Sudden death in epilepsy: an analysis of potential underlying mechanisms and risk factors

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Signed declaration

I, Robert Jan Lamberts confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

Signature: **Date:**

01-10-2014

Abstract

People with epilepsy have a 16 to 24 fold higher risk of sudden death than the general population. Autonomic dysfunction, cardiac electrical abnormalities, and use of potentially arrhythmic antiepileptic drugs (AEDs) have all been reported in epilepsy and suggest that the heart may be involved. Peri-ictal ventricular arrhythmia has been described in video-EEG recordings of people with severe epilepsy i.e. individuals at high risk of sudden unexpected death in epilepsy (SUDEP): a predominantly seizure-related type of sudden death without known anatomical or toxicological cause. Ventricular tachycardia/ventricular fibrillation (VT/VF) in epilepsy and its association with SUDEP have not yet been investigated in people with less severe epilepsy in the community.

Postictal generalized EEG suppression (PGES)>20s after convulsive seizures (CSs) has been proposed as a new SUDEP risk marker, but these results have not been confirmed in a second study. Conflicting findings regarding the value of PGES>20s as a SUDEP risk marker may be explained by high intraindividual variability.

I have undertaken three studies to obtain a better understanding of the pathophysiology of sudden death in epilepsy, directly by analysing a potential underlying cardiac mechanism (VT/VF in epilepsy) and evaluating whether this mechanism could be one of the causes of SUDEP in the community. Indirectly, the pathophysiology of sudden death in epilepsy was approached by analysing the intraindividual consistency and the facilitating co-factors of the recently proposed SUDEP risk marker PGES.

Study 1

I compared the proportions of people with active epilepsy in 1019 cases with ECG-documented VT/VF from the prospective community-based ARREST-database of out-of-hospital resuscitations in the Dutch region of Noord-Holland and 2834 controls matched by age, gender, and index date from the HAG-net-AMC-database containing the general practitioner's medical files of ≥60000 people in the same study area. I calculated whether people with active epilepsy had a higher risk of VT/VF than the general population after correction for cardiac risk factors. Active epilepsy was confirmed in 12 (1.2%) people among cases and 12 (0.4%) among controls, and was an independent risk factor for VT/VF: adjusted OR 2.9; 95% CI 1.1-8.0.

Study 2

I analysed whether 18 cases with active epilepsy and ECG-confirmed VT/VF fulfilled SUDEP criteria. These 18 cases were compared with 470 VT/VF controls without epilepsy from ARREST and 54 epilepsy controls without VT/VF matched by age and gender from the OPPEC pharmacy-based out-patient cohort with epilepsy. In most cases of VT/VF in epilepsy, there was an obvious (10/18) or presumed cardiovascular cause (5/18) in view of pre-existent heart disease. In two of the three remaining persons, VT/VF remained unexplained and a diagnosis of near-SUDEP was established after successful resuscitation. People with epilepsy and VT/VF were younger and more likely to have congenital heart disease than VT/VF controls without epilepsy. The onset of VT/VF in epilepsy was more likely to be unwitnessed and occur at/near home. Clinically relevant heart disease (adjusted OR 6.9; 95% CI 1.3-36.6) and intellectual disability (adjusted OR 41.3; 1.4-1264.8) were independent risk factors for VT/VF in epilepsy.

Study 3

I collected data on 59 people with multiple recorded CSs (154 seizures in total) from the EEG database of two tertiary epilepsy referral centres (Heemstede and Bonn) and assessed the intraindividual variability of PGES>20s and its facilitating co-factors. PGES>20s was found in 37 (63%) of individuals and 57 (37%) of seizures. The number of people with consistent presence/absence of PGES>20s decreased as the number of recorded CSs increased. Sleep (adjusted OR 2.5, 95% CI 1.3-5.0) or AED reduction before a CS (adjusted OR 3.7, 95% CI 1.4-9.7) were independent risk factors for PGES>20s.

People with active epilepsy are at higher risk of VT/VF, which mostly occurs in the context of acute or pre-existing heart disease. VT/VF in epilepsy and SUDEP partially overlap suggesting that ventricular arrhythmia may be an underlying mechanism of SUDEP in the community. PGES>20s after a CS is unlikely to be a reliable predictor of SUDEP due to its high intraindividual variability. Sleep and AED reduction before the onset of a CS appear to facilitate PGES>20s, which may provide more insight into the process underlying this EEG characteristic.

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Author's contributions

Study 1: prospective, community-based case-control study of epilepsy as a risk factor for sudden cardiac arrest due to ECG-confirmed VT/VF

The author collected the data of all people with epilepsy in the control cohort and was responsible for writing up the study results for publication together with Abdennasser Bardai and Marieke Blom from the cardiology department at the Academic Medical Centre (AMC) in Amsterdam, the Netherlands.

Study 2: prospective, community-based case-control study of the circumstances and risk factors of sudden cardiac arrest due to ECG-confirmed VT/VF in epilepsy

The author collected all data from the ARREST-database and OPPEC-database (together with Merel Wassenaar). The author, Marieke Blom, and Merel Wassenaar conducted the statistical analyses advised by Dr. Gail S. Bell. The author was responsible for writing up the study results for publication together with Marieke Blom from the cardiology department at the Academic Medical Centre (AMC) in Amsterdam, the Netherlands.

Study 3: retrospective assessment of PGES >20s in people with multiple CSs recorded on video-EEG in two epilepsy referral centres

The author collected all data from both epilepsy referral centres (Heemstede & Bonn), conducted the statistical analyses, and was responsible for writing up the study results for publication.

Publications

Parts of this thesis have been published as follows:

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Glossary

5-HT	**5-hydroxytryptamine**
AED	**antiepileptic drug**
CS	**convulsive seizure**
ECG	**electrocardiogram**
EEG	**electroencephalogram**
EMU	**epilepsy monitoring unit**
ERP	**early repolarization pattern**
GP	**general practitioner**
GTCS	**generalized tonic clonic seizure**
HR	**heart rate**
HRV	**heart rate variability**
IGE	**idiopathic generalized epilepsy**
PGES	**postictal generalized EEG suppression**
SCA	**sudden cardiac arrest**
SIDS	**sudden infant death syndrome**
SSRI	**selective serotonin reuptake inhibitor**
SUDEP	**sudden unexpected death in epilepsy**
VNS	**vagal nerve stimulator**
VT/VF	**ventricular tachycardia/ventricular fibrillation**

Introduction

Epilepsy is a chronic neurological condition affecting an estimated over 65 million people worldwide (Ngugi et al., 2010). Overall, the risk of premature mortality in people with epilepsy is 2 to 3 times as high as in the general population (Cockerell et al., 1997; Neligan et al., 2011). Causes of death in people with epilepsy can be subdivided into three main categories: unrelated to epilepsy (e.g. pancreatitis); the underlying aetiology of epilepsy (e.g. stroke, brain tumour); and directly epilepsy-related causes such as sudden unexpected death in epilepsy (SUDEP), seizure-related accidents, and status epilepticus (Hitiris et al., 2007 a). The term SUDEP has been coined to describe sudden deaths in people with epilepsy that remain unexplained even after detailed postmortem investigations (Annegers, 1997; Nashef, 1997). SUDEP was believed to be a rare phenomenon until a nationwide audit of epilepsy-related deaths demonstrated that SUDEP frequently went unrecognized (Hanna et al., 2002). Since then, it has become increasingly clear that SUDEP is a considerable public health burden: victims are most frequently between 20 and 40 years of age and in the prime of their lives (Ficker et al., 1998). Correspondingly, people with epilepsy in this age group have a 16 to 24-times higher risk of sudden death than the general population (Ficker et al., 1998; Holst et al., 2013). In a recent nationwide study of deaths in the young (1 to 35 years of age), SUDEP was shown to be responsible for 7% of deaths in those with epilepsy and almost 1% of deaths in the entire population (Holst et al., 2013). When compared with selected neurological diseases (stroke, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, bacterial meningitis), SUDEP ranked second only to stroke in potential years of life lost (Thurman et al., 2014).

To reduce the considerable societal burden of SUDEP, it is important to gain a better understanding of its pathophysiology. Several lines of evidence suggest that the heart, or more specifically cardiac arrhythmias, may play a role in SUDEP: In those with chronic focal epilepsy progressive autonomic dysfunction and changes in cardiac electrical properties have been documented (Tomson et al., 2008), which may lower the threshold for ventricular arrhythmia. In addition, sudden cardiac death may present as SUDEP, as in a subset of SCA cases no clear cause of death is found at autopsy (van der Werf et al., 2010). In an analysis of 25 cases of SUDEP or near-SUDEP that occurred under video-EEG monitoring sudden cardiac arrest (SCA) due to seizure-related ventricular arrhythmia (VT/VF) was the reported underlying mechanism in one case (Ryvlin et al., 2013 a). This study may, however, not directly apply to out-of-hospital SUDEP cases in the general population with epilepsy: most video-EEG-recordings were performed in a selected group of people with severe refractory epilepsy for the purpose of presurgical evaluation. In addition, rapid AED tapering schedules may have been used to increase the odds of recording at least one seizure. This procedure can, however, lead to more severe seizures than those seen in everyday life (Rajakulendran & Nashef, 2015). To study SCA due to VT/VF, this potential underlying cardiac mechanism of sudden death, in a non-selected cohort more representative of the general population with epilepsy, I could make use of a prospective community-based registry of out-of-hospital resuscitations with ECG-confirmed VT/VF. My aim was to determine whether having epilepsy was a risk factor for SCA in the general population after accounting for cardiac risk factors and to assess the underlying causes, characteristics, and risk factors of SCA in epilepsy.

Apart from an analysis of potential underlying mechanisms, the pathophysiology of sudden death in epilepsy and SUDEP may also be approached indirectly by studying its potential risk factors such as postictal generalized EEG-suppression (PGES).

PGES occurs in the majority of fatal CSs, where it appears to be an EEG hallmark of SUDEP starting off a chain of postictal events culminating in death (Ryvlin et al., 2013 a). Elucidation of the process underlying PGES may therefore shed more light on the pathophysiology of SUDEP. PGES can also occur after non-fatal CSs and has been proposed as a risk factor for future SUDEP (Lhatoo et al., 2010), but findings as to the value of this EEG-characteristic have been conflicting (Surges et al., 2011). To find an explanation for these divergent results, my goal was to determine the level of intraindividual variability of prolonged PGES in people with multiple recorded CSs.

In recent years, SUDEP has steadily gained attention in both lay and medical circles (Brigo et al., 2014), which is hopeful news. The example of sudden infant death syndrome (SIDS), a better-known cause of sudden death, shows that the continuing concerted efforts of laymen and professionals can yield valuable results; in the last couple of decades the incidence of SIDS has plummeted in developed countries after the implementation of large-scale educational campaigns (Hauck & Tanabe, 2008).

1. A critical review of the literature

1.1 History of SUDEP

The first proposals to define SUDEP were made in 1997, but the phenomenon it describes has been documented for much longer. The first description of SUDEP was probably provided by George Washington, first president of the United States of America (Doherty, 2004). In 1773, Patsy Custis, his 17-year old stepdaughter, who had intractable epilepsy died in the aftermath of one of her seizures. In 1868, George MacKenzie Bacon, medical superintendent of the Cambridge County Asylum, described the phenomenon of SUDEP for the first time in medical literature as "sudden deaths in a fit" (MacKenzie Bacon, 1868). During the 19th century, having epilepsy was the second most common reason for committal to an asylum in Europe and the United States, as people with epilepsy (particularly those with intractable seizures) could not usually earn a living and were thought to display erratic behaviour (Spurzheim et al., 1835; Lannon, 2002). Unlike their colleagues in the regular medical establishment, the physicians working in these asylums were able to monitor a large population with epilepsy continuously and, therefore, were in a much better position to recognize that those with epilepsy would regularly succumb to sudden death. As George MacKenzie Bacon notes: "of the causes enumerated, that of suffocation in bed is far from uncommon in asylums (five cases having occurred in a large asylum in one year); but this does not seem to be recognized as such in the outside world" (MacKenzie Bacon, 1868). In the late 19th century epilepsy was increasingly being viewed in the medical community as a brain disorder rather than the result of "spiritual punishment or feeble-mindedness".
Due to continuing stigma, however, people with epilepsy were still ostracized from their families and communities.

Philanthropists in Europe and the USA then started to establish isolated, self-financing agricultural "colonies", where "sane epileptics" could work, providing them with "healthy occupation" (Sander et al., 1993; Lannon, 2002; Novy et al., 2013). The 'colonies' included Stichting Epilepsie Instellingen Nederland (SEIN) in the Netherlands, the Epilepsy Centre Bethel in Germany, the Chalfont Centre near London and the Craig Colony in New York State. The physicians in these "colonies" continued to recognize and describe the phenomenon of sudden death in epilepsy without apparent cause. Spratling, one of the founders of the Craig Colony, described epilepsy as "a disease which destroys life suddenly and without warning through a single brief attack, unaided by an accident to the patient at the moment, such as suffocation, or fracture to the skull from falling, and does so in 3 to 4 per cent of all who suffer from it" (Spratling, 1904). Munson, another founder who conducted a study on 582 deaths in the Craig Colony described "a definite and fairly large group where neither accident of any kind nor suffocation can be assigned as the cause of death" (Munson, 1910). In a later section he added: "each patient must be seen every few minutes, for as has been noted these deaths occur very rapidly at times" (Munson, 1910). These physicians, therefore, considered SUDEP to be a rather common phenomenon that might be preventable with good quality care. In the years after the world wars, however, this view completely changed and earlier research on the subject was largely ignored. In later years, therefore, it became common belief that epilepsy was not a fatal condition. In 1954 it was stated in a review of 77 deaths in people with epilepsy that "the epileptic under adequate medical control with patient and critical guidance and understanding of his problem, is substantially a mortality risk no greater than the average normal person" (Schwade & Otto, 1954).

A lonely opposing view was espoused by Rodin: “it appears to be quite obvious that the life expectancy of the epileptic individual does not reach that of the average person. It is also quite impressive that the figures have not shown a dramatic improvement during the past five decades. Although death from a seizure is relatively rare, it does occur on occasion and is not preventable under all the circumstances at the present time” (Rodin, 1968). Livingston, the author of a key textbook in this period stated: “As far as longevity is concerned, the patient should definitely understand that epilepsy per se rarely causes death and that there is no reason why an epileptic should not live as long as he would if he did not have epilepsy” (Livingston, 1963). Paradoxically, the advent of better treatment options in the field of epilepsy including the introduction of new AEDs and the deinstitutionalization of people with epilepsy may have been responsible for this reduced awareness of SUDEP (Nashef, 1995 a). The expansion of treatment options may have given rise to the false belief that complete seizure control and, thereby, a normalization of the prognosis of epilepsy was now finally within reach. In addition, the closure of asylums limited the opportunities for long-term observation of people with severe epilepsy, those at highest risk of SUDEP. SUDEP did not become the focus of attention again until the autopsy studies by Leestma et al., in the 1980s (Leestma et al., 1984; Leestma et al., 1985; Leestma et al., 1989). Since then, interest in SUDEP has steadily risen culminating in the proposal of two SUDEP definitions in 1997 (Annegers, 1997; Nashef, 1997). In addition, the National Sentinel Clinical Audit of Epilepsy-related Deaths was performed in the UK in 2002, providing a detailed assessment of SUDEP incidence while highlighting the inadequate recognition of this phenomenon by medical professionals (Hanna et al., 2002).

When looking back at the evolution of SUDEP research in these past 150 years, it is a sobering realization that aspects discussed more than a hundred years ago (incidence, the tendency to occur after a single brief seizure, and the potential benefit of supervision), had to be relearned in the last two decades. The greater should be the determination of the general and scientific community to keep SUDEP on the agenda and continue research efforts in this area.

1.2 Definition of SUDEP

In 1997 two separate but similar definitions of SUDEP were adopted (Annegers, 1997; Nashef, 1997). While Nashef's main criteria are now most widely used, the additional classification of diagnostic certainty by Annegers has also been adopted (Annegers, 1997; Nashef, 1997). SUDEP is the "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death"(Nashef, 1997). Three categories of diagnostic certainty have also been specified: definite, probable, and possible (Annegers, 1997). Definite SUDEP meets all criteria including a negative post-mortem examination, whereas in probable SUDEP no post-mortem examination has been performed. In possible SUDEP there is either a competing cause of death or insufficient information regarding the circumstances of death. In this case, the diagnosis can neither be confirmed nor ruled out (Annegers, 1997). Recently, the amendment of these criteria has been proposed, as the potential contribution of somatic comorbidity to SUDEP may not have been addressed adequately thus far (Nashef et al., 2012).

The authors of these new unified SUDEP criteria proposed the following changes: the establishment of a "SUDEP plus" category to designate those cases with a (non-lethal) concomitant condition discovered before or after a death which would fulfil all the original criteria of SUDEP (Nashef et al., 2012). "Possible SUDEP" will only be used for those in whom a competing cause of death is present, whereas a case will remain unclassified if insufficient information is available. The timeframe in which death should occur after a witnessed terminal event (e.g. seizure) has been set to within one hour to minimize the possibility that other causes of death are involved. The term "near-SUDEP" pertains to those cases that satisfy all criteria, but who are successfully resuscitated after the life-threatening event.

1.3 Incidence of SUDEP

The incidence of SUDEP varies considerably depending on which population is studied. The lowest numbers are found in unselected, community-based cohorts of people with incident epilepsy: 0.09 to 0.41/1,000 person years: table 1. Other study methodologies may approximate SUDEP incidence in a population with prevalent epilepsy: (1) cases are found by reviewing postmortem records and incidence is calculated using the assumed prevalence of epilepsy in the catchment area (0.9-2.3/1000 person years) or (2) people with epilepsy with and without SUDEP are identified through AED prescription databases (0.54-1.3/1000 person years). In addition, SUDEP incidence has been analysed in cohorts from a hospital discharge registry (1.5/1000 person years) or epilepsy clinics (1.1-5.9/1000 person years): table 2. Similar numbers are found in selected groups who cannot live independently: long term residents at a tertiary epilepsy referral centre (2.1/1000 person years), pupils with epilepsy and a learning disability at a special residential school (3.4/1000 person years), and people with epilepsy and mental retardation (1.97-3.6/1000 person years).

SUDEP incidence has also been reported in populations with presumably refractory epilepsy: those on AED polytherapy (2.2/1000 person years), participants in AED trials (2.52-3.8/1000 person years), and people with an implanted vagal nerve stimulator (VNS) device (3.3-4.1/person years): table 3.

Table 1: Community-based studies of SUDEP incidence in adults

Study	Country	Population	Cases (n)	Total person years	SUDEP incidence (per 1000 person years)
Lhatoo et al., 2001	UK	Community (age 1-90 years)	1	11400	0.09
Ficker et al., 1998	USA	Community	9	25940	0.35
Holst et al., 2013	Denmark	Community (age 1-35 years)	50	120096	0.41
Terrence et al., 1975	USA	Community (autopsy records)	37	Not mentioned	0.9#
Opeskin & Berkovic, 2003	Australia	Community (autopsy records)	50	Not mentioned	1.3#
Langan et al., 1998	Ireland	Community (autopsy records)	15	Not mentioned	1.5#
Leestma et al., 1984	USA	Community (autopsy records)	66	Not mentioned	1.9#
Leestma et al., 1989	USA	Community (autopsy records)	60	Not mentioned	2.3#
Tennis et al., 1995	USA	AED prescription database (age 15-49 years)	18	33299	0.54
Jick et al., 1992	USA	AED prescription database (age 15-49 years)	11	8460	1.3

#The number of person years is calculated based on an assumed prevalence of epilepsy in the coroner's catchment area.

Table 2: Studies of SUDEP incidence in selected populations with epilepsy

Study	Country	Population	Cases (n)	Total person years	SUDEP incidence (per 1000 person years)
Nilsson et al., 1999	Sweden	Epilepsy cohort from hospital discharge centre (age 15-70 years)	62	40508	1.5
Mohanraj et al., 2006	UK	Epilepsy clinic (newly diagnosed)	7	6482	1.1
Vlooswijk et al., 2007	Netherlands	Tertiary referral centre	29	Not mentioned	1.2¶
Walckzak et al., 2001	USA	Three epilepsy centres	20	16463	1.2
Timmings, 1993	UK	Epilepsy clinic	14	7000	2
Mohanraj et al., 2006	UK	Epilepsy clinic (chronic patients)	55	22935	2.5
Nashef et al., 1995 b	UK	Tertiary referral centre	11	1849	5.9
Klenerman et al., 1993	UK	Residential care, epilepsy	7	3392	2.1
Nashef et al., 1995 c	UK	Residential care, epilepsy and learning disability	14	4135	3.4
Kiani et al., 2014	UK	Residential care or supported living, epilepsy and mental retardation (age ≥20 years)	26	13201	1.97
McKee & Bodfish, 2000	USA	Residential care, epilepsy and mental retardation	11	3012	3.6

¶The number of person years is calculated based on an assumed mean number of people with epilepsy treated per year at the tertiary referral centre.

Table 3: Studies of SUDEP incidence in cohorts with presumably chronic, refractory epilepsy

Study	Country	Population	Cases (n)	Total person years	SUDEP incidence (per 1000 person years)
Derby et al., 1996	UK	AED prescription database (patients on >2 AEDs; age <50 years)	15	6784	2.2
Tomson et al., 2013	USA/UK	Lamotrigine add-on trials	8	3168	2.52
Leestma et al., 1997	USA/UK	Lamotrigine add-on trials	20	6721	2.98
Ryvlin et al., 2011	International	AED add-on trials (entire cohort)	20	5589	3.58
Ryvlin et al., 2011	International	AED add-on trials (efficacious AED dose)	14	2022	6.9
Ryvlin et al., 2011	International	AED add-on trials (add-on placebo)	3	3297	0.9
Racoosin et al., 2001	USA	AED add-on trials	52	13617.1	3.8
Racoosin et al., 2001	USA	AED monotherapy trials	0	982.5	0
Granbichler et al., 2015	International	VNS cohort	10	2993.8	3.3
Annegers et al., 2000	International	VNS cohort	13	3176.3	4.1

SUDEP occurs most frequently in candidates or former candidates for epilepsy surgery (e.g. those who were rejected for surgery or who declined surgery): 5.94-9.3/1000 person years. The incidence of SUDEP, therefore, increases in tandem with epilepsy severity. This trend is also reflected in the estimated individual life-time risk of SUDEP, which was recently calculated based on pooled data from higher quality population-based studies of SUDEP incidence (Thurman et al., 2014): the individual life-time risk of SUDEP was calculated as 8% for the entire population with epilepsy, and 35% for those with refractory epilepsy (Thurman, 2013).

Interestingly, in people with drug-resistant epilepsy who participated in randomized controlled trials comparing add-on AED treatment to placebo, those receiving an efficacious add-on dose had a much lower incidence of SUDEP (0.9/1,000 person years) than those allocated to placebo: 6.9/1,000 person years (Ryvlin et al., 2011). People who received a temporal lobectomy, the most successful type of epilepsy surgery, appeared to have a lower incidence of SUDEP (0.51-3.99/1000 person years) than those who were evaluated for epilepsy surgery: table 4. In addition, SUDEP occurred less frequently in those who became seizure free after surgery than in people with persistent seizures: 7.49 vs. 0/1000 person years. This suggests that measures to achieve seizure control, such as AED optimization and epilepsy surgery, may prevent SUDEP (at least in some individuals). It should be stressed, however, that firm evidence that epilepsy surgery itself reduces SUDEP incidence is lacking. In children, SUDEP appears to occur less frequently than in adults with a similar epilepsy severity: unselected, community-based cohorts of children with incident epilepsy (0.176-0.26/1000), cases found by reviewing postmortem records while using an assumed prevalence of epilepsy in the catchment area to calculate an incidence (0.2/1000 person years), children identified through an AED prescription database (0.33/1000 person years), cases who were treated at a children's hospital (0.43/1000), and a cohort from an epilepsy clinic (0.8/1000): table 5. In children as in adults, however, SUDEP incidence appears to be higher in those with more severe epilepsy

Table 4: Studies of SUDEP incidence in (former) epilepsy surgery candidates, and cohorts after surgery

Study	Country	Population	Cases (n)	Total person years	SUDEP incidence (per 1000 person years)
Bell et al., 2010	UK	After epilepsy surgery	2	3905	0.51
Seymour et al., 2012	UK	After epilepsy surgery	6	3569	1.68
Salanova et al., 2002	USA	After epilepsy surgery	3	1514	1.98
Nilsson et al., 2003	Sweden	After epilepsy surgery	6	2455	2.4
Sperling et al., 2005	USA	After epilepsy surgery (entire cohort)	6	1502.6	3.99
Sperling et al., 2005	USA	After epilepsy surgery (seizure free)	0	701.1	0
Sperling et al., 2005	USA	After epilepsy surgery (persistent seizures)	6	801.5	7.49
Bell et al., 2010	UK	Surgery candidates, no surgery performed	20	3365	5.94
Nilsson et al., 2003	Sweden	Surgery candidates, no surgery performed	4	635	6.3
Ryvlin et al., 2013 a	International	During presurgical video-EEG monitoring	10	1334	7.5
Dasheiff, 1991	USA	Surgery candidates, no operation	7	_	9.3

Table 5: Studies of SUDEP incidence in children

Study	Country	Population	Cases (n)	Total person years	SUDEP incidence (per 1000 person years)
Holst et al., 2013	Denmark	Community (age 1-17 years)	10	57703	0.176
Berg et al., 2013	USA/UK/Canada/ Netherlands	Community (pooled analysis of four studies)	8	30284	0.26
Donner et al., 2001	Canada	Community (autopsy records)	27	_	0.2
Ackers et al., 2011	UK	AED prescription database (age 0-18 years)	9	26890	0.33
Weber et al., 2005	Switzerland	Epilepsy cohort from children's hospital	4	9295	0.43
Grønborg & Uldall, 2014	Denmark	Tertiary referral centre	9	11309	0.8

1.4 Descriptive and risk factor studies

Case series

It is estimated that >60% of SUDEP cases are unwitnessed (Nashef et al., 1998; Kloster & Engelskjøn, 1999; Langan et al., 2000; Langan et al., 2005). Most victims are found in or next to their bed, which suggests that they died during sleep (Nashef et al., 1998; Langan et al., 2005). Signs of a recent seizure such as a lateral tongue bite, urinary incontinence, posturing, and secretions/blood are frequently found: 64-88% (Nashef et al., 1998; Kloster & Engelskjøn, 1999; Langan et al., 2005).

Most victims (70-73%) are discovered in the prone position, although body position at time of death is not always accurately recorded (Kloster & Engelskjøn, 1999; Liebenthal et al., 2015). If witnessed, most witnesses confirm that victims had experienced a seizure shortly before death (Langan et al., 2000). This was usually a convulsive seizure (CS). Most witnesses reported seeing respiratory problems (cyanosis, laboured breathing), although one should be cautious when interpreting testimony from non-medical individuals (Langan et al., 2000).

Autopsy studies

Autopsy plays an important role in establishing the diagnosis of SUDEP and may be indispensable for a correct classification: in 14/35 (40%) people who would have been diagnosed clinically as probable SUDEP, an alternative cause of death was found after postmortem investigations (Novy et al., 2013). A structural cause of death is, by definition, not found in SUDEP victims, but (non-lethal) abnormalities such as pulmonary oedema (30 to 100%) and cerebral oedema (25 to 55%) have been frequently reported (Terrence et al., 1981; Leestma et al., 1984; Leestma et al., 1989; Earnest et al., 1992; Antoniuk et al., 2001; Salmo & Connolly, 2002, Zhuo et al., 2012). The pulmonary findings may suggest neurogenic pulmonary oedema, a condition thought to be triggered by the surge in central sympathetic activity accompanying CSs (Swallow et al., 2002). Alternatively, it may be the result of premortem congestive or "backward" cardiac failure (Thom, 1997). Various cardiac pathologies have also been reported in SUDEP victims: myocardial fibrosis (14 to 57%) (Earnest et al., 1992; Natelson et al., 1998; Zhuo et al., 2012), mild to moderate coronary atherosclerosis (4 to 16%) (Leestma et al., 1989; Zhuo et al., 2012), moderate left ventricular hypertrophy 10% (Zhuo et al., 2012), old myocardial infarction 4% (Leestma et al., 1989).

Myocardial fibrosis was more frequently found in SUDEP victims (71%) than in controls without epilepsy who died suddenly (4%), which may suggest that these lesions play a role in their deaths (Natelson et al., 1998). Autopsy findings support the notion that SUDEP deaths may be seizure-related: tongue biting is described in 23 to 28% of cases (Coyle et al., 1994; Salmo & Connolly, 2002; Pollanen & Kodikara, 2012). In addition, markers of acute cerebral injury such as HSP-70 and c-jun were more frequently found in SUDEP victims than in controls with and without epilepsy, thus also favouring a seizure-related cause (Thom, 2003).

Case-control studies (SUDEP vs. deceased controls with epilepsy)

Risk factors for SUDEP can be analysed by comparing SUDEP victims (cases) with 1) those with epilepsy who died of other causes (controls) or with 2) living people with epilepsy (controls) (Tomson et al., 2008). The first design appears to be most suitable for elucidating SUDEP circumstances. In these studies, the most consistent risk factor associated with SUDEP is evidence of a recent seizure and a younger age at time of death (Téllez-Zenteno et al., 2005 a). In addition, the AED concentration variability measured in scalp hair was higher in SUDEP victims than in controls with epilepsy who died of other causes or living controls with epilepsy, suggesting that AED non-compliance may increase SUDEP risk (Williams et al., 2006).

Case-control studies (SUDEP vs. living controls with epilepsy)

Comparing SUDEP victims with living controls may be more clinically relevant, because it can help to determine which people with epilepsy have the highest risk of SUDEP. In a combined analysis pooling data from four large case-control studies (Nilsson et al., 1999; Walczak et al., 2001; Langan et al., 2005; Hitiris et al., 2007 b), a high frequency of CSs was found to be the strongest risk factor for SUDEP after adjustment for data source, gender, duration of epilepsy, and age at death (Hesdorffer et al., 2011).

To a lesser degree, the variables male gender, structural/metabolic epilepsy, young age of onset, long duration of epilepsy, polytherapy (≥2 AEDs), and lamotrigine use were also associated with increased SUDEP risk (Hesdorffer et al., 2011). In addition, lamotrigine use among individuals with idiopathic generalized epilepsy (IGE) was found to be a risk factor for SUDEP in univariable analysis. Previously, four SUDEP cases involving young women with IGE who were on lamotrigine monotherapy had been reported (Aurlien et al., 2009). In addition, female SUDEP victims were taking lamotrigine more frequently than living controls with epilepsy matched by age and gender in a subsequent case-control study (Aurlien et al., 2012). There are several possible explanations for the association between lamotrigine use and SUDEP, particularly in those with IGE and young women: lamotrigine may not be as effective as valproic acid in achieving seizure control in people with IGE (Bauer et al., 2008). In addition, young women with IGE may be more likely to switch from valproate to lamotrigine monotherapy, because use of lamotrigine carries a smaller risk of foetal congenital malformation (Tomson et al., 2011). Women exposed to lamotrigine monotherapy in pregnancy were less likely to be seizure free than those using other AEDs as monotherapy (Battino et al., 2013).

Recently, it was shown that lamotrigine use and AED polytherapy were no longer significant risk factors for SUDEP after correction for CS frequency (Hesdorffer et al., 2012). In a meta-analysis of 42 lamotrigine randomized controlled trials, this drug was not associated with a higher risk of SUDEP (Tomson et al., 2013). All together, these data suggest that lamotrigine use in IGE and AED polytherapy appear to be surrogate markers for poor seizure control rather than independent risk factors for SUDEP. Achieving seizure freedom, therefore, appears to be of greater importance than limiting the number of AEDs.

In the largest of the four case-control studies the effect of possible preventive measures was evaluated (Langan et al., 2005). The presence of an individual of normal intelligence and ≥10 years of age in the same bedroom was found to reduce the risk of SUDEP by 2.5 times. The use of special precautions (regular checks throughout the night or the use of a listening device) was even associated with a 10 times lower risk of SUDEP. It is still unclear, however, how these measures also known as nocturnal supervision may be protective and which patients would benefit most.

1.5 Ictal recordings of (near-)SUDEP

In total, twenty-two cases of people who (almost) died of SUDEP while under (video)/EEG monitoring have been reported (Dasheiff & Dickinson, 1986; Purves et al., 1992; Thomas et al., 1996; Bird et al., 1997; Lee, 1998; So et al., 2000; Tavee & Morris III, 2008; Espinosa et al., 2009; Lhatoo et al., 2010; Bateman et al., 2010 a; Tao et al., 2010; Lanz et al., 2011; Ryvlin et al., 2013 a; Jeppesen et al., 2014). At first glance, this appears to be in contrast with the reported high incidence of SUDEP in those with refractory epilepsy. This finding, however, emphasizes the notion that SUDEP most readily occurs when there is least supervision: at home rather than in the hospital, and unwitnessed rather than witnessed.

Ictal recordings of (near-)SUDEP appear to confirm the findings of descriptive studies: all (near) deaths were seizure-related and occurred in the first 30 minutes after seizure end (Ryvlin et al., 2013 a). In most cases the (near-)fatal seizure was a CS (82%; 18/22), whereas focal seizures with alteration of awareness were seen less frequently (18%; 4/22). Despite the high level of supervision in an epilepsy monitoring unit (EMU), a surprising number of events were unwitnessed (32%; 7/22); another 32% (7/22) of cases were witnessed, while in the remaining case reports (36%; 8/22) this issue was not mentioned.

Seizures started during sleep in 50% (11/22) of events, during wakefulness in 41% (9/22), and seizure timing was not mentioned in 9% (2/22). In a recent retrospective survey of EMUs that incorporated most of the 22 previously mentioned (near-)SUDEP cases, 14/16 (88%) of individuals in whom body positions could be evaluated were lying in the prone position at seizure end (Ryvlin et al., 2013 a). In spite of the similar clinical presentation of all (near)-SUDEP cases, three peri-ictal pathomechanisms were observed that preceded (near)-SUDEP:

1. The sequence of pronounced post-ictal generalized attenuation of EEG activity followed by respiratory and cardiac arrest
2. Central and/or obstructive peri-ictal apnoea
3. Peri-ictal cardiac arrhythmias including VT/VF or asystole

1.6 Peri-ictal pathomechanisms of SUDEP

Postictal generalized EEG suppression

In earlier studies postictal attenuation of EEG activity or the "flat EEG" was described as "abruptly attenuated termination pattern" or "electrocerebral shutdown" (Kim et al., 2006; Bird et al., 1997), but in recent years the term "postictal generalized EEG suppression" (PGES) has been coined (Lhatoo et al., 2010). PGES has been defined as "the immediate postictal (within 30 seconds) generalized absence of electroencephalographic activity <10μV in amplitude, allowing for muscle, movement, breathing, and electrode artifacts" (Lhatoo et al., 2010). In subsequent studies additional criteria have occasionally been used such as a minimum PGES duration of 1s (Surges et al., 2011; Tao et al., 2013) or 2s (Seyal et al., 2012). In most ictal recordings of SUDEP, PGES is the first discernible abnormality before cardiorespiratory deterioration and cessation, suggesting that this EEG characteristic may reflect an underlying SUDEP mechanism.

PGES: facilitating co-factors

PGES does not occur exclusively in (near)-SUDEP cases, but can also be found after non-lethal seizures (Lhatoo et al., 2010; Surges et al., 2011). This has made the search for clinical determinants of this EEG characteristic much more achievable. PGES appears to be more prevalent in adults than in children (Freitas et al., 2013; Pavlova et al., 2013). Seizure type appears to be the most important determinant of PGES, as this EEG phenomenon is found more frequently after CSs than focal seizures with alteration of awareness (Lhatoo et al., 2010; Surges et al., 2011). In addition, PGES duration was significantly longer in focal seizures evolving into a bilateral convulsive seizure with tonic and/or clonic components than in GTCSs (Freitas et al., 2013). Seizure duration was not associated with PGES (Lhatoo et al., 2010; Surges et al., 2011; Poh et al., 2012; Semmelroch et al., 2012; Seyal et al., 2012; Freitas et al., 2013; Lee et al., 2013; Moseley et al., 2013; Pavlova et al., 2013; Tao et al., 2013), but a longer duration of the tonic phase may promote PGES (Freitas et al., 2013; Tao et al., 2013). PGES has also been associated with more severe peri-ictal hypoxaemia and postictal coma (Semmelroch et al., 2012; Seyal et al., 2012). AED changes may facilitate PGES; after the withdrawal of AED therapy, the introduction of levetiracetam decreased the severity of postictal EEG suppression and coma (Tilz et al., 2006).

PGES: aetiology

Three hypotheses regarding the origin of PGES have been proposed based on the aforementioned facilitating co-factors. PGES was suggested as being the result of a “passive” process such as seizure-related neuronal fatigue or neurotransmitter depletion (Lhatoo et al., 2010; Surges et al., 2011). This appears unlikely, however, given the sudden onset of this EEG phenomenon and the lack of correlation between PGES and seizure duration.

The second theory proposes that PGES may be due to the activation of inhibitory neuronal networks triggered by ongoing seizure activity. In an intracranial video-EEG-recording, EEG flattening originated in the right hemisphere ipsilateral to the seizure onset zone before spreading to the rest of the brain and evolving into PGES (Bird et al., 1997). The association between PGES and the severity of postictal coma further suggests that it reflects an endogenous seizure termination process that may not only suppress ongoing seizure activity but also modalities such as consciousness.

It is important to realize that the exact sequence of (post)ictal events in SUDEP remains incompletely understood. Even in video-EEG recordings of SUDEP critical physiological parameters such as BP or O_2 saturation were not assessed. In a study where O_2 saturation was continuously analysed, PGES following non-fatal CSs was found to be associated with preceding hypoxaemia (Seyal et al., 2012). In addition, early peri-ictal nursing interventions including oxygen administration were reported to reduce the duration of PGES (Seyal et al., 2013). In a recent case report, prolonged PGES after a non-fatal GTCS coincided with profound postictal hypotension, the end of PGES correlating closely with blood pressure normalization (Bozorgi et al., 2013). The third hypothesis regarding the origin of PGES, therefore, suggests that this EEG pattern is, at least in some cases, secondary to preceding hypoxia, hypotension, or asystole as seen in ictal recordings of (near-)SUDEP and vasovagal syncope.

PGES: SUDEP risk marker?

It has been hypothesized that PGES following non-fatal CSs may predict SUDEP risk. In a retrospective electroclinical case-control study (SUDEP cases (n=10, living epilepsy controls (n=30), recorded seizures (n=122)), those individuals who exhibited prolonged PGES of >20s after a CS were 13 times more likely later to die of SUDEP (Lhatoo et al., 2010).

These findings, however, could not be replicated in a second case-control study (Surges et al., 2011): SUDEP cases (n=17), living epilepsy controls (n=17), recorded seizures (n=80). The value of PGES >20s after non-lethal CSs as a risk marker for SUDEP, therefore, remains unclear.

Peri-ictal respiratory disturbances

Ictal respiratory abnormalities such as apnoea or hypoxaemia are not uncommon. In a landmark study, evidence of central apnoea was found in 44% of 100 seizures for which nasal airflow and abdominal excursion data were available (Bateman et al., 2008). In addition, mixed apnoea (with central and obstructive components) was reported in 7% of seizures and obstructive apnoea in 2% of seizures. Hypoxaemia (i.e. oxygen saturation <90%) was found in 33% of all seizures (Bateman et al., 2008). Apnoea and hypoxaemia were also frequently encountered in other studies with apnoea in 30 to 50% and hypoxaemia in 25-87% of seizures (Walker & Fish., 1997; O'Regan & Brown, 2005; Seyal & Bateman, 2009; Seyal et al., 2010; Moseley et al., 2010; Moseley et al., 2011; Moseley et al., 2013; Singh et al., 2013; Pavlova et al., 2013; Moseley & Britton, 2014). Ictal apnoea appears to be more common in children than adults, possibly because children have a lower apnoeic threshold (Rowley et al., 2006). Ictal hypoxaemia, however, was found to be more prevalent in adults (Moseley et al., 2011). Mechanisms other than apnoea such as diffusion-perfusion mismatch due to pulmonary oedema may, therefore, also contribute to seizure-related respiratory dysfunction (Seyal et al., 2010). In a recent study where consecutive chest X-rays were performed following a CS, pulmonary oedema was found in 29% of individuals and pulmonary oedema was most likely to occur after seizures with a longer duration (Kennedy & Seyal, 2015).

Both central apnoea and hypoxaemia were mostly related to temporal lobe seizures, to the contralateral spread of ictal activity, and longer seizure duration (Bateman et al., 2008; Seyal & Bateman, 2009; Singh et al., 2013). In fact, brief apnoeic responses could be reproduced after electrical stimulation of sections of the limbic system such as the cingulate gyrus in humans (Penfield & Jasper, 1954). This suggests that the spread of seizure activity to the limbic system, which modulates autonomous cardiac and respiratory control, can trigger ictal respiratory changes.

Mixed/obstructive ictal apnoea is far less common than the central type, but is described at least equally frequently as the underlying pathophysiological mechanism in ictal recordings of (near-)SUDEP (Thomas et al., 1996; So et al., 2000; Tavee & Morris III, 2008). Postictal laryngospasm due to inhalation of stomach contents during a CS and the frequent assumption of a prone position after seizure end may both aggravate upper airway obstruction (Tavee & Morris III, 2008; Blum, 2009). On a cellular level, dysfunction of the 5-hydroxytryptamine (5-HT) neurotransmitter system or release of the endogenous anticonvulsant adenosine may partially explain the link between ictal respiratory changes and SUDEP. 5-HT is found in the raphe and other related brain stem nuclei in control of a variety of functions including stimulation of autonomous breathing control (Ptak et al., 2009). Mice with defects in the 5-HT system exhibited postictal respiratory arrests (Tecott et al., 1995; Tupall & Faingold, 2006; Uteshev et al., 2010). Stimulation of breathing by the 5-HT system is likely to be particularly relevant in the aftermath of a CS when an individual with epilepsy may be prone, hypoxic and incapacitated. At this point, failure of the autonomic respiratory drive may eventually lead to SUDEP. Interestingly, defects of the 5-HT system have been reported in SIDS, another condition characterized by unwitnessed nocturnal sudden death (Richerson & Buchanan, 2011).

The incidence of SIDS decreased dramatically after advising parents to position their children in a supine rather than a prone sleeping position (Kinney & Thach, 2009). This further underscores the need to determine the effectiveness of similar measures (nocturnal supervision, body repositioning after seizure end) in preventing SUDEP.

Adenosine is an inhibitor of neuronal activity and is released in elevated levels during seizures (During & Spencer, 1992).The activation of adenosine receptors in the brainstem triggered severe respiratory depression in rats (Barraco et al., 1990). In another animal model, seizures were induced with kainic acid in mice while inhibiting adenosine clearance in some, thus leading to a build-up of adenosine (Shen et al., 2010). All animals with impaired adenosine clearance died within 20 minutes after the onset of seizures, whereas controls with normal adenosine clearance survived their seizures. The authors, therefore, suggested that excessive adenosine build-up plays a role in the pathophysiology of SUDEP. It should be noted, however, that sudden death in this study occurred during prolonged induced CSs, a model of status epilepticus rather than SUDEP. Caution should, therefore, be used when extending these results to SUDEP (Massey et al., 2014).

Peri-ictal cardiac arrhythmias

Various seizure-related cardiac arrhythmias have been described, but only two types have been reported in ictal recordings of (near-)SUDEP: cardiac asystole (Lanz et al., 2011) and ventricular tachycardia/fibrillation (VT/VF) (Dasheiff & Dickinson, 1986; Espinosa et al., 2009). The cross-sectional prevalence of ictal asystole was found to be relatively low when databases of video-EEG-recordings were retrospectively analysed: 0.3 to 0.4% of people with epilepsy (Rocamora et al., 2003; Schuele et al., 2007; Lanz et al., 2011).

A much higher prevalence was found when heart rhythm was measured continuously for 18 months using implantable cardiac loop recorders: 21% (4/19) of participants had clinically relevant ictal bradycardia or asystole necessitating pacemaker implantation (Rugg-Gunn et al., 2004). In a second study, (ictal) asystole was found in 6% (1/19) of participants (Nei et al., 2012). The discrepancy in prevalence between long-term ECG registries and video-EEG-databases may suggest that many ictal periods of asystole (of potential clinical relevance) go unnoticed in regular clinical practice. Ictal asystole occurs predominantly in people with temporal lobe epilepsy during focal seizures with alteration of awareness; the side of seizure onset does not appear to be of consequence (Rocamora et al., 2003; Schuele et al., 2007; Lanz et al., 2011). The aetiology of ictal asystole is incompletely understood. Electrical stimulation of parts of the limbic system such as the insula and cingulate gyrus was found to reproduce this arrhythmia analogous to the brief apnoeic responses described earlier (Oppenheimer et al., 1992; Altenmüller et al., 2004). The spreading of seizure activity to the limbic system may, therefore, trigger both asystole and ictal respiratory changes. Alternatively, this arrhythmia may be mediated by a transient increase in vagal tone after seizure onset, since ictal asystole has similar characteristics to those seen in cardioinhibitory vasovagal syncope (Schuele et al., 2008). It has further been suggested that ictal asystole may function as a seizure termination mechanism by causing cerebral ischaemia, which then both ends the seizure and the ictal asystole itself (Schuele et al., 2010). Ictal asystole may, therefore, be a benign self-limiting condition.

Seizure-related VT/VF has been described far less extensively than ictal asystole: only three cases have been reported (Dasheiff & Dickinson, 1986; Espinosa et al., 2009; Ferlisi et al., 2013). VT/VF appears to be triggered by CSs thus suggesting a different aetiology than asystole.

CSs have a number of proarrhythmic effects: a sympathetic surge activity triggers dramatic increases in the level of circulating catecholamines (Simon et al., 1984) and pronounced peri-ictal HR acceleration (Surges et al., 2010 a). Catecholamines affect cardiac repolarization resulting in prolongation of the QTc-interval (Magnano et al., 2006). Accordingly, abnormal peri-ictal QTc-lengthening has been described in several studies (Brotherstone et al., 2010; Surges et al., 2010 a; Surges et al., 2010 b). QTc-prolongation has been associated with an increased risk of cardiac arrhythmia, specifically torsade de pointe VT (Straus et al., 2006; Feldman & Gidal, 2013). Seizure-related QTc-shortening has also been described, but the clinical implications of this finding are less clear (Surges et al., 2010 a; Surges et al., 2010 b). Transient myocardial ischaemia reflected by ST-segment depression was seen in 40% of seizures in one study, predominantly in CSs and those with a higher maximum HR (Tigaran et al., 2003).Together, these seizure-related changes may lower the threshold for VT/VF, thus explaining why CSs can trigger this arrhythmia. In conclusion, ictal asystole appears to be more common than VT/VF, but its lethality and, therefore, its role in SUDEP pathophysiology remain unclear. There is stronger evidence for a link between VT/VF and SUDEP, as this arrhythmia was reported in three cases of (near-)SUDEP and is less likely to be self-limiting.

1.7 Predisposing interictal factors

In addition to potential peri-ictal pathomechanisms of SUDEP, various interictal abnormalities that may lower the threshold for (seizure-related) cardiac arrhythmias and thus contribute to SUDEP have been described. These predisposing interictal factors may be subdivided into intrinsic susceptibility (genetic modifiers of cardiac arrhythmias) and acquired susceptibility (autonomic alterations, cardiac electrical changes, effects of AED therapy).

Genetic modifiers of cardiac arrhythmias

With the advent of population genotyping, certain IGE syndromes have been associated with inherited sodium channelopathies (Hirose et al., 2005). In addition, the importance of sodium and potassium channel mutations in various cardiac arrhythmias has been established (Antzelevitch et al., 2005; Brenyo et al., 2012): KCNQ1, KCNH2, and SCN5A variants in the long-QT-syndrome and the Brugada syndrome. While these inherited syndromes are relatively rare, other mutations causing mild ion channel dysfunction may be more common and might enhance the susceptibility to arrhythmia. It is conceivable, therefore, that some patients with epilepsy may be genetically susceptible to arrhythmias due to expression of the same mutation in the heart and the brain. In a retrospective study of 343 individuals with long-QT-syndrome, those with subtype 2 (due to mutations in the KCNH2 gene) were much more likely to have a personal history of seizures than other subtypes (Johnson et al., 2009). In addition, a missense SCN5A mutation was recently described in three different family members who exhibited both epilepsy and the Brugada syndrome (Parisi et al., 2013).

Several ion channel gene mutations have been found in either SUDEP victims or their immediate family; in a family with a mutation in the sodium channel SCN1A and generalized epilepsy with febrile seizures plus (GEFS+) syndrome two cases of SUDEP were reported (Hindocha et al., 2008). An SCN1A mutation was also described in a young boy who died of SUDEP (Le Gal et al., 2010). An SCN5A mutation was found at post-mortem in a SUDEP victim (Aurlien et al., 2009). In a third sodium channel gene, SCN8A, a *de novo* pathogenic mutation was found in an individual with infantile epileptic encephalopathy who died of SUDEP (Veeramah et al., 2012).

After genetic analysis of postmortem DNA samples of 68 SUDEP victims, two variants in the KCNH2 and SCN5A genes were found, which were absent in control alleles and therefore potentially pathogenic (Tu et al., 2011 a). In postmortem DNA samples from 48 SUDEP victims, two non-synonymous variants in HCN2 and one non-synonymous variant in HCN4 (all absent in control alleles) were reported (Tu et al., 2011 b). The HCN genes encode for a mixed sodium potassium channel that is involved in generating spontaneous rhythmic activity in cardiac pacemaker and neuronal cells (Tu et al., 2011 b). The finding of these variants of neuro-cardiac ion channel genes (SCN1A, SCN5A, SCN8A, KCNH2, HCN2, and HCN4) in SUDEP victims further supports the notion of a pathogenic link between heart and brain, which may be involved in SUDEP (Tu et al., 2011 b). SCN1A mutations are found in up to 80% of individuals with clinical signs of Dravet syndrome, a severe epileptic encephalopathy with onset in infancy characterized by refractory seizures (Marini et al., 2011). The rate of SUDEP, particularly in older children and young adults with Dravet syndrome, appears to be extremely high (12.5% before age 50), even when compared with other childhood-onset epileptic encephalopathies with a similar seizure burden (Genton et al., 2011). The evidence, therefore, for a link between SCN1A mutations and SUDEP is stronger than for other ion channels.

Autonomic alterations

In people with epilepsy the prevalence of interictal cardiac arrhythmias appears to be similar to that of the general population (Blumhardt et al., 1986; Massetani et al., 1997). In those with epilepsy, however, interictal HR was faster, thus suggesting a changed autonomic balance (Evrengül et al., 2005; Shobha et al., 2007; Harnod et al., 2008; Harnod et al., 2009). The measure most commonly used to study changes in the autonomous nervous system is heart rate variability (HRV): the beat-to-beat change in heart rate (HR) thought to be regulated by sympathetic and parasympathetic activity (Stein & Kleiger, 1999).

HRV decrease has been associated with a higher risk of cardiac mortality and sudden cardiac death in healthy people and in individuals with cardiac disease (Tsuji et al., 1996; Stein & Kleiger 1999). In a recent meta-analysis, people with epilepsy were found to have lower HRV measures than healthy controls, with increased sympathetic and/or decreased parasympathetic tone (Lotufo et al., 2012). People with chronic temporal lobe epilepsy had significantly lower HRV measures than healthy controls, especially during the night (Tomson et al., 1998; Ronkainen et al., 2005). In addition, HRV changes appear to be progressive in refractory epilepsy, but not in well-controlled epilepsy; in a cross-sectional study comparing children with refractory and well-controlled epilepsy and normal controls, HRV measures were significantly lower in the first group (Raju et al., 2012). It was found that HRV measures progressively decreased during a period of six years in people with refractory, but not in those with well-controlled, temporal lobe epilepsy (Suorsa et al., 2011). These findings may have relevance for SUDEP pathophysiology: most SUDEP cases occur at night and individuals with refractory epilepsy have a higher SUDEP risk. In fact, in an individual with refractory temporal lobe epilepsy, progressive HRV deterioration was measured over the course of nine months after which he died from SUDEP (Rauscher et al., 2011).

Baseline HRV measures were not found to be predictive of SUDEP risk (Surges et al., 2009; Surges et al., 2010 b). The association between long-term HRV progression and SUDEP risk has, to my knowledge, not yet been systematically investigated. Other autonomic functions tests also appear to be abnormal in people with epilepsy, confirming the results found in HRV studies. In people with focal epilepsy, blood pressure variability differed significantly when compared with healthy controls, reflecting an impairment of baroreceptor function (Devinsky et al., 1994). In addition, decreased baroreceptor sensitivity was documented in people with epilepsy (Dütsch et al., 2006).

Cardiac electrical changes & the effects of AED therapy

Several interictal cardiac electrical changes have been documented in people with epilepsy. In seven studies the QTc-interval in people with and without epilepsy was compared: in three studies those with epilepsy had a slightly longer QTc-interval (Drake et al., 1993; Neufeld et al., 2009; Dogan et al., 2010), in two studies QTc-durations were found to be similar in both groups (Akalın et al., 2003; Krishnan & Krishnamurthy, 2013), and in two other studies those with epilepsy had a shorter QTc-interval (Teh et al., 2007; Ramadan et al., 2013). The co-incidence of a prolonged baseline QTc-interval and peri-ictal QTc-lengthening may increase the risk of ventricular arrhythmia further than either of those conditions separately. Neither baseline QTc-duration nor the level of peri-ictal QTc-prolongation differed, however, between later SUDEP victims and living controls with epilepsy (Surges et al., 2010 b). AED use may contribute to the QTc-abnormalities found in people with epilepsy. Widely-used AEDs such as carbamazepine and phenytoin have sodium channel blocking or QTc-prolonging effects (Smits et al., 2008; Feldman & Gidal, 2013). These drugs may, therefore, adversely affect the cardiac depolarization and repolarization process.

AEDs that induce the CYP450 enzyme system (again carbamazepine and phenytoin) may also have other negative effects on the heart. Use of enzyme-inducing AEDs has been associated with elevated levels of serological vascular risk markers (total cholesterol, LDL), and may, thus, lead to accelerated atherosclerosis and cardiac disease (Mintzer & Mattson, 2009; Mintzer, 2010). In addition, abrupt AED reduction or withdrawal may carry negative effects. Abrupt withdrawal of carbamazepine can increase sympathetic tone, especially during sleep, and may facilitate the occurrence of cardiac arrhythmias (Kennebäck et al., 1997; Hennessy et al., 2001). In addition, AED cessation/reduction may worsen seizure control leading to a higher risk of SUDEP.

As stated earlier, no individual AED has unequivocally been associated with an increased risk of SUDEP .In a meta-analysis of randomized controlled AED trials SUDEP incidence was found to be lower in those subjects with add-on treatment than in those receiving add-on placebo. The positive effects of AED use on seizure control, therefore, seem to outweigh the negative effects with respect to SUDEP.

1.8 Comorbidity and SUDEP

The new category of SUDEP plus has been defined to include cases where comorbidity may in part contribute to SUDEP (Nashef et al., 2012). Comorbidity has come to be defined as a greater than co-incidental association of two conditions in the same individual (Téllez-Zenteno et al., 2005 b; Ng et al., 2012). Major epidemiological studies have consistently shown that people with epilepsy have a higher prevalence of somatic comorbidity than those without epilepsy (Li et al., 1997; Gaitatzis et al., 2004; Strine et al., 2005; Téllez-Zenteno et al., 2005 b; Nuyen et al., 2006; Kobau et al., 2008; Elliott et al., 2009; Hinnell et al., 2010; Ivanova et al., 2010 a; Ivanova et al., 2010 b; Ottman et al., 2011; Eccher et al., 2012; Kaiboriboon et al., 2012; Kessler et al., 2012; Kadima et al., 2013; Selassie et al., 2014).

In a recent nationwide study of sudden, unexpected death in the young, people with epilepsy had a significantly higher prevalence of comorbidity (23%) than the non-epilepsy population (5%) (Holst et al., 2013): $p<0.001$. Specifically, those with epilepsy had an increased risk of neurological disease (13 vs. 0.9%), psychiatric disease (2.7 vs. 0.1%), mental retardation (2 vs. 0.1%), cerebral palsy (5 vs. 0.2%), and congenital disease (8 vs. 1%) (Holst et al., 2013). The increased burden of comorbidity, therefore, appears to be distributed across the entire spectrum of disease in the population with epilepsy without predilection for a specific condition or group of conditions.

Several biases have to be taken into account when addressing the association between epilepsy and comorbidity: people with epilepsy are consistently found to have a significantly lower socio-economic status, an important determinant of overall health and mortality, than the general population (Mackenbach et al., 1997; Mackenbach et al., 2000). In addition, people with epilepsy may be more likely to receive and report an additional diagnosis (i.e. comorbidity) due to their more intensive use of medical care services ("medical diagnosis bias") (Ottman et al., 2011). Epilepsy may be associated with specific comorbid conditions, because these diseases (such as stroke or brain tumours) are the cause of the epilepsy (causal bias). Other conditions may be more prevalent in epilepsy because they result from the effects of epilepsy or its treatment (resultant bias) (Gaitatzis et al., 2004; Gaitatzis et al., 2012). Evidence suggests, however, that people with epilepsy have a significantly higher prevalence of somatic comorbidity even when taking these biases into account (Strine et al., 2005; Ottman et al., 2011; Neligan et al., 2011).

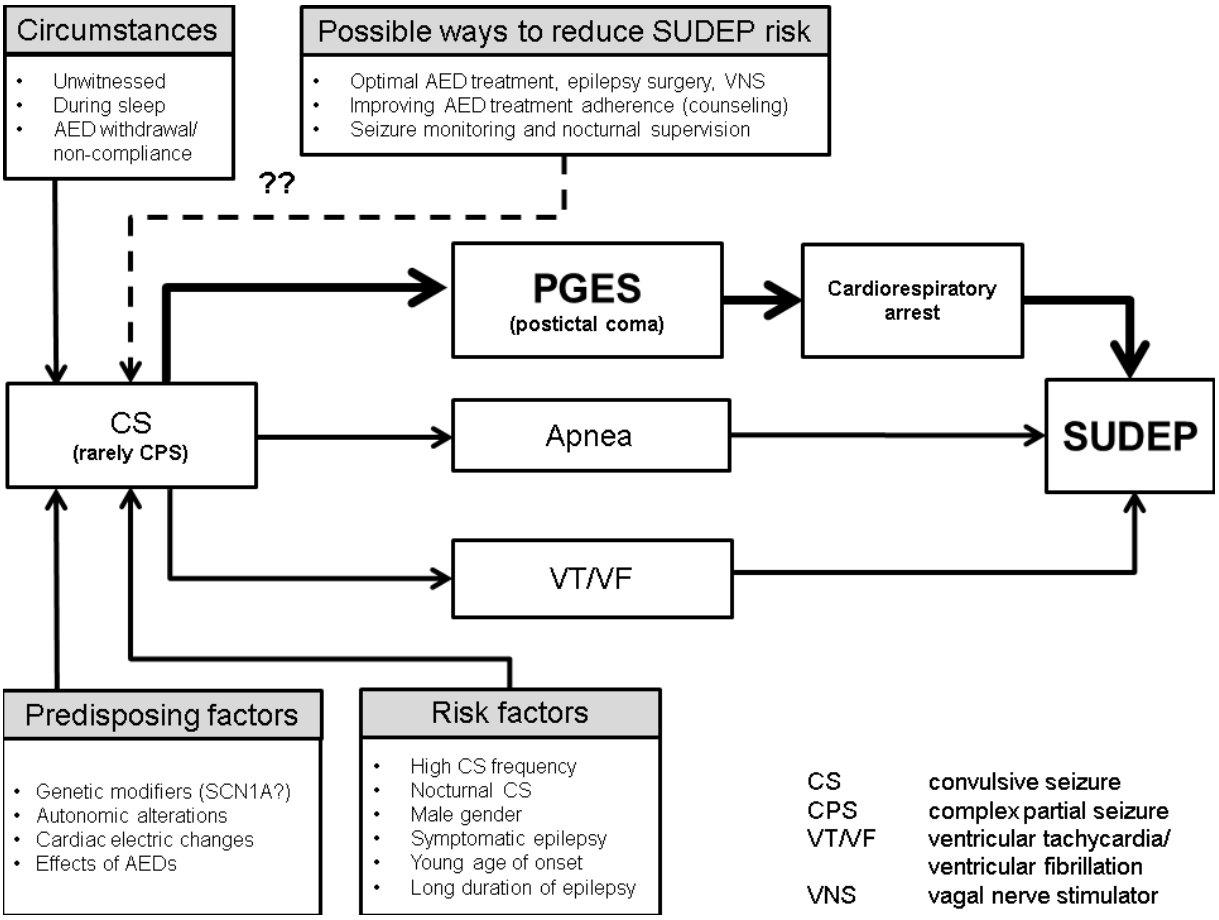
Cardiovascular comorbidity is the most likely group of conditions to play a contributory role in SUDEP considering that it is the most prevalent cause of sudden death in the general population; in clinicopathological series, approximately 70% of all sudden deaths under 40 years of age were ascribed to an anatomical cardiac cause, 20% to non-cardiac causes, and in 10% the underlying cause could not be determined (sudden unexplained death) (Van der Werf et al., 2010). A further analysis of this last category (autopsy-negative sudden unexplained death victims) through non-targeted screening of genes associated with primary arrhythmia syndromes established a putative cardiac cause in over a third of individuals (Tester & Ackerman, 2007). Postmortem investigations may be negative, therefore, in a considerable number of SCAs in the general population (Puranik et al., 2005), and a negative postmortem is also the hallmark of SUDEP.

As stated before, non-lethal cardiac pathology was found in a considerable number of SUDEP victims at autopsy. Analogous to the predisposing factors discussed earlier, (occult) cardiovascular comorbidity may lower the threshold for ventricular arrhythmia in people with epilepsy, so that peri-ictal changes can trigger SUDEP.

1.9 Model of SUDEP pathophysiology

SUDEP is presumably the result of a complex interplay of various predisposing and peri-ictal factors: figure 1. Predisposing factors may increase the vulnerability of an individual with epilepsy to the (cardiovascular) effects triggered by CSs or rarely focal seizures with alteration of awareness. Risk factors generally reflect how many potentially lethal CSs an individual with epilepsy is likely to experience. When CSs occur they may set off three distinct pathophysiological cascades that may end in SUDEP if left unchecked. External circumstances may further aggravate peri-ictal (respiratory) distress, further contributing to SUDEP.

Figure 1: Pathophysiological model of SUDEP.



1.10 Preventive measures

The fact that SUDEP usually occurs unwitnessed suggests that the (immediate) presence of a caregiver at the scene may be preventive. Timely medical intervention may save lives. The MORTEMUS study demonstrated that cardiopulmonary resuscitation was always started within 3 minutes after seizure end in those with non-fatal near-SUDEP and delayed for >10 minutes or not performed in all SUDEP cases. Laypersons may also be able to prevent SUDEP; in a cohort with severe epilepsy and learning disabilities at a special residential school, all deaths were unwitnessed and occurred when the students were not under the close supervision of the school (Nashef et al., 1995 c). In addition, nocturnal supervision at home was found to be protective (Langan et al., 2005). Why untrained witnesses may be capable in part of preventing SUDEP is unclear; postictal attempts at arousal and body repositioning might be effective. For caregivers, the most crucial time to check-up on their family members with epilepsy is at night, as SUDEP predominantly occurs at night. There has, therefore, been increasing interest in developing new types of seizure-surveillance systems that may facilitate the recognition of nocturnal seizures. Seizures can be detected by registering changes in environmental noise, body and limb movements, HR, breathing pattern, blood oxygenation level, electrodermal activity or a combination of some of these modalities (van de Vel et al., 2013). Most devices are capable of detecting CSs at rather high sensitivity; other seizure types are missed far more frequently (Poppel et al., 2013). Unfortunately, none of the current devices are fit for long-term monitoring of high-risk individuals in the home environment; the rate of false-positive alerts remains too high and most systems are too uncomfortable if worn continuously in everyday life (Carlson et al., 2009; Beniczky et al., 2013; Narechania et al., 2013; van de Vel et al., 2013).

1.11 Improving AED treatment adherence

An important goal of SUDEP counselling is treatment adherence. It is estimated that approximately 40% of those with epilepsy take fewer antiepileptic medications than prescribed (Davis et al., 2008). Non-compliance has been shown to be associated with a three-fold higher mortality rate in people with epilepsy (Faught et al., 2008). It may lead to a higher CS frequency and thus increase the risk of SUDEP. The higher AED concentration variability found in the scalp hair of SUDEP victims provides further evidence for a link between treatment non-adherence and SUDEP. In other studies, however, no differences in AED treatment adherence were found between SUDEP victims and living controls with epilepsy (Nilsson et al., 2001; Walczak et al., 2001). There are, broadly speaking, two schools of thought about which people with epilepsy should receive SUDEP counselling, which is nicely illustrated in a paper contrasting the views of a Scottish and an American epileptologist (Brodie & Holmes, 2008). The Scottish physician provides each of his patients with both written and oral information preferably shortly after diagnosis, while the American physician favours a more individualized approach. He communicates SUDEP risk at a later stage only to those who ask about epilepsy-related death or are estimated to be at high-risk. This contrast is also evident in national epilepsy guidelines: the UK and Scottish epilepsy guidelines espouse "routine disclosure", whereas the recently published Dutch guideline appears to favour "tailored disclosure" (NICE clinical guideline 137, NVN Richtlijn Epilepsie). When asked, the majority of patients and family members prefer to be told about SUDEP at the time of diagnosis (Gayatri et al., 2010; Ramachandrannair et al., 2013). In some individuals, however, this may inadvertently cause stress culminating in a higher seizure frequency (Lathers & Schraeder, 2006; Yuen et al., 2007; Brodie & Holmes, 2008).

Most healthcare professionals appear to favour tailored disclosure: in surveys the majority of neurologists (82 to 90%) informs only specific individuals of SUDEP, while approximately 5 to 10% of doctors routinely mention SUDEP, and 7 to 10% never discuss the subject at all (Morton et al., 2006; Vegni et al., 2011; Abdalla et al., 2013; Friedman et al., 2014). In a survey among US neurologists (Friedman et al., 2014), important reasons not to discuss SUDEP were the estimated small risk of SUDEP in a particular individual (53.6%), fear of negatively affecting mood or quality of life of people with epilepsy (32.8%), and lack of proven prevention (33.8%). A clear disadvantage of tailored disclosure is that it may come too late for a significant number of people, since SUDEP may also affect those with a recent diagnosis or those with infrequent seizures (Hanna, 1997). Detailed data are not available to the best of my knowledge, but the collection of stories by bereaved relatives at least gives the impression that it is not rare: 11/37 (30%) of SUDEP cases had a similar presentation (SUDEP: continuing the global conversation, 4rd edition). In addition, many people with epilepsy may, by this stage, have already absorbed information on the internet that may not always be accurate: the interest in SUDEP as measured by Google search terms has increased enormously in recent years (Brigo et al., 2014).

1.12 Summary

SUDEP is the most common seizure-related cause of death. To establish the diagnosis no anatomical or toxicological cause of death should be found at autopsy. Most deaths are unwitnessed and occur at night. SUDEP predominantly affects people with refractory epilepsy in the aftermath of a CS. The strongest SUDEP risk factors are associated with poor seizure control. Achieving seizure freedom is, therefore, the best strategy to prevent SUDEP.

Ictal recordings have demonstrated three potential seizure-related pathomechanisms of SUDEP: the sequence of PGES followed by cardiorespiratory arrest; central/obstructive apnoea; cardiac arrhythmias. Predisposing factors may increase the vulnerability for seizure-related (cardiac) effects. Comorbidity (especially occult cardiovascular disease) may play a contributory role. Specific preventive strategies are not yet available: nocturnal supervision is a promising measure if stronger scientific evidence of its effectiveness is produced. An important goal of SUDEP counselling is to promote treatment adherence. Disagreement remains on the most optimal counselling strategy: routine vs. tailored disclosure.

2. Aims of the studies

3.1 Prospective, community-based, case-control study of epilepsy as a risk factor for sudden cardiac arrest due to ECG-confirmed VT/VF

a) To assess whether having active epilepsy is a risk factor for sudden cardiac arrest due to ECG-confirmed VT/VF in the general population

3.2 Prospective, community-based case-control study of the circumstances and risk factors of sudden cardiac arrest due to ECG-confirmed VT/VF in epilepsy

a) To describe the causes, circumstances, and characteristics of SCA due to VT/VF in epilepsy and review them against (near)-SUDEP criteria
b) To compare patient and event characteristics in people with SCA due to VT/VF with and without epilepsy and determine whether the aetiology of SCA differs between these two groups
c) To search for determinants of SCA due to VT/VF risk in epilepsy

3.3 Retrospective assessment of PGES >20s in people with multiple CSs recorded on video-EEG in two epilepsy referral centres

a) To assess the intraindividual consistency of PGES >20s in people with multiple CSs and reconcile previous conflicting studies on the clinical value of this EEG-characteristic as a predictor of SUDEP
b) To analyse co-factors that facilitate the occurrence of PGES >20s and gain a better understanding of its underlying cause

3. Methods

3.1 Prospective, community-based case-control study of epilepsy as a risk factor for sudden cardiac arrest due to ECG-confirmed VT/VF

Study design

This investigation was conducted in a community-based study in the Netherlands: the Amsterdam Resuscitation Studies (ARREST). ARREST was designed to study the determinants of SCA in the general community (Bardai et al., 2011; Bezzina et al., 2010; Arking et al., 2011; Blom et al., 2014). Data were retrieved in the study period July 2005 to January 2010. This study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all participants who survived the SCA. The Medical Ethics Committee of the Academic Medical Centre in Amsterdam approved the use of data from patients who did not survive the SCA, and approved this study (Appendix 1).

Design of ARREST

ARREST is a prospective, community-based study aimed at establishing the genetic and clinical determinants of SCA in the general community in a contiguous region (urban and rural communities, ~2.4 million inhabitants) of the Netherlands. The ARREST research group, in collaboration with all Emergency Medical Services (EMS) in the study region, prospectively collects data of all cardiopulmonary resuscitation efforts using a mandatory multiple-source notification system (involving personnel of dispatch centres, ambulance services and all 14 area hospitals). This ensures a complete coverage of the study region and inclusion of >95% of all patients with out-of-hospital SCA (Bardai et al., 2011).

The data collection infrastructure used records all out-of-hospital SCA parameters, from ambulance dispatch to discharge from the hospital or to death. Cases are included as follows. After each suspected out-of-hospital SCA, the dispatch centre notifies the study centre (providing information on the place and circumstances of SCA). Ambulance personnel are obliged by protocol to send the ECGs by modem to the study centre directly after resuscitation, and to call the study centre to provide extra information (e.g., whether SCA onset was witnessed, whether basic life support was provided before arrival of ambulance personnel, whether the patient died at the resuscitation site or was transported to a hospital). If an automated external defibrillator was used, the study centre is notified by the dispatch centre, ambulance personnel and/or the user of this device (most automated external defibrillators in the study region carry a label requesting that the study centre is notified after the device has been used). ARREST personnel visit the resuscitation site upon notification to collect the ECG recording from the device. The electrocardiograms are stored and analysed with dedicated software (Code Stat Reviewer 7.0, Physio Control, Redmond, Washington). Rhythms are categorized as shockable (VT/VF) or non-shockable (asystole or pulseless electrical activity). Data items concerning the cardiopulmonary resuscitation procedure are stored according to the Utstein recommendations (Jacobs et al., 2004). ECG recordings from the ambulance monitor/defibrillator or automated external defibrillator are used to determine whether VT/VF had occurred. SCA cases are defined as patients with cardiac arrest in an out-of-hospital setting with ECG-documented VT/VF. Patients with an obvious non-cardiac cause of VT/VF (e.g., trauma, intoxication, drowning, suicide) or those in whom no ECG-documented evidence of VT/VF was available (these patients typically had asystole or pulseless electrical activity) are excluded. Medical histories are obtained from the general practitioner (GP) and/or hospital (Appendix 2).

In the Netherlands, every individual has a GP who acts as gatekeeper for all medical care. Thus GPs have a full overview of all diagnoses made by medical specialists. Complete medication histories of the year preceding VT/VF are obtained from the community pharmacies. Controls who had never experienced VT/VF were randomly drawn from the same source community as cases, using the HAG-net-AMC database of GPs. HAG-net-AMC contains the complete medical records of ~60,000 patients from a large group of GPs in the study area (van Doormaal et al., 2010). Each case was matched with up to 5 controls by age (± 5 years), gender, and index date (date of VT/VF in cases; in the accompanying controls data acquired after this index date was excluded from analysis).

Definition of active epilepsy and risk factors

We ascertained which cases and controls had a diagnosis of epilepsy; all GP records with the terms "epilepsy" or "epileptic seizure" in the diagnosis list were reviewed by two epileptologists (RD Thijs, JW Sander). Epilepsy was confirmed if the diagnosis was established by a neurologist in accordance with national guidelines (NVN Richtlijn Epilepsie). Additional information was requested from the attending neurologist if needed. Only people with a diagnosis of active epilepsy were included in the analysis as having epilepsy. Active epilepsy was defined as current treatment with AEDs or seizures within the previous 2 years (Fisher et al., 2005). For all cases and controls, we also assessed the following established risk factors for VT/VF: ischaemic cardiovascular disease, heart failure, hypertension, diabetes mellitus and hypercholesterolaemia. This was established from GP records based on a formal diagnosis, or by use of medication.

Statistical analysis

A conditional logistic regression model was used to estimate the association of various cofactors, including epilepsy, with VT/VF. Univariable analysis (matched for age, gender, and index date) was employed, as well as two models: multivariable analysis including all variables for which $p < 0.1$ in the univariable analysis; multivariable analysis including all variables (other than epilepsy) which had $p<0.1$ in univariable analysis, and which changed the point estimate of the univariable association between epilepsy and VT/VF by >5%; the only such covariates were ischaemic cardiovascular disease, diabetes, and heart failure. Subanalyses were performed using multivariable logistic regression, adjusting for age, gender and risk factors.

3.2 Prospective, community-based case-control study of the circumstances and risk factors of sudden cardiac arrest due to ECG-confirmed VT/VF in epilepsy

Design & setting

Two case-control studies were conducted using one case group and two control groups of individuals ≥12 years of age who were drawn from two community-based databases: cases were defined as people with epilepsy who suffered VT/VF. They were compared to those without epilepsy who experienced VT/VF (VT/VF controls) and to individuals with epilepsy who had not suffered VT/VF (epilepsy controls). Cases and VT/VF controls were drawn from the Amsterdam Resuscitation Studies (ARREST) registry, while epilepsy controls were drawn from the Out-Patient Population-based Epilepsy Cohort (OPPEC). ARREST was approved by the Medical Ethics Committee of the Academic Medical Centre (AMC) in Amsterdam and OPPEC by the Medical Ethics Committee of the University Medical Centre Utrecht (UMC).

In ARREST, written informed consent was obtained from all survivors of VT/VF and the use of observational data from non-survivors was allowed by the Medical Ethics Committee. In OPPEC, all participants provided written informed consent (Appendix 3, 4).

ARREST registry

The methodology of ARREST has been explained in detail in the methods section of study 1 (Blom et al., 2014).

OPPEC database

OPPEC is a cross-sectional, community-based study, designed to assess the clinical, demographic, genetic, and pharmacological determinants of AED treatment response in an out-patient cohort with epilepsy in a (sub)urban region in the centre of the Netherlands (het Gooi-Utrecht) (Wassenaar et al., 2013; Wassenaar et al., 2014): appendix 5, 6. Subjects were recruited during an 18-month period (July 2010 to December 2011) from the databases of 30 pharmacies, covering a population of about 250,000 inhabitants. Those who had at least two prescriptions for any AED dispensed in the previous two years (indicating long-term use) were asked to participate (Appendix 5): response rate 30% (Wassenaar et al., 2013).

Cases

People with SCA due to VT/VF and a presumed diagnosis of epilepsy based on the terms "epilepsy" or "epileptic seizure" listed in their GP or hospital records were extracted from all subjects enrolled in ARREST with complete GP and hospital records during a 7-year period (July 1st 2005 to July 31st 2012). Only those individuals with a confirmed diagnosis of active epilepsy were subsequently included in the study as cases (Appendix 6). To determine whether those with a confirmed diagnosis of active epilepsy could be classified as SUDEP, patient and event characteristics were evaluated by two neurologists with a special interest in epilepsy (JW Sander, RD Thijs) and one cardiologist (HL Tan).

In cases of disagreement, the reviewers discussed to reach consensus. SUDEP was defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration ≥30 min or seizures without recovery in between), in which postmortem examination does not reveal a cause of death (Nashef et al., 2012). Cases without autopsy results were classified as either probable or possible SUDEP depending on whether a potentially competing cause of death was found after cardiac evaluation. Near-SUDEP was defined as "an individual with epilepsy who survived resuscitation for more than 1 hour after a cardiorespiratory arrest that has no structural cause identified after investigation" (Nashef et al., 2012).

Controls

The VT/VF control group consisted of all those with VT/VF without a history of epilepsy in ARREST in 2007-2008 with complete GP and hospital records. Each case was also matched by age (±5 years) and gender to three epilepsy controls from OPPEC.

Definition of active epilepsy

The data of all people with a presumed diagnosis of epilepsy in ARREST and of all participants in OPPEC was reviewed by two members of the OPPEC diagnostic confirmation team who are neurologists with a special interest in epilepsy (F Leijten and GJ de Haan), who independently rated the likelihood of this diagnosis on a scale of 0-100% (Wassenaar et al., 2013; Wassenaar et al., 2014). People with an average score of ≥80% were considered to have epilepsy. Only individuals with active epilepsy, which was defined as current treatment with AEDs or a seizure within the previous two years were included as having active epilepsy (Fisher et al., 2005).

Collection of clinical information

The following clinical data were obtained from GP, pharmacy and hospital records in ARREST and OPPEC: epilepsy characteristics (aetiology, seizure freedom in the last two years, age of onset and duration of epilepsy), intellectual disability (yes/no), cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes mellitus, and stroke/TIA), and clinically relevant heart disease (yes/no). Cardiac pathologies included ischaemic (myocardial infarction, heart failure), valvular, or congenital/inherited heart disease (aortic coarctation, hypertrophic obstructive cardiomyopathy) with or without cardiac arrhythmia (atrial fibrillation, atrioventricular block). Complete medication histories of the year before VT/VF (ARREST) or inclusion in the study (OPPEC) were obtained from community pharmacies. We defined three drug categories: 1) QT-prolonging medication (www.azcert.org) including the AEDs phenytoin and felbamate (Feldman & Gidal, 2013), 2) depolarization-blocking drugs (www.brugadadrugs.org) including the AEDs carbamazepine, oxcarbazepine, phenytoin, and lamotrigine (Rogawski & Löscher, 2004), and 3) cardiovascular drugs (β-adrenoreceptor blockers, calcium channel antagonists, angiotensin-converting enzyme inhibitors, diuretics, angiotensin-II receptor blockers, nitrates, platelet aggregation inhibitors, and/or statins). Drugs may belong to more than one category.

Statistical analysis

Patient and event characteristics were described and compared between cases and VT/VF controls using $\chi 2$ statistics (Pearson/Fisher's Exact where appropriate) for categorical data and the Student's t-test/Mann Whitney U test for continuous data. Variables found significant in univariable analysis were included in a logistic regression model to determine whether the characteristics of VT/VF in cases and VT/VF controls differed.

To identify risk factors for VT/VF (cases vs. epilepsy controls), univariable and multivariable conditional logistic regression was employed, thereby accounting for matched data. In this model, Firth correction for rare events was used for seldom occurring variables (intellectual disability). P-values of <0.05 were considered to be significant. Statistics were performed in SPSS (cases vs. VT/VF controls; version 17.0 for Windows, Chicago IL, USA) and in R (cases vs. epilepsy controls 2; R statistical package, version 3.10, package clogit and logistf, version 1.10).

3.3 Retrospective assessment of PGES >20s in people with multiple CSs recorded on video-EEG in two epilepsy referral centres

Sample selection

We reviewed reports of digital video-EEGs from two tertiary epilepsy referral centres (Bonn and Heemstede) from the period 2003 to 2011 and selected people ≥15 years old who had two or more CSs recorded on long-term monitoring. The study size was determined by the number of available video-EEGs. This study was approved by the ethics committees at both sites; because of its observational nature, informed consent was not required at either site (Appendix 7).

Collection of variables

We collected data on: gender, age, presence of intellectual disability (yes/no), epilepsy classification (structural/metabolic vs. unknown), lesion on MRI (yes/no), age of onset, duration of epilepsy, frequency of CSs, AED regimen (prior to admission and for each subsequent monitoring day), state of wakefulness prior to seizure onset (awake/asleep), sleep stage prior to seizure onset (REM, NREM I-III), localization of EEG seizure onset (temporal/extratemporal), duration of the tonic and tonic-clonic phase as well as entire seizure duration.

Tapering was defined as any reduction of the total AED drug load during the recording period, compared with the regimen prior to admission. The overall drug load (prior to admission and each subsequent monitoring day) was estimated as the sum of the prescribed daily dose (PDD)/defined daily dose (DDD) ratios for each AED (Canevini et al., 2010). HR was measured during the last minute before seizure onset and the first minute after seizure end. This study was approved by the ethics committees at both sites; due to its observational nature informed consent was not required at either site. Conventional scalp EEG recordings (International 10–20 System) (Stellate Harmonie, Stellate Systems, Montreal, QC, Canada; Schwarzer GmbH/Natus, Germany) were performed at a sampling rate of 200 Hz. A modified lead-I electrocardiogram (ECG) (Stellate Harmonie; Schwarzer GmbH/Natus) (adhesive electrode(s) placed below the clavicle) was simultaneously recorded. Random numbers were assigned to all individual seizures in order to blind patient status. Two board-certified clinical neurophysiologists (A Gaitatzis, RD Thijs) independently analysed the presence or absence of PGES>20s and duration of the tonic phase in all CSs. PGES was defined as the immediate postictal (within 30s), generalized absence of EEG activity >10 μV in amplitude, allowing for muscle, movement, breathing, and electrode artefacts (Lhatoo et al., 2010).

Only PGES of >20s after CSs were scored as these were previously associated with increased SUDEP risk (Lhatoo et al., 2010). Due to privacy rules, video-recordings from Bonn could not be evaluated off-site, thus PGES was assessed using only EEG recordings in this site. In Heemstede both EEG and video were assessed. The onset of the tonic phase was defined as the occurrence of bilateral, symmetrical or asymmetrical, continuous muscle activity obscuring EEG background activity. Muscle activity was evaluated in the frontotemporal regions using a bipolar montage. The end of the tonic and onset of the clonic phase was defined by a sustained pattern of bilateral and synchronous bursts of muscle artefact with burst intervals ≥150 ms, and absence of muscle activity between bursts.

Statistical analysis

The proportion of people in whom PGES consistently occurred (presence or absence of PGES >20s in all CSs) was calculated and related to the number of recorded CSs. Associations between PGES >20s and person- or seizure-specific variables were assessed with Fisher's exact probability test, chi-square, or Mann-Whitney U tests, where appropriate. A mixed linear regression model was used to determine which variables were independently associated with PGES >20s after correction for individual effects and the varying number of seizures contributed by each person. Only those variables with $p<0.05$ at univariable analysis were entered and adjustments for multiple comparisons were made using the Holms-Bonferroni method. Statistical analysis was performed with SPSS (version 17 Chicago, IL, U.S.A.), and STATA 12 software (StataCorp LP, TX, USA).

4. Results

4.1 Prospective, community-based case-control study of epilepsy as a risk factor for sudden cardiac arrest due to ECG-confirmed VT/VF

We identified 1019 cases with VT/VF with an available medical and/or medication use history prior to the event; these cases were matched with 2834 controls. Mean age was 63.5 years in cases (76.5% male), and 58.3 years in controls (68.5% male). We confirmed that the established risk factors for VT/VF were also associated with VT/VF in our study: table 6. Twelve cases (1.2%) and 12 controls (0.4%) had a diagnosis of active epilepsy at index date. Epilepsy was associated with an almost three-fold increased risk for VT/VF (adjusted OR 2.9 [95%CI 1.1, 8.0], p= 0.034, model 2, table 7). Sub-analyses suggested that the adjusted VT/VF odds are higher in people with epilepsy aged <50 years (N=4, adjusted OR_{young} 4.6, p=0.210) compared with people aged ≥50 years (N=8, adjusted OR_{old} 2.4, p=0.128), and in females (N=5, adjusted $OR_{females}$ 4.6, p=0.044) compared with males (N=7, adjusted OR_{males} 2.0, p=0.309). Epilepsy characteristics of cases and controls are listed in table 8.

Table 6: demographics and distribution of covariates in cases with sudden cardiac arrest, controls without sudden cardiac arrest, and cases with sudden cardiac arrest and epilepsy

	Cases n=1019	Controls n=2834	Cases with epilepsy n=12
Gender			
Male	780 (76.5)	1855 (68.5)	7 (58.3)
Female	239 (23.5)	979 (31.5)	5 (41.7)
Mean age, years (SD)	63.5 (13.7)	58.3 (14.5)	60.0 (16.0)
Covariates			
Ischaemic CVD	443 (43.5)	141 (5.0)	3 (25)
Stroke/TIA	49 (4.8)	71 (2.5)	1 (8.3)
Hypertension	529 (51.9)	433 (15.3)	7 (58.3)
Diabetes mellitus	219 (21.5)	294 (10.4)	1 (8.3)
Heart failure	199 (19.5)	29 (1.0)	4 (33.3)
Hypercholesterolemia	290 (28.5)	170 (6.0)	5 (27.8)

Data are expressed as number (%) unless otherwise indicated. CVD = cardiovascular disease. TIA = transient ischaemic attack. SD, Standard deviation.

Table 7: multivariable analysis of risk factors for ECG-confirmed sudden cardiac arrest

	OR*(95% CI) p-value	Model 1 OR** (95% CI) p-value	Model 2 OR*** (95% CI) p-value	Univariable analysis p-value
Epilepsy	3.3 (1.4-7.5)	2.8 (0.9-9.0) p=0.076	2.9 (1.1-8.0) p=0.034	p=0.005
Ischaemic CVD	11.2 (8.8-14.3)	6.7 (5.0-8.8) p<0.001	9 (7-11.7) p<0.001	p<0.001
Stroke/TIA	1.7 (1.1-2.5)	0.8 (0.4-1.6) p=0.53	Not applicable	p=0.012
Hypertension	5.8 (4.8-7.0)	3.7 (2.9-4.7) p<0.001	Not applicable	p<0.001
Diabetes mellitus	2.0 (1.6-2.4)	0.8 (0.6-1.1) p=0.1	1.2 (0.9-1.5) p=0.2	p<0.001
Heart failure	20.5 (13.1-32.1)	9.9 (5.8-17) p<0.001	12.9 (7.9-21.1) p<0.001	p<0.001
Hypercholesterolemia	5.6 (4.5-7.0)	2.9 (2.2-3.9) p<0.001	Not applicable	p<0.001

Abbreviations as in table 6.

*****Odds Ratios estimated with conditional logistic regression, matched by age, gender, and index date.

** Model 1: Odds Ratios estimated with conditional logistic regression, matched by age, gender, and index date. All covariates that were significantly associated with ventricular tachycardia/fibrillation (at a p<0.1 level) were included in the regression analyses (ischaemic cardiovascular disease, stroke/transient ischaemic attack, hypertension, diabetes mellitus, heart failure and hypercholesterolemia).

*** Model 2: Odds Ratios estimated with conditional logistic regression, matched by age, gender, and index date. All covariates that were significantly associated with ventricular tachycardia/fibrillation (at a p<0.1 level) were included in the regression analyses if they changed the point estimate of the association between epilepsy and sudden cardiac arrest due to ventricular tachycardia/fibrillation by >5%; the only such covariates were ischaemic cardiovascular disease, diabetes, and heart failure.

Table 8: distribution of epilepsy and cardiovascular characteristics in cases with sudden cardiac arrest and epilepsy and controls with epilepsy

	Cases (n=12)	**Controls (n=12)**
Epilepsy aetiology		
Structural/metabolic	8 (67%)	5 (42%)
Unknown¶	4 (33%)	5 (42%)
Genetic	0 (0%)	2 (17%)
Seizure type[1]		
Convulsive seizures	9	10
Focal seizures with alteration of awareness	3	4
Focal seizures without loss of awareness	1	1
Absence seizures	1	0
Age at onset of epilepsy, yr (Median, Range)	46.5 (9-79)	42 (6-63)
Duration of epilepsy, yr (Median, Range)	11 (0-52)	17.5 (2-33)
Polytherapy (>1 antiepileptic drug)		
Yes	4 (33%)	3 (25%)
No	8 (67%)	9 (75%)
Antiepileptic drug use[1]		
Valproic acid	7	4
Carbamazepine	4	5
Phenytoin	3	2
Phenobarbital	1	1
Topiramate	1	1
Clobazam	1	0
Lamotrigine	0	2
History of underlying heart disease		
Ischaemic heart disease	3 (25%)	2 (17%)
Heart failure	4 (25%)	0 (0%)
Structural heart disease[2]	3 (25%)	1 (8%)

No history	4 (33%)	9 (75%)
Cardiac medication use		
Platelet aggregation inhibitors	5	1
Antihypertensives[3]	8	2
Antiarrhythmic agents[4]	1	0
Statins	5	0
Evidence of acute myocardial infarction[5]		
Postmortem[6]	3	
Clinical[7]	8	
Not Available	4	
Deceased before hospital discharge		
Yes	12 (100%)	
No	0 (0%)	

[1]Some patients had more than one type of seizure/antiepileptic drug/cardiac drug, therefore the number of seizure types/ antiepileptic drug used exceeds the total number of patients. [2]Valve abnormalities and/or aortic coarctation. [3]Diuretics, β-adrenoceptor blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists. [4] Amiodarone. [5] Patients may fall in more than one category. [6]Evidence of acute myocardial infarction found during autopsy. [7]Evidence of acute myocardial infarction found during clinical diagnosis and treatment of ventricular tachycardia/fibrillation (ECG, cardiac enzymes, coronary angiography).

4.2 Prospective, community-based case-control study of the circumstances and risk factors of VT/VF in epilepsy

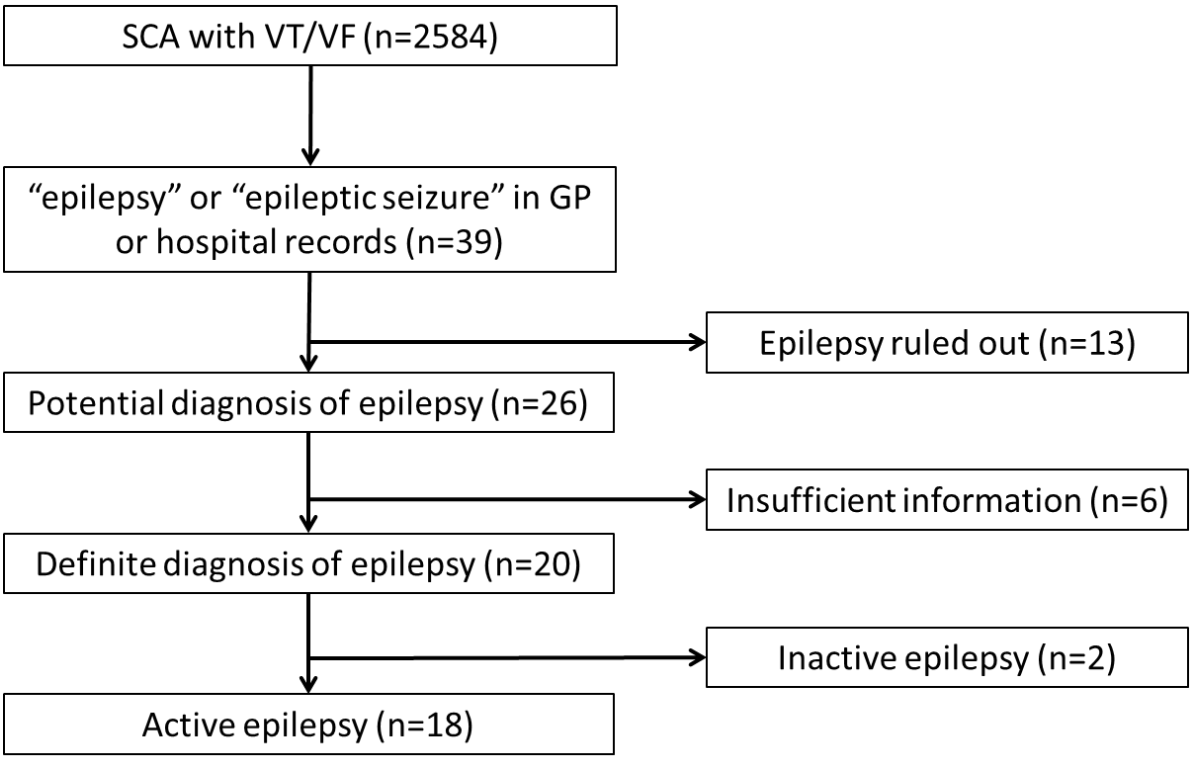
Cases

During the study period 2584 people with VT/VF were enrolled, 39 of whom had a presumed diagnosis of epilepsy: figure 2. After exclusions due to inaccurate diagnosis (n=13), insufficient information to validate a diagnosis (n=6), or inactive epilepsy (n=2), 18 cases (mean age 57 years, 67% male) with VT/VF and active epilepsy were included in the final analysis: tables 9-11. The majority of cases from my first thesis study (10/12; 83%) were also included in this cohort.

An underlying cardiovascular cause of VT/VF was found in 10 cases (56%): acute myocardial infarction, hypertrophic obstructive cardiomyopathy, and co-incidence of transient cardiac ischaemia and drug-induced QTc-prolongation. In five other cases (28%) an underlying cardiovascular cause was presumed: they had recent-onset cardiac symptoms (severe recurrent chest pains <1 week before VT/VF) or clinically relevant pre-existing heart disease. These suspicions could, however, not be confirmed as all died before hospital admission and autopsy was not performed. In the three remaining individuals (16%) no definite cardiovascular cause of VT/VF could be established after further investigations. In the first case, VT/VF was attributed to a high fever (42°C) secondary to autopsy-confirmed bilateral pneumonia. It did, therefore, not fulfil SUDEP criteria. The remaining two individuals died a few days later in the hospital after initial successful resuscitation and did not have autopsy: one of these, an apparently seizure-related case was classified as probable near-SUDEP in view of a normal comprehensive diagnostic work-up. In this case prolonged convulsive movements were reported by witnesses and rectal diazepam was administered.

The second case, apparently non-seizure-related, was classified as having possible near-SUDEP case: slight ECG abnormalities without cardiac enzyme changes were found, and these were considered insufficient evidence for a diagnosis of myocardial infarction.

Figure 2: Selection of cases with ventricular tachycardia/fibrillation and epilepsy



2584 individuals of ≥12 years of age with ventricular tachycardia/fibrillation and complete GP or hospital records were enrolled in ARREST in the period from July 1st 2005- July 31st 2012. From this cohort 18 cases with active epilepsy were selected for this study after exclusions for various reasons. In 13 individuals a diagnosis of epilepsy was ruled out: data entry errors (n=3), alcohol-induced seizures (n=3), non-epileptic transient loss of consciousness (n=3), single seizure (n=3), revision of epilepsy diagnosis (n=1). In some individuals (n=6) there was insufficient information either to confirm or to rule out a diagnosis of epilepsy. In these cases, either the attending general practitioner and/or neurologist could not be located (n=4), or the diagnosis was established ≥20 years ago and full medical records were no longer available (n=2).

Table 9: characteristics of people with ventricular tachycardia/fibrillation and epilepsy (n=18)

Male gender	12 (67%)
Age, years	
0-20	1 (5.5%)
21-40	2 (11%)
41-60	7 (39%)
61-80	7 (39%)
>80	1 (5.5%)
History of brain dysfunction or injury¶	
Intellectual disability	5
Traumatic brain injury	3
Stroke	4
Cerebral asphyxia	2
Cerebral abscess	1
None	7
Witnessed onset of SCA	13 (72%)
Prolonged convulsive movements	2 (11%)
Clinically relevant pre-existent heart disease ¶#	
Ischaemic	4
Valvular	2
Congenital	3
Atrial fibrillation	2
3rd degree atrioventricular block	1
Underlying cause of sudden cardiac arrest	
Acute myocardial infarction	8 (44%)
Other cardiovascular cause*	2 (11%)
Presumed cardiovascular cause	5 (28%)
No cardiovascular cause established after further investigations**	3 (17%)

Diagnostic work-up¶	
Ancillary tests	13
Autopsy	4
No ancillary tests or autopsy	5
Evidence of acute myocardial infarction¶	
Ischaemic ECG	5
Elevated cardiac enzymes	4
Regional wall motion abnormalities on echocardiogram	1
Percutaneous coronary intervention	3
Coronary artery bypass graft	1
Autopsy	3
Deceased before hospital discharge	
Yes	14 (78%)
No	4 (22%)

¶People may fall under more than one category.

#Clinically relevant heart disease was defined as ischaemic (myocardial infarction, heart failure), valvular, or congenital heart disease (aortic coarctation, hypertrophic obstructive cardiomyopathy) with or without cardiac arrhythmia (atrial fibrillation, 3rd degree atrioventricular block). *Hypertrophic obstructive cardiomyopathy, transient cardiac ischaemia and drug-induced QTc-prolongation. **Fever-associated ventricular tachycardia/fibrillation secondary to bilateral pneumonia, probable near-SUDEP, possible near-SUDEP.

VT/VF characteristics in people with and without epilepsy

In the 18 cases and 470 VT/VF controls general and event characteristics were analysed: table 10. Acute myocardial infarction was the most common cause of VT/VF in both groups. In cases, events generally occurred at younger age (mean age 57 vs. 64 yr, p=0.023), and SCA onset was less likely to be witnessed (72 vs. 89%, p=0.048) and more likely to occur at/near home (89 vs. 58%, p=0.009) than in controls. In addition, the prevalence of congenital heart disease was higher in cases (17 vs. 1%, p=0.002). In multivariable analysis, these four variables were independently associated with SCA due to VT/VF in epilepsy: table 10.

Epilepsy and other characteristics in people with and without VT/VF

General and epilepsy characteristics were compared in 18 cases and 54 epilepsy controls: table 11. Cases were more likely to have clinically relevant heart disease (50 vs. 15%, p=0.005) and intellectual disability (28 vs. 2%, p<0.001). In multivariable analysis, these variables were independently associated with VT/VF in epilepsy: table 11.

Table 10: Comparison of people with ventricular tachycardia/fibrillation and epilepsy and controls with ventricular tachycardia/fibrillation

	Cases (n=18)	VT/VF controls (n=470)	Crude OR (95% CI)	Adjusted OR (95% CI)
Demographics:				
Male gender	12 (67%)	376 (80%)	0.500 (0.183-1.367)	
Mean age, yr (SD)	57 (16.9)	64 (14.0)	**0.965 (0.936-0.995)**	**0.961 (0.931-0.993)**
Cardiac risk factors:				
History of myocardial infarction	4 (22%)	136 (29%)	0.702 (0.227-2.170)	
Congenital heart disease	3 (17%)	5 (1%)#	**18.560 (4.056-84.937)**	**19.806 (3.461-113.343)**
Stroke/transient ischaemic attack	4 (22%)	48 (10%)#	2.506 (0.793-7.919)	
Hypertension	10 (56%)	207 (44%)	1.588 (0.616-4.096)	

Hypercholesterolaemia	5 (28%)	156 (33%)#	0.772 (0.270-2.203)	
Diabetes mellitus	1 (6%)	99 (21%)	0.220 (0.029-1.677)	
Circumstances of event:				
Witnessed onset	13 (72%)	415 (89%)#	**0.326 (0.112-0.951)**	**0.303 (0.096-0.954)**
Event during night-time¶	2 (11%)	83 (18%)	0.583 (0.131-2.583)	
Event at/near home	16 (89%)	272 (58%)	**5.824 (1.324-25.617)**	**6.620 (1.420-30.868)**
Underlying cause of event:				
Acute myocardial infarction	8 (62%)□	247 (57%)□	1.192 (0.384-3.703)	
Deceased before hospital discharge				
All SCA	14 (78%)	264 (56%)	2.731 (0.886-8.421)	
SCA¶ (onset before EMS arrival)	13 (76%)	255 (60%)	2.179 (0.699-6.796)	

Dichotomous data are expressed as n (%) and continuous data as mean (standard deviation). #These variables were unknown in 1-3 people with ventricular tachycardia/fibrillation without epilepsy: congenital heart disease (1), stroke/transient ischaemic attack (1), hypercholesterolaemia (1), and presence of witnesses (3). □The underlying cause of ventricular tachycardia/fibrillation was undetermined in 5 people with epilepsy and 39 individuals without epilepsy. In 17 individuals with epilepsy and 426 people without epilepsy SCA onset occurred in the absence of EMS personnel. Night-time was defined as the period between 23:00 and 07:00. Associations were expressed as odds ratios with 95% confidence intervals. Significant associations are in bold. All covariates that significantly differed between cases and VT/VF controls ($p<0.05$) (age, presence of congenital heart disease, presence of witnesses, and occurrence of VT/VF at home) were entered in a logistic regression model to calculate adjusted odds ratios.

Table 11: Comparison of people with epilepsy and ventricular tachycardia/fibrillation and controls with epilepsy

	Cases (n=18)	Epilepsy controls (n=54)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Demographics:				
Male gender	12 (67%)	36 (67%)	n.a	n.a
Mean age, yr (SD)	57 (16.9)	57.3 (15.9)	n.a	n.a
Intellectual disability#	5 (28%)	1 (2%)	**43.31 (2.07-908.26)**	**41.35 (1.35-1264.8)**
Epilepsy characteristics				
Structural/metabolic aetiology	11 (61%)	24 (44%)	1.87 (0.65-5.42)	n.a
Recent seizure	8 (44%)	31 (57%)	0.56 (0.18-1.75)	n.a
Age of onset, years	38 (1-79)	39.5 (1-79)	0.99 (0.96-1.02)	n.a
Duration of epilepsy, years	13 (0-67)	11.5 (0-76)	1.01 (0.98-1.04)	n.a
Cardiac risk factors:				
Clinically relevant heart disease	9 (50%)	8 (15%)	**6.84 (1.79-26.18)**	**6.87 (1.29-36.56)**
Stroke/transient ischaemic attack	4 (22%)	7 (13%)	1.88 (0.49-7.24)	n.a
Hypertension	10 (56%)	25 (46%)	1.54 (0.48-4.98)	n.a
Hypercholesterolemia	5 (28%)	14 (26%)	1.10 (0.34-3.58)	n.a
Diabetes mellitus	1 (6%)	4 (7%)	0.72 (0.07-7.36)	n.a
Medication use:				
Polytherapy (>1 antiepileptic drug)	5 (28%)	22 (41%)	0.62 (0.22-1.80)	n.a
QT-prolonging drugs	5 (28%)	13 (24%)	1.20 (0.37-3.92)	n.a
Depolarization-blocking drugs	10 (56%)	27 (50%)	1.25 (0.43-3.61)	n.a
Cardiovascular drugs	13 (72%)	27 (50%)	3.65 (0.90-14.73)	n.a

Dichotomous data are expressed as n (%), and continuous data as mean (standard deviation) or median (range). OR: Odds Ratio, CI: confidence interval. Odds ratios with 95% confidence intervals were calculated using conditional logistic regression matched by age and gender. Significant associations are in bold. All covariates that significantly differed between cases and epilepsy controls ($p<0.05$) (intellectual disability, presence of clinically relevant heart disease) were entered in multivariable analysis to calculate adjusted odds ratios.

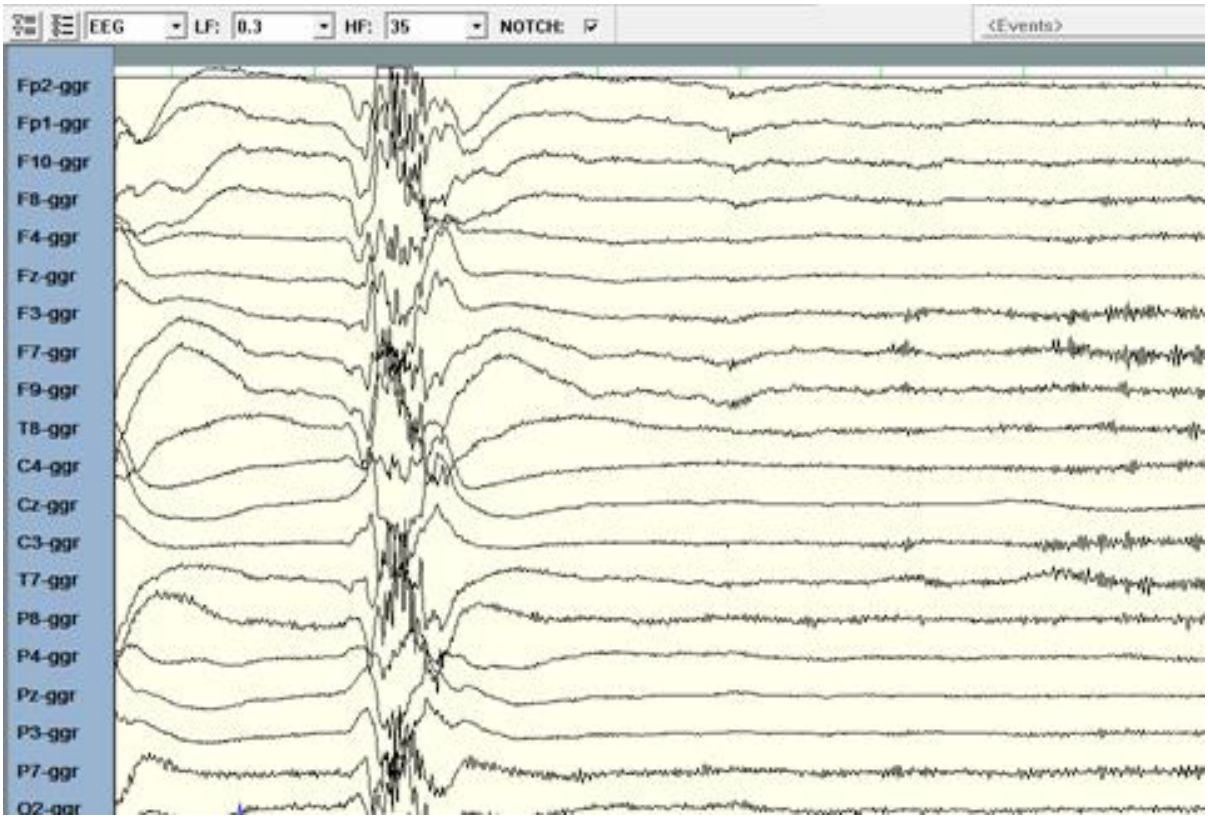
4.3 Retrospective assessment of PGES >20s in people with multiple CSs recorded on video-EEG in two epilepsy referral centres

Prevalence and intraindividual consistency of PGES >20s

We identified 170 CSs in 64 individuals. EEG recordings with less than one minute postictal recording time (n=13) and those of insufficient quality due to lead disconnection (n=3) were discarded, leaving 59 people with 154 CSs (19 with 47 seizures from Heemstede and 40 with 107 seizures from Bonn). All these seizures were classified as focal seizures evolving into a bilateral convulsive seizure with tonic and/or clonic components. The median number of monitoring days was 5 (range 1 to 13). In two CSs from Bonn, PGES based on EEG alone could not be scored due to uncertainty about the presence of movement artefacts, so a local clinical neurophysiologist (R Surges) analysed both EEG and video for a final decision. In the remaining 152 CSs PGES was evaluated by two examiners (R Thijs, A Gaitatzis); in case of disagreement the examiners discussed to reach consensus. Interobserver agreement on PGES>20s was good: κ=0.77 (Cohen's kappa).

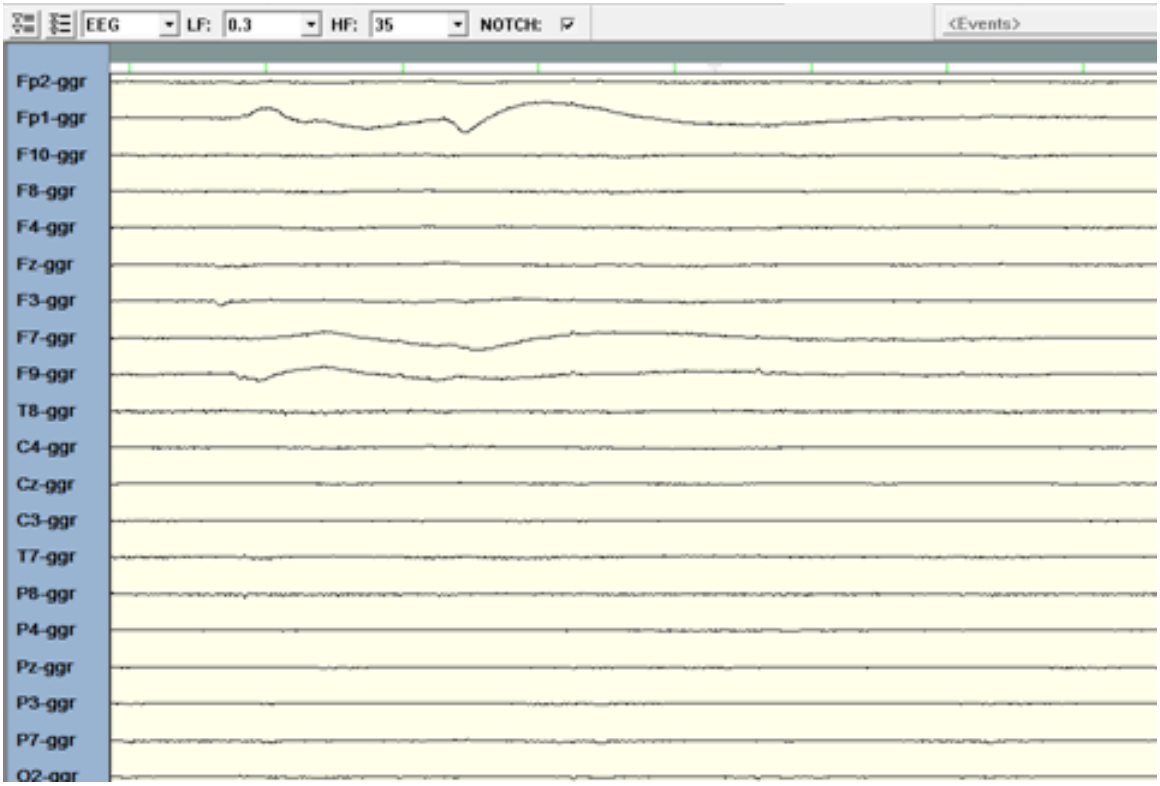
PGES >20s occurred in (37/59) 63% of individuals and in (57/154) 37% of CSs: tables 12-13. In figures 3 and 4 an example of a prolonged period of PGES is shown, whereas figure 5 displays a postictal period without PGES. Presence or absence of PGES >20s was a consistent finding in (34/59) people (presence 12/59; absence 22/59), whereas 25/59 people had a mixture of CSs with and without PGES >20s: figure 6. The number of people with 'consistent' results decreased as the number of CSs recorded increased: table 12, figure 6. None of the individuals described in this study had died at the time of data collection (July 2012).

Figure 3: Start of PGES of 95s immediately after seizure end



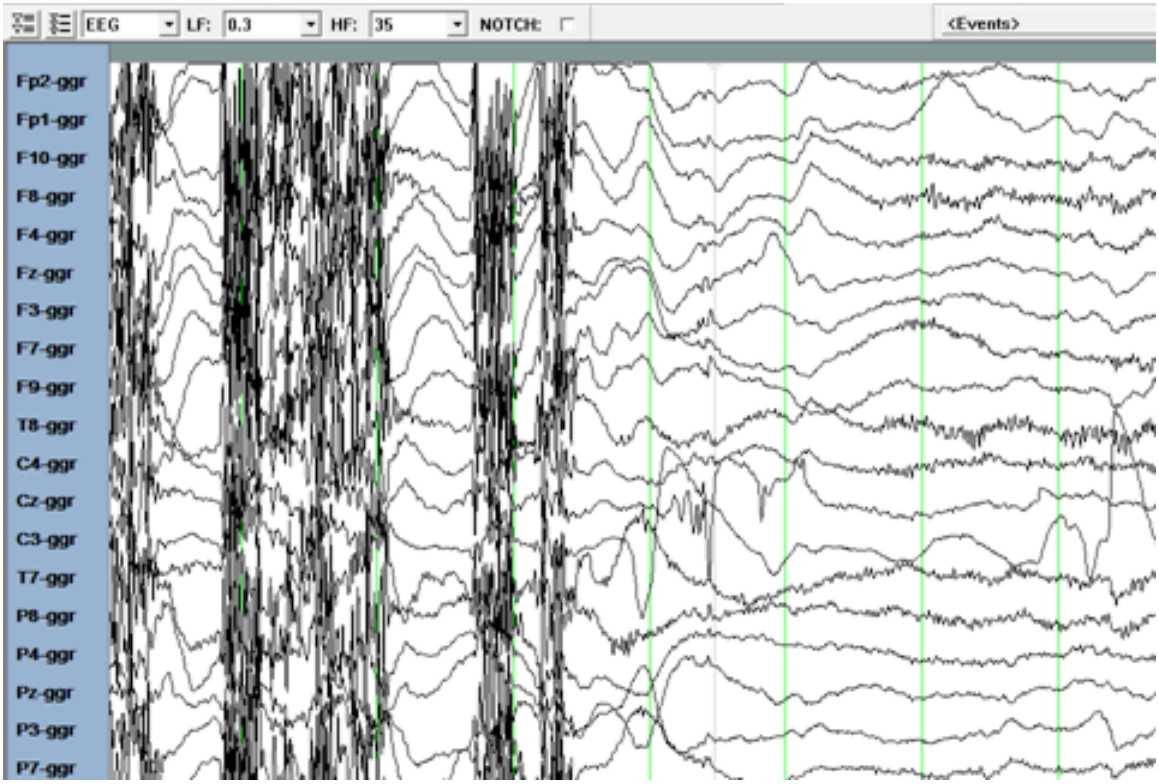
Flattening of EEG-activity in all channels is observed immediately after the end of a convulsive seizure barring muscle artefacts. The low frequency filter is set at 0.3 Hz and the high frequency filter at 35 Hz.

Figure 4: Continuation of PGES of 95s shown 50s after seizure end



The low frequency filter is set at 0.3 Hz and the high frequency filter at 35 Hz.

Figure 5: The start of a postictal period without PGES



No generalized flattening of EEG-activity is observed after the end of a convulsive seizure. The low frequency filter is set at 0.3 Hz and the high frequency filter at 35 Hz.

Table 12: Characteristics of people with a mixture of CSs with and without PGES >20s (n=25), and those in whom PGES >20s was either consistently present (n=12) or absent (n=22).

Variables	**CSs +/-PGES>20s (n=25)**	**All CSs + PGES>20s (n=12)**	**All CSs - PGES>20s (n=22)**
No. of recorded CSs (%)			
2	11 (44%)	9 (75%)	15 (68%)
>2	14 (56%)	3 (25%)	7 (32%)
Gender (%)			
Male	17 (68%)	6 (50%)	11 (50%)
Female	8 (32%)	6 (50%)	11 (50%)
Age at time of EEG, yr (Median; Range)	29 (16-63)	29 (15-49)	26 (16-57)
Duration of epilepsy, yr (Median; Range)	16 (1-44)	14 (1-47)	17 (0-53)
Epilepsy aetiology (%)			
Structural/metabolic	11 (44%)	8 (67%)	16 (73%)
Unknown	14 (56%)	4 (33%)	6 (27%)
Lesion on MRI (%)*			
Yes	11 (44%)	7 (64%)	16 (73%)
No	14 (56%)	4 (36%)	6 (27%)
Frequency of CSs (%)			
1-2 CSs/year	7 (28%)	6 (50%)	13 (59%)
≥3 CSs/year	18 (72%)	6 (50%)	9 (41%)
Mental retardation (%)			
Yes	2 (8%)	1 (8%)	2 (9%)
No	23 (92%)	11 (92%)	20 (91%)

*In one person with symptomatic generalised epilepsy no MRI was performed.

Table 13: Characteristics of CSs with PGES>20s versus CSs without PGES>20s

Variables	***CSs with PGES>20s n=57***	***CSs without PGES>20s n=97***	***Test***
Age at onset of epilepsy yr (Median; Range)	14 (0-55)	12 (0-55)	MW=0.09
State of wakefulness (%)			**χ2, p=0.009**
Asleep	40 (70%)	47 (48%)	
Awake	17 (30%)	50 (52%)	
Sleeping stage (%)			NA
NREM1	6 (15%)	6 (13%)	
NREM2	25 (63%)	31 (66%)	
NREM3	9 (22%)	10 (21%)	
AED reduction (%)			**χ2, p=0.005**
Yes	51 (89%)	66 (68%)	
No	6 (11%)	29 (32%)	
Location (%)			χ2, p=0.35
SEIN	20 (35%)	27 (28%)	
Bonn	37 (65%)	70 (72%)	
Ictal EEG onset (%)*			χ2, p=0.76
Temporal	32 (56%)	52 (53%)	
Extratemporal	25 (44%)	45 (47%)	
Time from seizure onset to generalization, s (Median; Range)	28 (2-367)	28 (0-121)	MW, p=0.69
Duration of tonic phase, s (Median; Range)	32.5 (16-58)	31.5 (0-75)	MW, p=0.59
Duration of tonic-clonic phase, s (Median; Range)	58 (22-118)	58.5 (11-138)	MW, p=0.95

Total seizure duration, s (Median; Range)	92 (25-430)	91.5 (29-486)	MW, p=0.85
Pre-ictal HR, bpm (Median; Range)	73 (49-137)	73 (50-140)	MW, p=0.91
Postictal HR, bpm (Median; Range)	132 (71-159)	136 (83-177)	MW, p=0.16

NREM=non-rapid eye movement

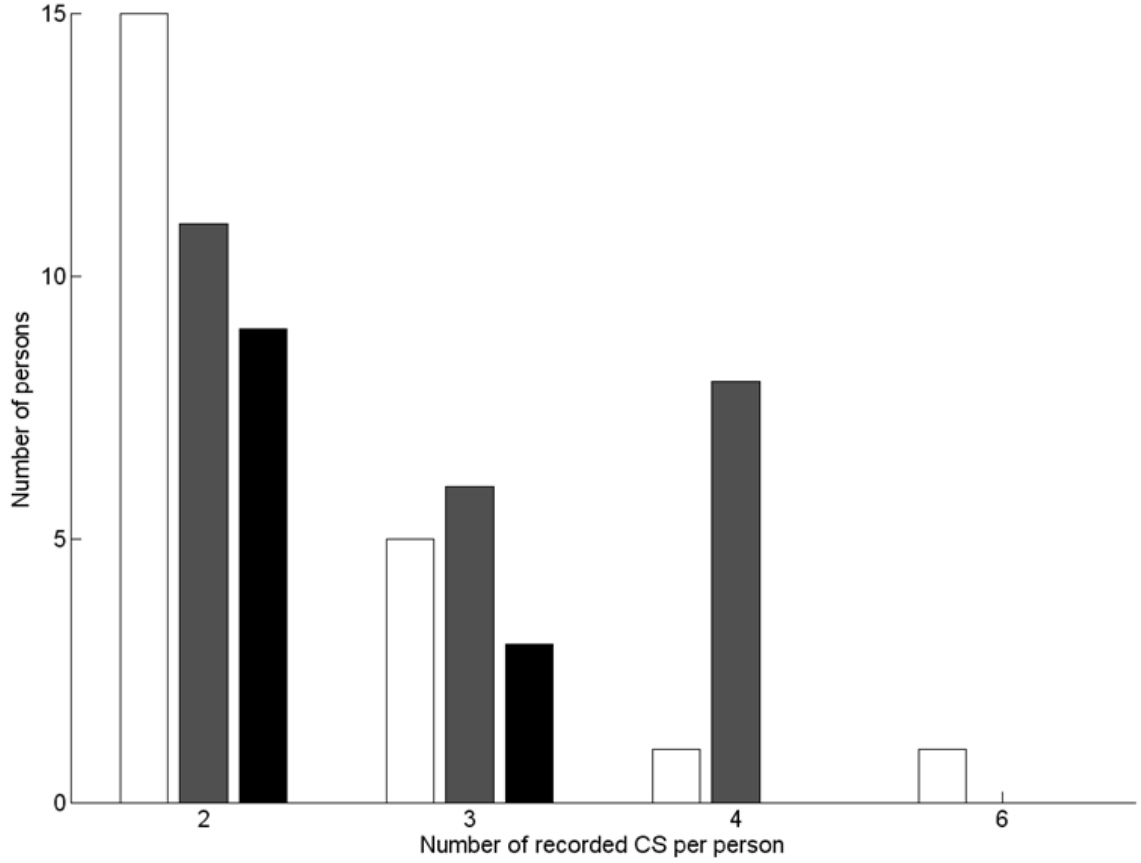
AED= anti-epileptic drug

HR= heart rate

NA=not applicable

*all people with symptomatic generalized epilepsy (n=3) had focal seizures evolving into a bilateral convulsive seizure with tonic and/or clonic components.

Figure 6: Intraindividual variability of PGES>20s in people with multiple recorded CSs.



Most people (25/59) had a mixture of CSs with and without PGES >20s (grey bars). In 22/59 persons PGES >20s was consistently absent (white bars), whereas in 12/59 persons it was consistently present (black bars). Consistency of PGES >20s seemed dependent on the number of recorded CSs.

Factors that facilitate the occurrence of PGES >20s

In univariable analysis, PGES >20s was more frequently found after CSs that started from sleep (OR 2.5, 95% CI 1.3-5.0) and in CSs where medication was tapered (OR 3.7, 95% CI 1.4-9.7). Other person or seizure-related variables did not differ between groups: tables 12-13. In multivariable analysis the variables “sleep” and “AED reduction” remained independent risk factors for PGES >20s after introduction into a mixed linear regression model: sleep OR 3.29, 95% CI 1.21-8.96; AED reduction OR 4.80, 95% CI 1.27-18.14.

5. Discussion

5.1 Prospective, community-based case-control study of epilepsy as a risk factor for sudden cardiac arrest due to ECG-confirmed VT/VF

Strengths & weaknesses

In this study, we provide first evidence that people with epilepsy may have a higher risk of VT/VF than the population without epilepsy. A major strength was the community-based design which ensured that selection bias was minimal. The inclusion of people with epilepsy and those with VT/VF was systematic. All individuals with the terms “epilepsy” or “epileptic seizure” in the GP diagnosis list were reviewed by a panel of experts to avoid overdiagnosis. The point prevalence of active epilepsy in controls was 0.4%. This agrees well with previous estimates in the general population and suggests that we included all people with active epilepsy (Forsgren et al., 2005). The mandatory multiple source notification system ensured that we included data from all potential resuscitations, so that no cases of ECG-documented VT/VF were missed. The study design and access to GP and hospital records enabled us to collect extensive information on the circumstances surrounding VT/VF, comorbidity, and potential confounders. We limited our analysis to cases of VT/VF with known medical and/or medication use history in order to have sufficient information to confirm or reject a diagnosis of active epilepsy. Selection bias can, therefore, not be entirely excluded. There is no reason to assume, however, that the proportion of people with epilepsy would differ in people with VT/VF with or without known medical and/or medication use history. We believe, therefore, that our results are still valid.

Comparison with literature

SCA is a difficult condition to study in the general population given its unpredictability, the short time period before death occurs, and its low survival rate. In ECG-documented SCA, one of three presenting rhythms is generally found: bradycardia/asystole, pulseless electrical activity, or VT/VF. The first two conditions are the final common outcome of every SCA due to cardiac or non-cardiac causes (e.g. respiratory failure), precluding establishment of the causative mechanism. ECG-documentation of VT/VF is probably the best way in a community-based study to ensure that SCA is due to cardiac causes. People with epilepsy had an increased risk of VT/VF, which was even higher in women and the young. Cardiac disease, by far the most common cause of VT/VF (Huikuri et al., 2001), is less prevalent in these two groups, further supporting an important role for epilepsy in VT/VF risk.

VT/VF risk & SUDEP

The association between epilepsy and increased VT/VF risk may suggest that cardiac causes contribute to SUDEP in the community. It should be stressed, however, that VT/VF in epilepsy, and not SUDEP, was the subject of this study. We do not exclude the possibility that other proposed pathomechanisms (PGES followed by cardiorespiratory arrest, central/obstructive apnoea) also contribute to SUDEP in the community. Excess VT/VF risk may also extend to people with epilepsy beyond those with SUDEP: the higher risk was documented in a community-based sample of individuals with less severe epilepsy who are expected to have a lower SUDEP risk. The role of epilepsy as a risk factor for VT/VF may be underestimated under the traditional definition of SUDEP: those who die suddenly with evidence of acute ischaemic heart disease at autopsy would not be classified as SUDEP. In these individuals, epilepsy would be excluded as a contributing factor to sudden death.

Epilepsy or associated autonomic and cardiac (electrical) changes may, however, trigger a lethal cardiac arrhythmia after the threshold for VT/VF has been lowered by ischaemic heart disease (multiple-hit model). The similar prevalence of cardiovascular VT/VF risk factors in people with and without epilepsy who experienced VT/VF appears to support the multiple-hit model: cardiac comorbidity alone does not seem to explain the increased risk of VT/VF, but having epilepsy may lower the threshold for ventricular arrhythmia in those with cardiac conditions even further.

Potential explanations for excess VT/VF risk in epilepsy

As discussed previously, epilepsy and VT/VF share underlying pathophysiological changes that may facilitate ventricular arrhythmias in the presence or absence of seizures. In the majority of those with epilepsy who experienced VT/VF (92%) preceding seizure activity was not reported, suggesting that sudden death in epilepsy is not always seizure-related. Impaired cardiac autonomic function has been described in people with epilepsy and those who suffered VT/VF (Tsuji et al., 1996). Cardiac repolarization abnormalities (e.g. QTc-lengthening and/or shortening) were reported in individuals with epilepsy. Mutations in ion channel genes that are expressed in heart and brain have been described in people with certain types of epilepsy, inherited cardiac arrhythmia syndromes, and SUDEP cases. Use of AEDs, particularly those with depolarization-blocking or QT-prolonging effects may also lower the threshold for ventricular arrhythmia. Lastly, epilepsy characteristics such as seizure frequency/type and epilepsy severity may modulate the risk of VT/VF in a similar way to that in SUDEP. Due to the small number of people with epilepsy who experienced VT/VF, the causes of excess VT/VF risk in this population could not be described further. In the second study of my thesis, therefore, our goal was to determine the underlying aetiologies of VT/VF in epilepsy.

5.2 Prospective, community-based case-control study of the circumstances and risk factors of sudden cardiac arrest due to VT/VF in epilepsy

Main findings

In this study, we collected a larger number of people with epilepsy who experienced VT/VF over a longer period of time from the same community-based registry in order to obtain in further detail the characteristics, aetiology, and risk factors of VT/VF in this population. An underlying (cardiovascular) aetiology, myocardial infarction, was the most common cause of VT/VF in those with and without epilepsy. General (age, prevalence of congenital heart disease) and event characteristics (presence of witnesses, location), however, differed significantly between both groups. Comorbidities (clinically relevant heart disease, intellectual disability) rather than epilepsy characteristics had the strongest associations with VT/VF in epilepsy compared with people with epilepsy without VT/VF.

Study strengths

The major strength of this study is its community-based approach that allowed me to analyse the full spectrum of SCA cases of definite cardiac origin in epilepsy: ECG-confirmed VT/VF. Each case was reviewed against (near-)SUDEP criteria. Due to this methodology, the contrasts and overlaps between SCA in epilepsy and (near-)SUDEP could be defined further. Ventricular arrhythmia may, therefore, be one of the underlying mechanisms of SUDEP not only in those with severe epilepsy, but also in community-dwelling people with epilepsy. Our approach is more rigorous than in two previous studies that analysed SCA in epilepsy in the community. In the first study conducted in Oregon only 26% (28/106) of SCA victims with epilepsy presented with VT/VF and the remaining individuals with bradycardia/asystole or pulseless electrical activity (Stecker et al., 2013).

In the second study set in Melbourne only 22% (185/841) of resuscitated young individuals (including those with epilepsy) presented with VT/VF (Deasy et al., 2011). No distinction between cardiac and non-cardiac SCA could be made due to the inclusion of all presenting rhythms, unlike in my study.

Study limitations

We found two near-SUDEP cases in this study that were categorized as probable/possible rather than definite SUDEP because autopsy was not performed. Those with epilepsy who experienced VT/VF and living controls with epilepsy were selected from two different community-based cohorts (ARREST & OPPEC). OPPEC was based on AED prescription records; this may have introduced bias since each control with epilepsy was by definition using AEDs unlike people with epilepsy who experienced VT/VF from ARREST. Controls could, therefore, potentially have had a higher prevalence of AED use and more severe epilepsy. In practice, however, every individual from both groups was taking AEDs, and the proportion of people with recent seizures (in the last two years) did not differ significantly.

VT/VF in epilepsy & SUDEP

In people both with and without epilepsy, the aetiology of VT/VF was mostly cardiovascular. In contrast, we found that general characteristics and event circumstances differed significantly between the two groups with VT/VF: people with epilepsy were younger and had a higher prevalence of congenital heart disease. In addition, the circumstances of SCA differed between those with and without epilepsy: The onset of VT/VF in epilepsy was less likely to be witnessed and more frequently occurred at/near home. Similar circumstances have been reported in most SUDEP cases. This further supports the notion that cases of VT/VF in epilepsy in the general population can present as SUDEP and may be diagnosed as such.

Taken together, our data suggest that cardiovascular events constitute the predominant cause of VT/VF in epilepsy, whereas in a minority with unexplained ventricular arrhythmia a diagnosis of (near) SUDEP may be established. This may explain why common SUDEP risk factors such as the presence of recent seizures were not associated with VT/VF risk in epilepsy in this study.

Potential explanations for excess VT/VF risk in epilepsy

Shared genetics, shared aetiology, or shared (cardiovascular) comorbidity are potential explanations for the increased risk of VT/VF in epilepsy. A single mutation in an ion channel gene such as SCN1A may confer intellectual disability, a propensity for epilepsy, and an innate vulnerability to lethal cardiac arrhythmia (especially in the presence of new-onset or pre-existent heart disease) (Johnson et al., 2009; Glasscock, 2014). Epilepsy, intellectual disability, and congenital heart disease may result from a multiple malformation syndrome: genetic defects may affect the development of both heart and brain or abnormal cardiovascular function may lead to poor (intrauterine) brain growth (Miller & Vogel, 1999). The incidence of lethal arrhythmia appears to be much higher in adults with (repaired) congenital heart disease than in the general population (Silka et al., 1998; Oechslin et al., 2000), thus linking epilepsy, intellectual disability, and VT/VF. A higher prevalence of (occult) cardiovascular comorbidity in those with epilepsy may also explain excess VT/VF risk. There are several clues linking epilepsy, cardiac comorbidity, and VT/VF. Firstly, people with epilepsy appear to have a worse cardiovascular risk profile than the general population: large health interview surveys have shown that those with a “history of epilepsy” are more likely to be cigarette smokers (Kobau et al., 2004; Elliott et al., 2008a; Elliott et al., 2008b; Kobau et al. 2008; Hinnell et al., 2010; CDC, 2013), and tend to exercise less (Kobau et al., 2004; Strine et al., 2005; Elliott et al., 2008 b; Kobau et al. 2008; Hinnell et al., 2010; CDC, 2013).

In people with epilepsy, obesity appears to be more common (Kobau et al., 2004; Kobau et al., 2008; Hinnell et al., 2010; CDC, 2013), and a higher prevalence of high blood pressure, pre-diabetes and stroke has been reported (CDC, 2013). AED use may further worsen the cardiovascular risk profile: weight gain is a commonly reported side effect of frequently used AEDs such as carbamazepine, and valproic acid (Katsiki et al., 2014). As discussed previously, enzyme-inducing AEDs may also be arteriosclerogenic, since they have been associated with elevated levels of serological vascular risk markers. Secondly, people with epilepsy have been found to have a higher prevalence of a variety of heart diseases and heart disease in general than the general population: in health interviews surveys, the categories "previous myocardial infarction" or "any heart disease" were more frequently reported in those with a "history of epilepsy" (Strine et al., 2005; Elliott et al., 2008b; CDC et al., 2013). In one study comparing the prevalence of somatic comorbidity between a large, unselected cohort with epilepsy and the general population, several types of heart disease were found to be more common in people with epilepsy (Gaitatzis et al., 2004): table 14. In a nationwide cohort study from Denmark, AED-treated people with epilepsy without previous stroke had a higher risk of myocardial infarction and cardiovascular death than the general population (Olesen et al., 2013).

Table 14: Prevalence ratios of different types of heart disease in people with epilepsy when compared to the general community without epilepsy

Types of heart disease	**Prevalence ratios (95% CIs)**
Congenital cardiac abnormalities	7.34 (4.58-11.75)
Heart failure	1.68 (1.45-1.95)
Ischemic heart disease	1.34 (1.19-1.50)

In a long-term follow-up study of a cohort with convulsive epilepsy in rural China, the mortality risk due to myocardial infarction was increased three-fold compared with the general population (Ding et al., 2013). Thirdly, cardiac comorbidity may more easily trigger life-threatening arrhythmias or cardiac death in people with epilepsy. In SCA survivors who were implanted with a cardioverter-defibrillator device, people with epilepsy had a higher risk of recurrent life-threatening cardiac tachyarrhythmia and cardiac death (Badheka et al., 2010). In a prospective case-control study, the odds of incident acute myocardial infarction was 4.8 times as high in people with epilepsy as in the general population (Janszky et al., 2009). Those with epilepsy also had a worse prognosis after suffering acute myocardial infarction after correction for traditional cardiovascular risk factors: a 3.5 times increased risk of cardiac death. Chronic inflammation (e.g. the inflammatory cytokine interleukin-6 (IL-6)) may be a link between epilepsy, intellectual disability, and cardiovascular comorbidity by promoting atherosclerosis or arrhythmogenesis (Hussein et al., 2013). The levels of IL-6 appear to be chronically elevated in people with epilepsy (Nowak et al., 2011), those with intellectual disability (Lehtimäki et al., 2011), and, to an even further extent, in individuals with both conditions (Lehtimäki et al., 2011). High concentrations of this cytokine were found to be associated with an increased risk of sudden cardiac death in a prospective community-based study after correction for traditional risk factors (Hussein et al., 2013).

Recommendations

In conclusion, our study proposes that VT/VF risk in epilepsy is mainly determined by comorbid conditions such as pre-existing heart disease. Careful attention to cardiovascular risk factors in people with epilepsy may reduce the rate of sudden death in this population.

5.3 Retrospective assessment of PGES >20s in people with multiple convulsive seizures recorded on video-EEG in two epilepsy referral centres

Main findings

We focused on the intraindividual variability of PGES >20s in people with multiple CSs and found that PGES consistency became progressively lower when more CSs were evaluated per individual. The prevalence of PGES >20s was higher after CSs arising from sleep or when medication had been reduced. PGES >20s had limited consistency in people with multiple CSs. High intraindividual variability may explain conflicting findings in previous studies regarding the value of PGES as a SUDEP risk marker (Lhatoo et al., 2010; Surges et al., 2011). Interestingly, intraindividual variability of PGES was higher in the study that found no relationship between PGES and SUDEP risk (Surges et al., 2011). Overall, these findings stress that the occurrence of PGES is critically dependent on the number of seizures analysed and, therefore, unlikely to be a reliable SUDEP risk marker.

Comparison with literature

A potential association between duration of the tonic phase and PGES has been reported previously (Tao et al., 2013), but this was not found in our study. Differences in seizure selection may explain these conflicting results. In the former study, 18.5% of seizures had no tonic phase compared with 0% in our sample. Presence of a tonic phase was highly predictive of PGES: OR 180 (Tao et al., 2013). The reported association between tonic duration and PGES may predominantly rely on the contrast between seizures with and without a tonic phase. Differences in seizure type rather than in tonic duration may, therefore, be responsible for the proposed relation between tonic duration and PGES.

Peri-ictal HR changes were similar in CSs with and without PGES>20s confirming our previous findings (Lamberts et al., 2013 a). In other electroclinical studies, peri-ictal HR acceleration was found to be either higher (Moseley et al., 2013) or lower in CSs with PGES than in those without PGES (Tao et al., 2013). Unfortunately, our findings cannot be easily compared, since these latter studies used a different definition of tachycardia (Moseley et al., 2013) or did not report the HR measurement periods (Tao et al., 2013).

Strengths and limitations

PGES was scored differently in Heemstede (EEG and video) and Bonn (EEG only), which may have introduced bias. This is unlikely, however, since the prevalence of PGES>20s was similar in both centres: table 13. All EEG studies were independently scored by two observers with good interobserver agreement. We could not analyse the effect of peri-ictal hypoxaemia on PGES due to the lack of concurrent oximetry measurements. The link between sleep and PGES may be explained by underlying peri-ictal hypoxaemia. Currently, it is unclear whether more severe hypoxaemia occurs during CSs arising from sleep. In a previous study hypoxaemia was equally frequent during nocturnal and daytime seizures, but mostly focal seizures were analysed (Bateman et al., 2008). Similarly, underlying hypoxaemia may explain the association between AED reduction and PGES. This appears unlikely, however, since no relationship between AED withdrawal and ictal hypoxaemia was found in a systematic analysis of seizure-related respiratory dysfunction (Bateman et al., 2008). Ideally, an analysis of the association between AED withdrawal and PGES would take into account the amount and speed of AED reduction. Unfortunately, such an analysis could not be performed in this study due to its retrospective nature and the great variety in AEDs and reduction schedules.

Aetiology of PGES

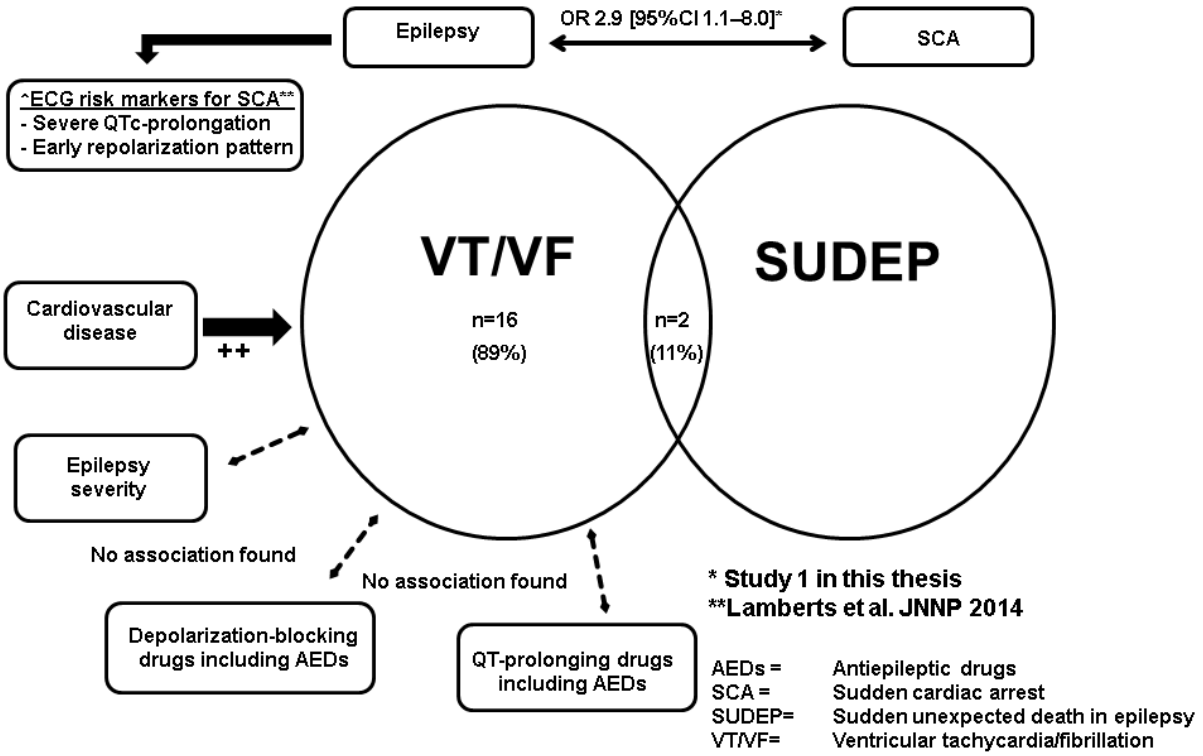
As discussed previously, there are several theories regarding the aetiology of PGES. In this study, we did not see an association between seizure duration and PGES, thus confirming the findings of all previous electroclinical studies on PGES. It is unlikely, therefore, that PGES is the result of neuronal exhaustion. The second hypothesis states that PGES may be due to preceding cardiovascular or respiratory dysfunction. Concurrent oximetry and blood pressure measurements were not available in this study, and our findings, therefore, neither support nor disprove this theory. It has been proposed that PGES results from the increased activity of inhibitory neuronal networks in response to ongoing seizure activity (Lhatoo et al., 2010). This theory may explain the association between sleep and PGES, since inhibitory neuronal network activation is also involved in the process of sleep (Steriade et al., 1993). Similarly, AED use may modulate seizure-related inhibitory neuronal network activation (Tilz et al., 2006), as AED reduction in the EMU can lead to an increase in seizure intensity and frequency (Zhou et al., 2002; Wang-Tilz et al., 2005). It may be speculated that changes in these seizure characteristics can trigger an exaggerated termination response by inhibitory neuronal networks. A further elucidation of the link between different AED withdrawal schedules, changes in seizure characteristics, and PGES may be of interest.

6. My findings in context

6.1 General aim of thesis

The general aim of my thesis was to elucidate further the role of the heart in sudden death in epilepsy. To accomplish this goal, I investigated the association between VT/VF and epilepsy from various angles: a community-based approach was used to determine the association between VT/VF and epilepsy, and to assess the potential overlap between this condition and SUDEP. Our search yielded several new clues favouring a link between VT/VF, epilepsy and SUDEP, which are summarized in figure 7.

Figure 7: Links between epilepsy, sudden cardiac arrest due to ventricular tachycardia/fibrillation, and sudden unexpected death in epilepsy



I found that people with epilepsy had a three times higher odds of VT/VF than the general population irrespective of traditional cardiac risk factors using a prospective community-based registry of resuscitation efforts. In a recent study I took a different approach and analysed the prevalence of three ECG risk markers for SCA in the ECGs of 185 people with refractory epilepsy and 178 controls without epilepsy (Lamberts et al., 2015):

1. severe QTc-prolongation: >450ms in males, >470ms in females (Algra et al., 1991; Straus et al., 2006; Soliman et al., 2011)
2. ERP or early repolarization pattern: figure 8 (Tikkanen et al., 2009; Sinner et al., 2010; Haruta et al., 2011; Rollin et al., 2012)
3. Brugada ECG-pattern (Matsuo et al., 2001)

People with epilepsy were found to have a longer mean QTc-interval (405 vs 394 ms, $p<0.001$) than controls without epilepsy and were more likely to display severe QTc-prolongation (5% vs 0%, $p=0.002$). Those with epilepsy also more frequently displayed ERP (34% vs. 13%, $p<0.001$), whereas the prevalence of the Brugada ECG pattern was similar in both groups (2% vs. 1%, $p>0.999$). The results in this study thus appear to further support a link between epilepsy and SCA. To further explore this link, I analysed the effect of three potential risk factors of VT/VF in epilepsy in a larger group of 18 cases with epilepsy and VT/VF: use of AEDs with depolarization-blocking or QT-prolonging properties, epilepsy severity, cardiovascular comorbidity.

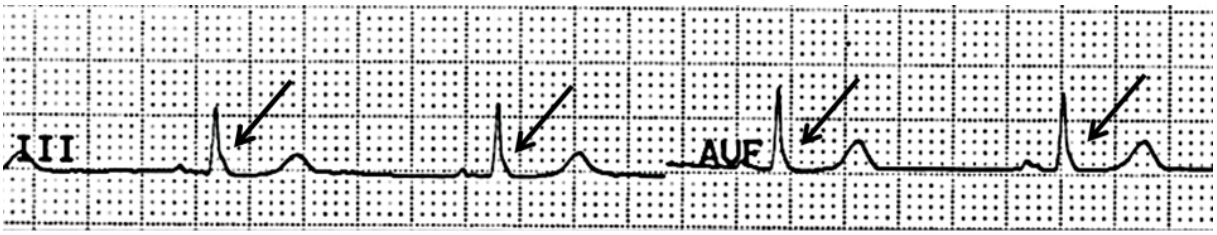


Figure 8: Person with epilepsy and early repolarization pattern in the inferior leads. J-point elevation of ≥ 0.1 mV with slurring morphology in two adjacent leads (III and aVF).

Depolarization-blocking and QT-prolonging AEDs

I did not find an association between the use of potentially arrhythmogenic AEDs (with depolarization-blocking or QT-prolonging properties) and VT/VF in epilepsy. My study was, however, neither powered nor designed to exclude every possibly negative effect of these AEDs. In another recently published community-based study, AED use was reported to give a higher risk of sudden cardiac death in people with and without epilepsy in another recently published community-based study (Bardai et al., 2015). There were, however, a number of possible methodological flaws: the authors used an epidemiological definition of sudden cardiac death in which all sudden natural deaths were attributed to cardiac causes in the absence of a competing cause. In people with epilepsy, however, SUDEP of a non-cardiac origin is a major diagnostic alternative in such cases. Sudden unexplained deaths (i.e. without a definite anatomical or toxicological cause) in this population, therefore, cannot be assumed to be of cardiac origin without additional ECG-documentation, a proof that was present in the first two studies of this thesis. The reported association between AED use and sudden cardiac death may thus have been confounded by epilepsy and its association with both AED use and SUDEP. Carbamazepine and gabapentin were the only AEDs that were individually associated with an increased risk of sudden cardiac death, which the authors attributed to their purported depolarization-blocking properties.

It is unclear, however, to what extent indication bias might have played role. Carbamazepine is a drug of first choice in people with focal epilepsy, and stroke is a leading cause of this type of epilepsy, particularly in the elderly (Ryvlin et al., 2006). Gabapentin is rarely used in refractory epilepsy, but in controls without epilepsy chronic diabetic neuropathic pain is an important indication (Moore et al., 2014). It is, therefore, possible that the excess risk of sudden cardiac death in carbamazepine and gabapentin users was caused by a worse baseline cardiovascular status rather than depolarization-blocking properties.

In conclusion, more research is needed to determine whether the use of potentially antiarrhythmic AEDs may trigger SCA. My recently conducted ECG-study may provide a starting point for addressing this issue, as it raises the question whether those individuals with epilepsy and severe QTc-prolongation or ERP may be at highest risk for the potentially negative effects of these AEDs.

Epilepsy severity

Epilepsy severity was not found to be a major determinant of VT/VF risk. Most people with epilepsy (56%; 10/18) had been seizure free for the last two years before SCA. Only 28% (5/18) of cases was on polytherapy, thus further suggesting that the seizure burden was relatively mild in our sample. Correspondingly, VT/VF in epilepsy rarely appeared to be seizure-related: 11%, 2/18. I cannot exclude the possibility, however, that our sample of SCA cases with epilepsy may have been biased towards those with less severe forms of epilepsy. In individuals with severe refractory epilepsy living in specialized institutions the presentation of VT/VF may be more likely to be mistaken for seizure-like movements and emergency medical services may, therefore, not be contacted or only contacted after a delay.

This would reduce the odds of ECG-confirmation of VT/VF in these individuals and, therefore, of their entering into the ARREST database. Nevertheless, my findings of an excess risk of life-threatening ventricular arrhythmia in people with epilepsy that is not associated with epilepsy severity appear to correspond with data on overall mortality in epilepsy. In the National General Practice Study of Epilepsy (NGPSE), the first prospective population-based cohort study of children and adults with epilepsy from the time of diagnosis, seizure recurrence did not affect the mortality rate after a median follow-up of 11.8 years (Lhatoo et al., 2001). After a median follow-up of 22.8 years, the standardized mortality ratio was still elevated in the remaining people in the cohort, even though 80% were in 5-year terminal remission, and 60% were off AEDs for ≥5 years (Neligan et al., 2011).

In other recent studies where mortality in community-dwelling people with epilepsy was investigated, the association between seizure frequency and risk of death was not addressed, presumably because this data was unavailable (Berg et al., 2013; Ding et al., 2013; Fazel et al., 2013; Holst et al., 2013; Nevalainen et al., 2013). In contrast, in selected cohorts with more severe epilepsy a high seizure frequency was found to be predictive of mortality (Sillanpää & Shinnar, 2010; Nevalainen et al., 2012; Trinka et al., 2013; Novy et al., 2013). In the latter study, this variable was found to be an independent risk factor of premature mortality even in non-seizure-related deaths due to, for example, cardiovascular disease (Novy et al., 2013). Overall, there appears to be an increased risk of non-seizure-related mortality (and life-threatening arrhythmia) in community-based samples with epilepsy. High seizure frequency may further aggravate this risk, but this will presumably only become apparent in selected cohorts with severe epilepsy.

Cardiovascular comorbidity

I found that cardiovascular comorbidity was the strongest determinant of VT/VF in people with epilepsy. Intellectual disability was also associated with an increased risk of VT/VF in epilepsy, but should probably be interpreted as a proxy for cardiovascular comorbidity rather than as a cause. As discussed previously, intellectual disability may be linked with cardiovascular comorbidity in several ways: e.g. a multiple malformation syndrome of both brain and heart or enhanced vasculosclerogenesis due to chronic inflammation. In people with intellectual disability, cardiovascular disease may also be more likely to go unrecognized and untreated because of the inability to express symptoms clearly (van den Akker et al., 2006).

In the first study of this thesis, I established that people with epilepsy had a higher risk of VT/VF than the general population. In the second study, it was found that cardiovascular comorbidity was the strongest determinant of VT/VF in epilepsy.

The excess VT/VF risk in this population may, therefore, either be explained by 1) a higher prevalence of (occult) cardiovascular comorbidity or 2) an increased vulnerability to the proarrhythmic effects of cardiovascular disease (multiple hit model). People with epilepsy may have a worse cardiovascular baseline status than the general population at the time of diagnosis due to underlying causes of epilepsy such as stroke. The effects of an unhealthier life-style or epilepsy-associated changes such as genetic modifiers, (progressive) autonomic dysfunction, cardiac electrical properties, and AED treatment may further accelerate the development of cardiovascular disease. For example, genetic modifiers affecting the function of ion channels in the brain and heart may increase the likelihood of developing epilepsy, severe QTc-prolongation, ERP, and fatal cardiac arrhythmias and thus potentially explain the findings of my recent ECG-study (Hirose et al., 2005; Johnson et al., 2009; Watanabe et al., 2011). Alternatively, an increased vulnerability in people with epilepsy to the (proarrhythmic) effects of cardiovascular disease may be suggested by the fact that this population had a higher recurrence of life-threatening cardiac arrhythmias (Badheka et al., 2010) and a worse prognosis after acute myocardial infarction than controls without epilepsy (Janszky et al., 2009). My main goals in the first two studies of this thesis were to assess whether people with epilepsy had an increased risk of VT/VF and to identify the underlying determinants. The question why cardiovascular disease leads to an excess risk of VT/VF in people with epilepsy should be addressed in future studies.

VT/VF in epilepsy

In the majority of cases of VT/VF in epilepsy (89%; 16/18), an underlying cardiac cause was found or suspected. In two remaining individuals (11%; 2/18) VT/VF remained unexplained after additional investigations and they were, therefore, classified as near-SUDEP.

As expected, the most important cause of VT/VF in people with and without epilepsy was acute myocardial infarction. Those with epilepsy had different patient characteristics, however, as they were significantly younger (57 vs. 64 years of age) and more likely to have congenital heart disease at the time of SCA (17 vs 1%). This may suggest that VT/VF in epilepsy has a different underlying aetiology. In people with epilepsy the prevalence of congenital heart abnormalities was found to be 7x higher than in those without epilepsy (Gaitatzis et al., 2004). Conversely, people with congenital heart disease were reported to be at increased risk of developing epilepsy when compared to age- and sex-matched controls without congenital heart disease (Billett et al., 2008). Congenital heart disease appears to be a more important cause of sudden cardiac death in the young (<40 years of age), whereas coronary artery disease accounts for the majority of cases over 40 (Van der Werf, 2010). The link between epilepsy and congenital heart disease may, therefore, partially explain why those with epilepsy experienced SCA at a younger age. The circumstances surrounding SCA in people with and without epilepsy also differed: The onset of SCA in epilepsy more frequently occurred at or near home (89 vs. 58%) and unwitnessed (28 vs 11%). The negative socioeconomic impact of having epilepsy may be a possible explanation: people with epilepsy are less likely to be married or to be employed (mcCagh et al., 2009), which may cause them to spend a greater portion of their time in or around the house and alone. Interestingly, the tendency to occur at/near home and unwitnessed has been described in most SUDEP cases, suggesting that a proportion of cases of VT/VF in epilepsy in the general population can present as probable SUDEP and may be diagnosed as such.

SUDEP

It is nigh impossible to study the pathomechanisms of SUDEP in the community for the following reasons: SUDEP predominantly occurs unwitnessed at night, and there is only a short time frame before death ensues. Cause of death can only be determined ad hoc and not retrospectively by postmortem investigations. A portable device providing continuous monitoring of multiple body systems (EEG, HR, O2 saturation, blood pressure) would, therefore, be required to "catch" SUDEP cases in the community and accurately determine the underlying pathophysiological cascade. This is not feasible in view of the invasiveness together with the required number needed to monitor over a long period of time. In the first two studies of this thesis I, therefore, took advantage of the infrastructure of ARREST, a prospective community-based database of ECG-confirmed VT/VF aimed at establishing the genetic and clinical determinants of SCA. The great advantage of focusing on ventricular arrhythmia as a potential underlying mechanism of SUDEP is its unquestionable cardiac origin. Simultaneous measurements of multiple body systems to determine the underlying pathophysiological cascade could, therefore, be dispensed with. My studies were, unavoidably, limited to one specific potential underlying mechanism of SUDEP. Presumably, some unwitnessed cases where emergency medical services were either not alerted or arrived too late to detect VT/VF were missed as well as those SUDEP cases due to non-cardiac mechanisms. It is impossible, therefore, to indicate what proportion of all SUDEP cases is caused by VT/VF. Non-cardiac mechanisms may be responsible for a majority of SUDEP cases in the community: in a previous study of out-of-hospital SCA, 93% of autopsy-confirmed SUDEP cases presented with asystole, which may suggest a cardiac but also a non-cardiac origin (Deasy et al., 2011). Overall, my work is a first attempt to characterize the importance of VT/VF in premature sudden death in epilepsy in a community-based sample.

6.2 The mechanisms of premature sudden death in epilepsy

Ventricular arrhythmia: a contributor to premature mortality in epilepsy?

The increased risk of VT/VF in people with epilepsy cannot be explained by SUDEP alone, as only 2/18 cases of SCA in epilepsy were classified as (near)-SUDEP. VT/VF in epilepsy was, generally, not seizure-related and tended to occur in middle age in the presence of pre-existing heart disease. In the community-based NGPSE cohort with epilepsy the premature mortality rate remained two-fold increased after 22.8 years of follow-up even though the majority of individuals were seizure-free by then and off AED treatment (Neligan et al., 2011). At this point in time, the risk of death due to ischaemic heart disease also became significantly elevated. A mortality survey in residents of a tertiary epilepsy referral centre confirmed that early mortality in epilepsy (defined as occurring at ~45–50 years) was not always a consequence of seizures, but also due to other causes such as cardiovascular disease (Novy et al., 2013). My findings of an increased VT/VF risk in people with epilepsy may partly explain non-seizure-related excess mortality in the general population with epilepsy. The contribution of life-threatening ventricular arrhythmias to premature death in epilepsy may first become apparent in middle age, when the prevalence of cardiovascular disease in the population increases. Little is known about the aetiology and risk factors of VT/VF in epilepsy in the community. My work is a first step to better understanding of this important issue.

Sudden unexpected vs. sudden cardiac death in epilepsy

People with SUDEP typically have a different profile from those with VT/VF and epilepsy: young (20-40) versus middle-aged, refractory vs. well-controlled epilepsy, absence vs. presence of additional cardiovascular comorbidity.

These conditions, however, are likely to present both ends of a continuum rather than two sharply delineated entities: in SUDEP seizures appear to be the dominant trigger, whereas in VT/VF in epilepsy a combination of epilepsy-related effects and cardiovascular disease may be involved. Sudden death cases with pre-existing conditions that could have contributed to death such as coronary insufficiency are generally excluded from SUDEP research studies under current definitions (Nashef et al., 2012). If excess sudden death mortality in people with epilepsy is, therefore, exclusively considered through the lens of SUDEP, the effects of both epilepsy and of co-existing disease as risk factors are probably underestimated. Under the new unified SUDEP criteria, the category of "SUDEP Plus" has been created in order to investigate the role that epilepsy and/or co-existing disease may have in causing SUDEP. If I had used the category of SUDEP plus in the second study of this thesis, the overlap between SUDEP and VT/VF in epilepsy would have probably been larger. In one case of VT/VF in epilepsy who had a history of hypertrophic obstructive cardiomyopathy, ventricular arrhythmia appeared to be triggered by a seizure-like episode for which diazepam was administered. This case was not classified as SUDEP due to the presence of pre-existing cardiac comorbidity, but would presumably have fulfilled the criteria for SUDEP plus (Nashef et al., 2012). It may be exceedingly difficult in a community-based setting, however, to determine reliably whether VT/VF is caused by the effects of cardiac comorbidity, epilepsy, or both. For instance, sudden death cases with a pre-existing heart condition (e.g. long-QT-syndrome) and an ECG-documented fatal arrhythmia can only be classified as SUDEP plus if there is a preceding seizure trigger (Nashef et al., 2012). In a community-based setting, however, reports of seizure-like events occurring just before ECG-documentation of VT/VF may represent either genuine epileptic activity or epilepsy mimics such as hypoxaemia-induced seizures due to SCA. My co-authors and I, therefore, decided not to use SUDEP plus criteria.

To appreciate fully the role of epilepsy and accompanying comorbidity in causing premature sudden death mortality, the following approach may be better: an analysis of all sudden deaths in people with epilepsy regardless of the underlying cause of death.

PGES: SUDEP risk factor?

The value of a new potential risk marker for SUDEP, PGES>20s, was assessed in the last study of this thesis. The intraindividual variability of this EEG characteristic was critically dependent on the number of CSs recorded per person and is, therefore, unlikely to be a reliable predictor of SUDEP risk. Sleep and AED reduction were found to be facilitating co-factors of PGES>20s.

Aetiology of PGES

The relationship between sleep, AED reduction, and PGES may suggest that these postictal EEG changes reflect the enhanced activity of inhibitory neuronal networks responding to ongoing seizure activity: neuronal inhibition also plays a role in the sleep process and may be modulated by AED use. Interestingly, a recent study has documented enhanced inhibitory neuronal activity towards the end of focal seizures. In intracerebral recordings of guinea pig and human brains the final stage of focal seizures was characterized by recurring, synchronous bursts of increasing amplitude (excitatory activity) and progressively longer interburst intervals: inhibitory activity (Boido et al., 2014). To test neuronal excitability during bursts the dentate gyrus of the guinea pig brains was stimulated using a fork electrode: it became progressively more difficult to elicit a field response with the fork electrode in the late interburst intervals towards the end of a seizure. Together, these findings suggest that seizure termination is caused by the simultaneous and opposite enhancement of excitation (during bursts) and inhibition (between bursts).

Another study assessing EMG signals in CSs, further supports the concept that active neural inhibition plays a role in seizure termination (Conradsen et al., 2013). There was an increase in EMG frequency which reached its peak in the late tonic phase. During the clonic phase the energy of clonic discharges progressively decreased, whereas the silent period between discharges progressively increased. The energy in the last clonic discharge was extinguished in some seizures but not in others, suggesting that neuronal exhaustion was not the only mechanism involved in seizure termination. In seizures with a higher peak EMG frequency longer silent periods were found. The progressive changes in these periods might, therefore, at least partially be explained by neural inhibitory mechanisms.

Next to the theory that PGES may be caused by excessive activation of inhibitory neuronal networks, a second hypothesis suggests that it results from preceding hypoxia, hypotension, or asystole. In this context, I have mentioned a few studies where PGES was preceded by peri-ictal hypoxaemia (Seyal et al., 2012; Seyal et al., 2013) or hypotension (Borzorgi et al., 2013), but have not yet detailed the relationship between PGES and peri-ictal HR(V) change. In an electroclinical study, I compared peri-ictal HR(V) changes between CSs with and without PGES at 1 minute before seizure onset and 1, 3, 5, 15 and 30 minutes after seizure end in a group of 50 people with epilepsy (Lamberts et al., 2013 a): changes in HR and HRV were associated with neither presence nor duration of PGES. In other studies, peri-ictal HR acceleration was found to be either higher (Moseley et al., 2013) or lower (Tao et al., 2013) in CSs with PGES than in those without PGES. Longer PGES duration was associated with measures of higher postictal sympathetic (Poh et al., 2012) and lower parasympathetic activity (Poh et al., 2012; Freitas et al., 2013).

These contradictory results highlight the probable heterogeneity of PGES, as its presence is not associated with definite abnormalities that are known to trigger fatal cardiac disturbances. These findings also underscore the fact that PGES is not likely to be predictive of SUDEP, as SUDEP is a multifactorial process: figure 1. A CS followed by PGES may be prerequisite for most cases of SUDEP, but death will presumably only ensue when the perfect combination of predisposing factors, a seizure trigger, and unfavourable peri-ictal circumstances occurs.

Sleep, PGES, and SUDEP

The link between PGES, an EEG hallmark of SUDEP, and sleep is intriguing because most SUDEP cases also occur during sleep. In fact, in a reanalysis of the data from the largest SUDEP case-control study (154 SUDEP victims, 616 living controls with epilepsy) to date, I found that SUDEP risk may not only be determined by CS frequency, but also by CS timing (Lamberts et al., 2012). Sleep-related SUDEP cases were four times more likely to be unwitnessed than SUDEP cases that occurred during the day. In addition, those with sleep-related SUDEP more frequently had a history of nocturnal seizures: OR 3.6, 95% CI 1.4, 9.4. After correction for CS frequency and other covariates, a history of nocturnal seizures remained a significant risk factor for SUDEP: OR 2.6, 95% CI 1.3, 5.0. Nocturnal CSs may, therefore, not only increase the risk of PGES, but also of SUDEP.

Nocturnal CSs may be associated with less favourable circumstances than daytime CSs, thus explaining the higher risk of PGES and SUDEP. Nocturnal CSs are more likely to go unwitnessed. Early intervention by nursing staff, however, (e.g. oxygen administration) may shorten the duration of subsequent PGES (Seyal et al., 2013). The presence of a family member or caregiver in the immediate aftermath of a CS may also reduce the risk of SUDEP (Langan et al., 2005; Ryvlin et al., 2013 a).

In conclusion, there appears to be a link between sleep, PGES, and SUDEP. This highlights the importance of further studies to determine the effectiveness of preventive measures including night supervision (Lamberts et al., 2012).

6.3 SUDEP prevention: current perspectives

Demonstrating the effectiveness of preventive measures

Inaccurate individual risk assessment and an insufficient understanding of the underlying pathophysiological mechanisms of SUDEP are currently the two major problems that impede the implementation and development of preventive measures. Before such measures can be used in routine clinical care, their value should be demonstrated in a high risk population.

Unfortunately, we still cannot characterize those at high-risk accurately enough to make such studies feasible. The highest incidence of SUDEP to date was reported in those undergoing presurgical evaluation or individuals who failed epilepsy surgery: 9.3/1,000 (Dasheiff, 1991). To demonstrate a reduction of SUDEP incidence by 50% during a 6-month preventive intervention, would require the enrolment of approximately 12,000 participants with epilepsy (Ryvlin et al., 2013 b). This would present considerable (and perhaps insurmountable) financial and logistical efforts. Alternatively, the effectiveness of preventive measures could be tested in high risk populations using surrogate endpoints for SUDEP. SUDEP can generally be considered to be the fatal result of a CS. Other, more frequently occurring, consequences of such seizures e.g. severe fractures, traffic accidents may, therefore, have value as potential substitute endpoints (Persson et al., 2002). A strong association between such variables and SUDEP should first be established in epidemiological studies before they can be used as alternative endpoints in smaller, more feasible clinical trials.

Analysing the effect of preventive interventions in well-defined high-risk communities with validated SUDEP registers (e.g. residents of tertiary epilepsy referral centres) would be another option. People with Dravet syndrome constitute another promising group for clinical intervention trials, because they appear to have a very high risk of SUDEP: 12.5% may die before age 50. In addition, the underlying cause of this syndrome, mutations in the neuro-cardiac ion channel gene SCN1A, has been identified. This population may, therefore, be a more obvious target for cardiac preventive interventions. The value of postictal interventions may also be assessed in the EMU using biological surrogate markers of SUDEP such as PGES or the depth and duration of postictal coma.

Current targets for intervention

A better understanding of SUDEP pathophysiology may lead to improved risk profiling, and thus enable us to select those individuals with a sufficiently high SUDEP risk for clinical intervention trials. SUDEP pathomechanisms could also be targeted more directly, thus opening new avenues for prevention. At this point in time, we know that in most SUDEP cases peri-ictal cardiorespiratory dysfunction appears to play a role. In addition, the surrounding circumstances may adversely affect both conscious and autonomous breathing efforts in the postictal phase. Minimizing the CS burden and reducing postictal respiratory distress, therefore, currently constitute our most promising preventive options.

Minimizing CS burden

When confronted with an individual with epilepsy who continues to have seizures despite AED treatment, reassessment of the diagnosis of epilepsy should be the first point of concern (Lamberts et al., 2013 b): figure 9.

Unfortunately, misdiagnosis of epilepsy is not rare. Of 94 people who presented at a tertiary epilepsy referral centre because of "refractory epilepsy", 13% (12/94) eventually received an alternative diagnosis (Smith et al., 1999). Of the remaining 82 individuals, 16 (19%) eventually became seizure-free. Only 44% (7/16) of the seizure-free group had genuine refractory epilepsy. The most important cause of "pseudo-refractoriness" was misclassified IGE treated with aggravating narrow spectrum AEDs. If misdiagnosis or misclassification of epilepsy is ruled out, avoidance of seizure-precipitating factors such as alcohol and drug abuse or sleep-deprivation should be discussed (Lamberts et al., 2013 b). Confirming AED adherence may be in order considering that 40% of people with epilepsy take fewer AEDs than prescribed (Davis et al., 2008), which is associated with a three times higher mortality risk (Faught et al., 2008). When all these factors have been addressed, dose adjustment or expansion of the number of AEDs should be considered. Unfortunately, approximately 30% of the population with epilepsy will ultimately remain refractory for treatment despite these measures (Kwan & Sander, 2004). Timely referral for presurgical evaluation or other alternative treatment options such as vagal nerve stimulation should then become a priority. Successful surgical treatment of refractory epilepsy may be one of the most effective options currently available to achieve seizure freedom and reduce the risk of SUDEP. As discussed previously, people who achieved seizure freedom after epilepsy surgery were found to have a lower risk of SUDEP than those who failed surgery: table 4. It remains unclear, however, if this can be ascribed to the effect of epilepsy surgery or to pre-existing biological differences between the two groups (Ryvlin et al., 2005).

Vagal nerve stimulation (VNS) is most frequently used in people with refractory epilepsy who do not qualify for epilepsy surgery. Those who start VNS may sporadically become seizure free (El Tahry et al., 2010). The SUDEP incidence rate in cohorts treated with VNS, however, appears to be similar to other populations with severe epilepsy (Annegers et al., 2000; Schachter, 2006; Granbichler et al., 2015). New treatment modalities involving neurostimulation such as stimulation of the anterior nuclei of the thalamus and responsive neurostimulation have recently become available (Liu et al., 2013). It remains to be seen whether these future treatment options will have additional beneficial effects on seizure frequency and SUDEP incidence compared to optimal AED treatment.

Figure 9: Strategy when confronted with "refractory epilepsy"

Step	**Question**	**Action**
1	Has AED treatment really failed?	Check: 1) Diagnosis 2) Classification 3) Treatment adherence 4) Precipitating factors
2	Can the current AED regime be improved?	Dosage adjustment or AED switch/addition
3	Other therapies possible?	Referral to epilepsy centre for: 1) Presurgical evaluation 2) Vagal nerve stimulation 3) Other treatment options

Reducing postictal respiratory distress

Sleeping materials and an unfavourable postictal body position, may exacerbate seizure-related postictal respiratory distress and should be corrected, if possible. Most SUDEP cases are found in bed, at night, while lying prone, whereas in the general population only ~3% of males and 6% females prefer a prone sleeping posture (Gordon et al., 2007). This position, therefore, appears to be conspicuously common in SUDEP cases. It has been suggested that a prone posture may increase postictal respiratory distress especially when lying face-down and rebreathing into a pillow. Body repositioning may not automatically occur at this time, if there is profound postictal depression of consciousness.

Low airflow resistance lattice foam pillows have, therefore, been developed to reduce the risk of postictal asphyxia. Simulated rebreathing tests using a ventilator suggested that the risk of reaching a clinically relevant inspiratory CO2 concentration of 10% was lower when using lattice pillows as opposed to standard pillows (Catcheside et al., 2014). The effect of lattice pillows on postictal respiratory parameters such as O2 saturation has, however, not yet been investigated in humans. If a caregiver or family member is present during the immediate postictal period, turning a person with epilepsy onto his side may further reduce seizure-related respiratory distress and prevent SUDEP: analogous to the effect of sleeping posture on the incidence of SIDS (Kinney & Thach, 2009). In addition, physical stimulation of people with epilepsy during the immediate postictal phase may reduce central hypoventilation (Ryvlin et al., 2013 b).

Nocturnal supervision can increase the likelihood of bystander presence during the time period when those with epilepsy may be at highest risk of SUDEP. Definitive evidence of its effectiveness, however, is still lacking. Abnormalities in the serotonergic 5-HT arousal system (Tupal & Faingold, 2006) and respiratory depression due to enhanced secretion of the anticonvulsant adenosine (Shen et al., 2010), may also play a role in seizure-related respiratory dysfunction, thus presenting targets for SUDEP prevention. It has been suggested that the use of selective serotonin reuptake inhibitors (SSRIs) may activate the 5-HT arousal system, thus reducing peri-ictal respiratory abnormalities. In mice with defects in the 5-HT system exhibiting postictal respiratory arrests (Tupall & Faingold, 2006), the subsequent introduction of the SSRI fluoxetine was found to abolish these symptoms. In a retrospective study, peri-ictal hypoxaemia (<85% O2 desaturation) was less frequently seen after focal seizures in people with epilepsy on SSRIs than in those without these medications (Bateman et al., 2010 b). In the same study SSRI treatment had no significant effect, however, on peri-ictal hypoxaemia resulting from CSs. In CSs central hypoventilation may not be the only cause of hypoxaemia, as a ventilation/perfusion mismatch due to pulmonary oedema may also occur. This may explain why SSRI treatment appears to be less effective in CSs than in focal seizures with alteration of awareness. It remains unclear whether SSRIs may be of value in preventing death, considering that CSs are the seizure type most commonly associated with SUDEP. High peri-ictal levels of adenosine may not only suppress ongoing seizure activity but also impede respiratory function (Shen et al., 2010). When mice with impaired adenosine clearance were pretreated with either caffeine (an adenosine receptor inhibitor) or saline, the caffeine group's survival after seizure onset was significantly longer (Shen et al., 2010). Caffeine may, therefore, reduce seizure-related breathing abnormalities. Use of this drug is not likely to become a measure to prevent SUDEP, however, due to its proconvulsant effects (Shapira et al., 1985).

Ambulatory SUDEP prevention devices

The use of pacemakers and implantable cardioverter defibrillators to prevent sudden cardiac death in high risk individuals with heart disease has been very rewarding. Similarly, the use of ambulatory devices to prevent SUDEP in the remaining population at risk would be conceivable. In contrast to sudden cardiac death, however, there appears to be simultaneous involvement of multiple body systems (brain, lungs, cardiovascular system) in most cases of SUDEP. It remains unclear, therefore, which specific abnormality should trigger an intervention by the preventive device. A device that would react to PGES or an equivalent (e.g. a sharp decrease in spectral energy of the EEG) may become a viable option with the advent of responsive neurostimulation. In addition, the type of intervention that should be administered remains unclear. An implantable cardioverter defibrillator can correct the underlying problem in one system (ventricular arrhythmia), thus preventing sudden cardiac death. In most impending SUDEP cases, however, simultaneous interventions in multiple systems (respiration, heart rhythm, blood pressure) is likely to be required as VT/VF only plays a role in minority of cases. At this point in time, therefore, there is no place for SUDEP devices as high risk individuals cannot yet be identified. Devices detecting seizures in general, irrespective of potential effects on cardiorespiratory control, are currently the most effective preventive measure as they can notify bystanders or caregivers.

6.4 SUDEP and the future

SUDEP awareness and documentation

Substantial deficiencies in the documentation of epilepsy-related deaths were reported in the National Sentinel Clinical Audit of Epilepsy-related Deaths in the UK, suggesting that a considerable proportion of SUDEP cases may have been misdiagnosed (Hanna et al., 2002).

Between September 1999 and August 2000 2412 deaths (1023 with post-mortem records, 1389 without post-mortem records) were registered with epilepsy mentioned somewhere on the death certificate. Of these deaths, 43% (439/1023) of cases with post-mortem records and 11% (156/1389) of cases without post-mortem records were audited. The investigation of cause of death was found to be inadequate in 87% (383/439) of audited cases with post-mortem records: requisite post-mortem investigations such as a toxicological analysis for alcohol and drugs, a histological examination of major organs, and a neuropathological examination of the brain were not always performed. In addition, variable phrasings of a single cause of death were frequently used or a cause of death was cited despite a lack of pathological evidence. Of audited cases without post-mortem records, 25% (39/156) were specifically certified as due to epilepsy. Of these deaths, 38% (15/39) were sudden and/or unwitnessed and should, therefore, have been subject to post-mortem. The term SUDEP, defined in 1997 (Annegers, 1997; Nashef, 1997), was cited in 9% (54/595) of all audited cases (with and without post-mortem records). To summarize, post-mortem investigations were not standardized nor always performed, a number of death certificates listed the incorrect cause of death, and autopsy was withheld in a number of sudden and/or unwitnessed deaths thus precluding a diagnosis of definite SUDEP.

The documentation of epilepsy-related deaths and diagnosing of SUDEP cases may be equally deficient in the Netherlands, where the main studies described in my thesis were performed. Recently, Dutch investigative journalists reported that the standard procedures for "schouwartsen" (forensically trained physicians) when assessing a possible unnatural death (many of which may be sudden) vary considerably across the Netherlands: during the external examination routine procurement of blood and urine samples was carried out only in the most urbanized regions of the Netherlands (KRO Brandpunt, 2014).

SUDEP awareness and the registration of epilepsy-related deaths may improve in the future as SUDEP is steadily gaining more attention in both medical and layman's circles (Brigo et al., 2014). Accordingly, a number of interdisciplinary SUDEP meetings for epilepsy care professionals have recently been organized in the Netherlands and the first steps were taken to establish a national registry and develop educational material.

Greater recognition and better documentation of SUDEP may enable the comparison of incidence data in the community between different countries. Across European nations epilepsy care is organized very differently and this may, therefore, give us more insight into the effect of health care availability on SUDEP incidence. For example, the number of board-certified neurologists per 100.000 inhabitants is much higher in the Netherlands than in the UK: 4.7 vs. 0.9/100.000 (Struhal et al., 2011). A negative trend that may hinder accurate SUDEP diagnosing is the progressive decline in clinically indicated autopsy rates in most developed countries: from 42.7% in 1979 to 15.3% in 2001 in the UK (Burton & Underwood, 2007). An important differential diagnosis of SUDEP is suicide, which is also likely to be sudden, unexpected, and unwitnessed and 3x more common in people with epilepsy than in the general population (Bell et al., 2009) or in siblings without epilepsy (Fazel et al., 2013). In the absence of autopsy, suicides in people with epilepsy may be misdiagnosed as probable SUDEP (Kapusta et al., 2011). In addition, in 40% (14/35) of sudden deaths in a tertiary epilepsy referral centre that might have been classified as probable SUDEP, autopsy results suggested a different (usually cardiovascular) diagnosis (Novy et al., 2013): this further underscores the importance of this procedure for correct classification. Definite SUDEP can, therefore, only be established when alternative causes of death have been ruled out by post-mortem investigations (Annegers, 1997; Nashef, 1997).

To (partially) compensate for the growing lack of autopsies, the additional collection of health information regarding the deceased through interviews with family members (i.e. verbal autopsy) may become more important in determining whether epilepsy-related deaths are due to SUDEP. Future research may yield more clues as to which data should be collected to most accurately predict autopsy-negative epilepsy-related sudden deaths, so that a reliable diagnosis of SUDEP will remain possible.

SUDEP: subdivisions by underlying mechanism

Over the last few decades it has time and again been re-iterated that epilepsy is a disorder or a family of disorders rather than a uniform disease (Fisher et al., 2014). In fact, "Epilepsy is not a disease, but a collection of diverse syndromes, some of which are secondary to other derangements, and some of which are seemingly primary" (Fisher, 1989). If the epilepsies can be considered a heterogeneous group, it is reasonable to assume that SUDEP, a definition by exclusion of a type of sudden death in people suffering from the epilepsies may include a heterogeneous set of conditions as well. This view appears to be supported by the analysis of ictal video-EEG-recordings of SUDEP, which has yielded multiple potential pathomechanisms rather than a single all-encompassing cause of death (Dasheiff & Dickinson, 1986; Purves et al., 1992; Thomas et al., 1996; Bird et al., 1997; Lee, 1998; So et al., 2000; Tavee & Morris III, 2008; Espinosa et al., 2009; Lhatoo et al., 2010; Bateman et al., 2010 a; Tao et al., 2010; Lanz et al., 2011; Ryvlin et al., 2013 a; Jeppesen et al., 2014). Partly to re-emphasize this heterogeneity, I chose to focus mostly on (peri-ictal) cardiac arrhythmia as a less prevalent potential underlying mechanism of SUDEP in my thesis, as opposed to "the early, centrally mediated, severe alteration of both respiratory and cardiac functions after CSs" (PGES followed by gradual cardiorespiratory arrest) which has recently been proposed as the predominant underlying pathomechanism (Ryvlin et al., 2013 a).

Each condition under the umbrella term SUDEP may have its own distinctive risk factors, pathophysiological mechanisms, and may require unique preventive measures, thus explaining why individual risk assessment nor scientifically proven prevention have yet been achieved. By pooling resources of epilepsy research centres across the globe the identification and definition of SUDEP's subordinate conditions along with their associated risk factors, pathomechanisms, and preventive strategies may be accelerated. The MORTEMUS study in which the SUDEP incidence in EMUs was estimated by collecting data from centres in Europe, Israel, Australia, and New Zealand serves as a successful example of this strategy (Ryvlin et al., 2013 a). Recently, the National Institutes of Health have awarded a large grant to a consortium of epilepsy research centres that have pledged such a far-reaching collaboration in the field of SUDEP research (NIH, 2014; The Lancet Neurology, 2015). Regardless of future breakthroughs, however, there exists a current, urgent need for effective preventive strategies.

SUDEP: genetic screening

As I have explained earlier, genetic modifiers may play a role as predisposing factors in the pathophysiology of SUDEP: figure 1. Screening for such modifiers in those at highest risk of SUDEP (people with refractory epilepsy) may, therefore, contribute to improved individual risk assessment. Suitable screening target(s) may be found among the mutations that have previously been reported in SUDEP victims: see section 1.7. Some of the implicated genes are associated with epileptic encephalopathies (SCN1A, SCN8A), and others with the inherited cardiac arrhythmogenic disease long QT-syndrome (SCN5A, KCNH2). HCN2 and HCN4 are involved in generating spontaneous rhythmic activity in cardiac pacemaker and neuronal cells, but are not associated with a specific disease.

Genetic testing in SUDEP victims has, thus far, focussed predominantly on those genes that may facilitate fatal cardiac arrhythmia (e.g. SCN5A). The findings I have presented in this thesis, however, and in particular the MORTEMUS study, suggest that the commonest SUDEP pathomechanism is not (seizure-related) cardiac arrhythmia but rather the sequence of PGES and cardiorespiratory arrest. It is currently unfeasible to identify genetic modifiers that facilitate this sequence as its underlying cause is incompletely understood.

In a recent study, generalized seizures were evoked in anaesthetized mice carrying mutations in the KCNQ1 gene (involved in long QT syndrome) or the SCN1A gene and wild-type mice, while electrophysiological signals in the cortex and brain stem as well as heart and respiratory parameters were recorded (Aiba & Noebels, 2015). In mutant but not in wild-type mice, the electrophysiological hyperactivity caused by generalized seizures was found to trigger spreading depression, a self-propagating wave of inhibition that depolarizes neuronal membranes in such a way that action potentials can no longer be generated (Bernard, 2015). Spreading depression was then followed by PGES, respiratory arrest, asystole, and death. The same manifestations could also be evoked by directly triggering spreading depression in the brain stem of mutant mice (i.e. without a preceding seizure), thereby proving causality. These results suggest that genetic modifiers may facilitate seizure-triggered spreading depression, and thereby, the sequence of PGES and cardiorespiratory arrest. Interestingly, spreading depression is also thought to be the underlying cause of migraine aura (Tolner et al., 2015). Genes associated with familial hemiplegic migraine (CACNA1A, ATP1A2, and SCN1A), a rare monogenic migraine with aura subtype (Tolner et al., 2015), may, therefore, be promising targets for genetic testing in SUDEP victims. If the search for genetic modifiers of spreading depression in SUDEP victims is successful, genetic screening in high-risk groups to improve individual SUDEP risk assessment may come within reach.

Nocturnal supervision and seizure detection

As explained previously, achieving seizure freedom may be the best way to reduce SUDEP risk, but this can only be achieved in approximately 70% of people with epilepsy despite optimal treatment. In addition, a considerable number of individuals with epilepsy may have a relapsing-remitting course, thus hindering early identification of drug-refractory epilepsy, timely referral, and institution of appropriate treatment until it might be too late (Shorvon, 1984; Shorvon & Luciano 2007). Every (convulsive) seizure can kill, and people may, therefore, still die suddenly even after years of seizure freedom. In hospital settings, seizure-surveillance systems may be used to promote the timely arrival of medical personnel in the (post)ictal period.

In the community, SUDEP cases were predominantly nocturnal and unwitnessed, and most likely to be triggered by nightly CSs (Lamberts et al., 2012). Supervision at night, i.e. by a family member sleeping in the same room or alerted by a listening device, has so far been the only documented preventive factor (Langan et al., 2005). For these reasons, and given the relatively smaller impact of surveillance at night on everyday life, it is likely that nocturnal supervision in a home environment using seizure monitoring devices will become more commonplace in the future. Unfortunately, many currently available seizure-surveillance systems that use a combination of multiple factors to detect seizures are unsuitable for long-term monitoring at home due to a high rate of false-positive alerts (Carlson et al., 2009; Beniczky et al., 2013; Narechania et al., 2013; van de Vel et al., 2013).

The best scientific evidence of the preventive value of nocturnal supervision using a particular seizure monitoring device would be a randomized controlled trial comparing the effects of this measure versus no intervention on SUDEP incidence in a cohort of people with refractory epilepsy. As explained previously, SUDEP incidence is too low even in high-risk groups to make such a trial financially and logistically feasible. In addition, depriving the control group of a potentially life-saving intervention raises severe ethical concerns. I, therefore, do not foresee the emergence of evidence-based SUDEP prevention measures. Alternative approaches could be considered, however, including retrospective case-control studies comparing seizure monitoring devices and nocturnal supervision measures in SUDEP cases and living controls with epilepsy. This may be most rewarding in the residential population of a tertiary epilepsy referral centre as these are well-defined high-risk cohorts where valid SUDEP registers are likely to be in place and a variety of (nocturnal) seizure-monitoring devices has come into use over the last few decades.

When seizure detection devices become more accurate and widely used in the home environment, family members will more frequently encounter patients during the early postictal period at the brink of dying from SUDEP. “What is to be done?” is then the crucial question. In practice, a number of actions will be taken simultaneously such as patient repositioning from the prone to the side, physical stimulation, or even cardiopulmonary resuscitation. In all likelihood, it will remain impossible to separate the effects of each measure and determine which have preventive value and which do not. I believe, therefore, that a protocol detailing the steps to be taken once called by the bedside by a seizure alarm should be developed based on expert consensus. This information may then be divulged to the patient and his/her family members by the treating neurologist, once they have expressed an interest in implementing nocturnal supervision.

In this thesis I have drawn a number of analogies between SUDEP and SIDS, another autopsy-negative sudden death syndrome predominantly occurring during sleep, which may also be seizure-related in some cases. In SIDS, a single measure, i.e. putting children to sleep in the supine position, was eventually found to be a major preventive factor (Kinney & Thach, 2009), seemingly belying my scepticism regarding the discovery of a similar preventive magic bullet in SUDEP. The major difference between SIDS and SUDEP, however, is that there was a major (iatrogenic) rise in the incidence of SIDS in the 1970 and 1980s due to the medical recommendation to put children to sleep in the prone position (to prevent regurgitation) (Högberg & Bergström, 2000). Sleeping position, therefore, became an obvious focus of subsequent studies designed to explain this SIDS epidemic. In the post "back-to-sleep" era the analogy between SIDS and SUDEP has become even stronger, as both are syndromes with a complex, multifactorial aetiology including putative genetic factors and preventive measures are lacking (Tomson et al., 2008; Kinney & Thach, 2009).

Seizure-related & non-seizure-related cardiac arrhythmia

In this thesis I discussed various potentially negative effects of epilepsy on the heart: genetic modifiers of ion channel genes expressed in heart and brain may convey a tendency to develop epilepsy and an increased vulnerability to cardiac arrhythmia. Progressive autonomic dysfunction, i.e. decreasing HRV measures, was reported in people with refractory temporal lobe epilepsy (Suorsa et al., 2011), and was associated with a higher risk of cardiac mortality and sudden cardiac death (Tsuji et al., 1996; Stein & Kleiger 1999). ECG risk markers of SCA (severe QTc-prolongation and ERP) were found to be more common in people with refractory epilepsy than in controls without epilepsy (Lamberts et al., 2015).

In the first study of my thesis, I provided evidence that people with epilepsy in the community had a 3x higher risk of ECG-confirmed VT/VF than those without epilepsy. In the second study, it was established that most cases of VT/VF with epilepsy in the community were non-seizure-related and that pre-existing cardiac comorbidity was the strongest associated risk factor. I suggested various theories for the higher risk of non-seizure-related VT/VF in people with epilepsy such as the possible arteriosclerogenic or arrhythmogenic properties of AEDs, a worse cardiovascular risk profile and higher prevalence of cardiac comorbidity, or an innate vulnerability for life-threatening cardiac arrhythmia. Unfortunately, the relatively modest number of cases with VT/VF in epilepsy precluded a deeper analysis of its aetiology and risk factors. Continuing efforts to identify prospectively and fully characterize all cases with epilepsy and ECG-confirmed VT/VF in the community-based ARREST-database may help to further elucidate the underlying causes of non-seizure-related VT/VF and sudden death in epilepsy. Research on premature mortality in the middle-aged with comorbidity should not be neglected in favour of understanding sudden death in the young and healthy.

Apart from peri-ictal VT/VF which does not appear to be common, asystole is a far more frequent seizure-related arrhythmia thought to be implicated in SUDEP. The point prevalence of ictal asystole in hospital-based studies of EEG-recordings was reported to be 0.3-0.4% (Rocamora et al., 2003; Schuele et al., 2007; Lanz et al., 2011), but much higher figures (6-19%) were found in long-term monitoring studies using a Reveal, an implantable loop recorder (Rugg-Gunn et al., 2004; Nei et al., 2012). The asystolic responses in these latter studies were not captured in the hospital, which suggests that the majority of these arrhythmias may go unnoticed in routine clinical practice.

The unexpectedly high prevalence of clinically relevant ictal asystole in both Reveal studies (i.e. resulting in pacemaker implantation) have not yet lead to the adoption of new standards of epilepsy care such as preventive cardiac screening in people with severe epilepsy. This may be due to the small numbers of individuals with only the severest forms of epilepsy who were analysed. The results, therefore, could not be translated to the larger and clinically more important group of people with drug-refractory epilepsy representing 30% of the entire population with epilepsy. The unresolved pathophysiology of ictal asystole, particularly regarding its lethality, may be a second reason why preventive cardiac screening in people with drug-refractory epilepsy has not yet been adopted. As discussed in the introduction to this thesis, ictal asystole may have similar characteristics to those seen in cardioinhibitory vasovagal syncope (Schuele et al., 2008). As such, it may constitute a self-limiting seizure termination mechanism: a seizure triggers ictal asystole causing brain ischemia, thus terminating seizure activity which resolves the cardiac arrhythmia (Schuele et al., 2010).

A long-term ECG monitoring study in a larger representative group of people with drug-refractory focal epilepsy after performing initial autonomic function tests (e.g. tilt table) in each individual may resolve these two issues: the prevalence of ictal asystole in a larger, representative group of people with drug-refractory focal epilepsy can be determined.

In addition, a better insight of the underlying mechanism of ictal asystole may be gained: those with ictal asystole may be more prone to VVS and have a higher proportion of positive tilt table tests. The findings of such a study may have the potential to launch a wider debate on the necessity of preventive cardiac screening and treatment (e.g. pacemaker implantation) in people with drug-refractory focal epilepsy to decrease the incidence of SUDEP in this high-risk population.

As explained previously, people with Dravet syndrome may be another promising target for preventive cardiac screening, as this population appears to have an extremely high risk of SUDEP and the underlying cause of this epilepsy syndrome is known: mutations in the neuro-cardiac ion channel SCN1A (Genton et al., 2011). In an animal model of Dravet syndrome, mice in which SCN1A was knocked out in the brain developed prolonged atropine-sensitive ictal bradycardia at the end of a CS culminating in terminal asystole (Kalume et al., 2013). This suggests that in this population (seizure-related) cardiac arrhythmia, particularly asystole, may play a more prominent role in the pathophysiology of SUDEP than in others with epilepsy. Currently, the prevalence of ictal cardiac arrhythmia in people with Dravet syndrome is unknown. Performing long-term ECG monitoring in this population using an implantable loop recorder is unfeasible, however, as most people with Dravet syndrome suffer from intellectual disability. Alternatively, such a study may be performed using cotton T-shirts containing recently developed wireless wearable ECG sensors for long-term monitoring (Nemati et al., 2012).

Seizure termination, PGES, and SUDEP

Individual SUDEP risk assessment remains out of reach, thus hindering attempts to institute targeted preventive measures. In 2010 the EEG characteristic PGES was proposed as a promising new risk marker for SUDEP in a retrospective electroclinical study, in which those with PGES>20s after CSs had a 13x higher risk of dying of SUDEP in the future than living controls with epilepsy (Lhatoo et al., 2010). This association between PGES and SUDEP could not be replicated in a second, larger study (Surges et al., 2011).

In the last main study of this thesis, I demonstrated that the intraindividual variability of PGES>20s was very high, thus explaining these contrasting results. My findings implied that PGES>20s after CSs may have little clinical usability as a SUDEP risk marker. This does not at all mean, however, that the concept of PGES is useless. Individual video-EEG case reports of SUDEP showed and the MORTEMUS study confirmed that PGES represents the first step in a pathophysiological cascade followed by gradual cardiorespiratory cessation in the majority of recorded SUDEP cases (Dasheiff & Dickinson, 1986; Purves et al., 1992; Thomas et al., 1996; Bird et al., 1997; Lee, 1998; So et al., 2000; Tavee & Morris III, 2008; Espinosa et al., 2009; Lhatoo et al., 2010; Bateman et al., 2010 a; Tao et al., 2010; Lanz et al., 2011; Ryvlin et al., 2013 a; Jeppesen et al., 2014). The aetiology of PGES remains unclear, but requires elucidation as this may also improve our understanding of SUDEP. In my thesis I have tried to take a first step in this direction. I found significant associations between sleep, AED reduction, and PGES, suggesting that this EEG characteristic may result from an increased activity of inhibitory neuronal networks. As discussed previously, progressive lengthening of interburst intervals (EEG) or interclonic intervals (EMG) may represent increasing inhibitory activity before seizure offset (Conradsen et al., 2013; Boido et al., 2014), and the speed of lengthening of successive intervals may be a measure for the strength of seizure inhibition (Conradsen et al., 2013). It would be interesting to determine whether the rate of increase in interburst/interclonic interval durations during CSs is associated with the presence or duration of ensuing PGES. If so, this would provide further evidence that this EEG characteristic may result from the increased activation of inhibitory neuronal networks in response to ongoing seizure activity. The next step may then be to compare electroclinical characteristics in fatal CSs (ending in SUDEP) and non-fatal CSs. Such a study should be feasible due to the collection of video-EEG-recordings of SUDEP in the recent systematic retrospective survey of EMUs (MORTEMUS) (Ryvlin et al., 2013 a).

Earlier in the discussion of this thesis, I posited the question as to what extent PGES in fatal and non-fatal CSs represented the same process. Unfortunately, this EEG characteristic cannot be directly compared in fatal and non-fatal CSs, as it is of infinite duration in fatal CSs. An analysis of interburst/interclonic interval frequency in video-EEG-recordings of fatal and non-fatal CSs may clarify whether and how the process of seizure termination differs between these groups. This may potentially improve our understanding of SUDEP pathophysiology. In addition, if a cut-off point for interburst/interclonic interval frequency can be determined to distinguish between fatal and non-fatal CSs, this may become a valuable trigger for a future ambulatory SUDEP prevention device.

In conclusion, I have briefly outlined some developments that are expected to take place within the next decade in epilepsy care and SUDEP research and have suggested several research approaches to further stimulate those developments: a growing awareness and more accurate diagnosing of SUDEP, the founding of new international networks in the scientific community (centre without walls) dedicated to further elucidating the pathophysiology of SUDEP including the role of seizure inhibition mechanisms, risk profiling tailored to separate SUDEP pathomechanisms e.g. those at risk for lethal arrhythmias as this may require specific interventions (implantable cardioverter defibrillator, pacemaker), screening for genetic modifiers in high risk groups, and improving the accuracy of seizure detection devices. It is my expectation that due to these developments we will be able to reduce the incidence of SUDEP in the coming decade.

7. Conclusions

I analyzed ventricular arrhythmia, a presumed pathomechanism in ictal recordings of SUDEP,in people with epilepsy in the community. Those with epilepsy in the community were found to have a 3x higher risk of ECG-documented VT/VF than the general population irrespective of traditional cardiac risk factors. The most common cause of VT/VF in epilepsy was acute myocardial infarction. Comorbidity such as clinically relevant pre-existent heart disease rather than epilepsy characteristics were the strongest risk factors for VT/VF in epilepsy. In two persons with epilepsy who were successfully resuscitated, VT/VF remained unexplained after additional investigations and a diagnosis of near-SUDEP could be established. Ventricular arrhythmia may, therefore, also be an underlying SUDEP mechanism in the community. My findings may partly explain long-term non-seizure-related excess mortality in people with epilepsy in the community, as has been documented in the NGPSE study. Little is known is known about the aetiology and risk factors of VT/VF in epilepsy in the community. My work represents a first step to better understanding this important issue.

PGES occurs in the majority of fatal CSs and appears to be an EEG hallmark of SUDEP. A better understanding of the process underlying PGES is, therefore, important. PGES >20s after non-fatal CSs has been proposed as a new SUDEP risk marker, but its clinical value remains unclear. Conflicting findings between studies may be explained by the varying number of seizures per individual that was analyzed. I found that the intraindividual variability of PGES >20s in people with multiple recorded CSs was high, suggesting that the clinical usability of this potential SUDEP risk marker is limited.

Sleep and AED reduction before CS onset appeared to facilitate the occurrence of PGES >20s, suggesting that PGES may result from the increased activity of inhibitory neuronal networks in response to ongoing seizure activity. Other electroclinical characteristics such as progressive lengthening of interburst intervals (EEG) or interclonic intervals (EMG) may also result from the increased activity of inhibitory neuronal networks in response to ongoing seizure activity, and the speed of lengthening of successive intervals may be a measure for the strength of seizure inhibition. If the rate of increase in interburst/interclonic interval durations during CSs is associated with the presence or duration of ensuing PGES, this would provide further evidence that PGES results from this seizure termination mechanism. A further comparison of electroclinical seizure characteristics in fatal CSs (ending in SUDEP) and non-fatal CSs may then clarify whether and how seizure termination differs between these two groups. This may potentially improve our understanding of SUDEP pathophysiology.

I have briefly outlined some developments that are expected to take place within the next decade in epilepsy care and SUDEP research and have suggested several research approaches to further stimulate those developments: a growing awareness and more accurate diagnosing of SUDEP, the founding of new international networks in the scientific community (centre without walls) dedicated to further elucidating the pathophysiology of SUDEP including the role of seizure inhibition mechanisms, risk profiling tailored to separate SUDEP pathomechanisms e.g. those at risk for lethal arrhythmias as this may require specific interventions (implantable cardioverter defibrillator, pacemaker), and improving the accuracy of seizure detection devices. It is my hope that due to these developments we will be able to reduce the incidence of SUDEP in the future.

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Appendix 1: medical ethical approval ARREST

Academisch Medisch Centrum

Universiteit van Amsterdam

Dr. H.L. Tan
Cardiologie
M0 - 105

Amsterdam, 28 maart 2007
uw kenmerk:
ons kenmerk: 07.17.0430
betreft:

Medisch Ethische Commissie
E2-162
doorkiesnummer: 566 5880
fax: 5669015

uw project:
Pharmacogenetics of sudden arrhythmic death from common cardiac depolarization blocking drugs: a population-based study.

Geachte heer Tan,

Bovengenoemd onderzoek, ons voorgelegd met uw brief d.d. 13 maart 2007, is besproken in onze vergadering van 22 maart jongstleden. Daarbij kwam het volgende aan de orde.

Wij onderschrijven uw oordeel dat er in casu geen sprake is van onderzoek in de zin van de Wet medisch-wetenschappelijk onderzoek met mensen (WMO). Hieruit vloeit echter mede voort dat de paragrafen 6.1 en 8.5 van het protocol geschrapt dienen te worden: artikel 10 van de WMO en de WMO-verzekering zijn uitsluitend van toepassing bij onderzoek dat wél onder deze wet valt. Tevens dient de verzekeringsbijlage bij de patiënteninformatie te vervallen.

Voor het overige hebben wij geen bezwaar tegen dit onderzoek.

Met vriendelijke groet,
namens de Medisch Ethische Commissie,

Mw.mr. M.L.M. van der Hulst,
secretaris

Appendix 2: questionnaire for general practitioner ARREST

Gaarne Ja, Nee of Onbekend aankruisen: **(Let op: Medische voorgeschiedenis tot aan de reanimatie)**

Cardiaal	**Onbekend**	**Ja**	**Nee**
Hartinfarct in de voorgeschiedenis: (jaar: .....)	☐	☐	☐
Angina pectoris:	☐	☐	☐
Angina pectoris in het jaar voor de reanimatie:	☐	☐	☐
Hartfalen:	☐	☐	☐
Aangeboren structurele hartafwijkingen:(*specificeer*:.....)	☐	☐	☐
Hartkloppingen	☐	☐	☐
Boezem-fibrilleren / boezem-flutter: (*specificeer*:.....)	☐	☐	☐
Kamer-ritmestoornissen: (*specificeer*:.....)	☐	☐	☐
Cardiomyopathie: (*specificeer*:.....)	☐	☐	☐
Klep-pathologie: (*specificeer*:.....)	☐	☐	☐

Risico profiel HVZ			
Hypercholesterolemie:	☐	☐	☐
Obesitas: (geschatte BMI;.....)	☐	☐	☐
Roken:	☐	☐	☐
Excessief alcohol gebruik:	☐	☐	☐
Acute hartdood in de familie:	☐	☐	☐
(*zo ja*: welk familielid? ..... leeftijd: .....)			
Tekenen van infectie (in de week voor reanimatie:	☐	☐	☐
(*specificeer*: ..... koorts: JA/ NEE temp: .....)			
Bezoek aan de huisarts in de week voor de reanimatie:	☐	☐	☐
(*zo ja*: reden van het bezoek: .....)			

Algemeen			
Hypertensie:	☐	☐	☐
Diabetes Mellitus: (*zo ja, kies*: type I/ type II)	☐	☐	☐
(indien bekend, HbA1c: ..... laatst gemeten: .....-.....-.....)			
CVA/TIA: (jaar: .....)	☐	☐	☐
Depressie:	☐	☐	☐
Angststoornis:	☐	☐	☐
Schizofrenie:	☐	☐	☐
Epilepsie: (zo ja: specificeer: .....)	☐	☐	☐
Migraine:	☐	☐	☐
Hyperthyreoïdie:	☐	☐	☐
Hypothyreoïdie:	☐	☐	☐
Astma:	☐	☐	☐
COPD:	☐	☐	☐
Maligniteit: (specificeer:..... jaar: .....)	☐	☐	☐
Reumatische aandoeningen:	☐	☐	☐
Leverfunctiestoornis: (lab.waarden:.....)	☐	☐	☐
Nierfunctiestoornis: (ureum: ..... creatinine: .....)	☐	☐	☐

Is patiënt(e) gevaccineerd tegen de Mexicaanse griep (H1N1) voor de reanimatie: ☐ ☐ ☐

Andere medische voorgeschiedenis:

.....

.....

Etniciteit: Kaukasisch/ Negroïde/ Aziatisch/ Arabisch/ Turks/ anders nl: .....

Apotheek: .....

.....

Vriendelijk bedankt voor uw medewerking aan het onderzoek.

Appendix 3: medical ethical approval OPPEC

Universitair Medisch Centrum
Utrecht

Divisie Hersenen
Afdeling Klinische Neurofysiologie
t.a.v. Dr. F.S.S. Leijten
Huispost : F02.230

Uw kenmerk
Ons kenmerk AvG/vb/10/05110
CCMO-nummer NL30427.041.09
Datum 24 februari 2010
Betreft METC-protocolnummer 09-372/K
Toestemming Raad van Bestuur

Raad van Bestuur

Contactpersoon METC
Mw. M.A.C. van Groenestijn, secretaris

Tel 088-7556376
(ma t/m do 09.30-12.00uur)
metc@umcutrecht.nl

Geachte heer Leijten,

Hierbij geeft de Raad van Bestuur, gehoord hebbende het positieve oordeel in de zin van de WMO van de Medisch Ethische Toetsingscommissie van het UMC Utrecht d.d. 24 februari 2010, toestemming voor de uitvoering van onderzoeksvoorstel met METC-protocolnummer 09/372, getiteld **"OPPEC: OutPatient Population based Epilepsy Cohort to study genetic, etiologic, clinical and pharmacological factors in treatment response"**.

De Raad van Bestuur verplicht, conform landelijke afspraken, onderzoekers die WMO-plichtig onderzoek opzetten en/of uitvoeren, de "Basiscursus regelgeving en organisatie voor klinisch onderzoekers" (BROK) te doorlopen en het bijbehorende certificaat te behalen. In enkele gevallen kan de door de Raad van Bestuur ingestelde UMC Utrecht BROK commissie hiervoor vrijstelling verlenen.

De Raad van Bestuur stelt dat, indien dit nu nog niet het geval is, de onderzoekers van het hierboven genoemde onderzoek maximaal 6 maanden na aanvang van het onderzoek aan deze verplichting voldaan hebben.

Ik wens u veel succes bij de uitvoering van uw onderzoek.

Met vriendelijke groeten,
namens de Raad van Bestuur,

i.o.

Prof. dr. J.L.L. Kimpen,
voorzitter

Bezoekadres:
Heidelberglaan 100
3584 CX Utrecht

Postadres:
Huispostnummer D 01.343
Postbus 85500
3508 GA Utrecht

www.umcutrecht.nl/metc

cc: METC

Prof. dr M Joëls, Neurowetenschappen en Farmacologie Divisie Hersenen, Postbus 85500, 3508GA Utrecht, STR.5.203

bijlage: positief oordeel brief

Appendix 4: informed consent form OPPEC

TOESTEMMINGSFORMULIER

OPPECstudie: OutPatient Population based Epilepsy Cohort to study genetic, etiologic, clinical and pharmacological factors in treatment response

Studie naar de oorzaken voor het wel of niet werken van medicijnen bij epilepsie.

Onderzoeksnummer:

Naam: _____

Adres (straat, huisnummer, toevoegingen): _____

Postcode: _____

Woonplaats: _____

Geboortedatum: ____ / ____ / _____

Geslacht:

- o man
- o vrouw

Wij zouden het waarderen als u de uitgebreide vragenlijst online zou willen invullen. Dit kunt u al gelijk doen door te gaan naar onze website: : http://www.epilepsieonderzoek.nl
Indien u dit op een later tijdstip wilt doen kan dat natuurlijk ook, wij zouden dan graag uw e-mail adres willen gebruiken om u de vragenlijst online toe te sturen.

e-mailadres: _____

Als u graag op de hoogte blijft van nieuws over de OPPEC studie kunnen wij uw e-mail adres ook gebruiken voor toesturen van de nieuwsbrief.
Wilt u 2x per jaar een digitale nieuwsbrief ontvangen:

- o ja
- o nee

Ik heb de informatiebrief voor de proefpersoon gelezen. Ik heb al dan niet gebruik gemaakt van de mogelijkheid vragen te stellen. Ik heb genoeg tijd gehad om te beslissen of ik meedoe.

Onderzoeksnummer:

Ik weet dat sommige mensen mijn gegevens kunnen zien. Die mensen staan vermeld in de Algemene brochure.

Ik weet dat meedoen helemaal vrijwillig is. Ik weet dat ik op ieder moment kan beslissen om niet meer mee te doen. Daarvoor hoef ik geen reden te geven.

Graag bij elk van onderstaande punten doorstrepen wat niet van toepassing is:

- Ik geef **wel/ geen*** toestemming om mijn gegevens te gebruiken, voor de doelen die in de informatiebrief staan.

- Ik geef **wel/ geen*** toestemming voor deelname aan onderzoek naar genetische factoren die verantwoordelijk zijn voor de werking van medicijnen, d.m.v. bloed onderzoek.

- Ik geef **wel/ geen*** toestemming om mijn lichaamsmateriaal (DNA) nog maximaal 15 jaar na afloop van dit onderzoek te bewaren, zodat dit in de toekomst gebruikt kan worden voor nieuw onderzoek.

- Ik geef **wel/ geen*** toestemming om in de toekomst opnieuw benaderd te worden voor nader onderzoek of follow- up onderzoek.

- Ik geef **wel/ geen*** toestemming om mijn medische gegevens over mijn epilepsie op te vragen bij mijn huisarts of specialist(en). Ik besef dat mijn huisarts of specialist dan ook weet dat ik meedoe aan dit onderzoek.

Gegevens huisarts en/ of behandelend specialist, bij wie gegevens mogen worden opgevraagd:
Naam huisarts:_____
Adres: _____
_____
Naam specialist:_____
Adres: _____
_____

Ik wil **WEL/ NIET*** deelnemen aan dit onderzoek

Naam proefpersoon: _____

Handtekening: _____ Datum : ____ / ____ / _____

Appendix 5: introductory questionnaire OPPEC

VRAGENLIJST

Onderzoeksnummer:

U krijgt deze brief omdat u onderstaand(e) geneesmiddel(en) gebruikt:

(Sticker met merknaam voorgeschreven anti epilepticum of anti epileptica)

1) Gebruikt u een of meerdere van bovenstaande medicijnen voor epilepsie (epileptische aanvallen/ insulten/ wegrakingen/ absences)?
   - o Ja
   - o Nee

2) Gebruikt u een of meerdere van bovenstaande medicijnen voor migraine, pijn of depressie?
   - o Ja
   - o Nee

U hoeft de volgende vragen alleen te beantwoorden indien u bij vraag 1 ja heeft ingevuld.

3) Hoeveel epileptische aanvallen heeft u de afgelopen 2 jaar gehad?
   (Eén antwoord aankruisen)
   - o een of meer keer per dag
   - o een of meer keer per week
   - o een of meer keer per maand
   - o een of meer keer per jaar
   - o minder dan een keer per jaar
   - o geen aanvallen

4) Wanneer was uw laatste epileptische aanval? *(Eén antwoord aankruisen)*
   - o vandaag
   - o deze week
   - o deze maand
   - o het afgelopen half jaar

- o meer dan een half jaar geleden
- o meer dan 1 jaar geleden
- o meer dan 2 jaar geleden

5) Wie schrijft uw medicijnen tegen epilepsie voor?
   - o huisarts
   - o neuroloog in een algemeen ziekenhuis
   - o neuroloog in een universitair ziekenhuis
   - o neuroloog in een speciale epilepsiepolikliniek
   - o kinderarts
   - o anders namelijk; _____

6) Hoe vaak ziet u de arts die u medicijnen voorschrijft?
   - o Nooit (herhalingsrecepten via de doktersassistente)
   - o _____ keer per jaar

7) Wanneer was uw laatste bezoek aan de arts die uw epilepsie behandelt?
   - o 1 maand geleden
   - o 3 maanden geleden
   - o 6 maanden geleden
   - o 12 maanden geleden
   - o meer dan 12 maanden geleden

8) Heeft u het laatste jaar over uw epilepsie gesproken met uw behandelend arts?
   - o ja
   - o nee

DANK VOOR UW MEDEWERKING!

Indien u gelijk ook de uitgebreide vragenlijst wilt invullen dan kunt u deze vinden via de website: http://www.epilepsieonderzoek.nl

Appendix 6: follow-up questionnaire OPPEC

VRAGENLIJST

Onderzoeksnummer:

U heeft aangegeven mee te willen werken aan het OPPEC onderzoek.
Dit is een groot nationaal onderzoek naar de oorzaken voor het wel of niet werken van medicijnen tegen epilepsie.
Wij zouden het erg op prijs stellen als u deze vragenlijst zou willen invullen. Let op deze vragenlijst is dubbelzijdig geprint, dus vergeet niet ook de achterkant in te vullen.
Eventueel kunt u deze vragenlijst ook online invullen via: www.epilepsieonderzoek.nl

Vult u hier de datum in waarop u deze vragenlijst invult (dd/ mm/ jjjj): ____/____/ 20___

1. Wat is uw geslacht? *(kies een van de volgende mogelijkheden)*
   - o vrouw
   - o man

2. Wat is uw geboortedatum? (dd/ mm/ jjjj) ____/____/19____

3. Wat is uw hoogst genoten opleiding?*(kies een van de volgende mogelijkheden)*
   - o geen opleiding
   - o lagere school/ basisonderwijs
   - o middelbare school of lager beroepsonderwijs (LBO)
   - o middelbaar beroepsonderwijs (MBO) of vakopleiding
   - o hoger beroepsonderwijs (HBO) of universiteit
   - o anders nl: _____

4. Hoe is uw arbeidssituatie? Ik heb: *(kies een van de volgende mogelijkheden)*
   - o een betaalde baan
   - o geen betaalde baan
   - o ik studeer of zit op school
   - o anders nl: _____

5. Hoe woont u? *(kies een van de volgende mogelijkheden)*
    - o alleen
    - o ik woon samen of ben getrouwd
    - o bij mijn ouders
    - o in een woongroep, begeleid of beschermd wonen
    - o anders nl: _____

6. Wat is uw lengte: _____ (cm)

7. Wat is uw gewicht: _____ (kg)

8. Rookt u? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o ik heb vroeger gerookt

9. Gebruikt u wel eens alcoholhoudende drank? *(kies een van de volgende mogelijkheden)*
    - o vaak (dagelijks)
    - o regelmatig (een/ meer keer per week)
    - o af en toe (een/ meer keer per maand)
    - o zelden (een/ meer keer per jaar)
    - o nooit

10. Gebruikt u wel eens drugs/ verslavende middelen? *(kies een van de volgende mogelijkheden)*
    - o vaak (dagelijks)
    - o regelmatig (een/ meer keer per week)
    - o af en toe (een/ meer keer per maand)
    - o zelden (een/ meer keer per jaar)
    - o nooit

De volgende vragen gaan over uw familie

11. Heeft u kinderen? *(kies een van de volgende mogelijkheden)*

- o ja; ik heb *(graag aantal invullen)* _____ zoons
  _____ dochters
- o nee → *ga naar vraag 13*

12. Indien u kinderen heeft: *(kies een van de volgende mogelijkheden)*

Heeft een of meer van uw kinderen epilepsie of epileptische aanvallen?

- o ja:
  Zo ja, hoeveel van uw kinderen hebben epilepsie/ epileptische aanvallen *(graag aantal invullen)* _____ van mijn kinderen
- o nee
- o weet ik niet

13. Heeft u broers en/ of zussen? *(kies een van de volgende mogelijkheden)*

- o ja; ik heb *(graag aantal invullen)* _____ broers
  _____ zussen
- o nee → *ga naar vraag 15*

14. Indien u broers en/ of zussen heeft:

Heeft een of meer van uw broers en/ of zussen epilepsie of epileptische aanvallen?

- o ja:
  Zo ja, hoeveel van uw broers en/of zussen hebben epilepsie/ epileptische aanvallen *(graag aantal invullen)* _____ van mijn broers/zussen
- o nee
- o weet ik niet

15. Komt er in uw gezin of familie epilepsie voor?*(kies per vraag een van de mogelijkheden)*

	ja	nee	weet ik niet
Vader	o	o	o
Moeder	o	o	o
Grootouders of verdere familie (ooms/ tantes/ neven/ nichten)	o	o	o

16. Indien u heeft aangegeven dat een of meer van uw grootouders of verdere familieleden epilepsie of epileptische aanvallen hebben,
    Kunt u aangeven bij hoeveel van deze familieleden epilepsie (of epileptische aanvallen) voorkomt? *(graag aantal invullen)*
    - ♦ bij _____ van mijn grootouders (opa's en oma's)
    - ♦ bij _____ van mijn verdere familie (ooms/ tantes/ neven/ nichten)

17. Zijn al uw grootouders (opa's en oma's) geboren in Nederland? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o weet ik niet

18. Bent u in de afgelopen 2 jaar zwanger geweest? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o ja; maar dit leidde tot een miskraam
    - o nee → *ga naar vraag 21*
    - o niet van toepassing → *ga naar vraag 21*

19. Bent u op dit moment zwanger? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee

20. Is de behandeling van uw epilepsie veranderd tijdens uw laatste zwangerschap? *(kies een van de volgende mogelijkheden)*
    - o ja, ik moest meer anti-epileptica innemen
    - o ja, ik moest minder anti-epileptica innemen
    - o ja, het soort anti-epilepticum werd gewijzigd
    - o ja, ik ben gestopt met de anti-epileptica
    - o nee

De volgende vragen gaan over uw huidige of eerdere medicatie gebruik

21. Gebruikt u op dit moment anti-epileptische medicijnen? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee → *ga naar vraag 23*

22. Vindt u dat uw huidige medicijnen tegen epilepsie voldoende helpen tegen uw aanvallen? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o weet ik niet

23. Hoeveel verschillende medicijnen tegen epilepsie heeft u sinds uw eerste epileptische aanval gehad? *(kies een van de volgende mogelijkheden)*
    - o ik heb nog steeds hetzelfde medicijn als in het begin → *ga naar vraag 25*
    - o ik heb 2 verschillende medicijnen geprobeerd
    - o ik heb 3 verschillende medicijnen geprobeerd
    - o ik heb meer dan 3 verschillende medicijnen tegen epilepsie gehad
    - o weet ik niet → *ga naar vraag 25*
    - o niet van toepassing → *ga naar vraag 25*

24. Indien u ooit veranderd bent van medicijnen tegen epilepsie, wat was hiervoor de reden? *(u mag meerdere antwoorden aankruisen)*
    - o medicijn was niet (voldoende) effectief of de aanvallen namen toe → *ga naar vraag 26*
    - o ik had last van bijwerkingen
    - o zwangerschap → *ga naar vraag 26*
    - o weet ik niet → *ga naar vraag 26*
    - o anders namelijk: _____ → *ga naar vraag 26*

25. Indien u last heeft of had van bijwerkingen van uw anti-epileptica, wat waren uw klachten? *(u mag meerdere antwoorden aankruisen)*
    - o geheugen problemen of vergeetachtigheid
    - o concentratie problemen
    - o moeite met spreken of het vinden van woorden
    - o suf, slaperig of extra moe
    - o rusteloos gejaagd, agressief of geïrriteerd
    - o piekeren, terneergeslagen, droevig of depressief
    - o duizelig, trillerig, coördinatie problemen
    - o dubbel of wazig zien
    - o hoofdpijn
    - o gewichtsverandering (toename/ afname), weinig eetlust of maag/ darmproblemen
    - o huiduitslag, huidproblemen, haaruitval of allergische reactie
    - o weet ik niet
    - o anders nl: _____

26. Hebt u ooit, zelf of met hulp van uw arts, geprobeerd om uw medicijnen tegen epilepsie helemaal te stoppen? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee → *ga naar vraag 28*
    - o niet van toepassing → *ga naar vraag 28*

27. Indien u heeft geprobeerd te stoppen bleef u aanvalsvrij? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee

28. Vergeet u wel eens om uw medicijnen in te nemen? *(kies een van de volgende mogelijkheden)*
    - o nooit
    - o heel soms
    - o regelmatig (een of meer keer per maand)
    - o vaak (een of meer keer per week)
    - o zeer vaak

De volgende vragen gaan over uw gezondheid en uw epilepsie.

29. Hoe oud was u toen u uw eerste epileptische aanval kreeg? _____ jaar

30. Heeft u “grote” aanvallen? *(kies een van de volgende mogelijkheden)*
    - o Ja;
      zo ja, hoeveel grote aanvallen heeft u in het afgelopen jaar gehad? *(graag aantal invullen)* _____ aanvallen
    - o nee
    - o weet ik niet

31. Heeft u “kleine” aanvallen? *(kies een van de volgende mogelijkheden)*
    - o Ja;
      zo ja, hoeveel kleine aanvallen heeft u in het afgelopen jaar gehad? *(graag aantal invullen; een schatting voldoet)* _____ aanvallen
    - o nee
    - o weet ik niet

32. Indien u nog epileptische aanvallen heeft, zijn deze voor u ‘acceptabel’? dat wil zeggen: vindt u het niet noodzakelijk dat er wat aan gedaan wordt als dat mogelijk zou zijn? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee

33. Hoeveel invloed heeft uw epilepsie op uw dagelijks leven? *(omcirkel één cijfer op de schaal hieronder)*

1 2 3 4 5 6 7 8 9 10

Weinig tot geen invloed ⟷ Veel invloed

34. Heeft u voor uw 6e jaar koortsstuipen gehad? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o weet ik niet

35. Komen koortsstuipen, voor de leeftijd van 6 jaar, in uw familie voor? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o weet ik niet

36. Heeft u ooit een status epilepticus (een aanval die langer dan een half uur duurde en waarvoor de meeste mensen naar het ziekenhuis worden gebracht) gehad? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o weet ik niet

37. Bent u ooit voor een aanval acuut in het ziekenhuis opgenomen of heeft u hiervoor de eerste hulp/spoedeisende hulp bezocht? *(u mag meerdere antwoorden aankruisen)*
    - o ja, bij de 1e aanval
    - o ja, bij een latere aanval
    - o nee
    - o weet ik niet

38. Heeft u ooit een hersenoperatie gehad? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee → *ga naar vraag 40*
    - o weet ik niet → *ga naar vraag 40*

39. Was deze operatie voor epilepsie? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee; deze was voor: _____

40. Heeft u ooit een zware hersenschudding gehad? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee → *ga naar vraag 42*
    - o weet ik niet → *ga naar vraag 42*

41. Was deze hersenschudding voor of na het begin van uw epilepsie? *(kies een van de volgende mogelijkheden)*
    - o voor
    - o na

42. Heeft u naast uw epilepsie, nog andere ziekten/ aandoeningen? *(u mag meerdere antwoorden aankruisen)*
    - o Ja; namelijk:
        - o Suikerziekte
        - o Beroerte/ hart en vaatziekten
        - o Leverziekte
        - o Nierziekte
        - o Darmziekte
        - o Anders namelijk: _____
    - o Nee

43. Zijn er, voor uw epilepsie, behalve medicijnen, ook andere behandelingen geprobeerd?*(u mag meerdere antwoorden aankruisen)*
    - o Ja; een hersenoperatie
    - o Ja; een nervus vagus stimulatie
    - o Ja, een ketogeen dieet
    - o Anders, namelijk: _____
    - o Nee → *ga naar vraag 45*

44. Zo ja was/ waren deze behandeling(en) effectief? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o weet ik niet

De volgende vragen gaan over de epileptische aanvallen die u heeft of heeft gehad. Vult u onderstaande vragen, indien mogelijk, samen of in overleg met uw partner of huisgenoten in.

45. Heeft u in de afgelopen 2 jaar aanvallen gehad? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee

46. Wanneer was uw laatste aanval?
    - o _____ jaar geleden
    - o _____ maanden geleden
    - o _____ weken geleden
    - o _____ dagen geleden

47. Beginnen uw epileptische aanvallen altijd hetzelfde? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o weet ik niet

48. Zijn er bepaalde omstandigheden/ prikkels die uw aanvallen meestal uitlokken? *(u mag meerdere antwoorden aankruisen)*
    - o ja; namelijk:
        - o slaaptekort
        - o stress
        - o flikkerend zonlicht
        - o tv
        - o videogames
        - o disco
        - o geluiden/ muziek
        - o menstruatie
        - o alcohol
        - o koort
        - o Anders namelijk: _____
    - o nee
    - o weet ik niet

49. Voelt u soms een epileptische aanval heel kort (seconden) van tevoren aankomen?
(u mag meerdere antwoorden aankruisen)
    - o ja; namelijk door:
        - o een beeld of geluid
        - o een geur, smaak of opstijgend gevoel vanuit de buik
        - o een plotseling angstig gevoel
        - o een gevoel iets al eerder gezien of meegemaakt te hebben
        - o hoofdpijn
        - o duizeligheid
        - o een gevoel dat ik herken, maar moeilijk kan beschrijven
        - o anders namelijk: _____
    - o nee
    - o weet ik niet

50. Heeft u aanvallen tijdens de slaap? *(kies een van de volgende mogelijkheden)*
    - o ja, de meeste aanvallen zijn tijdens slaap
    - o ja, sommige aanvallen zijn tijdens slaap
    - o ja, vooral bij het ontwaken
    - o nee
    - o weet ik niet

51. Valt u wel eens bij een aanval? *(kies een van de volgende mogelijkheden)*
    - o ja, altijd
    - o ja, soms
    - o nee
    - o weet ik niet

52. Heeft u aanvallen die bestaan uit een korte spierschok (of myoclonieen) van ca. 1 seconde? *(kies een van de volgende mogelijkheden)*
    - o ja, dat kan op ieder tijdstip van de dag
    - o ja, vooral ’s ochtends na het ontwaken
    - o ja, bij het inslapen
    - o nee
    - o weet ik niet

53. Heeft u wel eens een tonisch-clonische aanval gehad? Dat is een grote aanval of insult met verlies van bewustzijn en trekkingen van armen en benen. *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o weet ik niet

54. Heeft u absences? Dat zijn aanvallen met kortdurende afwezigheid, waarin u niet op anderen reageert. *(kies een van de volgende mogelijkheden)*
    - o ja
    - o nee
    - o weet ik niet

55. Heeft u verschillende soorten epileptische aanvallen? *(kies een van de volgende mogelijkheden)*
    - o ja, ik heb geheel verschillende aanvallen
    - o ja, de aanvallen lijken erg op elkaar (zelfde begin) maar verschillen in zwaarte, of ze lijken op elkaar maar sommige aanvallen zijn groot en andere aanvallen klein
    - o nee
    - o weet ik niet

De volgende vragen hebben alleen betrekking op uw meest voorkomende type aanvallen. Het is goed mogelijk dat u meerdere typen aanvallen heeft. Beantwoordt u echter de volgende vragen alleen voor het meest voorkomende soort aanvallen.

56. Hoe oud was u toen u uw eerste epileptische (meest voorkomende type) aanval kreeg? _____ jaar

57. Hoeveel van deze epileptische aanvallen heeft u in uw leven (ongeveer) gehad? *(kies een van de volgende mogelijkheden)*
    - o 1 aanval
    - o minder dan 5
    - o tussen de 5 en 10
    - o meer dan 10
    - o meer dan 100

58. Voelt u soms deze (meest voorkomende type) epileptische aanvallen heel kort (seconden) van tevoren aankomen? *(u mag meerdere antwoorden aankruisen)*
    - o ja; namelijk door:
        - o een beeld of geluid
        - o een geur, smaak of opstijgend gevoel vanuit de buik
        - o een plotseling angstig gevoel
        - o een gevoel iets al eerder gezien of meegemaakt te hebben
        - o hoofdpijn
        - o duizeligheid
        - o een gevoel dat ik herken, maar moeilijk kan beschrijven
        - o anders namelijk: _____
    - o nee
    - o weet ik niet

59. Kunt u tijdens deze aanval praten? *(kies een van de volgende mogelijkheden)*
    - o ja
    - o soms wel, soms niet
    - o nee
    - o weet ik niet

60. Hoeveel van deze epileptische aanvallen heeft u de afgelopen 2 jaar gehad? *(kies een van de volgende mogelijkheden)*
    - o een of meer keer per dag
    - o een of meer keer per week
    - o een of meer keer per maand
    - o een of meer keer per jaar
    - o minder dan een keer per jaar
    - o geen aanvallen

61. Hoelang duren deze aanvallen meestal? *(kies een van de volgende mogelijkheden)*
    - o een paar seconden
    - o een paar minuten
    - o een paar uren
    - o wisselend
    - o weet ik niet

62. Wat geldt voor deze epileptische aanvallen? *(kies een van de volgende mogelijkheden)*
    - o ik kan me niets van de aanval herinneren, het zijn altijd anderen die vertellen dat ik er een gehad heb
    - o ik kan me iets van de aanval herinneren, maar het meeste ben ik kwijt
    - o ik maak het grootste deel van mijn aanval gewoon mee
    - o ik weet zelf precies wat er tijdens mijn aanval gebeurt

63. Heeft u bij deze aanvallen wel eens? *(u mag meerdere antwoorden aankruisen)*

	ja	nee	weet ik niet
Wilde bewegingen in de slaap	o	o	o
Een tongbeet	o	o	o
In de broek geplast	o	o	o
Veel speeksel verloren	o	o	o

64. Moet u na een epileptische aanval herstellen? *(kies een van de volgende mogelijkheden)*
    - o Ja; na deze aanval geldt meestal:
        - o ik ben verward
        - o ik kan niet goed uit mijn woorden komen
        - o ik herken mensen niet
        - o ik weet niet goed waar ik ben
        - o anders nl: _____
    - o nee

65. Weet u hoe uw type epilepsie of deze aanvallen genoemd worden? *(kies een van de volgende mogelijkheden)*
    - o focale epilepsie of partiële epilepsie o.a. temporaalkwab epilepsie, frontaalkwab epilepsie
    - o gegeneraliseerde epilepsie o.a. absences, myoclonieen, tonische (clonische) aanvallen, clonische aanvallen, atonische aanvallen, juveniele myoclonus epilepsie (JME)
    - o anders o.a. syndroom van West, syndroom van Lennox-Gastaut
    - o weet ik niet
    - o anders nl: _____

De volgende5 vragen gaan over de hierboven gestelde vragen. Deze zijn niet verplicht maar we zouden het fijn vinden als u deze toch wilt invullen, zodat we, indien nodig, de vragenlijst nog beter kunnen maken.

Hierna kunt u verder gaan met het 2e deel van de vragenlijst .

1. Door wie is deze vragenlijst ingevuld? *(kies een van de volgende mogelijkheden)*
   - o mijzelf (degene die de epileptische aanvallen heeft)
   - o anders nl: _____

2. Hoeveel tijd heeft het invullen van de vragenlijst tot nu toe ongeveer gekost?
   _____ minuten

3. Hoe duidelijk vond u de gestelde vragen over het algemeen?
   - o zeer helder/ zeer begrijpelijk
   - o begrijpelijk/ duidelijk
   - o onbegrijpelijk/ onduidelijk
   - o zeer onbegrijpelijk/ vaag
   - o anders nl: _____

4. Hoe moeilijk vond u de vragen over het algemeen?
   - o zeer ingewikkeld
   - o moeilijk
   - o makkelijk
   - o zeer eenvoudig
   - o anders nl: _____

5. Heeft u verdere vragen of opmerkingen over dit eerste deel van de vragenlijst?
   _____
   _____
   _____
   _____
   _____

Deel 2 van de vragenlijst:

Dit deel gaat over de kwaliteit van uw leven (uw gezondheid en uw dagelijkse bezigheden) bij epilepsie als ook over eventuele bijwerkingen die u zou kunnen ondervinden door het gebruik van anti-epileptica.

Deze vragen gaan over hoe u zich **VOELT** en hoe het met u ging in **de afgelopen 4 weken**. Wilt u a.u.b. bij elke vraag het antwoord geven dat het best benadert hoe u zich voelde. Hoe vaak gedurende de **afgelopen 4 weken**. (omcirkel één cijfer)

		Altijd	Meestal	Vaak	Soms	Zelden	Nooit
1.	Had u veel energie?	1	2	3	4	5	6
2.	Voelde u zich somber en neerslachtig?	1	2	3	4	5	6

De volgende vraag gaat over problemen die u misschien heeft bij bepaalde **ACTIVITEITEN**. **Hoe veel** problemen hebben uw epilepsie of anti-epileptische medicijnen gedurende de **afgelopen 4 weken** veroorzaakt bij… (omcirkel één cijfer)

		Heel veel	Veel	Enigszins	Maar weinig	Helemaal niet
3.	Autorijden, motorfiets rijden, etc.	1	2	3	4	5

De volgende vraag gaat over hoe u zich **VOELT** over uw **epileptische aanvallen.** (omcirkel één cijfer)

		Heel bang	Enigszins bang	Niet erg bang	Helemaal niet bang
4.	Hoe bang bent u ervoor in de komende 4 weken een epileptische aanval te hebben?	1	2	3	4

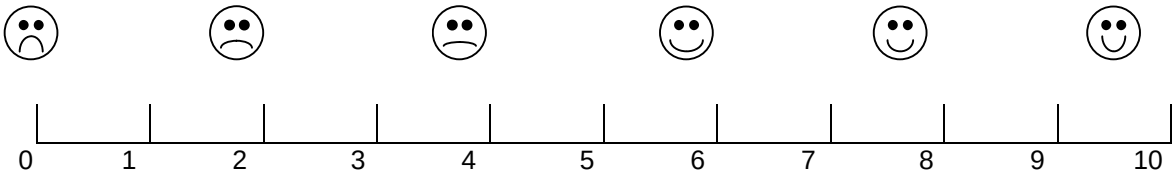
Omcirkel één cijfer bij elk van deze **PROBLEMEN** om aan te geven **hoe veel last u ervan heeft** op een schaal van 1 tot 5, waarbij 1 = Helemaal geen last van, en 5 = Heel veel last van.

		Helemaal geen last van				Heel veel last van
5.	Geheugenproblemen	1	2	3	4	5
6.	Beperkingen wat betreft werk	1	2	3	4	5
7.	Beperkingen in uw sociale contacten	1	2	3	4	5
8.	Lichamelijke bijwerkingen van anti-epileptische medicijnen	1	2	3	4	5
9.	Psychische bijwerkingen van anti-epileptische medicijnen	1	2	3	4	5

10. Hoe was de **KWALITEIT VAN UW LEVEN** gedurende de **afgelopen 4 weken** (dat wil zeggen: hoe ging het met u)?

		Heel goed kon nauwelijks beter	Vrij goed	Ongeveer even goed als slecht	Vrij slecht	Heel slecht kon nauwelijks slechter
	Kwaliteit van leven	1	2	3	4	5

11. Hoe zou u, over het geheel genomen, de kwaliteit van uw leven beoordelen? (Omcirkel één cijfer op de schaal hieronder)



Slechtst mogelijke Kwaliteit van Leven (zo slecht als, of erger dan, dood zijn)

Best mogelijke Kwaliteit van Leven

Deze vragen gaan over hoe u zich **VOELT** en hoe het met u ging in **de afgelopen 4 weken**. Wilt u a.u.b. bij elke vraag het antwoord geven dat het best benadert hoe u zich voelde.
Hoe vaak gedurende de **afgelopen 4 weken**…(omcirkel één cijfer)

		Altijd	Meestal	Vaak	Soms	Zelden	Nooit
12.	Voelde u zich levenslustig?	1	2	3	4	5	6
13.	Was u erg zenuwachtig?	1	2	3	4	5	6
14.	Zat u zo in de put dat niets u kon opvrolijken?	1	2	3	4	5	6
15.	Voelde u zich rustig en tevreden?	1	2	3	4	5	6
16.	Voelde u zich uitgeput?	1	2	3	4	5	6
17.	Was u een gelukkig mens?	1	2	3	4	5	6
18.	Voelde u zich moe?	1	2	3	4	5	6
19.	Maakte u zich er zorgen over weer een epileptische aanval te krijgen?	1	2	3	4	5	6
20.	Had u moeite met redeneren en het oplossen van problemen (bijvoorbeeld plannen maken, besluiten nemen, nieuwe dingen leren)?	1	2	3	4	5	6
21.	Heeft uw gezondheid u beperkt bij uw sociale activiteiten (zoals vrienden of familie bezoeken)?	1	2	3	4	5	6

De volgende vraag gaat over het **GEHEUGEN**…(omcirkel één cijfer)

		Ja, veel	Ja, enigszins	Maar weinig	Nee, helemaal niet
22.	Heeft u in de afgelopen 4 weken problemen gehad met uw geheugen?	1	2	3	4

Met de volgende vraag willen we te weten komen **hoe vaak** u in de **afgelopen 4 weken** moeite had om iets te *onthouden* of **hoe vaak** dit geheugenprobleem u gehinderd heeft bij uw normale werk of dagelijkse leven. …(omcirkel één cijfer)

		Altijd	Meestal	Vaak	Soms	Zelden	Nooit
23.	Moeite om dingen te onthouden die mensen u vertelden	1	2	3	4	5	6

De volgende vragen gaan over **CONCENTRATIE** problemen die u misschien heeft. **Hoe vaak** heeft u in de **afgelopen 4 weken** moeite gehad om u te concentreren of **hoe vaak** hinderden deze problemen u bij uw normale werk of dagelijkse leven? …(omcirkel één cijfer)

		Altijd	Meestal	Vaak	Soms	Zelden	Nooit
24.	Moeite met concentreren bij het lezen	1	2	3	4	5	6
25.	Moeite om u op één ding tegelijk te concentreren	1	2	3	4	5	6

De volgende vraag gaan over problemen die u misschien heeft bij bepaalde **ACTIVITEITEN**. **Hoe veel** problemen hebben uw epilepsie of anti-epileptische medicijnen gedurende de **afgelopen 4 weken** veroorzaakt bij... …(omcirkel één cijfer)

		Heel veel	Veel	Enigszins	Maar weinig	Helemaal niet
26.	Activiteiten in uw vrije tijd (zoals hobbies, uitgaan)	1	2	3	4	5

De volgende vragen gaan over hoe u zich **VOELT** over uw **epileptische aanvallen.** …(omcirkel één cijfer)

			Veel zorgen	Een beetje zorgen	Helemaal geen zorgen
27.	Maakt u zich zorgen dat u zichzelf bezeert tijdens een epileptische aanval?		1	2	3
		Heel bezorgd	Enigszins bezorgd	Niet zo erg bezorgd	Helemaal niet bezorgd
28.	Hoe bezorgd bent u dat u in de komende 4 weken in verlegenheid gebracht zal worden of dat u andere problemen in uw sociale contacten zal hebben tengevolge van een epileptische aanval?	1	2	3	4
29.	Hoe bezorgd bent u dat de medicijnen die u inneemt slecht voor u kunnen zijn als u ze langdurig inneemt?	1	2	3	4

Omcirkel één cijfer bij onderstaand **PROBLEEM** om aan te geven **hoe veel last u ervan heeft** op een schaal van 1 tot 5, waarbij 1 = Helemaal geen last van, en 5 = Heel veel last van.

		Helemaal geen last van				Heel veel last van
30.	Epileptische aanvallen	1	2	3	4	5

31. Hoe goed of slecht denkt u dat uw gezondheid is? Op de thermometer-schaal hieronder staat 100 voor de best denkbare gezondheidstoestand en 0 voor de slechtst denkbare gezondheidstoestand. Geef a.u.b. aan wat u van uw gezondheid vindt door een cijfer op de schaal te omcirkelen **Beschouw bij het beantwoorden van deze vraag uw epilepsie als onderdeel van uw algehele gezondheid**.

0 10 20 30 40 50 60 70 80 90 100

Slechts denkbare gezondheidstoestand

Best denkbare gezondheidstoestand

De volgende vragen gaan over mogelijke bijwerkingen van anti-epileptische medicatie.

Kunt u hieronder aangeven of u last heeft van deze problemen en zo ja, hoe lang u al last heeft van deze klachten?

		Geen probleem	Een mild probleem	Matig probleem	Ernstig probleem	Sinds enkele weken	Enkele maanden	Een half jaar of langer
1	Mijn tandvlees geeft problemen	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
2	Mijn gewicht is afgenomen (ik val af)	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
3	Ik heb problemen bij het onthouden van namen	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
4	Ik voel me vaak suf en slaperig	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
5	Ik moet me soms vasthouden anders val ik	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
6	Ik vergeet van alles zoals afspraken	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
7	Ik vind het moeilijk me te concentreren	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
8	Ik word snel moe en heb weinig energie	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
9	Ik word snel agressief	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
10	Ik kan me maar een korte tijd concentreren op iets	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
11	Ik stoot me voortdurend tegen tafels, deurposten etc	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
12	Ik voel me gejaagd en rusteloos	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
13	Ik merk dat ik traag reageer op anderen	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
14	Ik kan niet lang achter elkaar met iets bezig zijn	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
15	Ik merk dat ik traag spreek	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
16	Ik voel me de hele tijd druk en opgewonden	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
17	Ik voel me vaak duizelig	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
18	Ik heb weinig eetlust	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
19	Mijn menstruatie begint soms later of eerder	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
20	Ik merk dat ik af en toe moeilijk uit mijn woorden kom	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
21	Ik voel me vaak misselijk	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
22	Ik ben de hele dag aan het piekeren	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
23	Ik heb vaak last van diarree	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
24	Mijn handen trillen voortdurend	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
25	Ik heb last van veel speeksel	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
26	Ik zie regelmatig dubbel	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
27	Ik heb huiduitslag of andere huidproblemen	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
28	Mijn gewicht is toegenomen (ik word dikker)	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
29	Ik denk trager dan ik gewend was	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ
30	Ik ben snel geïrriteerd	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ	ɔ

		Geen probleem	Een mild probleem	Matig probleem	Ernstig probleem	Sinds enkele weken	Enkele maanden	Een half jaar of langer
31	Ik voel me teneergeslagen en droevig	ə	ə	ə	ə	ə	ə	ə
32	Ik heb vaak moeizame ontlasting	ə	ə	ə	ə	ə	ə	ə
33	Ik heb moeilijkheden met het vinden van woorden	ə	ə	ə	ə	ə	ə	ə
34	Ik kom tot minder en ben minder aktief	ə	ə	ə	ə	ə	ə	ə
35	Ik kan niet in slaap komen en lig vaak wakker	ə	ə	ə	ə	ə	ə	ə
36	Ik heb minder zin in sex	ə	ə	ə	ə	ə	ə	ə
37	Er zijn dagen dat ik niets kan doen door de hoofdpijn	ə	ə	ə	ə	ə	ə	ə
38	Mijn haren vallen uit	ə	ə	ə	ə	ə	ə	ə
39	Ik zie wazig	ə	ə	ə	ə	ə	ə	ə
40	Ik heb veel meer beharing	ə	ə	ə	ə	ə	ə	ə
41	Als ik iets wil pakken beginnen mijn handen te trillen	ə	ə	ə	ə	ə	ə	ə
42	Ik voel me niet goed in staat de gewone dingen te doen	ə	ə	ə	ə	ə	ə	ə
43	Ik heb veel last van hoofdpijn	ə	ə	ə	ə	ə	ə	ə
44	Het vrijen is minder plezierig geworden	ə	ə	ə	ə	ə	ə	ə
45	Ik heb last van mijn maag	ə	ə	ə	ə	ə	ə	ə
46	Ik voel me licht in het hoofd	ə	ə	ə	ə	ə	ə	ə

Dank u voor het invullen van deze vragenlijst

Appendix 7: medical ethical approval PGES study

commissie

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Medisch EthischeToetsingscommissie
VU medisch centrum
voorzitter: Prof. dr. J.A. Rauwerda
intern postadres: BS7, kamer H-565

dhr. R. Lamberts
SEIN
Postbus 540
2130AM Hoofddorp

VU medisch centrum

datum
24 augustus 2011

onderwerp
niet WMO advies

ons kenmerk
2011/273

doorkiesnummer
(020) 44 43488
e-mail subcom-ethiek.org@vumc.nl

Geachte heer Lamberts,

De Medisch Ethische Toetsingscommissie VUmc adviseert in positieve zin omtrent de uitvoering van het onderzoek: **"Heart rate changes in PGES positive generalized tonic clonic seizures: a retrospective case-control study."** Het onderzoek valt niet onder de WMO.

De goedkeuring, waartoe besloten is in het overleg tussen voorzitter en secretaris d.d. 9-8-2011, is gebaseerd op de volgende documenten:

- Begeleidende brief, d.d. 9-6-2011 (ontvangen d.d. 25-7-2011)
- Onderzoeksprotocol, d.d. 9-6-2011
- Privacy reglement, getekend d.d. 9-6-2011

Met vriendelijke groet,
namens de METC VUmc,

prof. dr. J.A. Rauwerda, voorzitter

drs. W.E. van der Voet, secretaris

Samenstelling commissie

prof. dr. J.A. Rauwerda	voorzitter, chirurg		
dr. K. Hoekman	plv. voorzitter, internist-oncoloog		
mw. M. Baak	verpleegkundige	dr. M. Klein	neuropsycholoog
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