Heart rate controversies in epilepsy: autonomic metrics and predictions

Thijs RD[1,2,3] Sander JW [2,3,4]

[1] Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands

[2] NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London, UK

[3] SEIN - Stichting Epilepsie Instellingen Nederland, Heemstede, The Netherlands

[4] Chalfont Centre for Epilepsy, Chalfont St Peter, Bucks SL9 ORJ, UK.

Word count: 794

References: 10

Keywords: autonomic nervous system, arrhythmia, sudden cardiac death

Should we pay a closer look at the beat-to-beat heart rate variations in people with epilepsy? The report by Sivathamboo et al. [1] in this issue of Neurology encourages us to do so. The investigators examined heart rate variability (HRV) among people who later died seemingly due to sudden unexpected death in epilepsy (SUDEP) and found lower HRV than in living epilepsy controls. These findings thus raise the question of whether autonomic metrics could help us to improve SUDEP risk stratification.

SUDEP is a devastating and difficult-to-predict fatality affecting approximately 1 per 1000 adults with epilepsy annually.[2] SUDEP is hard to ascertain as the fatal events are typically unattended and unrecorded, thus lacking the opportunity to uncover the full pathophysiological cascade. SUDEP is likely heterogeneous with a succession of convulsion-triggered postictal cerebral suppression leading to apnoea and asystole as the dominant pathway.[3] Convulsions triggering primary cardiac arrhythmias seem to be responsible for only a small number of cases.[3] Other rare variants include the sequence of cerebral suppression, apnoea and asystole without an initial seizure. The inclusion of SUDEP in epilepsy counselling has been much praised, but we still fail to predict individualized SUDEP risk accurately. SUDEP risk estimates predominantly rely on clinical parameters with the presence and frequency of convulsive, mainly nocturnal, seizures as the most decisive factor, [2] thus stressing the need for reliable biomarkers.

Impaired HRV has long been proposed as a candidate SUDEP biomarker given its well-established role in predicting sudden death in people with cardiac conditions. Certainly, several studies have established that HRV is impaired in people with epilepsy and particularly severe in people with temporal lobe epilepsy and difficult-to-treat epilepsies.[4] The etiology of the HRV imbalances in epilepsy is, however, complex. Seizures may transiently impact the central and peripheral autonomic networks or cause structural changes affecting autonomic control in the long term.[3] Undeniably, there is evidence that the heart and the coronary vasculature is incrementally damaged by repeated seizures, resulting in electrical and mechanical dysfunction, a condition labelled as ‘epileptic heart’.[5] Alternatively, chronic refractory epilepsy may impact the central autonomic network, as exemplified by the association between excessive brainstem atrophy and blunted HRV in focal epilepsy.[6] Another factor to consider is the use of antiseizure medications, notably those with sodium channel blocking properties. Apart from these epilepsy-related factors, there are many other contextual factors to consider when assessing HRV, including age, body position, physical fitness, clock time, sleep/wake stage, and non-epilepsy medications (notably beta blockers)

and cardiac comorbidities.[3] Not surprisingly, small scale SUDEP case-control studies assessing HRV metrics yielded inconclusive results.[7,8,9] Sivathamboo et al. present a retrospective, multicenter, nested case-control study in a larger cohort and carefully controlling for several factors known to affect HRV.[1] Normalized low-frequency power (LFP) during wakefulness appeared to be lower in SUDEP cases than living epilepsy controls. In contrast, normalized high-frequency power (HFP) during wakefulness and HFP & LFP during sleep were similar between groups. The investigators found a negative correlation within the SUDEP cases between LFP and SUDEP latency, whereas higher HFP was associated with increased survival, suggesting a cardioprotective role.

While the report energizes enthusiams for HRV as a biomarker in epilepsy, it also raises questions. How could impaired HRV contribute to the transition from a 'usual' to a fatal convulsive seizure? One may hypothesize that HRV instability may lower the threshold to arrhythmias in response to post-convulsive hypoxia. Indeed, arrhythmias were more common in convulsive seizures with hypoxemia,[10,] but it is not yet known whether these changes are mediated by low HRV. Another question that deserves further consideration relates to the circadian HRV changes. The investigators reported lower HRV in SUDEP cases during wakefulness, while SUDEP typically occurs at night.[3] HRV impairment is a consistent finding among people with refractory epilepsy vs. well-controlled epilepsy; HRV profiles vary across reports.[4] It is therefore essential to confirm the reported LFP impairments are consistent among SUDEP victims. Like many other SUDEP studies, the study population was skewed towards those with refractory focal epilepsy, while risk assessment is critically needed to identify those with seemingly, well-controlled epilepsy. More importantly, the authors did not demonstrate that low HRV has independent predictive value. We, therefore, still do not know whether HRV complements routine risk assessment using clinical variables such as seizure control.

Further research is warranted to assess interictal HRV metrics comprehensively and their alterations in non-fatal and ideally fatal seizures. Apart from studies in epilepsy monitoring units, the widespread availability of attractive wearable sensors holds promise for large-scale longitudinal HRV studies in epilepsy.

References

1. Sivathamboo S, Friedman D, et al. Short-term heart rate variability predicts sudden unexpected death in epilepsy. Neurology (in press)

2. Harden C, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 88, 1674-1680 (2017).

3. Thijs RD, et al. Autonomic manifestations of epilepsy: emerging pathways to sudden death? Nat Neur Rev (in press)

4. Myers, KA, Sivathamboo, S. & Perucca, P. Heart rate variability measurement in epilepsy: how can we move from research to clinical practice? *Epilepsia* **59**, 2169-2178 (2018).

5. Verrier RL, Pang TD, Nearing BD, Schachter SC. The Epileptic Heart: Concept and clinical evidence. *Epilepsy Behav* **105**, 106946, doi:10.1016/j.yebeh.2020.106946 (2020).

6. Mueller SG, *et al.* Brainstem network disruption: a pathway to sudden unexplained death in epilepsy? *Hum. Brain Mapp.* **39**, 4820-4830 (2018).

7. Odom N, Bateman LM. Sudden unexpected death in epilepsy, periictal physiology, and the SUDEP-7 Inventory. *Epilepsia* 2018 Oct;59(10):e157-e160.

8. Myers KA, Bello-Espinosa LE, Symonds JD, Zuberi SM, Clegg R, Sadleir LG, Buchhalter J, Scheffer IE. Heart rate variability in epilepsy: A potential biomarker of sudden unexpected death in epilepsy risk. *Epilepsia* 2018 Jul;59(7):1372-1380.

9. Surges R, Henneberger C, Adjei P, Scott CA, Sander JW, Walker MC. Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy? Epilepsy Res 2009 Dec;87(2-3):277-80.

10. Park KJ, Sharma G, Kennedy JD, Seyal M. Potentially high-risk cardiac arrhythmias with focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures are associated with the duration of periictal hypoxemia. Epilepsia 2017 Dec;58(12):2164-2171.