Heart rate variability & baroreflex sensitivity in epilepsy: Their potential role in SUDEP

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Introduction

Patients with epilepsy have a mortality rate two to three times that of the general population [1]. A proportion of this increased risk can be attributed to an underlying disease process presenting with seizures particularly in newly diagnosed epilepsy, but excess mortality is also known to occur in the chronic epilepsy population [2]. Seizure related causes of death include accidents, drowning & status epilepticus, but the most common cause of death in this group is sudden unexpected death in epilepsy (SUDEP) [3]. Incidence rates will vary depending on the population studied. Community based rates are reported between 0·09 to 2.3 per 1000 patient-years [4] [5] [6] [7] [8] [9] [10] [11] [12]. Not surprisingly, a higher incidence of 1.1 to 6.0 per 1,000 patient years is found in selected populations from epilepsy clinics, tertiary referral centres and residential care facilities [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25]. The highest rates are quoted in the surgical referral population and these range from 6.3 to 9.3 per 1,000 patient years [26] [27] [28] [29].

Case-control studies have managed to elucidate risk factors and clues to the mechanism of SUDEP. Poorly controlled seizures and in particular, generalized tonic-clonic seizures, are at the forefront of increased risk [13] [21] [16] [30] [31]. Anticonvulsants, namely carbamazepine and lamotrigine, have also been suggested as potential risk factors through cardiovascular modulation [15] [32] [30]. However, a recent meta-analysis of HRV and anti-convulsants could not establish any adverse effect of these medications on autonomic function [33]. SUDEP is typically unwitnessed, but for cases that are witnessed, a terminal seizure is documented in the majority of cases [34] [31]. And although it remains largely hypothesis driven, SUDEP is almost certainly a multifactorial condition. The direct observation of both SUDEP and near-SUDEP cases indicate a cardio-respiratory pathway including apnoea, cardiac arrhythmias & cerebral shutdown [35]. In relation the cardiovascular system, dysfunction of the autonomic nervous system (ANS) could potentially precipitate a fatal arrhythmia causing SUDEP [36]. Both heart-rate variability (HRV) and baroreflex sensitivity (BRS) are used to assess the cardiovascular ANS and a decrease in these parameters following a myocardial infarction is known to increase the risk of sudden cardiac death [37]. Heart-rate variability is reduced in chronic temporal lobe epilepsy compared to a healthy population, which may be relevant to SUDEP [38] [39]. Baroreflex sensitivity on the other hand, has been little studied in epilepsy with one prior case-control study in the literature at the time of writing [40] Therefore, we decided to conduct a larger

study on BRS, with associated HRV testing on a cohort of active epilepsy patients compared to healthy controls, to determine any differences that may play a role in sudden unexpected death in epilepsy.

Patients and Methods

We examined 25 men and 17 women aged 19 to 46 years (median 31.5, lower quartile 28.0, upper quartile 39.25) with active epilepsy of all syndrome types and compared their results to 42 age (+/- 5 years) and sex-matched healthy controls (median 30 years, lower quartile 27.5, upper quartile 37.0). Active epilepsy was defined as any seizure in the last 5 years. Any individual with a co-existing condition or on medication, other than anticonvulsants, that may alter autonomic function were excluded.

34 patients had localisation related epilepsy; 23 temporal lobe epilepsy (TLE), 5 frontal lobe epilepsy (FLE) and 6 symptomatic. 8 patients had generalized epilepsy; 5 idiopathic generalized epilepsy (IGE) and 3 juvenile myoclonic epilepsy (JME).

23 (54.8%) patients were diagnosed with epilepsy in the last 10 years with 19 (45.2%) diagnosed more than 10 years ago. 17 (40.5%) suffered a generalized tonic-clonic seizure in the previous 6 months with 25 (59.5%) having their most recent generalized tonic-clonic seizure more than 6 months previously. 11 (26.2%) patients had nocturnal seizures, 31 (73.8%) had daily only seizures. 41 patients were taking anticonvulsants, with 1 patients choosing not to take any treatment. 22 (52.4%) were on monotherapy with 19 (45.2%) on two or more anticonvulsants.

Patients were recruited through the epilepsy out-patient and neurophysiology department in St. James's Hospital. There was also an online call for volunteers on the 'Epilepsy Ireland' research page. Ethical approval was granted by the St. James's Hospital/Adelaide and Meath Hospital research and ethics committee. Informed consent was obtained from all participants prior to testing. Participants had a full physical examination which was unremarkable in all.

Testing was carried out in the Falls & Blackout unit in St. James's Hospital. This is a dedicated unit for autonomic assessment. On the day of testing, participants were asked to refrain from caffeine, alcohol and nicotine 18 hours before their assessment.

After an adjustment period of at least 10 minutes, time-domain cardiovascular reflex testing was evaluated via heart-rate response (HRR) to 6 breaths/min metronomic breathing and Valsalva manoeuvre.

HRR to metronomic breathing was calculated as follows: Mean of R-R maximum in expiration minus R-R minimum in inspiration in five consecutive samples.

Valsalva ratio (VR) was calculated as follows: R-R maximum in 30 seconds post manoeuvre divided by R-R minimum during manoeuvre. The manoeuvre consisted of blowing into a mouthpiece at a pressure of 40mmHg for 15 seconds and breathing normally for the remaining minute. The mean value of three ratios was taken as the VR.

Frequency-domain analysis was assessed during 5 minutes of normal respiration with Medilog® DARWIN software via a Medilog® 5-lead holter monitor AR12. Frequency-domain analysis consists of splitting the cardiac tracing into its underlying components; high frequency (HF) (0.15-0.4Hz) and low frequency (LF) (0.04-0.15Hz).

Baroreflex sensitivity testing was evaluated during 10 minutes of controlled breathing at 15 breaths/minute via a finometer and BeatScope® software.

Final analysis for HRV in the time domain and BRS was carried out on the 42 cases and controls. Frequency domain analysis was included after the study had begun and was carried out on 36 cases and controls.

Results

Statistical analysis was carried out with SSPS version 19. Data was non-normal and therefore a Mann-Whitney U test was used to evaluate any differences between HRV and BRS in the two groups. A Pearson's correlation test was also used to evaluate any relationship between patient demographics and autonomic function.

Time-domain analysis

HRV in the time domain was not significantly different in the two groups ($p>0.05$; Table 3). HRR during metronomic breathing did not differ between cases 14 (9; 19) and controls 17 (10; 23). An abnormal HRR is ≤10bpm. VR were identical in cases 1.6 (1.5; 1.8) and controls 1.6 (1.5; 1.8). A normal VR should exceed 1.2.

Frequency-domain analysis

The absolute power of LF-modulation of HR 613ms^2 (285; 1549) in the patient group was lower than the LF-modulation of HR 1241ms^2 (526; 2017) in the healthy control group ($p<0.05$; Table 3). Similarly, the absolute power of HF-modulation of HR 293ms^2 (124; 559) was also lower in the patient group than the controls 619ms^2 (208; 1042) ($p=0.05$; Table 3). Normalized units (nu) of LF (LF/(total power-VLF) x 100) and HF (HF/(total power-VLF x 100) did not differ significantly between cases and controls ($p>0.05$; Table 3).

The LF:HF ratio of HR was only marginally lower in the epilepsy patients 0.315 (0.149; 0471) than in controls 0.318 (0.174; 0.515) ($p>0.05$; Table 3).

Baroreflex sensitivity

In the epilepsy patients, BRS values were significantly lower 11.21ms/mmHg (7.13; 14.97) than in controls 14.34ms/mmHg (10.42; 19.79) ($p<0.05$; Table 3).

Finally, no correlation was found between these autonomic parameters and patient age, gender, ILAE classification, duration of epilepsy, most recent GTCS, nocturnal seizures, monotherapy and treatment with carbamazepine, oxcarbazepine and lamotrogine ($p>0.05$; Table 4)

Discussion

Both HRV and BRS are measures of autonomic function. Reductions in these parameters are indicative of impaired cardiovascular homeostasis [41]. This type of autonomic dysfunction predicts mortality following a myocardial infarction and is also increasingly used as a prognostic marker in various other disease processes such as congestive heart failure, atherosclerotic plaque progression, stroke, diabetes and even depression [42] [43] [44] [45] [46]. Of particular note, impaired autonomic function is well described in chronic epilepsy and this has led to suggestions that it plays a potential role in SUDEP [38] [47] [48].

Various case-control studies have evaluated risk factors for SUDEP, with uncontrolled seizures and in particular generalized tonic-clonic seizures consistently being found to increase risk [13] [16] [21] [30] [35]. Interestingly, a reduction in HRV has been shown to be progressive in patients with temporal lobe epilepsy, but more so in those with refractory seizures compared to their well controlled counterparts [49]. Studies on epilepsy surgery have suggested similar findings in terms of HRV decline & seizure control, with autonomic parameters shown to improve following surgery in those with a good outcome [50] [51].

Studies looking at the circumstances of death in SUDEP have frequently found that patients are more likely to be found in bed with more deaths occurring at night [30] [38] [52]. This may be relevant as night-time recordings of HRV are significantly lower than day-time recordings in patients with temporal lobe epilepsy [39]. Recent work by Lamberts et al. [53] in collaboration with our group re-evaluated the cases and controls available from Langan et al. [30]. The original data found that patients were indeed more likely to die at night, but our review found that patients who suffered SUDEP were also more likely to have nocturnal seizures compared to their living controls [53]. In addition, anticonvulsant medications have been implicated in SUDEP and specifically carbamazepine in relation to HRV [54]. Hennessey et al. described an increase in sympathetic tone at night following the abrupt withdrawal of carbamazepine [55]. The clinical relevance of

anticonvulsants in SUDEP however, remains to be fully evaluated and no evidence exists to avoid any specific anticonvulsant [33].

Diminished autonomic function is a reflection of impaired sympathovagal balance, but how exactly this imbalance is manifested in epilepsy remains unclear. This is most likely related to the assorted methods used to quantify HRV [33]. Overall, there has been a trend towards a definite reduction in parasympathetic tone and likely increase in sympathetic tone [50] [56] [57]. HRV measures are broadly categorized into time domain analysis & frequency domain analysis [58] . Frequency domain analysis is recommended for short term recordings with time domain analysis better suited to recordings of at least 24 hours [41]. This may be the reason for significant findings in the frequency domain and not the time domain. Frequency analysis consists of two main components; low frequency (LF) & high frequency (HF) representing sympathetic and parasympathetic tone respectively [58]. As with other studies, we report a reduction in vagal activity, but also a reduction in sympathetic activity. However, the sympathetic representation of LF values has recently been called into question with the suggestion that perhaps it is more a reflection of parasympathetic tone and perhaps even BRS [59]. Our analysis used validated software for the calculation of frequency-domain parameters. This method was chosen with a view to the potential future of clinical based testing should HRV become a standard measure of prognosis in epilepsy. We acknowledge that further work is needed using Medilog® DARWIN to ensure its reliability as a test method.

While HRV is well researched, BRS has been little studied in epilepsy. Dütsch et al. reported a lower BRS in patients with temporal lobe epilepsy compared to healthy controls [40] but at the time of writing, no other case-control studies on BRS in epilepsy were found in the literature. Arterial baroreceptors are stretch receptors that are stimulated by distortion of the arterial wall when pressure changes. The baroreceptors can identify changes blood pressure with each heart beat which subsequently elicits a reflex response to either increase or decrease heart rate and blood pressure [60]. BRS is a measure of this activity. Validated Beatscope® software was used to calculate BRS values, again with the view to any future clinical application.

The mechanism behind autonomic dysfunction in epilepsy remains ill-defined. The autonomic centres of the brain are anatomically in close relationship to the temporal lobes. The insular cortex is one of the chief centres for cardiovascular control and has widespread connections with other autonomic centres such as the lateral hypothalamus, nucleus of the solitary tract and the ventrolateral medulla [61] [62]. Theoretically, both ictal and inter-ictal activity may interfere with the normal function of these central areas with a negative impact on HRV and BRS. While HRV & BRS were found to be significantly reduced in our epilepsy patients compared to controls, we did not find any correlation with epilepsy syndrome, duration of epilepsy, seizure frequency, nocturnal seizures or

anti-convulsant medications. It should be noted that while our patient selection included active epilepsy and a record was made of their last generalized tonic-clonic seizure, this did not necessarily translate to seizure frequency as a record of all seizure activity in the preceding six months to a year was not recorded.

The relevance of nocturnal seizures should be evaluated in future work, as we know that SUDEP occurs more often at night in association with nocturnal seizures [30] [53]. In addition, there is limited evidence to suggest that night-time supervision could be protective [20] [30].

While no association was found with medication, numbers were small in this study and larger groups would be necessary to fully determine their role, if any, in SUDEP. We also included all epilepsy syndromes, but overall the majority of cases were temporal lobe epilepsy and no clear conclusions can be drawn in relation to epilepsy syndrome.

In summary, our work has added to the literature on HRV in epilepsy which almost certainly to some extent is involved in SUDEP. Also, BRS was found to be reduced in the epilepsy group which has not been as widely studied as HRV. We also studied a larger patient group that previous work by Dütsch et al. [40]. Given that impaired HRV and BRS are predictors of cardiovascular mortality post myocardial infarction, similar findings in epilepsy may indicate an increased cardiovascular risk in this group. It is likely a number of predisposing and precipitating factors work together as in the 'perfect storm' theory [63]. For example, ictal hypo- or hypertension in association with an impaired BRS may result in an insufficient response to maintain cerebral oxygenation with potentially fatal consequences.

Importantly, SUDEP does not occur in every individual with chronic epilepsy and further work is needed to identify what factors predispose one person over the next and how or why they come together in SUDEP. These factors will ultimately determine the future prevention of this devastating condition.

1. Gaitatzis, A. and J.W. Sander, *The mortality of epilepsy revisited.* Epileptic Disord, 2004. **6**(1): p. 3-13.
2. Cockerell, O.C., et al., *Mortality from epilepsy: results from a prospective population-based study.* Lancet, 1994. **344**(8927): p. 918-21.
3. Tomson, T., *Mortality in epilepsy.* J Neurol, 2000. **247**(1): p. 15-21.
4. Lhatoo, S.D., et al., *Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort.* Ann Neurol, 2001. **49**(3): p. 336-44.
5. Tennis, P., et al., *Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada.* Epilepsia, 1995. **36**(1): p. 29-36.
6. Jick, S., et al., *Sudden unexpected death in young persons with primary epilepsy.* Pharmacoepidemiol Drug Safety, 1992. **1**(2): p. 59-64.
7. Terrence, C.F., H.M. Wisotzkey, and J.A. Perper, *Unexpected, unexplained death in epileptic patients.* Neurology, 1975. **25**(6): p. 594-8.
8. Leestma, J.E., et al., *Sudden unexpected death associated with seizures: analysis of 66 cases.* Epilepsia, 1984. **25**(1): p. 84-8.
9. Leestma, J.E., et al., *A prospective study on sudden unexpected death in epilepsy.* Ann Neurol, 1989. **26**(2): p. 195-203.
10. Langan, Y., N. Nolan, and M. Hutchinson, *The incidence of sudden unexpected death in epilepsy (SUDEP) in South Dublin and Wicklow.* Seizure, 1998. **7**(5): p. 355-8.
11. Opeskin, K. and S.F. Berkovic, *Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases.* Seizure, 2003. **12**(7): p. 456-64.
12. Ficker, D.M., et al., *Population-based study of the incidence of sudden unexplained death in epilepsy.* Neurology, 1998. **51**(5): p. 1270-4.
13. Nilsson, L., et al., *Risk factors for sudden unexpected death in epilepsy: a case-control study.* Lancet, 1999. **353**(9156): p. 888-93.
14. Mohanraj, R., et al., *Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study.* Lancet Neurol, 2006. **5**(6): p. 481-7.
15. Timmings, P.L., *Sudden unexpected death in epilepsy: a local audit.* Seizure, 1993. **2**(4): p. 287-90.
16. Walczak, T.S., et al., *Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study.* Neurology, 2001. **56**(4): p. 519-25.
17. Nashef, L., et al., *Incidence of sudden unexpected death in an adult outpatient cohort with epilepsy at a tertiary referral centre.* J Neurol Neurosurg Psychiatry, 1995. **58**(4): p. 462-4.
18. Vlooswijk, M.C., et al., *SUDEP in the Netherlands: a retrospective study in a tertiary referral center.* Seizure, 2007. **16**(2): p. 153-9.
19. Klenerman, P., J.W. Sander, and S.D. Shorvon, *Mortality in patients with epilepsy: a study of patients in long term residential care.* J Neurol Neurosurg Psychiatry, 1993. **56**(2): p. 149-52.
20. Nashef, L., et al., *Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty.* Epilepsia, 1995. **36**(12): p. 1187-94.
21. McKee, J.R. and J.W. Bodfish, *Sudden unexpected death in epilepsy in adults with mental retardation.* Am J Ment Retard, 2000. **105**(4): p. 229-35.
22. Racoosin, J.A., et al., *Mortality in antiepileptic drug development programs.* Neurology, 2001. **56**(4): p. 514-9.
23. Leestma, J.E., et al., *Sudden unexplained death in epilepsy: observations from a large clinical development program.* Epilepsia, 1997. **38**(1): p. 47-55.
24. Derby, L.E., P. Tennis, and H. Jick, *Sudden unexplained death among subjects with refractory epilepsy.* Epilepsia, 1996. **37**(10): p. 931-5.
25. Annegers, J.F., et al., *Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death.* Epilepsia, 2000. **41**(5): p. 549-53.
26. Dasheiff, R.M., *Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death.* J Clin Neurophysiol, 1991. **8**(2): p. 216-22.
27. Nilsson, L., et al., *Mortality in a population-based cohort of epilepsy surgery patients.* Epilepsia, 2003. **44**(4): p. 575-81.

28. Sperling, M.R., et al., *Mortality after epilepsy surgery.* Epilepsia, 2005. **46 Suppl 11**: p. 49-53.
29. Hennessy, M.J., et al., *A study of mortality after temporal lobe epilepsy surgery.* Neurology, 1999. **53**(6): p. 1276-83.
30. Langan, Y., L. Nashef, and J.W. Sander, *Case-control study of SUDEP.* Neurology, 2005. **64**(7): p. 1131-3.
31. Hitiris, N., et al., *Sudden unexpected death in epilepsy: a search for risk factors.* Epilepsy Behav, 2007. **10**(1): p. 138-41.
32. Danielsson, B.R., et al., *Effects of the antiepileptic drugs lamotrigine, topiramate and gabapentin on hERG potassium currents.* Epilepsy Res, 2005. **63**(1): p. 17-25.
33. Lotufo, P.A., et al., *A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs.* Epilepsia, 2012. **53**(2): p. 272-82.
34. Langan, Y., L. Nashef, and J.W. Sander, *Sudden unexpected death in epilepsy: a series of witnessed deaths.* J Neurol Neurosurg Psychiatry, 2000. **68**(2): p. 211-3.
35. Tomson, T., L. Nashef, and P. Ryvlin, *Sudden unexpected death in epilepsy: current knowledge and future directions.* Lancet Neurol, 2008. **7**(11): p. 1021-31.
36. Ansakorpi, H., et al., *Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy.* Epilepsia, 2000. **41**(1): p. 42-7.
37. Huikuri, H.V. and P.K. Stein, *Clinical application of heart rate variability after acute myocardial infarction.* Front Physiol, 2012. **3**: p. 41.
38. Tomson, T., et al., *Heart rate variability in patients with epilepsy.* Epilepsy Res, 1998. **30**(1): p. 77-83.
39. Ronkainen, E., et al., *Suppressed circadian heart rate dynamics in temporal lobe epilepsy.* J Neurol Neurosurg Psychiatry, 2005. **76**(10): p. 1382-6.
40. Dütsch, M., M.J. Hilz, and O. Devinsky, *Impaired baroreflex function in temporal lobe epilepsy.* J Neurol, 2006. **253**(10): p. 1300-8.
41. Xhyheri, B., et al., *Heart rate variability today.* Prog Cardiovasc Dis, 2012. **55**(3): p. 321-31.
42. Bigger, J.T., et al., *Frequency domain measures of heart period variability and mortality after myocardial infarction.* Circulation, 1992. **85**(1): p. 164-71.
43. Kleiger, R.E., et al., *Decreased heart rate variability and its association with increased mortality after acute myocardial infarction.* Am J Cardiol, 1987. **59**(4): p. 256-62.
44. Huikuri, H.V., et al., *Heart rate variability and progression of coronary atherosclerosis.* Arterioscler Thromb Vasc Biol, 1999. **19**(8): p. 1979-85.
45. Chen, C.F., et al., *Relationship between ischemic stroke location and autonomic cardiac function.* J Clin Neurosci, 2013. **20**(3): p. 406-9.
46. Turker, Y., et al., *Heart rate variability and heart rate recovery in patients with type 1 diabetes mellitus.* Acta Cardiol, 2013. **68**(2): p. 145-50.
47. Frysinger, R.C., J. Engel, and R.M. Harper, *Interictal heart rate patterns in partial seizure disorders.* Neurology, 1993. **43**(10): p. 2136-9.
48. Massetani, R., et al., *Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability.* Epilepsia, 1997. **38**(3): p. 363-9.
49. Suorsa, E., et al., *Heart rate dynamics in temporal lobe epilepsy-A long-term follow-up study.* Epilepsy Res, 2011. **93**(1): p. 80-3.
50. Hilz, M.J., et al., *Decrease of sympathetic cardiovascular modulation after temporal lobe epilepsy surgery.* Brain, 2002. **125**(Pt 5): p. 985-95.
51. Persson, H., et al., *Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy.* Neurology, 2005. **65**(7): p. 1021-5.
52. Kloster, R. and T. Engelskjøn, *Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors.* J Neurol Neurosurg Psychiatry, 1999. **67**(4): p. 439-44.
53. Lamberts, R.J., et al., *Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk.* Epilepsia, 2012. **53**(2): p. 253-7.
54. Persson, H., M. Ericson, and T. Tomson, *Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy.* Epilepsy Res, 2003. **57**(1): p. 69-75.

55. Hennessy, M.J., et al., *Sudden withdrawal of carbamazepine increases cardiac sympathetic activity in sleep.* Neurology, 2001. **57**(9): p. 1650-4.
56. Diehl, B., et al., *Spontaneous oscillations in cerebral blood flow velocities in middle cerebral arteries in control subjects and patients with epilepsy.* Stroke, 1997. **28**(12): p. 2457-9.
57. Evrengül, H., et al., *Time and frequency domain analyses of heart rate variability in patients with epilepsy.* Epilepsy Res, 2005. **63**(2-3): p. 131-9.
58. *Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.* Eur Heart J, 1996. **17**(3): p. 354-81.
59. Reyes del Paso, G.A., et al., *The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies.* Psychophysiology, 2013. **50**(5): p. 477-87.
60. Heesch, C.M., *Reflexes that control cardiovascular function.* Am J Physiol, 1999. **277**(6 Pt 2): p. S234-43.
61. Oppenheimer, S.M., et al., *Cardiovascular effects of human insular cortex stimulation.* Neurology, 1992. **42**(9): p. 1727-32.
62. Oppenheimer, S., *The anatomy and physiology of cortical mechanisms of cardiac control.* Stroke, 1993. **24**(12 Suppl): p. I3-5.
63. Surges, R., et al., *Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms.* Nat Rev Neurol, 2009. **5**(9): p. 492-504.