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The Epileptic Heart Syndrome: Epidemiology, pathophysiology and clinical detection☆

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ABSTRACT

Population studies report elevated incidence of cardiovascular events in patients with chronic epilepsy. Multiple pathophysiologic processes have been implicated, including accelerated atherosclerosis, myocardial infarction, altered autonomic tone, heart failure, atrial and ventricular arrhythmias, and hyperlipidemia. These deleterious influences on the cardiovascular system have been attributed to seizure-induced surges in catecholamines and hypoxemic damage to the heart and coronary vasculature. Certain antiseizure medications can accelerate heart disease through enzyme-inducing increases in plasma lipids and/or increasing risk for life-threatening ventricular arrhythmias as a result of sodium channel blockade. In this review, we propose that this suite of pathophysiologic processes constitutes "The Epileptic Heart Syndrome." We further propose that this condition can be diagnosed using standard electrocardiography, echocardiography, and lipid panels. The ultimate goal of this syndromic approach is to evaluate cardiac risk in patients with chronic epilepsy and to promote improved diagnostic strategies to reduce premature cardiac death.

1. Cardiovascular disease in epilepsy

Extensive clinical studies indicate that chronic epileptic seizures exert a deleterious effect on electrical and mechanical function of the heart [1–3]. The lines of evidence are diverse, ranging from histology, echocardiography, and electrocardiography to population studies. Studies from extensive population databases, a type of investigation generally regarded as a gold standard mainly because of its complete case ascertainment, have reported evidence of increased incidence of cardiac events including cardiovascular death, ischemic heart disease/atherosclerosis, myocardial infarction, heart failure, sudden cardiac death (SCD)/cardiac arrest, and atrial and ventricular fibrillation (AF/VF), etc. (Table 1) [4–31]. This spectrum of cardiac abnormalities led us to formulate the concept of the "Epileptic Heart," which we defined as "a heart and coronary vasculature damaged by chronic epilepsy as a result of repeated surges in catecholamines and hypoxia leading to electrical and mechanical dysfunction" [1].

Premature demise in patients with epilepsy has generally been attributed to the clinical entity termed "sudden unexpected death in epilepsy" (SUDEP), which is due to respiratory failure in the post-ictal period leading to cardiac asystole [32]. There is growing evidence that cardiac mortality in patients with epilepsy may be 4.5-fold more frequent than SUDEP, which excludes deaths from known causes (Fig. 1) [1,26,33–38].

While deaths among patients with epilepsy nearly doubled in the United States between 1999 and 2017, the proportion of deaths due to ischemic heart disease in people with epilepsy declined by 34 % to 43% over the same time period [8,9]. The former effect has been ascribed to increased cerebrovascular disease and neoplasms, while the latter change has been attributed to widespread implementation of techniques and treatments that reduce cardiovascular risk [9].

Currently, we are considering whether the "Epileptic Heart"

Abbreviations: AF, atrial fibrillation; ASM, antiseizure medication; CASH, Cardiac Arrest Study Hamburg; CAST, Cardiac Arrhythmia Suppression Trial; CIMT, carotid intima media thickness; CYP450, cytochrome P450; HDL, high-density lipoprotein; HFpEF, heart failure with preserved ejection fraction; HRV, heart rate variability; PWH, P-wave heterogeneity; rMSSD, root mean square of successive differences of R-R intervals; SCD, sudden cardiac death; SUDEP, sudden unexpected death in epilepsy; TWA, T-wave alternans.

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Table 1
Population Studies of Cardiovascular Morbidity and Mortality in Patients with Epilepsy.

Cardiac condition	First author, year	Database	Study cohort	Significant Findings and Comparisons
Cardiovascular death, myocardial infarction	Janszky et al. 2009 [4]	Stockholm Heart Epidemiology Program	1799 epilepsy patients with first MI; 2339 matched controls	4.92-fold more MIs and 1.95-fold more cardiovascular deaths in patients with than without epilepsy
Cardiovascular death	Neligan et al. 2011 [5]	National General Practice Study of Epilepsy at the National Health Service Information Centre of the United Kingdom	>1000 patients with epilepsy	3.3-fold more deaths in epilepsy patients with ischemic heart disease than without
Cardiovascular death	Nevalainen et al. 2013, 2016 [6,7]	Social Insurance Institution of Finland	10,818 patients with epilepsy and 43,894 subjects in reference cohort	2.31-fold more cardiovascular deaths in patients with than without epilepsy
Cardiovascular death	DeGiorgio et al. 2020, 2021 [8,9]	United States Centers for Disease Control and Prevention WONDER online database	8052 deaths in patients with epilepsy	Cardiovascular deaths declined by 34 % to 43% of all deaths in patients with epilepsy
Cardiovascular death, heart failure, ventricular tachycardia/ fibrillation, cardiac arrest	Mayer et al. 2024 [10]	French Hospital National Database from 2014 to 2022	682,349 patients with epilepsy plus 682,349 matched patients without epilepsy	2.69-fold more all-cause deaths; 2.16-fold more cardiovascular deaths; 1.26-fold more heart failure cases; 2.08-fold more ischemic strokes; 1.10-fold more VT/VF events; 2.12-fold more cardiac arrests in patients with than without epilepsy
Ischemic heart disease	Chen et al. 2016 [11]	Census and Statistics Department, Hong Kong Special Administrative Region	7461 patients with newly diagnosed epilepsy	4.18-fold more ischemic heart disease cases in patients with newly diagnosed epilepsy
Ischemic heart disease/ atherosclerosis	Zack and Luncheon 2018 [12]	US National Health Interview Survey	95,196 respondents including 1705 with epilepsy	1.8-fold more ischemic heart disease cases in patients with compared to without epilepsy, especially in families with incomes below poverty line
Ischemic heart disease	Husein et al. 2021 [13]	Canadian Longitudinal Study on Aging	44,817 participants including 751 patients with epilepsy	1.27-fold more ischemic heart disease cases, 1.88-fold more peripheral vascular disease cases in patients with than without epilepsy
Ischemic heart disease	Josephson et al. 2021 [14]	National Health Service hospitals in England	10,916,166 adults; 31,479 adults with epilepsy free of cardiovascular disease at baseline	1.21-fold more heart disease cases in patients with epilepsy receiving enzyme-inducing ASMs
Ischemic heart disease, heart failure, cardiac arrest, ventricular arrhythmia, atrial fibrillation	Bucci et al. 2023 [15]	TriNetX Global Federated Health Research Network	271,172 patients with epilepsy	3.23-fold more cardiovascular events at 5 years after seizure in 15,210 patients with compared to without 30-day events
Ischemic heart disease, sudden cardiac death, atrial fibrillation, ventricular arrhythmia	Shah et al. 2023 [16]	UK Biobank	494,676 subjects without epilepsy; 7786 patients with epilepsy	6.65-fold more SCDs, 3.9-fold more all-cause deaths in patients with than without epilepsy
Ischemic heart disease	Mayer et al. 2024 [17]	TriNetX Global Federated Health Research Network	374,950 patients with epilepsy	Carbamazepine (1.39-fold) and sodium valproate (1.264-fold) were associated with more cardiac events compared to lamotrigine. Valproate was associated with a 10-year 1.226-fold higher risk of all-cause death than carbamazepine.
Myocardial infarction	Olesen et al. 2011 [18]	Danish National Patient Register	48,602 patients with epilepsy	1.09-fold more MIs in ASM-treated patients; 1.15-fold more MIs in non-ASM treated patients
Myocardial infarction	Renoux et al. 2015 [19]	U.K. Clinical Practice Research Datalink	252,407 ASM users and matched control patients	1.46-fold more MIs in patients using enzyme-inducing ASMs compared to noninducing ASMs; non-inducing ASMs were associated with fewer MIs (to 0.81-fold)

(*continued on next page*)

Table 1 (*continued*)

Cardiac condition	First author, year	Database	Study cohort	Significant Findings and Comparisons
Myocardial infarction	Wilson et al. 2018 [20]	South Carolina hospital and emergency department encounter data	39,203 patients with epilepsy, 119,559 patients without epilepsy	1.24-fold more MIs in patients with compared to without epilepsy
Myocardial infarction	Wellejus Albertsen et al. 2020 [21]	DANish Comorbidity Index for Acute Myocardial Infarction (DANCAMI)	36,685 patients with first MI	1.26-fold more MIs in patients with compared to without epilepsy
Myocardial infarction, arrhythmia, SCD	Cheng et al. 2021 [22]	Taiwan National Health Insurance Research Database 1997–2013	27,055 patients including 5411 with epilepsy	1.71-fold more MIs, 2.11-fold more arrhythmias, 1.83-fold more SCDs in patients with than without epilepsy
Heart failure	Doege et al. 2021 [23]	German outpatient cohort	9646 patients with epilepsy and matched nonepileptic referents	1.56-fold more heart failure cases
Heart failure deaths	Liang et al. 2022 [24]	Danish registries	1345 patients with epilepsy and matched nonepilepsy referents	2.35-fold more heart failure deaths,1.31-fold more all-cause deaths in 696 patients receiving valproate compared to 649 patients receiving lamotrigine or levetiracetam
Cardiac arrest/VF	Bardai et al. 2012 [25]	Amsterdam Resuscitation Studies (ARREST)	1019 sudden cardiac arrest patients, 2834 referents without SCA	2.9-fold more sudden cardiac arrests in patients with epilepsy
Cardiac arrest/VF	Stecker et al. 2013 [26]	Oregon Sudden Unexpected Death Study	~1,000,000-subject study population; 106 sudden cardiac arrests in patients with epilepsy; 2311 sudden cardiac arrests in patients without epilepsy	No seizure activity witnessed prior to 66 % of sudden cardiac arrests in patients with epilepsy
Cardiac arrest/VF	Bardai et al. 2015 [27]	Integrated Primary Care Information (IPCI)	926 sudden cardiac deaths, 9832 referents without SCD	5.8-fold more sudden cardiac arrests in patients with symptomatic epilepsy; 2.8-fold more sudden cardiac arrests in patients with sodium channel blocking ASMs
Cardiac arrest, arrhythmia	Rossi et al. 2021 [28]	New York, Florida, and California State Inpatient and Emergency Department Databases	1,270,304 encounters for cardiac arrhythmias including 8717 in patients with epilepsy	2.37- to 3.36-fold more encounters for cardiac arrest/arrhythmias across 180 days following seizure than in prior year
Out-of-hospital cardiac arrest (OHCA)	Eroglu et al. 2022 [29]	Danish registries	35,195 OHCA cases and 351,950 matched non-OHCA controls	1.76-fold more OHCAs in patients with epilepsy than in the general population
Ventricular arrhythmias, atrial fibrillation	Wang et al. 2023 [30]	UK Biobank	329,432 subjects including 2699 with epilepsy	1.80-fold more ventricular arrhythmias, 1.26-fold more atrial fibrillation events in patients with than without epilepsy
Atrial fibrillation	Desai et al. 2017 [31]	Nationwide Inpatient Sample (NIS) Database of patients with epilepsy	1,424,320 hospitalized patients with epilepsy including 277,230 with cardiac arrhythmia	AF was most frequent cardiac arrhythmia (9.7 %). Incidence of sudden cardiac arrest was 1.4 %; incidence of VT was 1.0 %

Key:
AF = atrial fibrillation
ASM = antiseizure medication
MI = myocardial infarction
OHCA = out-of-hospital cardiac arrest
SCD = sudden cardiac death
VF = ventricular fibrillation
VT = ventricular tachycardia

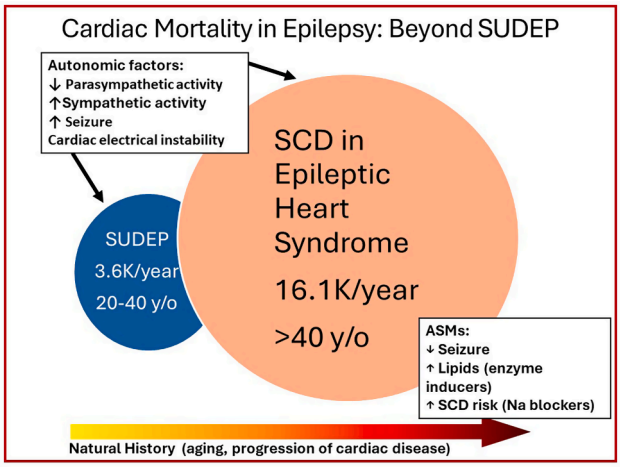

Fig. 1. Venn diagram of the interrelationship between sudden cardiac death (SCD) and sudden unexpected death in patients with epilepsy (SUDEP). SUDEP incidence data of 3600 cases/year are from Thurman et al. 2014 [35] and Harden et al. 2017 [37]. SCD incidence data are from Stecker et al. 2013 [26], Zack and Kobau 2015 [36], and Benjamin et al. 2018 [38]. ASMs = antiseizure medications. Republished with permission from Verrier et al. 2020 [1].

condition constitutes a syndrome, with a constellation of manifestations that can be assessed with standard clinical tools on an individual patient basis [2]. The main objectives of this review are to characterize the pathophysiologic basis of the "Epileptic Heart Syndrome" and to define candidate clinical criteria that could be used in developing a systematic, practical approach to its detection.

2. "Epileptic Heart Syndrome": Pathophysiology

The conceptual framework that characterizes the link between chronic epilepsy and the development of the "Epileptic Heart Syndrome" is illustrated in Fig. 2 [2]. The specific, well-documented abnormalities include changes in myocardial structure, with fibrosis, contraction-band necrosis, increased myocardial stiffness with diastolic dysfunction, and electrocardiographic abnormalities. The inciting factors include repeated seizure-induced hypoxemia [39–41] and myocardial ischemia [42,43], the cardiotoxic effects of excess catecholamines [44], and the potential exacerbating effects of certain antiseizure medications (ASMs). The involvement of myocardial ischemia is supported by the report from Tigaran et al. [43] that ST-segment changes are evident in up to 40% of seizures. The cardiotoxic effects of catecholamines during seizures are underscored by reports of myocardial stunning with markedly reduced left ventricular ejection fraction in patients admitted to the Epilepsy Monitoring Unit [45]. The magnitude of this depression in cardiac contractility is akin to Takotsubo cardiomyopathy [46]. Secondary Takotsubo cardiomyopathy has been estimated to occur in ~1 of 1000 in-hospital seizures, resulting in poor outcomes, including inpatient mortality (3.7%), arrhythmia (22.7%), cardiac arrest (3.9%), etc. [47]. This finding has led to the view that chronic epilepsy may be associated with a neurogenic cardiomyopathy phenotype.

Postmortem evidence of myocardial structural changes in patients with epilepsy has been reported by several groups. Falconer and Rajs [48] were the first to report postmortem evidence of cardiac fibrosis and myofibrillar degeneration. At autopsy, hearts of patients with epilepsy were characteristically dilated and were heavier than expected [48,49]. Dasheiff et al. [50] observed mild ventricular hypertrophy and focal myocardial fibrosis in 20% of autopsy cases. Natelson and coworkers [51] noted myocardial vascularization and perivascular and interstitial myocardial fibrosis in a majority of autopsied hearts of patients with chronic epilepsy. Thus, a generalized pattern of microfocal interstitial

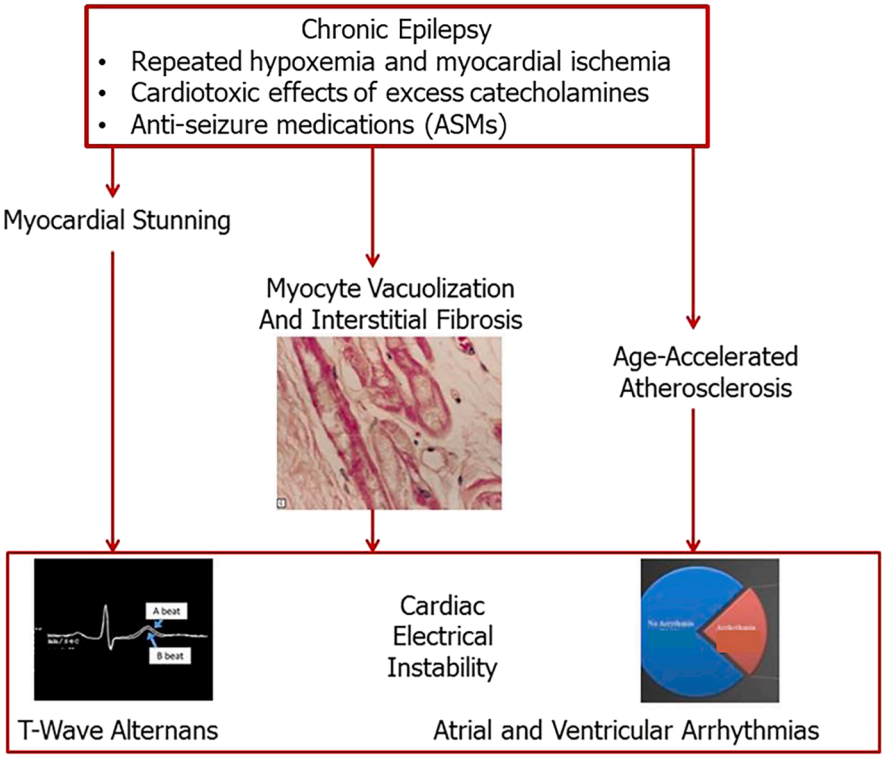

Fig. 2. Conceptual framework of the link between chronic epilepsy and development of the "Epileptic Heart Syndrome." The factors include cardiotoxic effects of catecholamines, repeated hypoxemia, and increased cardiac electrical instability manifest as T-wave alternans, a repeating ABAB beat-to-beat pattern in the ST segment and T wave of the electrocardiogram. ASMs = antiseizure medications. Republished with permission from Verrier et al. 2021 [2].

and/or patchy myocardial fibrosis [52,53] is a well-documented feature of the "Epileptic Heart Syndrome." Devinsky and coworkers [54] have emphasized the need for further study to define more precisely the potential role of cardiac fibrosis in SUDEP.

Echocardiography studies have confirmed that patients with chronic epilepsy exhibit abnormally high levels of left ventricular stiffness, increased ventricular pressure, and greater left atrial volume compared to healthy age- and sex-matched controls [55]. The investigators proposed that recurring seizures could lead to heart failure with preserved left ventricular ejection fraction (HFpEF) [55–58], a condition known to increase risk for premature death [57].

The convergence of the main pathologic pathways including myocardial stunning, histological changes involving myocardial vacuolization and interstitial fibrosis, and accelerated atherosclerosis lead to cardiac electrical instability of both the atria and ventricles. Increased incidence of atrial arrhythmias, particularly AF, has been documented in large populations [15,16,30,31]. Yassin and colleagues [59] reported AF during routine EEG recordings in 6.3 % of patients. AF incidence in patients with epilepsy deserves further attention, especially because this arrhythmia carries increased risk for stroke and myocardial infarction. There is growing evidence that P-wave heterogeneity (PWH) precedes AF and can be used for risk assessment [60].

Significant increases in ventricular arrhythmia incidence including ventricular fibrillation in patients with epilepsy compared to general populations have been reported [10,15,22,25–28,30]. Rossi and colleagues [28] reported a heightened incidence of cardiac arrhythmia/arrest across 180 days after a seizure. Sudden cardiac deaths and cardiac arrests were also more frequent in patients with than without epilepsy [10,15,16,22,25–29]. Seizure-induced electrical dysfunction of the ventricles is well-documented based on a number of clinically available electrocardiographic parameters such as QT interval prolongation and P-wave and T-wave alternans and heterogeneity.

It is well documented that epilepsy predisposes to cardiovascular death [4–10], ischemic heart disease [11–17], myocardial infarction [4,18–22], and heart failure [10,15,23,24].

An additional major compounding factor of the "Epileptic Heart Syndrome" is a role for certain ASMs. These agents introduce at least two potential major cardiac risks. First, as Mintzer and colleagues [61,62] proposed, ASMs that induce the cytochrome P450 (CYP450) system are linked to elevations in lipids, Lp_a, C-reactive protein, and homocysteine, contributors to atherosclerosis. Another important deleterious influence is that certain ASMs may increase risk for SCD and other cardiac events, notably, those with sodium channel-blocking effects, including carbamazepine, lamotrigine, and phenytoin [3,17,27,63]. Blockade of the cardiac sodium channels, particularly in patients with cardiovascular disease, can promote conduction abnormalities and predispose patients to serious cardiac arrhythmias such as wide-complex ventricular tachycardia. The Cardiac Arrhythmia Suppression Trial (CAST), which enrolled post-myocardial infarction patients with cardiac arrhythmias, showed that the sodium channel blockers flecainide and encainide were severely proarrhythmic and predisposed to higher incidence of death [64]. In addition, in the Cardiac Arrest Study Hamburg (CASH) trial, conducted in patients with prior cardiac arrest, the sodium channel blocker propafenone was shown to increase all-cause mortality significantly in the first year of the study [65]. Myocardial ischemia during seizures, especially GTCSs, may enhance risk for life-threatening ventricular arrhythmias in individuals receiving chronic ASMs with sodium channel-blocking activity. It is noteworthy that certain ASMs such as carbamazepine and phenytoin, which have both enzyme-inducing effects and sodium-channel blocking properties, pose a "double-hit" by increasing plasma lipid levels and predisposing to malignant arrhythmias [27,62].

3. Clinical criteria and methods for detection of the "Epileptic Heart Syndrome"

The candidate criteria and measurements that can be assessed with commercially available equipment are presented in Table 2. These criteria were derived from extensive Boolean searches of the medical literature using PubMed from National Library of Medicine (USA). We employed the terms "electrocardiographic," "echocardiography," "atherosclerosis," "left ventricular function," "heart rate variability," "autonomics," and "lipids." Based on this comprehensive evaluation, we formulated five conditions and criteria that provide the basis for establishing the syndromic components of an "Epileptic Heart Syndrome" with these diagnostic tools [2].

3.1. Criterion #1: Presence of chronic epilepsy with or without drug resistance

Confirmation of chronic epilepsy is fundamental to the determination of the "Epileptic Heart Syndrome." The basic rationale, as shown in our conceptual framework (Fig. 2) [2], is that seizures progressively injure the heart and coronary vasculature as a result of recurring bouts of myocardial ischemia and the cardiotoxic effects of excessive levels of catecholamines. A critical factor is age past 40 years [12,66], when

Table 2
Criteria for the Epileptic Heart Syndrome.*

- **Chronic Epilepsy with or without Drug-Resistance**
  - Based on ILAE standard diagnostic criteria
- **Myocardial Injury and Arrhythmia Risk on EKG**
  - Clinical signs and symptoms such as exercise intolerance, chest pain, irregular pulse and palpitations
  - Atrial and/or ventricular arrhythmias
  - P waves >2.5 mm tall and/or >110 ms wide may indicate atrial enlargement
  - Q waves—indicator of prior myocardial infarction
  - QRS complex >150 ms wide may indicate conduction abnormalities and electrical dyssynchrony
  - Severe QT interval prolongation (>450 ms in men, >470 ms in women) may indicate repolarization abnormalities or antiseizure medication use
  - ST-segment depression or elevation
  - T-wave alternans ≥47 μV
- **Altered Autonomic Tone as Assessed by HRV Measures**
  - rMSSD <27 ± 12 ms
  - LF/HF ratio >1.5–2.0
- **Diastolic Dysfunction on Echocardiography**
  - Increased left ventricle stiffness (β constant)
  - Elevated left ventricular diastolic filling pressure (mmHg)
  - Increased left atrial volume (ml)
- **Hyperlipidemia and Accelerated Atherosclerosis**
  - Triglycerides >149 mg/dl; high-density lipoprotein (HDL) <40 mg/dl male, <50 mg/dl female
  - Consider ultrasound measurement of carotid intima media thickness

Note: ILAE = International League Against Epilepsy.
* Requires the presence of chronic epilepsy and any two other criteria.

vulnerability to pathologic processes can be enhanced. Additionally, it is important to recognize the potential involvement of acquired channelopathies in epilepsy [67]. Experimental studies have shown that epilepsy can alter expression of ion channels in both the heart and brain, which in turn can predispose to cardiac dysfunction and mortality. This process may occur at younger ages than is the case for longer term progression of cardiovascular disease.

3.2. Criterion #2: Electrocardiographic markers of myocardial injury and risk for atrial and ventricular arrhythmias

With respect to atrial arrhythmia risk, the key clinical approach involves measurement of atrial enlargement in terms of P waves >2.5 mm tall or >110 ms wide. P-wave heterogeneity (PWH) may reveal increased susceptibility to AF and can be monitored from standard 12-lead EKGs. Recently, we have shown that patients with chronic epilepsy exhibit an increased PWH indicative of an arrhythmogenic atrial substrate that is comparable to levels observed in patients with AF [60]. The patients with epilepsy were ~20 years younger than the patients with AF but without epilepsy, consistent with acceleration in structural atrial changes and/or cardiac electrical instability of the atria.

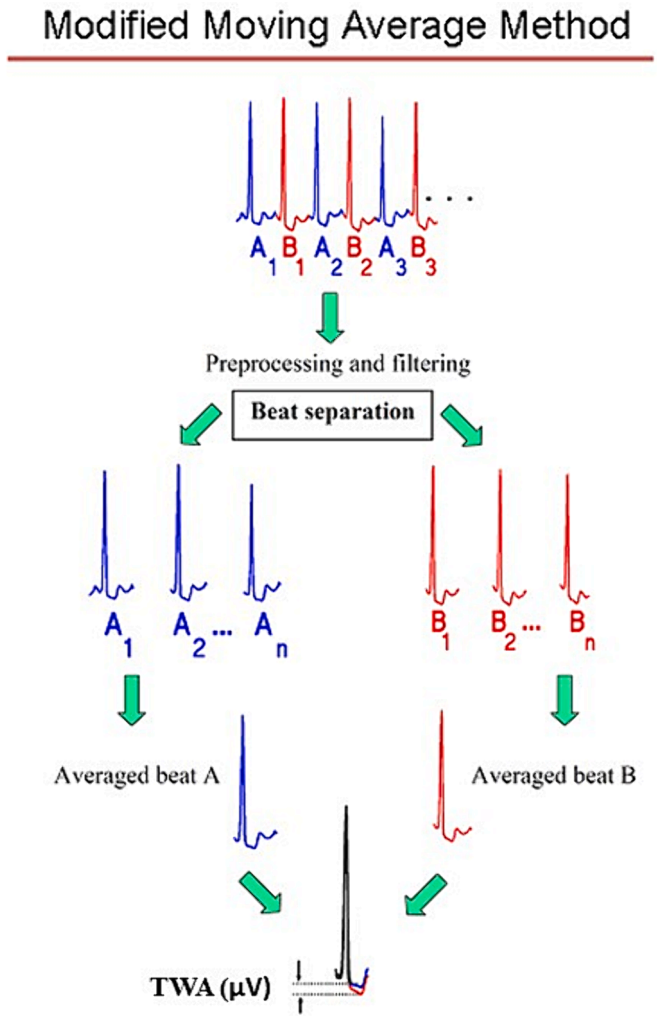

Fig. 3. Modified moving average technique for detection of T-wave alternans (TWA). Alternate beats are dichotomized into bins of "A" beats (blue) and "B" beats (red), and the T-wave morphologies in each bin are averaged. The averaged beats are then superimposed, and the difference in the magnitude of the T waves of the A and B averaged beats is quantified in microvolts. This difference is the TWA level, which indicates the degree of cardiac risk [67]. Republished with permission from Verrier et al. 2020 [1]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In terms of assessing ventricular injury and risk for ventricular arrhythmias, several measurements are available. These include presence of Q waves with large downward deflection, which may indicate prior myocardial infarction; QRS complex width >150 ms, which may indicate conduction abnormalities and electrical dyssynchrony; and severe QT interval prolongation (>450 ms in men, >470 ms in women), which may indicate repolarization abnormalities or ASM use. It has been shown, for example, that QT prolongation >448 ms was abnormal in nearly one-third of >18,000 patients with chronic epilepsy in the Mayo Clinic (Rochester MN) database and was associated with 1.48-fold increase in mortality [68].

Our group found that a widely studied measure of arrhythmogenic repolarization abnormality, T-wave alternans (TWA), a beat-to-beat fluctuation in T-wave morphology (Fig. 3) [1,69,70], is elevated in individuals with chronic epilepsy to the level observed in patients with cardiomyopathy and myocardial infarction (Fig. 4) [1,71]. TWA is a well-established marker of cardiac arrhythmia risk and is based on sound electrophysiologic principles, as it indicates heightened levels of heterogeneity of repolarization and sets the stage for unidirectional block and reentry. The capacity of TWA analysis to evaluate risk for malignant arrhythmias is supported by studies in ~4800 patients with diverse cardiac conditions [70], specifically, cardiomyopathy, ischemic heart disease, and heart failure. TWA is also useful for detecting the influence of anti- and proarrhythmic agents [72], enabling clinicians to select nonarrhythmogenic treatment drugs. The FDA-cleared commercially available modified moving average method for TWA analysis is illustrated (Fig. 3).

The utility of TWA in detecting latent arrhythmia risk is increased by EKG monitoring with multiday EKG patches, which are well-tolerated. Pang et al. [73] reported that TWA levels in chronic epilepsy patients were significantly higher than those in individuals with newly diagnosed epilepsy; the latter did not differ significantly from those observed in the healthy control group. In patients with chronic epilepsy, maximum TWA magnitude across 24 h exceeded the ≥47-μV TWA cut point for cardiac risk. It is of interest that during an interictal period, one of the patients experienced a crescendo in TWA level that heralded a brief run of ventricular tachycardia. This arrhythmia occurred on the fourth day of monitoring with an ambulatory EKG patch and would not have been detected by conventional Holter monitoring, which is typically limited to 1 or 2 days. Additional studies have indicated that heightened levels of T-wave alternans prior to EMU admission identify patients with greater likelihood of a seizure during their hospital stay [74]. We also found that T-wave heterogeneity, a precursor of TWA, can provide advance warning of seizure onset [75].

3.3. Criterion #3: Altered autonomic tone

An established feature of certain seizure types is the occurrence of bursts of sympathetic nerve activity. Heart rate variability (HRV) has proven to be a valuable marker of autonomic tone and has historically been used in ambulatory monitoring with 24-h EKG recorders. In recent years, HRV has been incorporated into multiday EKG patches and readers to characterize autonomic tone both intra- and interictally. The commonly employed metric of parasympathetic tone is "root mean square of successive differences of R-R intervals" (rMSSD). This time-domain HRV parameter appears to be inversely correlated with SCD risk in populations with cardiovascular disease [76–78]. A meta-analysis revealed that chronic epilepsy patients exhibit lower levels of rMSSD than are observed in the general population [79]. Our group [73] reported that during periods when rMSSD is reduced, TWA was reciprocally increased, indicating elevated levels of cardiac electrical instability. These findings point to an inverse relationship between parasympathetic autonomic activity and propensity for cardiac arrhythmias in patients with chronic epilepsy.

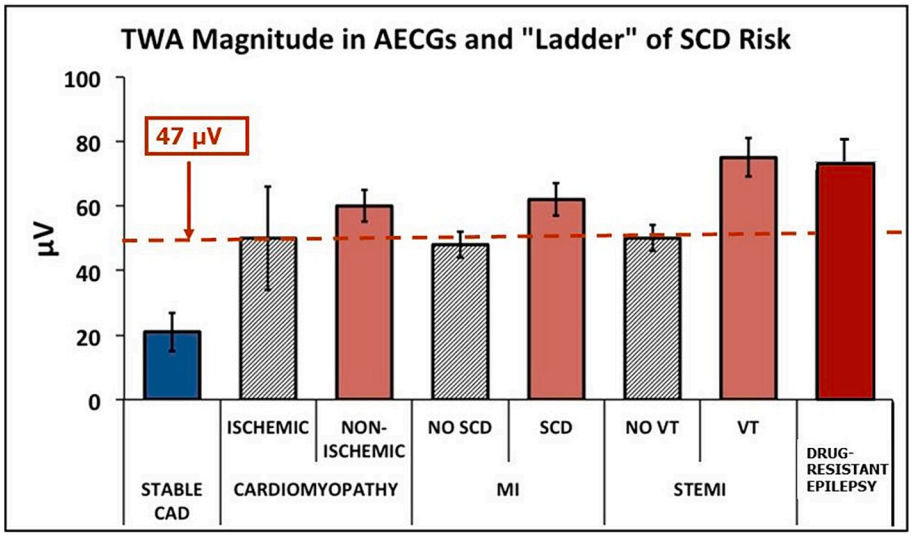

Fig. 4. T-wave alternans (TWA) ladder of risk. Patients with chronic epilepsy exhibit maximum 24-hour TWA in the severely abnormal range (>60 μV), similar to patients who experience ventricular tachycardia (VT) following ST-segment elevation myocardial infarction (STEMI). AECG, ambulatory electrocardiogram; MI, myocardial infarction. Republished with permission from Verrier et al. 2020 [1].

In Dravet syndrome, which is known to be associated with a heightened risk for premature death, HRV was found to be reduced, indicating relatively unopposed sympathetic nerve activity [80]. Also, markers of atrial and ventricular arrhythmia vulnerability, specifically, QT-interval and P-wave dispersion, were found to be abnormal.

3.4. Criterion #4: Echocardiographic evidence of myocardial stiffness and diastolic dysfunction

Several investigations applied state-of-the-art echocardiographic techniques to demonstrate that chronic epilepsy is associated with a type of stress-related cardiomyopathy typical of HFpEF [55,57,58,81–83]. They attributed the resulting cardiac effects to recurring bouts of sympathetic nerve overstimulation and to the corresponding release of catecholamines at the neurocardiac junction, resulting in cardiac myofilament damage, extracellular matrix deposition, fibrosis, and inflammation. Other investigators have provided evidence that recurring epileptic seizures can set the stage for diastolic heart failure, with potential for left ventricular hypertrophy [50,82]. Doege et al. [23] reported a 1.56-fold increase in heart failure diagnoses in patients with epilepsy. Collectively, these studies illustrate the potential for standard echocardiography to identify structural changes in the cardiac substrate that compromise cardiac mechanical function and promote risk for arrhythmia.

3.5. Criterion #5: Presence of hyperlipidemia and accelerated atherosclerosis

Growing evidence highlights the need for monitoring lipid levels and evidence of accelerated atherosclerosis in patients with chronic epilepsy. The normal limit for triglycerides is <149 mg/dl and for high-density lipoprotein (HDL) is >40 mg/dl, equivalent to the ranges established for ruling out the metabolic syndrome. In population studies enrolling >900 patients with epilepsy, hyperlipidemia was found to be ≥1.17-fold more common among patients with epilepsy than in comparison cohorts without epilepsy [84,85]. It is germane that use of ASMs that induce the CYP450 system is associated with elevated serum lipid levels and C-reactive protein, and that use of CYP450-inhibiting ASMs is associated with a reduced risk for myocardial infarction [19]. Mintzer and colleagues [61,62] also demonstrated that switching from CYP450-inducing agents (e.g., carbamazepine, phenytoin) to CYP450-noninducing ASMs (e.g., levetiracetam, lamotrigine, zonisamide) alone results in a persistent reduction in serum lipid and C-reactive protein levels and can decrease SCD risk by 3.2–5.7-fold. Liang and coworkers [24] reported that valproate was associated with 1.31-fold more all-cause deaths and 2.35-fold more heart failure deaths compared to treatment with lamotrigine or levetiracetam. The notable 34% to 43% decline in cardiovascular deaths in epilepsy patients from 1999 to 2017 has been attributed to primary prevention strategies and prescription of more modern ASMs [8,9].

In individuals with hyperlipidemia, particularly those receiving enzyme-inducing ASMs, there is evidence that evaluating carotid intima media thickness (CIMT) with echocardiography could prove helpful [86,87]. The presence of increased CIMT has the potential to signal more widespread atherosclerosis including coronary vascular stenosis and ischemic heart disease.

4. Diagnostic and therapeutic implications of the "Epileptic Heart Syndrome"

The proposed approach to the detection of the "Epileptic Heart Syndrome" in the adult population is rooted in sound pathophysiologic principles. The criteria include establishing chronic epilepsy with or without drug resistance as a centerpiece and is backed by electrocardiographic, autonomic, and echocardiographic measurements as well as plasma lipid level determinations. By combining these criteria, the soundness of diagnosis of the "Epileptic Heart Syndrome" is enhanced. Furthermore, the spectrum of variables assessed uncovers multiple potential therapeutic targets. The literature reviewed highlights the value of routine and multiday EKG-based assessment, which can help to disclose rhythm abnormalities, including atrial and ventricular arrhythmias. A number of attractive state-of-the-art wearable sensors including EKG patches and wristbands as well as minimally invasive insertable loop recorders hold promise to improve cardiac monitoring and to optimize therapeutic interventions in individuals afflicted with chronic epilepsy.

Ultimately, the body of evidence reviewed and the suggested syndromic approach provided [2] have the potential to impact day-to-day practice in patients suspected of an Epileptic Heart Syndrome. Particular attention to indications of cardiac dysfunction, including symptoms revealed in patient history such as palpitations, chest discomfort, and poor exercise performance, is recommended. The importance of hypertension, stroke, and diabetes mellitus in the morbidity and mortality of epilepsy patients has recently been emphasized with recommendation

of cardiovascular risk estimation by American College of Cardiology's atherosclerotic cardiovascular disease (ASCVD) estimator [88–90]. In addition to routine use of the 12-lead EKG during patient visits and hospital admission, we foresee that echocardiography could become an important additional tool in the armamentarium for determination of left ventricular ejection fraction and diastolic dysfunction, indicating a neurogenic cardiomyopathy phenotype [55,57,58].

The potential benefits of improved cardiovascular diagnostics and therapy in patients with epilepsy are supported by the reduction in cardiovascular deaths by primary prevention strategies [8,9] and by eliminating use of enzyme-inducing agents [19], which can accelerate atherosclerosis. Avoidance of sodium channel blocking ASMs has also been shown to reduce risk for sudden arrhythmic death [17,27,61–63]. In the future, studies should be directed to evaluate the potential cardioprotective effect of reducing the impact of excess catecholamines. Promising therapies include cardioselective beta-adrenergic blockade and vagomimetic interventions such as vagus nerve stimulation with chronically implanted electrical stimulators [71,91] or noninvasive tragus nerve stimulation [92,93], based on principles emphasized in the current review.

Clearly, there is need for a comprehensive management plan that addresses not only epilepsy but also long-term cardiovascular risk.

Ethical statement

This is a review article. It provides no new data based on clinical studies or preclinical experiments.

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CRediT authorship contribution statement

Richard L. Verrier: Writing – review & editing, Writing – original draft, Conceptualization. **Steven C. Schachter:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Verrier is coinventor of United States Patent #10,022,060, which protects analytical methodologies used by Dr. Fialho and colleagues in Reference #60. Dr. Verrier is a member of the Medical Advisory Board of StratusNeuro, Inc. (Houston TX, USA) and has received consulting fees from Union Chimique Belge (UCB) Pharma S.A. (Brussels, Belgium). Dr. Schachter reports no conflicts of interest.

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