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## **Case Series - General Neurology**

# Cardiac Structure and Function in Epilepsy Patients with Drug-Resistant Convulsive Seizures

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## **Keywords**

Cardiac MRI · Drug-resistant epilepsy · Echocardiography · Epilepsy · Sudden unexpected death in epilepsy

### Abstract

High frequency of convulsive seizures and long-lasting epilepsy are associated with an increased risk of sudden unexpected death in epilepsy (SUDEP). Structural changes in the myocardium have been described in SUDEP victims. It is speculated that these changes are secondary to frequent convulsive seizures and may predispose to SUDEP. The aim of this cross-sectional study was to investigate the impact of chronic drug-resistant epilepsy on cardiac function and structure in patients with a high frequency of convulsive seizures. We consecutively included 21 patients (17 women, 4 men) aged 18–40 years, with at least 10 years with epilepsy and a minimum of six convulsive seizures in the last year and without a history of status epilepticus or nonepileptic events. A complete clinical examination, resting 12-lead electrocardiogram, 72-h Holter monitoring, and echocardiography were recorded in all patients. Ten patients were assessed by 3-Tesla cardiac magnetic resonance imaging. Echocardiography and MRI data were compared with those from age- and sex-matched healthy control individuals. No significant changes in cardiac structure or function were found among patients with chronic



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drug-resistant epilepsy and high frequency of convulsive seizures. However, we cannot exclude that there are subgroups of patients who are more prone to epilepsy-associated cardiac alterations.

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## Introduction

Sudden unexpected death in epilepsy (SUDEP) is one of the leading causes of mortality in patients with epilepsy [1], with an incidence up to nine per 1,000 patient-years in drug-resistant epilepsy patients [2]. Chronic epilepsy, convulsive seizures, and early onset of epilepsy are considered to be risk factors for SUDEP [3]. After decades of research, the pathophysiological mechanisms of SUDEP are still only partially known. It is believed that SUDEP may be the result of a cascade of events that affect the autonomic nervous system, causing respiratory and cardiac failure [4]. Several studies have suggested that cardiac mechanisms may play a vital role in the pathophysiology of SUDEP [5]. Cardiac events, like tachycardia, bradycardia, and repolarization abnormalities, are frequent ictal manifestations [5]. Ictal malignant arrhythmias and asystole with fatal outcomes have occasionally been described [6].

Myocardial structural changes, like left ventricular (LV) hypertrophy and cardiac fibrosis (CF), have been found in many studies of SUDEP victims [7–9]. Based on this, it could be hypothesized that CF could act as an arrhythmogenic substrate, causing a fatal outcome in generalized convulsive seizures.

However, cardiac function and structure have, to date, not been studied in living epilepsy patients with a high risk of SUDEP. This pilot study aimed to investigate the impact of chronic epilepsy on cardiac function and structure in young-adult patients with long-lasting epilepsy with frequent convulsive seizures.

#### **Methods**

#### Study Population

This cross-sectional study consecutively recruited patients from The National Centre for Epilepsy, Oslo University Hospital, Norway, from February 2017 to June 2018. The inclusion criteria were age between 18 and 40 years with a diagnosis of epilepsy for at least 10 years and a minimum of 6 convulsive seizures in the last 12 months. Convulsive seizures were defined as including both generalized tonic-clonic seizures and focal to bilateral tonic-clonic seizures. Both lesional (nonprogressive) and non-lesional cases were included (Table 1). We excluded patients with a previous history of status epilepticus and history of nonepileptic events, patients using vagus nerve stimulation, patients who were unable to cooperate, and patients with severe renal insufficiency (glomerular filtration rate <30). In addition, patients with coronary heart disease and/or valvular disease were also excluded.

#### Clinical Examination

A complete clinical examination was carried out on each patient by the same neurologist (A.G.), consisting of demographic questions, cardiovascular diseases in the family, syncope, and sudden deaths. We registered the antiseizure medication being used at the time of inclusion and the number of convulsive seizures in the last 12 months.

Cardiovascular symptoms were defined as syncope, chest pain, and palpitations. Cardiovascular heredity was defined as first-degree relatives with heart disease, including



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Table 1. Demographics and	
clinical data	

	N = 21
Fomalo n (%)	
Female, <i>n</i> (%)	17 (80)
Age in years, mean (range)	28 (19-39)
Age of epilepsy debut in years, mean (range)	11 (3-18)
Duration of epilepsy in years, mean (range)	18 (10–30)
Epilepsy type, n (%)	
Generalized	6 (29)
Focal	13 (62)
Unknown	2 (9)
Seizure type, n (%)	
GTCSs or FBTCSs	21 (100)
FIAS	9 (43)
FAS	11 (52)
Myoclonic	2 (10)
Absence	5 (24)
Etiology, <i>n</i> (%)	
Structural	6 (29)
Genetic	7 (33)
Immunologic	0
Metabolic	0
Infectious	0
Unknown	8 (38)
ASM, <i>n</i> (%)	21 (100)
ASM in use, <i>n</i> , median (range)	2 (1-4)
Convulsive seizures over the last 12 months, <i>n</i> , mean (range)	10 (6->15)
Cardiac symptoms, <i>n</i> (%)	3 (14)
Cardiac disease in first-degree relatives, $n$ (%)	10 (48)
Comorbidities, <i>n</i> (%)	7 (33)*
Co-medication, n (%)	2 (10)**

ASM, antiseizure medication; *N*, number of patients; FAS, focal aware seizure; FBTCSs, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizure; GTCSs, generalized tonic-clonic seizures.

\*Comorbidities: 1 Asperger syndrome, 1 Morbus Crohn, 1 depression, 1 migraine, 1 delayed sleep phase syndrome, 1 hypothyroidism, and 1 anxiety.

\*\*Co-medication: Levothyroxine, Infliximab.

hypertension, supraventricular and ventricular arrhythmias, angina pectoris, myocardial ischemia, and familial hyperlipidemia.

## ECG

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All patients underwent a 12-lead ECG examination conducted with a MAC 3500 analysis system with 50 mm/s and standard amplitude of 10 mm/mV. We registered rhythm, PR-interval, QRS complex, and presence of atrioventricular block in addition to QT interval,

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which was heart rate (HR) corrected by Bazett's [10] formula. The ECG records were compared with normal reference values based on American Heart Association [11] guidelines.

#### Holter Monitoring

All patients underwent 72-h Holter monitoring (Medilog AR12 plus/AR4plus/FD5 plus, Schiller). The Holter records were analyzed based on normal reference values from Medilog AR12.

#### Echocardiography

One cardiologist (P.H.B.) performed transthoracic echocardiography in all patients using Vivid E95 ultrasound scanners (GE Vingmed Ultrasound, Horten, Norway) and examinations were analyzed using commercially available software (EchoPAC v 202, GEVU). LV ejection fraction (EF) and LV end-diastolic volume and end-systolic volume were calculated by Simpson's biplane method. From speckle tracking echocardiography, longitudinal strain was analyzed from three apical views with a frame rate >50/s. Peak strains from each segment were averaged to global longitudinal strain (GLS) from a 16-segment LV model. The lower limit of normal GLS was defined as -18% [12]. LV mechanical dispersion was defined as the standard deviation of time from Q/R to peak strain in the same 16 segments [13]. Speckle tracking was acquired in 15 of 16 segments in order to calculate GLS and mechanical dispersion. Echocardiographic analyses were performed blinded to data other than demographic variables.

The reference group consisted of 21 age- and sex-matched healthy individuals who gave written informed consent for using their echocardiographic recordings and were recruited from a database at the Department of Cardiology, Oslo University Hospital Rikshospitalet, for echocardiographic comparisons.

#### Cardiac MRI

Due to limited resources, cardiac magnetic resonance (CMR) images were assessed only in 10 patients. CMR was acquired in breath-hold expiration using ECG-gated Ingenia, Philips Healthcare, 3 T systems (Best, The Netherlands). Cine images were made with a balanced steadystate free precession (bSSFP) sequence, and modified look locker (MOLLI) images were acquired for T1 determination in one mid-ventricular short axis and one 4-chamber view. Following contrast medium administration of 0.2 mmol/kg gadoterate meglumine (Dotarem, Guerbet), 12 consecutive short-axis cine bSSFP images of 8 mm without gaps were acquired. Ten minutes after contrast medium, post-contrast MOLLI T1 mapping images were repeated, followed by short- and long-axis inversion recovery, 2D late gadolinium enhancement (LGE) images. The inversion time was adjusted to null normal myocardium signal intensity. Cardiac function was analyzed by manual demarcation of endocardial and epicardial contours on enddiastolic and end-systolic bSSFP short-axis images. LV volumes and myocardial mass were compared to reference ranges from the UK Biobank population cohort [14]. T1 was measured in 2 regions of interest in both basal and mid parts of septum and the lateral wall, avoiding endocardial and epicardial borders, and one circular regions of interest in the LV lumen on both pre- and post-contrast 4-chamber MOLLI views. Myocardial extracellular volume (ECV) fraction was calculated as the ratio of contrast medium-mediated relaxivity change in the myocardium to blood multiplied by ECV of blood (1-packed cell volume). T1 and ECV were compared to local reference levels obtained by measurements at the same magnet with similar sequences of 30 healthy individuals (age 42 ± 11 years) who gave written informed consent for using their CMR recordings and were recruited from a database at The Intervention Centre, Oslo University Hospital Rikshospitalet.

LGE images were visually analyzed independently by one experienced CMR cardiologist and radiologist. Any focally defined LGE was considered to be possible focal fibrosis. CMR images were analyzed blinded to clinical data.



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## Results

Age, Gender, and Clinical Characteristics

We included 21 patients with chronic epilepsy, 17 women and 4 men with an average age of 28 years (range 19–39 years). The mean age at epilepsy onset was 11 years (range 3–18 years), and the average duration of epilepsy was 18 years (range 10–30 years) (Table 1).

All patients had focal to bilateral tonic-clonic seizures or generalized tonic-clonic seizures; 52% (11/21) also had focal aware seizures, and 43% (9/21) had focal seizures with impaired awareness. Epilepsy type was focal in 13 (62%), generalized in 6 (29%), and unknown in 2 (9%) of the 21 patients. The etiology of epilepsy was unknown in 38% (8/21), genetic generalized epilepsy in 33% (7/21), and structural in 29% (6/21). Among the patients with structural etiology, 2 patients had mesial temporal sclerosis, one with possible low-grade glioma without progression for the last 10 years, one with cerebral cavernoma, one with polymicrogyria, and one with unknown structural etiology.

The patients used between one and four antiseizure medication, which included lamotrigine (13/21), valproic acid (11/21), phenobarbital (1/21), zonisamide (1/21), clobazam (3/21), levetiracetam (4/21), lacosamide (2/21), topiramate (4/21), carbamazepine (2/21), perampanel (2/21), brivaracetam (2/21), and eslicarbazepine (1/21). The median number of convulsive seizures in the last 12 months was 10 (range 6–>15). Two patients had experienced >15 seizures in the previous 12 months.

Fourteen percent (3/21) had a history of precordial pain or palpitations during the last year. The symptoms had occurred independently of epileptic seizures. Ten patients had at least one first-degree relative with heart disease; no patients had a family history of sudden death.

Seven patients (33%) had comorbidities, including Asperger syndrome, depression, migraine, anxiety, and delayed sleep phase syndrome. One patient had Morbus Crohn treated with infliximab and another patient had hypothyroidism treated with levothyroxine. No other patients had co-medication.

#### ECG

ECG showed sinus rhythm in all patients with PR-, QRS-, and QTc-values within normal limits for all patients (shown in Table 2).

#### Holter Analyses

The average HR was 79 beats per minute (bpm), with a minimum HR of 41bpm and a maximum HR of 151 bpm. Increased numbers of ventricular premature contractions (VPCs) were recorded in 2 patients; patient 16 had 1094 VPCs, and patient 9 had 514 VPCs. Patient number 9 had a pause of 5 s, and patient number 5 had a pause of 8 s during the recording, both pauses occurred during the night (Table 2). None of the patients had generalized seizures during the Holter recordings.

#### Echocardiography

Average values for LV function were within the normal range for the entire group, both by LV EF and by GLS. However, individual changes below reference values occurred in 3 patients (patients 5, 13, and 16) (Table 3). Sufficient GLS data were obtained from only 16 of 21 patients, due to inadequate speckle tracking in multiple segments.

#### Cardiac MRI

CMR was performed in 10 patients, in which T1 measurement was unsuccessful in one due to technical failure. Findings are shown in Table 3. Regarding LV volumes and myocardial



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Parameter	Patients, $n = 21$	Reference values*
ECG recordings (mean, SD)		
HR, bpm	68±9.5	60-100
PR, ms	163±21	120-200
QRS, ms	93±6	80-110
QT interval, s	388±85	400-440
QTc, ms all	406±89	>400
Males	389±27	390-450
Females	383±24	380-460
Holter recordings, mean, SD (range)		
Ventricular tachycardia, events/72 h	0.2±0.9 (0-4)	
Supraventricular premature beats, events/72 h	6 (0-91)	<100 beats/24 h
HR average, night, bpm	79±9 (68–99)	-
HR average, day, bpm	78±11(59-101)	-
HR average, bpm	79±8 (67–95)	-
HR max, bpm	151±22 (111–200)	-
HR min, bpm	41±11 (35-51)	-
Irregular rhythm, events/72 h	11±25 (0-111)	-
Pause (>3 s), events/72 h	1±2 (0-8)	-
QTc, ms	504±150 (472-555)	-

**Table 2.** Variables regarding cardiac function in epilepsy patients

mass, no changes were found outside the reference values. There were no signs of diffuse fibrosis in any of the study patients. The average native T1 and ECV were similar to normal control values measured on the same magnet, and no individual had ECV measurement >30%. Only 1 patient (patient 10) had an unspecific finding on the LGE images not considered to be of clinical relevance.

The time between the last convulsive seizure and the performance of the CMR varies from the same day up to 12 weeks. Three patients had seizures close to 48 h prior to the study; no structural or functional cardiac changes were detected among these patients.

## Discussion

This pilot study is the first to include echocardiographic and CMR in a detailed cardiological evaluation of young-adult patients with long-lasting epilepsy and frequent convulsive seizures. We found no evidence of significant changes in myocardial function or structure, and no indication of diffuse or significant myocardial fibrosis in patients with drug-resistant epilepsy. However, slight changes outside reference range were revealed in a few individuals. One had a subtle area of low-attenuating LGE combined with slightly increased LV mass, and three individuals had decreased contraction and/or dilated LV. The clinical relevance of these minor and isolated findings is uncertain and must be interpreted with caution.

Investigation of the pathophysiological mechanisms leading to SUDEP is a challenge due to its abrupt nature, which is why studies in patients at risk and of postmortem cases have



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Table 3. Variables of imaging studies regarding structure and function in patients with chronic epilepsy and	
controls	

Parameter		
cardiac MRI, mean (±SD)*	controls, $N = 30$	patients, $N = 10$
Myocardial native T1, ms $(n = 9)$	1,252 (±36)	1,262 (±52)
Myocardial ECV (%) $(n = 9)$	25.1 (±3.0)	25.4 (±1.5)
LGE findings	N/A	1 (subtle)
LV EF (%)	N/A	55 (±5)
LV end-diastolic volume index, mL	N/A	93 (±15)
LV end-systolic volume index, mL	N/A	42 (±10)
LV stroke volume index, mL LV	N/A	50 (±7)
LV myocardial mass index, g	N/A	56 (±16)
cardiac echocardiography, mean (±SD)**	controls, <i>N</i> = 21	patients, N = 16
LV global longitudinal strain (%)	-21 (±1.8)	-20 (±2)***
LV mechanical dispersion, ms	30±5	34±6****
LV EF (%)	61 (±3)	60 (±4)

No significant differences were found between patients and controls, significance level set to p < 0.05. \*All individual MR, data were compared to age- and sex-matched reference values based on Petersen

et al. [14].

\*\*No pathological values were found in any of the patients studied compared with age- and sex-matched controls.

Number of patients studied: \*\*\*5; \*\*\*\*14.

been vital for understanding the mechanisms behind this tragic complication of epilepsy [15]. High frequencies of convulsive seizures and long-lasting epilepsy have been considered significant risk factors for SUDEP [4, 15]. The individuals studied in our work have these clinical characteristics and represent, in our opinion, a group of patients at high risk of SUDEP.

Generalized seizures induce autonomic overstimulation [5]. It has been suggested that such repetitive overstimulation can generate structural cardiac changes that may increase the risk of arrhythmia and myocardial ischemia [5].

As early as 1976, Falconer et al. [16] described the presence of interstitial and subendocardial fibrosis detected by autopsy in 9 patients with epilepsy, with at least seven related to seizures or possible SUDEP. In a series of SUDEP cases compared with healthy controls who had committed suicide or died by drug overdose, interstitial and perivascular fibrosis was present in five of the seven SUDEP cases and none of the control cases [8]. In a literature review of 11 studies reporting cardiac pathology in SUDEP cases, cardiac abnormalities were found in approximately 25% of cases. The most common findings were myocyte hypertrophy and myocardial fibrosis [7]. Based on these reports, we assumed that changes in myocardial structure and function would be more common in patients with frequent generalized seizures and chronic epilepsy. However, in contrast to our expectations, our study did not find any evidence of myocardial pathology.

Nevertheless, it has been documented that cardiac troponin I, a marker with high specificity for cardiac injury, is commonly elevated in association with convulsive seizures [17]. Several studies have found seizure-related elevation of troponin without pathological changes in ECG and echocardiography, suggesting that no permanent cardiac damage occurs under these conditions [18]. Our work did not include troponin analysis since, for practical reasons, repetitive sampling was not possible after seizures. However, the methods used in our study 94



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are capable of detecting even small structural changes in the myocardium [19]. Our results suggest that permanent cardiac changes resulting from high-seizure frequency are not common. Nevertheless, we have not excluded the possibility that some epilepsy patients with preexisting cardiac pathology, such as CF, cardiomyopathy, or coronary artery disease, may have a higher risk of SUDEP when convulsive seizures occur.

A case-control study demonstrated that changes in the myocardium might also be present in patients with newly diagnosed and untreated temporal lobe epilepsy (TLE), suggesting that the cardiac changes detected, at least in this subgroup of epilepsy patients, may not be cumulative [20]. This study found greater diameters in the LV and volume in systole, and highlighted a decrease in the EF in TLE patients compared with controls [20]. A study that analyzed the relationship between sudden cardiac arrest and epilepsy in 106 patients with epilepsy found that 30 had a previous echocardiography. Among these, 12 patients (40%) had a reduction in the EF [21].

Interestingly, in our study, 3 patients with genetic generalized epilepsy had reduced EF, with values below 50%, as demonstrated by echocardiography (Table 2), indicating reduced cardiac systolic function [22]. Reduced cardiac contractility was suggested by Fialho et al. [23] to be secondary to CF, a factor known to promote arrhythmogenesis. In contrast with their results, we did not detect any structural changes in the myocardium that indicated diffuse fibrosis. Differences in patient selection and the low number of patients and controls in our study may explain the conflicting results between the 2 studies. Our study included patients with heterogeneous epilepsy etiologies, while Fialho et al. [23] focused on TLE patients. Furthermore, gender distribution differed between the 2 studies, with 60% men in the study of Fialho et al. [23] versus only 20% in our study. The impact of these various factors is unknown.

#### **Strengths and Limitations of the Study**

To our knowledge, this is the first study that combines CMR, ECG, echocardiography, and telemetry for studying structural and functional cardiac changes in young patients with long-lasting, drug-resistant epilepsy with a high frequency of convulsive seizures. The combination of several diagnostic modalities would generally increase the possibility of revealing any cardiac changes, if present. However, we are aware that there are also several weaknesses in our study, especially the low number patients. Other weaknesses in our study include: a heterogeneous population including both lesional (nonprogressive) and non-lesional cases, asymmetric gender distribution, patients with focal seizures in addition to convulsive seizures, and variable total lifetime number of seizures. Due to limited resources, only 10 patients underwent CMR.

## Conclusions

This pilot study did not reveal significant functional or structural cardiac changes in young patients with many years of epilepsy and high frequency of convulsive seizures. The theory that multiple generalized seizures over time induce cardiac structural changes with fibrosis, which may, in turn, increase the risk for SUDEP, does not gain support from our findings. However, the number of included patients in our study was limited and whether clinically significant cardiac abnormalities could have been found in a larger study with older patients or subgroups more prone to epilepsy-related cardiac changes and sudden death remains to be answered.



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# **Statement of Ethics**

This study protocol was reviewed and approved by The Regional Committee for Medical and Health Research Ethics, REC West, Norway (2014/1053/REK). Written informed consent was obtained from the patients for publication of this case report.

# **Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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# **Author Contributions**

A.G., D.A., and E.T. conceptualized and drafted the manuscript. K.H., P.H.B., E.H., S.Ø., and S.A. revised the manuscript. S.A. participated in patient collection. S.Ø. and E.H. contributed in CMR assessment and K.H. and P.H.B. with echocardiography and ECG assessment. All authors read and approved the manuscript.

# **Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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