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Heart rate variability regression and risk of sudden unexpected death in epilepsy

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ABSTRACT

The exact mechanisms of sudden unexpected death in epilepsy remain elusive, despite there is consensus that SUDEP is associated with severe derangements in the autonomic control to vital functions as breathing and heart rate regulation. Heart rate variability (HRV) has been advocated as biomarker of autonomic control to the heart. Cardiac dysautonomia has been found in diseases where other branches of the autonomous nervous system are damaged, as Parkinson disease and multiple system atrophy. In this perspective, an impaired HRV not only is a risk factor for sudden cardiac death mediated by arrhythmias, but also a potential biomarker for monitoring a progressive decline of the autonomous nervous system. This slope may lead to an acute imbalance of the regulatory pathways of vital functions after seizure and then to SUDEP.

Introduction

Sudden unexpected death in epilepsy interests about 1–6 persons every 1.000/year among epileptic patients that are refractory to medical therapy [1,2]. It is defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy, with or without evidence for a seizure, with exclusion of documented status epilepticus, and when post-mortem examination does not reveal a structural or toxicological cause for death [3]. Despite the exact mechanism leading to SUDEP remains elusive, there is growing evidence that death is the result of a derangement of the autonomic control to vital organs [1,2]. Measures of heart rate variability offer a simple, non invasive-tool to assess the function of the autonomic control to the heart. We hypothesize a new HRV parameter, the HRV regression over time, as the best predictor of SUDEP.

Heart rate variability measures and their association with severe derangements in heart rhythm

Measures of heart rate variability refer to beat-to beat or long-term (24 h) variability of the R-R intervals within a standard ECG Holter of 24 h or less (a few minutes), which is consequence of the sympathetic and parasympathetic modulatory activities through cardiac nerves [4–7]. Analysis in the time domain includes SDNN (the standard deviation of all normal R-R intervals in the 24-h recording), SDANN (the standard deviation of the mean of the 5-min intervals, averaged over a 24-h period), SDNNIDX (the average of the standard deviations of R-R intervals for each 5-min interval in 24 h), pNN50 (the proportion of adjacent R-R that are >50 ms apart, measured in percent) and r-MSSD (the root mean square successive differences: the square root of the averaged sum of the squared differences in length between all adjacent normal R-R in 24 h) [4–7].

Power spectral analysis is another way to assess the dynamic changes in R-R intervals over time and recognizes four patterns of periodic variations [4–7]. The high frequency power (HF) corresponds to changes in the R-R interval that occur with a frequency of 0.15–0.4 Hz. HF power strongly correlates with r-MSSD and pNN50; it is thought to represent the parasympathetic innervation and is related to respiratory variations. Low frequency power (LF) encompasses the 0.04 to 0.15 Hz band and it represents both the sympathetic and the parasympathetic arms of cardiac innervation modulated by oscillations in the activity of baroreceptors. Together with very low frequency power (VLF), which includes variations in the R-R with a frequency of 0.0033 to 0.04 Hz, LF correlates with SDNNIDX. VLF and ultra low frequency power (1.15×10^{-5} to 0.0033 Hz) may reflect both sympathetic and parasympathetic activities partially mediated by thermoregulation, peripheral

Abbreviations: SUDEP, sudden unexpected death in epilepsy; HRV, heart rate variability.

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vasomotor and renin-angiotensin systems. Total power (TP) represents the sum of all the frequencies and is the total variance of R-R intervals. Frequency domain analysis is expressed as ms^2 or natural logarithm (ln) [4].

Heart rate variability measures are stable over time in healthy subjects, although may be affected by ageing [8]. Any decline in HRV should be expected to predict a lower compliance of the cardiovascular autonomic system to stressors, such as seizures.

HRV has been studied in patients with chronic heart failure, who have a higher risk of sudden cardiac death. In this population it seems to have a prognostic value [9–11]. In the CARISMA study on 312 post-myocardial infarction patients with reduced left ventricular ejection fraction who were implanted a loop recorder, a VLF <5.7 ms^2 was associated with a 7-fold increase in the risk of lethal or near-lethal ventricular arrhythmias potentially treatable by an implantable cardioverter-defibrillator [12]. Similarly to heart failure, epileptic patients with a high burden of generalized tonic clonic seizures (e.g. $\geqslant$3 episodes per year) [13] may exhibit significant impairments in the autonomic control to the heart [14].

SUDEP: is there a role for lethal arrhythmias?

Lethal or near-lethal arrhythmias are infrequent during seizures, but they may play an important pathogenic role in those SUDEP cases that occur in patients with congenital anomalies of ion channels involving both the brain and the heart, or when a structural heart disease is present [1,2]. Given that a relatively high prevalence of mutations in genes involved in cardiac arrhythmias has been found in SUDEP (7% for definite arrhythmogenic mutations, 15% for candidate mutations in arrhythmia genes [15]), a significant number of sudden unexpected deaths in epilepsy could be linked to disturbances in heart rhythm.

Congenital syndromes associated with SUDEP include the long QT syndrome (LQTS), Dravet syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. A seizure phenotype interests about 29% of patients with LQTS, especially when the mutation of the gene KCNH2 (encoding a voltage-gated potassium channel) is present [2]. Dravet syndrome is usually due to a mutation in the sodium channel SCN1A gene, which causes seizures and is associated with low HRV [2]. Brugada syndrome most frequently involves a mutation in the sodium channel gene SCN5A and its phenotype includes seizures and ventricular tachycardia/fibrillation[2]. Catecholaminergic polymorphic ventricular tachycardia is associated with mutations in the calcium channel RyR2 and is characterized by exercise-induced ventricular arrhythmias and generalized tonic-clonic seizures [2].

Various cardiac rhythm disturbances have been described during seizures: tachyarrhythmias (both supraventricular and ventricular), bradycardia and asystole [1,2,16],. Jeppesen et al. described a case of SUDEP preceded by a great instability in heart rhythm, with tachycardia preceding bradycardia and asystole. The rhythm immediately before death was a ventricular tachycardia [17].

In the ongoing CARELINK-study (NCT01946776) a loop recorder will describe the 2-year incidence and prevalence of clinically relevant arrhythmias in patients with difficult-to-treat epilepsy, who have higher risk of SUDEP. Collected data will possibly clarify which proportion of SUDEP cases are arrhythmic deaths. HRV might predict the risk of lethal arrhythmias in epileptic patients.

The hypothesis: HRV changes as biomarker of autonomic imbalance and SUDEP risk

Autonomic dysfunction in epilepsies may involve several vital functions, including breathing, as demonstrated by hypoventilation and hypoxemia that often accompany seizures[2]. A meta-analysis on 39 studies has shown that interictal HRV in epileptic patients may be lower than in healthy subjects, especially in the HF component [14]. Given these premises, a reduced HRV may indicate an autonomic dysfunction that does not involve solely the heart. It is less clear whether the severity of anomalies in HRV directly correlates with the risk of SUDEP: in a case-control study by Surges and colleagues the interictal HRV of 7 patients who died of SUDEP was not significantly different from that of 7 epileptic controls [18]. However, there are two main limitations of this study: differences between groups may be missed owing to the small number of patients and all patients, both SUDEP cases and controls, had a high risk of SUDEP, because they all were refractory to medical therapy. For this reason also controls might have experienced SUDEP after the end of the study. DeGiorgio and colleagues studied baseline HRV parameters in epileptic patients and found a significant correlation between low r-MSSD and clinical predictors of SUDEP [19].

We hypothesize that SUDEP results from the impossibility of a deranged autonomous nervous system (ANS) to maintain vital functions during seizures. A balance between ANS regulatory functions and stressors (seizures) could explain why patients at low risk of SUDEP (those with epilepsy that is responsive to medical treatment) do not exhibit any significant decline over time of HRV, as observed by Suorsa and colleagues [20]. The neurons of the brainstem and cerebral cortex that are responsible for the autonomic control to vital functions may have a permanent damage caused by hyperactivation during seizures, a type of neuron death that has been termed excitotoxicity, which is linked to calcium ion overload during depolarization [21]. MRI findings in temporal lobe epilepsy show that brain areas involved in the genesis of seizures undergo atrophy after years of disease with uncontrolled symptoms [22]. As a result of these mechanisms, every episode of generalized tonic clonic seizures (GTCS) should be expected to increase the permanent damage to neurons that may have a function in regulating the ANS. This view finds support in the results by Suorsa and colleagues, where HRV significantly declined over 6 years only in patients with high seizure burden despite optimal therapy [20]. This may be particularly true for temporal lobe epilepsies, as it seems that the temporal lobe plays a prominent role in regulating the ANS [23].

There are two published case reports of patients who died of SUDEP and had serial HRV measurements before death that are consistent with the hypothesis of ANS progressive deterioration [24,25],. In one patient HRV parameters were obtained 9, 5 and 1 months before death [24]. r-MSSD, HF power and pNN50 decreased over time, with the sharpest decline between 5 months and 1 month before death. From this observation it could be hypothesized that a change in HRV, especially if acute, could predict SUDEP. An epileptic patient may have low but stable HRV, and this condition may not pose a risk for SUDEP as high as a progressively declining ANS function, which may anticipate the failure of the cardiac and respiratory systems to overcome a potentially life-threatening seizure. For this reason, HRV trends over time could be a more specific biomarker for SUDEP risk than HRV alone.

HRV progressive deterioration may also correlate with the number of seizures: Kolsal and colleagues reported significantly lower values of HRV among epileptic children that are refractory to medical therapy and have a higher disease burden [26].

How to test the hypothesis: validation trials

HRV regression analysis could be performed in two separate studies.