistaken for seizures, arrhythmias triggered by medication, animal studies, interictal cardiac arrhythmias and sinus tachycardia. Full texts of all remaining articles were screened and included when they reported cases with the following arrhythmias: asystole, bradycardia, AV block, postictal AV conduction block, atrial fibrillation/flutter, VT/VF and preexcitation syndromes including Wolff-Parkinson- White. For each individual case, it the peri-ictal phase (pre-ictal, ictal or postictal) in which the cardiac arrhythmia started was recorded. Asystole was defined as sinus arrest of ≥3s and bradycardia as <1st heart rate percentile for age and for adults <50 bpm (Fleming *et al.*, 2011). Reviews were screened to find additional cases. Only cases with simultaneous video-EEG recordings were included, apart from arrhythmias with fewer than five identified case reports with video-EEG.

The search resulted in 1167 articles. After titles and abstracts were reviewed, 989 were excluded. Full texts of 178 articles were reviewed and

65 articles reporting 162 cases with (post)ictal arrhythmias were included.

No pre-ictal cardiac arrhythmias were identified.

Appendix 3: User Manual ‘Cardiac Arrhythmias in Dravet Syndrome’

Thank you for participating in this study. The upcoming period we will measure your child’s heart rate with a special sensor. The aim is to investigate if people with Dravet syndrome are at risk for cardiac arrhythmias. Here, we provide a brief manual. If you have any questions or problems during the measurements, please feel free to contact the researcher, Sharon Shmuely (email: sshmuely@sein.nl, telephone (office hours): +31 23 5588 143).

1. Start a session

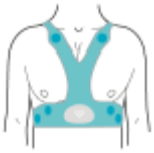
Turn on the sensor by turning the switch to the right, where it says ‘REC’. When the sensor is turned on, you will hear two beeps and the green REC-light will flash.

If the battery icon remains lit the battery should be charged. Contact the researcher if you only hear one long beep.

2. Putting on the chest strap

If the sensor is turned on, it can be attached to the chest strap. Make sure all six pushbuttons are closed properly and that the on-/off-switch is on the bottom. The chest strap should be in direct contact with the skin.

Put on the chest strap as follows: the chest strap should be placed in such a way that the sensor is located exactly in the middle of the chest and the clasps are located on the back. The shoulder straps should be tightened to optimize good contact with the skin.



Important: The chest strap should be closed with the same clasps every day.

3. Apply gel on the electrodes twice daily

To ensure optimal recordings we ask you to apply gel on the 5 electrodes in the strap twice daily. The gel is needed to ensure a good contact between the electrodes and the skin.

4. Charge battery once daily

The battery of the sensor needs to be charged once daily, for the duration of **1 hour**. Charging should take place around the same time every day. The chest strap should be taken off during this hour and the sensor should be switched off by sliding the switch to its central position ('Off'). The sensor can remain attached to the chest strap during charging.

When the sensor is connected to the charger you will hear a beep and the orange charge indicator on the sensor will light up. The sensor is

fully charged when the indicator changes from orange to green. In case the indicator is still orange after 1 hour of charging, the sensor is sufficiently charged and can be used again.

Important: Always use the supplied charger.

5. Diary

We ask you to fill in the seizure diary every day to the seizure characteristics as well as the sleeping times. If possible, we ask you to record the ear temperature every morning and note the temperature in the diary.

6. Washing the chest strap

Make sure you have turned the sensor off and removed the sensor from the chest strap before washing.

It is best to wash the chest strap by hand or with a cold washing machine program of less than 30°C. The chest strap can be used for the measurement once it has completely dried.

- Hand or machine wash on a cold program (<30°C)
- Do not use bleach
- Do not iron
- Do not dry clean
- Do not tumble dry

7. Send the files from the memory card to the researcher

In the first week of measurements the researcher will check the quality of the recordings. The recordings are saved on the micro SD memory card in the sensor. You will be asked to send the files from the memory card to the researcher.

- Check that the mode switch on the sensor is in its 'Off' position.
- Remove the memory card: press the card inwards, and when a click is heard, stop pressing. You will see that the card protrudes by itself so that you can pull it completely out.
- Insert the card into the USB stick (see figures below) and insert the USB stick into your computer.

- Open the folder of the USB stick on your computer, this name of the folder is '**NUUBO_SD**'.
- Copy the files to the desktop.
- Open the internet browser and go to the page **https://www.wetransfer.com**.
- Click on "**add files**", on the left side of the page.
- A small window will appear, where you can select the files which you placed on the desktop. Add these files.
- Type in the email address of the researcher: **sshmuely@sein.nl**.
- Type in your own email address.

- If you do not want to enter your email address on this website, you can type the email address of the researcher (sshmuely@sein.nl) here as well. In that case, we will ask you to send a separate email to the researcher to let her know you sent the files.

- On the browser page the button '**Transfer'** will light up blue and then you can click on it. The files will now be sent to the researcher.
- If you entered your own email address you will receive a confirmation email from We Transfer.

8. Completion

The recording is completed when the sensor has been worn for 20 days and the sensor has been returned to the researcher. The research team will then analyse the recordings. Your treating neurologist will receive the results after about six weeks.