Epilepsy Currents
2022, Vol. 22(3) 181–183

DOI: 10.1177/15357597221085892
journals.sagepub.com/home/epi
SAGE

When Seizures Trigger "Extreme (Cardiac) Makeover"

Alica M. Goldman, MD, PhD

Altered Cardiac Structure and Function is Related to Seizure Frequency in a Rat Model of Chronic Acquired Temporal Lobe Epilepsy

Powell KL, Liu Z, Curl CL, et al. *Neurobiol Dis*. 2021;159:105505. doi:10.1016/j.nbd.2021.105505.

Objective: This study aimed to prospectively examine cardiac structure and function in the kainic acid-induced post-status epilepticus (post-KA SE) model of chronic acquired temporal lobe epilepsy (TLE), specifically to examine for changes between the pre-epileptic, early epileptogenesis and the chronic epilepsy stages. We also aimed to examine whether any changes related to the seizure frequency in individual animals. Methods: Four hours of SE was induced in 9 male Wistar rats at 10 weeks of age, with 8 saline treated matched control rats. Echocardiography was performed prior to the induction of SE, two- and 10-weeks post-SE. Two weeks of continuous video-EEG and simultaneous ECG recordings were acquired for two weeks from 11 weeks post-KA SE. The video-EEG recordings were analyzed blindly to quantify the number and severity of spontaneous seizures, and the ECG recordings analyzed for measures of heart rate variability (HRV). PicroSirius red histology was performed to assess cardiac fibrosis, and intracellular Ca2+ levels and cell contractility were measured by microfluorimetry. Results: All 9 post-KA SE rats were demonstrated to have spontaneous recurrent seizures on the 2-week video- EEG recording acquired from 11 weeks SE (seizure frequency ranging from .3 to 10.6 seizures/day with the seizure durations from 11 to 62 s), and none of the 8 control rats. Left ventricular wall thickness was thinner, left ventricular internal dimension was shorter, and ejection fraction was significantly decreased in chronically epileptic rats, and was negatively correlated to seizure frequency in individual rats. Diastolic dysfunction was evident in chronically epileptic rats by a decrease in mitral valve deceleration time and an increase in E/E/ ratio. Measures of HRV were reduced in the chronically epileptic rats, indicating abnormalities of cardiac autonomic function. Cardiac fibrosis was significantly increased in epileptic rats, positively correlated to seizure frequency, and negatively correlated to ejection fraction. The cardiac fibrosis was not a consequence of direct effect of KA toxicity, as it was not seen in the 6/10 rats from separate cohort that received similar doses of KA but did not go into SE. Cardiomyocyte length, width, volume, and rate of cell lengthening and shortening were significantly reduced in epileptic rats. Significance: The results from this study demonstrate that chronic epilepsy in the post-KA SE rat model of TLE is associated with a progressive deterioration in cardiac structure and function, with a restrictive cardiomyopathy associated with myocardial fibrosis. Positive correlations between seizure frequency and the severity of the cardiac changes were identified. These results provide new insights into the pathophysiology of cardiac disease in chronic epilepsy, and may have relevance for the heterogeneous mechanisms that place these people at risk of sudden unexplained death.

Commentary

Patients with epilepsy face an increased risk of sudden unexpected death in epilepsy (SUDEP) and uncontrolled or medically refractory seizures magnify the chance for premature mortality. While the incidence of SUDEP in community samples is estimated at 0.09-2.65 per 1000 patient years, it is up to 9.3 per 1000 patient years in patients with medically and surgically refractory epilepsy.[1] The mechanisms predisposing or leading up to SUDEP are incompletely understood, however there is a mounting clinical and experimental evidence implicating autonomic dysfunction and progressive structural and functional impairment in cardiac function. Compared to general population, sudden cardiac death (SCD) occurs 2.8 times to 5.8 times more frequently in patients with epilepsy.[2] Moreover, sudden death in epilepsy seems rare at the onset and far more

Baylor College of Medicine, USA

common later in the course of the disease. Why? What happens in the months and years of active epilepsy to result in sudden death?

Powell and colleagues[3] turned to a kainic acid–induced rat model of acquired chronic temporal lobe epilepsy (TLE) in order to shed light on cardiac processes that ensue in response to recurrent seizures. The authors performed a detailed analysis of cardiac function and structure in a sample of nine animals with chronic epilepsy and in eight saline treated controls. The EEG was monitored with subdural electrodes placed in bilateral frontal and parietal regions for two weeks following the onset of chronic seizures at 11 weeks. They observed a common occurrence of bradycardia at or before the onset of discernible electro-clinical seizures. They also noted that, in some cases, it would take up to two minutes after the electro-clinical seizure offset before the heart rate returned to baseline. This is an interesting observation given that in humans, heart rate change may precede ictal onset from the mesial temporal structures by about 5 seconds when recorded by scalp EEG.[4] However, over 90% of human seizures are accompanied by tachycardia,[5] while ictal bradycardia with or without asystole is less common.[4,6] In the current model, mesial structures were not probed and respiratory functions were not evaluated. It remains unclear whether the "pre-ictal bradycardia" was in fact an ictal phenomenon that coincided with central apnea due to ictal spread to amygdala[7] or whether it indicated a diving reflex due to the activation of brainstem regions.[8] Follow up studies that include respiratory monitoring and recording from depth electrodes in the mesial structures would be helpful to elucidate these mechanisms. They may then also clarify whether ongoing subclinical seizures underlay the observed delay in postictal heart rate return to baseline.

In conjunction with monitoring peri-ictal and ictal heart rate, the authors made an interesting and important observation of progressive structural and functional cardiac changes in the chronic phase of the model epilepsy. By 10 weeks post KA-induced status epilepticus (SE), cardiac echocardiogram showed a significantly lower left ventricular (LV) mass and thinner LV posterior wall initially suggesting the possibility of LV dilatation or a diastolic failure. However, contrary to these assumptions, the investigators also observed a smaller LV diameter in diastole. Since the relative wall thickness, a ratio of the LV posterior wall diameter and LV internal diameter during diastole were not different between epileptic animals and controls, the abnormalities pointed towards a functional impairment of LV relaxation and filling, as also evidenced by the simultaneous 15% decrease in ejection fraction (EF). Moreover, decreased EF corresponded to seizure burden and the most affected animal had the lowest EF at 57.5%. These findings paralleled changes observed in the hearts of patients with TLE that manifested increased LV stiffness and filling pressures, albeit EF was either preserved or non-significantly lower.[9,10] Still, patients with TLE showed significantly higher burden of echocardiographic findings associated with sudden death, such as a dilatation of the left atrium[10] not reported in the chronically epileptic rats in the study by Powell et al. The absence of this change may be due to the type of epilepsy model or because of a relatively short length of follow up. In humans, left atrium dilatation was observed rather early in patients with generalized tonic-clonic seizures (mean age 25.2+/−9.3 years) but in relatively older patients with TLE (37.4+/−11.2 years of age).[10] Myocardial fibrosis is another often reported finding in sudden cardiac death and SUDEP.[11] It occurs as a consequence of myocardial stress leading to necrotic death of cardiomyocytes and their replacement with a fibrotic scar and is considered a risk factor for heart failure, arrhythmic events, and sudden death.[12] In the KA-induced TLE model of Powel et al, the burden of cardiac fibrosis positively correlated with seizure frequency and this finding aligns with observation in a DBA1 mouse model. Curiously, careful postmortem evaluation of cardiac samples from SUDEP cases showed a comparable extent of this cardiac pathology to matched cases that died due to trauma.[11,13] and the sample size did not allow to control for possible confounding factors (hypertension, diabetes, and others) that could trigger myocardial fibrosis and thus obscure potential difference. Adult myocardium has limited regenerative capacity and cardiac fibrosis is a non-specific reparative response to varied insults aimed to preserve a structural integrity of the heart.[14] However, it comes at a cost of increased risk for adverse outcomes and animal models, such as the KA-induced TLE may be useful to study preventative interventions. As the study in the KA-induced TLE model suggests the risk for sudden cardiac failure in epilepsy is modulated by a combination of cardiac structural pathology, functional deterioration, and chronic autonomic dysfunction reflective of increased sympathetic tone and these findings parallel previously published clinical data.[9,10]

Another important contribution of the study by Powell et al is the connection of the observed structural and functional myocardial changes on the organ level with an evaluation at a cellular level. The authors documented altered diastolic properties of cardiomyocytes from epileptic rats. They were shorter, thinner, and impaired in their relaxation and showed a corresponding decrease in Ca2+ reuptake into sarcoplasmic reticulum. This is an important observation, as similar analysis in living patients would be challenging. Further experimental studies will be important to elucidate mechanisms leading up to these cellular changes.

In conclusion, the work by Powell et al delivers experimental confirmation of published findings related to autonomic dysfunction and cardiac structural and functional changes that were previously observed in patients with chronic TLE. As prospective probing of cardiac structure and function at an organ or cellular level is challenging, model systems are indispensable when attempting to understand pathophysiology of processes facilitated by chronic epilepsy and predisposing to arrhythmic events or sudden cardiac death. Prior work in animal models of chronic epilepsy has shown transcriptomic changes leading to acquired channelopathies and to receptor dysregulation in response to recurrent seizures and resultant increased sympathetic tone.[15] Future research will be necessary to fully elucidate the

cascade of cardiac and autonomic molecular and cellular events launched by recurrent seizures and to identify points of intervention to ameliorate the all too high risk of premature mortality in epilepsy.

ORCID iD

Alica M. Goldman https://orcid.org/0000-0002-5491-5746

References

1. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol*. 2008;7:1021-1031.
2. Bardai A, Lamberts RJ, Blom MT, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. *PLoS One* 2012;7:e42749.
3. Powell KL, Liu Z, Curl CL, et al. Altered cardiac structure and function is related to seizure frequency in a rat model of chronic acquired temporal lobe epilepsy. *Neurobiol Dis*. 2021;159:105505.
4. Di Gennaro G, Quarato PP, Sebastiano F, et al. Ictal heart rate increase precedes EEG discharge in drug-resistant mesial temporal lobe seizures. *Clin Neurophysiol*. 2004;115:1169-1177.
5. Britton JW, Ghearing GR, Benarroch EE, Cascino GD. The ictal bradycardia syndrome: localization and lateralization. *Epilepsia*. 2006;47:737-744.
6. Monte CP, Monte CJ, Boon P, Arends J. Epileptic seizures associated with syncope: ictal bradycardia and ictal asystole. *Epilepsy & Behav*. 2019;90:168-171.
7. Nobis WP, Schuele S, Templer JW, et al. Amygdala-stimulation-induced apnea is attention and nasal-breathing dependent. *Ann Neurol*. 2018;83:460-471.
8. Villiere SM, Nakase K, Kollmar R, Silverman J, Sundaram K, Stewart M. Seizure-associated central apnea in a rat model: evidence for resetting the respiratory rhythm and activation of the diving reflex. *Neurobiol Dis*. 2017;101:8-15.
9. Bilgi M, Yerdelen D, Colkesen Y, Muderrisoglu H. Evaluation of left ventricular diastolic function by tissue Doppler imaging in patients with newly diagnosed and untreated primary generalized epilepsy. *Seizure* 2013;22:537-541.
10. Fialho GL, Pagani AG, Wolf P, Walz R, Lin K. Echocardiographic risk markers of sudden death in patients with temporal lobe epilepsy. *Epilepsy Res*. 2018;140:192-197.
11. Devinsky O, Kim A, Friedman D, Bedigian A, Moffatt E, Tseng ZH. Incidence of cardiac fibrosis in SUDEP and control cases. *Neurology* 2018;91:e55-e61.
12. Pezel T, Viallon M, Croisille P, et al. Imaging interstitial fibrosis, left ventricular remodeling, and function in stage A and B heart failure. *JACC Cardiovasc Imaging*. 2021;14:1038-1052.
13. Zhao H, Zhang H, Schoen FJ, Schachter SC, Feng HJ. Repeated generalized seizures can produce calcified cardiac lesions in DBA/1 mice. *Epilepsy & Behav*. 2019;95:169-174.
14. Frangogiannis NG. Cardiac fibrosis: cell biological mechanisms, molecular pathways and therapeutic opportunities. *Mol Aspects Med*. 2019;65:70-99.
15. Li MCH, O'Brien TJ, Todaro M, Powell KL. Acquired cardiac channelopathies in epilepsy: evidence, mechanisms, and clinical significance. *Epilepsia*. 2019;60:1753-1767.