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Review

Epilepsy and ultra-structural heart changes: The role of catecholaminergic toxicity and myocardial fibrosis. What can we learn from cardiology?

Guilherme L. Fialho[a,b,*], Peter Wolf[b,c,d], Roger Walz[b,c,e], Katia Lin[b,c,e]

[a] Cardiology Division, Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil
[b] Medical Sciences Post-graduate Program, Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil
[c] Neurology Division, Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil
[d] Danish Epilepsy Centre, Dianalund, Denmark
[e] Center for Applied Neurosciences (CeNAp), Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil

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ABSTRACT

In this article, we explore the interaction of brain and heart in patients with epilepsy (PWE), focusing on new insights into possible pathways from epilepsy, catecholaminergic toxicity, subtle cardiac changes and sudden death. Initial evidence and biological plausibility point to an interaction between autonomic dysfunction, higher sympathetic drive, myocardial catecholaminergic toxicity and cardiac fibrosis resulting in subtle myocardial changes in structure, function, arrhythmogenesis and/or a heart failure-like phenotype in PWE. Non invasive imaging and biomarkers of cardiac injury and fibrosis are emerging as possible diagnostic tools to better stratify the risk of such individuals. Translational lessons from cardiac models of disease and ultra-structural lesions are used to support these considerations.

1. Introduction

In 1628, Sir William Harvey, the famous English physician, stated that "*For every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart*" [1]. In this article, we explore the interaction of brain and heart in patients with epilepsy, focusing on new insights into possible pathways from epilepsy, catecholaminergic toxicity, subtle cardiac changes and sudden death. Translational lessons from cardiac models of disease and ultra-structural lesions are used to support these considerations.

2. Methods

We did a narrative review of articles published in English, Spanish or Portuguese at MEDLINE, LILACS and EMBASE, with no restriction in date of publication. Our search terms were "epilepsy" and "cardiac fibrosis"; "epilepsy" and "cardiac stiffness"; "epilepsy" and "autonomic dysfunction"; "epilepsy" and "takotsubo"; "epilepsy" and "catecholaminergic"; "epilepsy" and "catecholaminergic toxicity"; "antiepileptic drugs" and "autonomic dysfunction"; "antiepileptic drugs" and "heart". In view of the limited number of allowed references we selected those that were most relevant for our discussion.

3. Autonomic dysfunction and catecholamine toxicity

Brain-heart interactions are complex. The autonomic nervous system (ANS) is responsible for the heart´s chronotropic (heart rate), dromotropic (conduction velocity), inotropic (contractility), bathmotropic (excitability) and lusitropic (relaxation) function, as well as for myocyte homeostasis at a cellular/molecular level [2]. The extrinsic component of the ANS is composed by afferent and efferent sympathetic and vagal fibers that connect the central nervous system to the heart. After entering the pericardial sac, nervous fiber of the ANS are called intrinsic. The intrinsic fibers form nervous plexuses (around 7) in atrial and ventricular surfaces near the sinus node, atrioventricular node, coronary arteries and pulmonary veins. There are around 94 thousand neurons in children´s and 43 thousand in adults' hearts [2,3].

A great number of different heart responses occur after physiological and pathological brain activation. Stress-related cardiomyopathy syndromes include cardiac alterations (*e.g.* heart failure or arrhythmias) after brain insults, such as intracranial bleeding, head trauma, stroke or epilepsy, acute emotional stress as in Takotsubo cardiomyopathy, or other conditions such as cardiomyopathy secondary to medical illness,

* Corresponding author at: Departamento de Clínica Médica - 3° andar - Hospital Universitário Polydoro Ernani de São Thiago - Rua Prof. Maria Flora Pausewang S/N°, Caixa Postal 5199 - Campus Universitário – Universidade Federal de Santa Catarina - Trindade - 88040-900 - Florianópolis, SC, Brazil.
E-mail addresses: fialhog@gmail.com (G.L. Fialho), wolfcph@gmail.com (P. Wolf), rogerwalz@hotmail.com (R. Walz), linkatia@uol.com.br (K. Lin).

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surgery or drug use/abuse [4]. Interestingly, most of the stress-related cardiomyopathies share a common pathway of enhanced sympathetic stimulation promoting catecholamine release to the myocardium [4]. Catecholamine toxicity can promote myocyte apoptosis [5] and inflammation [6], with histological contraction band necrosis secondary to calcium overload [4,7].

4. Epilepsy, SUDEP and stress-related cardiomyopathy

Epilepsy can be viewed as a model for stress-related cardiomyopathy. It is a common neurological condition, with over 50 million people affected worldwide [8]. People with epilepsy (PWE) have 2–3 times greater risk of dying prematurely due to falls, drowns, traffic accidents, suicide and sudden death [9]. Those with untreated seizures have a 9.3–13.4 greater risk of death [9].

Sudden unexpected death in epilepsy (SUDEP) can be described as a sudden death in PWE not caused by status epilepticus and after excluding death from trauma, drowning, pulmonary aspiration, without anatomical or toxicological explanation detected by post-mortem examination [10]. It is considered the most important cause of death in PWE being responsible for 2–18% of deaths [11,12]. PWE have a 24–27 greater risk of dying suddenly compared to the general population, with a life time risk of SUDEP of 7 to 35% [11–14]. Early age onset disease, frequent uncontrolled generalized seizures, resistance to drug therapy and low adherence to treatment are markers of increased risk of SUDEP [11–17].

Autonomic dysfunction, with increased sympathetic tone and lower vagal tone is prevalent in PWE and may explain the increased risk of death in this population [18–21]. Chronic increased sympathetic tone is related to arrhythmia and sudden cardiac death as it promotes cardiac electrical remodeling secondary to increased intracellular calcium and reduction of the potassium current in the heart, disturbing the duration of the cellular action potential with consequent electrical repolarization heterogeneity [22,23]. This can lead to abnormal automatism, after-depolarization and arrhythmia [22,23]. The influence of the ANS on the heart has a dynamic characteristic, being intensified by myocardial ischemia [2,22,24]. Abnormal nervous fiber growth in the myocardium after ischemia (nerve sprouting) has been shown, which favors asymmetric electrical stimulation promoting arrhythmia [2,22,24]. Fluctuation of ANS stimuli on the heart has been shown to influence ion channel activity in the heart and have an important role in unmasking electrocardiographic markers of genetic arrhythmic syndromes such as Brugada phenotype or long QT [25]. Autonomic imbalance that occurs in epilepsy could favor this electrical heterogeneity, which is not necessarily present the whole time. These intermittent electrocardiographic and clinical manifestations, such as seen in some patients with cardiac disease, could also happen to epilepsy patients due to autonomic disturbances and predispose them to arrhythmia.

In murine models of *status epilepticus*, Bealer et al. demonstrated an increased risk of lethal arrhythmia 12–14 days after the event. They found a 60% decrease in the myocyte Kv4.2 ion channel, responsible for rapid potassium outflow current related to phase 1 of the membrane's action potential [26]. Beta-blockers used immediately before the seizure [26] or continuously during or after the seizure [27,28], was associated to a reduction in troponin levels, QT interval duration and lethal arrhythmias. We are not aware of studies such as this one in humans. There are studies on gross cardiac dysfunction in patients with *status epilepticus* [29].

5. Antiepileptic drugs and autonomic function

Polytherapy with antiepileptic drugs (AEDs) is related to SUDEP [30]. Bardai et al. found that AEDs related to sodium channel blockade were related do associated to sudden cardiac death, although one should recognize that distinction from SUDEP is sometimes difficult [31]. We know from cardiology that antiarrhythmic class I drugs (from Singh-Vaughan-Williams classification) acts through blockade of sodium channel. These drugs increase the risk of arrhythmias (*proarrhythmic effect*) such as ventricular tachycardia and death in individual with structural heart disease and thus should not be use is theses patients [32]. In murine models, Hubert et al. found that carbamazepine, lamotrigine and levetiracetam use were associated to a reduction in cardiac myocyte contraction and excitability compromising electromechanical coupling which was more intense with association of drugs [33].

The relation of AEDs with autonomic dysfunction is not clear. Lotufo et al. found a trend toward AED use and higher LF (low-frequency power spectrum of heart rate variability) values which is associated with a higher sympathetic drive [20]. Our previous work found that polytherapy with AEDs was associated to worse cardiovascular fitness in multiple linear regression analysis, but not to chronotropic incompetence [34]. In that same study, we found an association between age of onset of epilepsy and monthly number of generalized seizures, with impaired autonomic response to exercise [34].

6. Cardiovascular continuum, fibrosis and lessons from Takotsubo

The pathway from ANS dysfunction and sympathetic overdrive to a greater risk of arrhythmia and death might be explained by catecholaminergic toxicity leading to cell death and myocardial fibrosis. Acute sympathetic overstimulation (such as in Takotsubo cardiomyopathy, acute brain damage or *status epilepticus*) can cause overt myocardial damage and dysfunction easily detectable by cardiac exams such as electrocardiogram or echocardiogram [4,35]. On the other hand, chronic and repeated sympathetic overstimulation (as seen in epilepsy and possibly other stimuli such as anger or panic attacks), might cause subtle cardiovascular changes such as myofilament damage, extracellular matrix deposition and fibrosis, mostly not detected by usual exams [36,37]. Recently, it has been demonstrated that PWE have a higher left ventricular stiffness coefficient, which is related to fibrosis [36]. Schwarzl at al. found in a 15 thousand people cohort without prior cardiovascular disease that common cardiac risk facts such as age, hypertension, diabetes and obesity were associated with increased stiffness and mortality [38].

The extracellular matrix provides structural support to normal myocardium. Although fibrosis can be generally defined as an excessive accumulation of extracellular matrix [39], different pathways lead to this.Reparative fibrosis occurs as an organized scar after loss of myocytes due to myocardial infarction, which acts as a stabilizer of the lesion. Reactive fibrosis, on the other hand, occurs in non-ischemic cardiomyopathies, and is more interstitial and perivascular depending on the time of the insult. Models of and triggers to cardiac fibrosis are ischemic injury, pressure/volume overload such as in hypertension or valve disease, inflammation/infection such as occurs with myocarditis, genetic as in cardiomyopathies, aging and after catecholaminergic toxicity as in Takotsubo and possibly epilepsy/SUDEP [19,35,37,39]. There is much going on in fibrotic areas, since fibroblasts transform into myofibroblasts with extracellular matrix production, cross-linking and breakdown by metalloproteinases [39]. Anyway, the presence of fibrosis is related to systolic dysfunction, diastolic dysfunction, arrhythmia and death [38,40–42]. Shanbhag et al. demonstrated in 900 individuals that fibrosis was associated with death and heart failure hospitalization [43]. In that study individuals with non-ischemic patterns of fibrosis had worse outcomes compared to individuals with ischemic patterns, and the former was better than left ventricular ejection fraction to predict outcomes [43].

Takotsubo cardiomyopathy, also known as stress cardiomyopathy, broken heart syndrome or apical ballooning syndrome was first reported in Japan in 1990 [44]. Once believed to be a rare event, it is now well recognized with prevalence estimated in 1–2% of all patients suspected to have acute coronary syndrome [45]. It can be described as a transient (less than 21 days) acute left ventricular systolic and diastolic dysfunction related to emotional or physical stressful triggers [44,45]. Catecholaminergic toxicity and microvascular ischemia are believed to be potential causes. Although myocardial function recovery is expected, recently it has been shown that 74% of patients with prior Takotsubo in the long term develop fatigue, 43% shortness of breath, 8% chest pain and 8% palpitations [46]. Persistent myocardial deformation abnormalities (measured by strain in echocardiographic studies) and lower oxygen consumption (measured as VO2, which is related to fitness) occur in patients with prior Takotsubo [46]. A heart failure-like phenotype has been proposed for such individuals with symptoms and impaired metabolic and structural abnormalities [46].

7. Evidence of myocardial fibrosis in PWE

Although recurrence of Takotsubo is relatively common, occurring in 2 to 4% per year [44], much more common is the aggression on the heart caused by generalized seizures in PWE, possibly due to catecholamine toxicity and ischemia. Recently, Nass et al. have demonstrated that using a more sensitive myocardial damage biomarkers such as high sensitive troponin, 25% of PWE with generalized tonic-clonic seizures have cardiac lesions without clinically apparent symptoms [47].Troponin is released from myocardial cell after ischemic or non-ischemic cell injury [47]. Similar to Takotsubo, catecholaminergic toxicity secondary to seizure activity is one possible mechanism to explain this rise in myocardial injury biomarkers and subtle myocardial injury found in PWE. Acute and gross myocardial dysfunction is the hallmark of Takotsubo but less often found in epilepsy. In PWE, however, chronic and repeated cardiac aggressions secondary to seizures (which are a more frequent event than Takostubo events in an individual patient) could promote cardiac fibrosis and electrical remodeling that could increase one´s risk for lethal events or heart failure-like symptoms.

There is evidence of subtle alterations in myocardial function do to cell injury. Çelik et al. recently have shown abnormalities in myocardial deformation index, despite normal ejection fraction, using myocardial strain analyses by echocardiography in 60 children with epilepsy compared to controls [48]. Myocardial deformation is related to outcomes such as myocardial infarction and atrial fibrillation, and prognosis in patients with heart failure and cancer submitted to chemotherapy [49,50]. It is also related to myocardial fibrosis [49,51]. Fialho et al. demonstrated that PWE have a higher left ventricular stiffness coefficient, which is also related to fibrosis and mortality [36]. These findings on subtle myocardial damage could explain why studies on myocardial oxygen consumption or cardiac fitness in PWE points to lower performance in that group [34,52,53]. Possibly a heart failure-like phenotype occurs in these individuals, similarly to post Takotsubo patients (Fig. 1).

From pathological studies, P-Codrea et al. found signs of myocardial fibrosis in 22 (42%) individuals and myocardial hypertrophy in 11 (21%) among 52 SUDEP patients [54]. Zhuo et al. in 2012 found subendocardial multifocal fibrosis in 6 out of 15 (40%) SUDEP patients versus null in controls [55]. Others found coronary artery disease and cardiomegaly in pathological studies in PWE [56]. Not all studies, however, found higher prevalence in myocardial fibrosis in SUDEP patients, and less is known in non-SUDEP PWE [57]. In a recent article, Raju et al. found that “myocardial histological findings of uncertain significance” labeled by the authors as interstitial and replacement fibrosis, inflammatory infiltrate, myocyte hypertrophy and minor coronary artery plaque, were associated with sudden unexplained death in an unselected population [58].

8. Future directions

Better assessment of myocardial fibrosis is needed, and currently some groups have already taken the first step [39]. The gold standard of *in vivo* myocardial fibrosis assessment is through endomyocardial biopsies. However, even this technique is prone to pitfalls since sampling errors or small tissue fragments can occur.

Circulating biomarkers of fibrosis related to extracellular matrix proteins or cleaved products can be measured in blood samples [39]. However, costs and limited prediction power when adjusted to clinical variables have limited its use. In addition, since fibrosis can occur in extracardiac tissues, the presence of circulating products may not reflect cardiac fibrosis [59]. In heart failure patients, Lopez et al. found that, out of 28 biomarkers of cardiac fibrosis, only C-terminal propeptide of procollagen type I (CITP) and procollagen type III N-terminal propeptide (PIIINP) had correlation with cardiac histological findings [59].

Cardiac imaging is emerging as a tool to both fibrosis assessment and prognosis. Echocardiography is widely available and although classical Doppler and two -dimensional echocardiography gives us little information about subtle ultra-structural cardiac changes, new tools such as global longitudinal strain have been associated with fibrosis [48,60]. Assessment of left ventricle pressure-volume relationship, which demonstrates myocardial stiffness and is related to cardiac fibrosis is also feasible to measure by echocardiography [36,38,40].

Cardiac magnetic resonance imaging (MRI) can distinguish macroscopic (replacement) from microscopic (reactive) fibrosis, using late-gadolinium enhancement (LGE) imaging and T1 mapping [42]. T1 mapping is able to quantify the extracellular volume fraction (ECV) of the myocardium which is related to fibrosis, edema, lipid accumulation and iron and amyloid deposition [39]. Previous studies have shown that for each 3% increase in ECV measured by MRI, there is a 52% increase in death and hospitalization for heart failure [61]. The presence of ischemic or non-ischemic myocardial fibrosis detected by MRI is related to worse outcomes and is independent of prior cardiovascular events, probably reflecting disturbances in heart inflammation, thrombosis and arrhythmogenesis [39,42,62]. We are not aware of studies with cardiac magnetic resonance to investigate fibrosis in PWE.

There is no approved therapy directed at fibrosis. De Boer et al, have recently reviewed this topic [39]. Classic drugs used in cardiology, such as angiotensin-converting enzyme inhibitors and mineralocorticoid receptor antagonists, which are important for reducing mortality in heart failure patients, have some effect in reducing fibrosis, although that is not their primary utility [39,63]. Probably, depending on the trigger, fibrosis can be approached in better ways. For example, considering sympathetic overdrive in autonomic dysfunction, leading to catecholaminergic toxicity, beta-blockers could have a role. That is true for heart failure patients, which also have autonomic dysfunction and benefit from that drug class [63]. Modulation of autonomic dysfunction and, consequently, sympathetic overdrive, could also be achieved with cardiovascular rehabilitation programs and vagal stimulation [63].

9. Conclusion

Initial evidence and biological plausibility point to an interaction between autonomic dysfunction, higher sympathetic drive, myocardial catecholaminergic toxicity and cardiac fibrosis resulting in subtle myocardial changes in structure, function, arrhythmogenesis and/or a heart failure-like phenotype in PWE. This cardiovascular continuum could explain the increased mortality in this group of individuals. Non invasive imaging and biomarkers of cardiac injury and fibrosis are emerging as possible diagnostic tools to better stratify the risk of such individuals.

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Ethical publication statement

We confirm that we have read the Journal´s position on issues

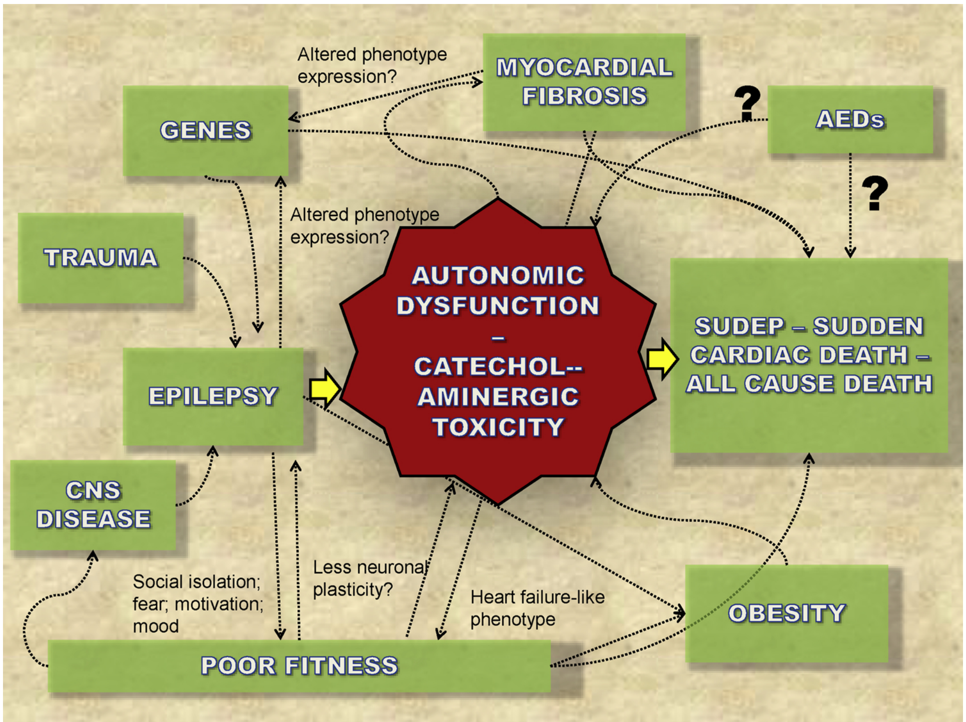

Fig. 1. *Cardiovascular continuum.* Chronic and recurrent adrenergic discharge seen in patients with epilepsy (PWE) could promote changes in the heart, initially in its ultra-structure without gross anatomic alterations. These recurrent aggressions could be part of a *cardiovascular continuum* of autonomic dysfunction, myofilaments lesion, extracellular matrix deposition, inflammation and fibrosis which promotes altered phenotypic ion channel gene expression, myocardial stiffness, heart failure-like symptoms (such as poor fitness), arrhythmogenesis and death. The association between antiepileptic drugs (AEDs), autonomic dysfunction and SUDEP is not entirely known (see text). Poor fitness, demonstrating lower functional reserve is linked to autonomic dysfunction and could be related to a heart failure-like phenotype. Myocardial fibrosis is related to worse cardiovascular outcomes, sudden death and all cause death, as seen in patients with heart failure, cardiomyopathy or ischemic heart disease (and possibly epilepsy). CNS – Central nervous system; AEDs – Antiepileptic drugs.

involved in ethical publication and affirm that this report in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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