Review

Cardiovascular complications of epileptic seizures

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ABSTRACT

Seizure disorders are associated with multisystem complications. Cardiovascular complications account for a significant proportion of morbidity and mortality in these patients. As such, particular attention must be paid to the incidence of cardiovascular complications especially in populations at increased risk. The background for cardiac dysfunction lies in the interplay of genetic/molecular, autonomic, and iatrogenic factors that contribute to its onset.

The purpose of this review was to summarize the state of literature in the last decade with regard to cardiac complications of epileptic seizures in order to increase awareness of short- and long-term debilitating cardiac complications as well as facilitate informed clinical decision-making.

Taken together, the evidence provided in this review suggests that cardiac dysfunction following seizures should not be viewed as a separate entity but as an important complication of epileptic seizures. Appropriate cardiac therapy should be instituted in the postictal medical management of epileptic seizures. In acute states, postictal cardiac troponinemia (elevated cTn) should be worked up. Longer-term, monitoring for the development of cardiac structural and functional abnormalities is prudent.

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1. Introduction

Status epilepticus (SE) is defined clinically or electrographically by the presence of continuous seizure activity at least 5 min in duration or recurrent seizure activity without recovery between seizures [1]. Although SE is a known independent risk factor for mortality [2], cardiac complications confer worse outcomes and increased risk of mortality [3–7]. Cardiovascular disease risk factors, including diabetes mellitus (DM), hypertension, dyslipidemia, and heart failure, are prevalent in patients who suffer from SE [1,8–10] and may determine the chronicity of resulting cardiac complications. However, even in the absence of coronary artery disease, cardiovascular dysfunction is possible [7].

1.1. Background for cardiac complications

The background for cardiac dysfunction lies in the interplay of genetic/molecular, autonomic, metabolic, and iatrogenic components that contribute to its onset. These are not limited to functional changes but include structural alterations as well [11], which appear to be mediated by dysregulation in sympathetic and parasympathetic outflow [7,12].

2. Pathogenesis

Neurohumoral malfunction occurs due to cortical damage from seizure activity with consequent cardiac dysrhythmias and altered vascular tone. In addition, iatrogenic factors (anticonvulsant pharmacokinetics) form the basis of cardiovascular dysfunction observed in patients with epilepsy.

2.1. Vascular alterations

Myocardial infarction and hypertension are observed vascular complications of chronic epilepsy and are the result of neurohumoral hyperstimulation and sympathetic overflow [11]. Hypertension is thought to potentiate a vicious cycle where it is not only a cause/trigger for but the effect of chronic epilepsy [10].

Cardiac troponinemia has been reported in the postictal state [13–17]. It is unclear whether this phenomenon is the result of a cause and effect relationship or merely an association. It appears that in patients with cardiovascular risk factors (smoking, diabetes) the risk of occurrence of myocardial injury/infarction following seizures is increased [13]. Postictal cardiac troponinemia (elevated cTn) should always be worked up for underlying coronary artery disease with the institution of appropriate revascularization therapies.

The ST-segment changes on electrocardiography may be nonspecific or include elevations and depressions, heralding underlying coronary obstruction/spasms as well as stress cardiomyopathy [4,18].

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2.2. Ictal arrhythmogenic myocardium

Autonomic imbalance, arrhythmogenetic mutations, and antiepileptic medications act in concert to increase the risk of arrhythmias in patients with chronic epilepsy. Ictal catecholamine surge is an underlying common mechanism for the development of fatal rhythm disturbances in convulsive epileptic seizures [19], especially in the context of other predisposing factors. It is important to note that myocardial damage is most likely to be seen with chronic, sustained epileptic seizures [10,20].

The insula region is a major player in the regulation of the heart-brain axis [11]. Insular cortical (and other limbic structures) dysregulation has been shown to cause cardiac dysrhythmias with their associated mortality [19,21,22]. Studies have shown that autonomic dysregulation leading to elevated maximum heart rate (HR) as well as decreased HR variability (HRV) is an important risk factor for sudden unexpected death in epilepsy (SUDEP) [6,23]. Decreased HRV is a prognostic indicator for the development of various conduction disturbances including atrial fibrillation [24]. Heart rate increases have been observed in the preictal period and may signal incoming seizure episodes [25]. Sinus tachycardia, QT prolongation, ventricular tachycardia, and ventricular fibrillation, AV nodal conduction disorders, bradyarrhythmia, and asystole are not infrequently encountered in SE [3,26].

Ictal-induced bradycardia (HR < 50 beats/min) and asystole are most frequently observed in seizures of temporal lobe origin. Although its etiology and risk factors are unclear, it is thought to be mediated by activation of key areas of the central autonomic network with subsequent parasympathetic overtone and/or direct postganglionic effect on the heart. Interestingly, ictal bradycardia may represent a homeostatic feedback loop in that the resulting decrease in cerebral perfusion leads to termination of electroencephalographic changes as well as seizure activity, which in turn allows for normalization of the arrhythmia. Surgical and/or medical control of seizures is an important preventive strategy for control of ictal bradyarrhythmias [61]. Symptoms, e.g., syncope, are more likely to be encountered with asystole duration > 6 s [62]. Ictal bradycardia and asystole are rare autonomic findings with a prevalence of less than 1% in monitored settings and 3% in the ambulatory setting [63]. Conversely, ictal tachycardia (HR > 100 beats/min) is the most commonly encountered cardiac autonomic disturbance in epileptic seizures [19,28,64] and manifests as sinus tachycardia (≥80%), ventricular tachycardia, or other fatal tachyarrhythmias. Risk factors include failure of therapy (≥ 3 failed AEDs) and seizure generalization [64,65]. Life-threatening consequences may be observed with longer duration of asystole or progression of tachycardia to fatal arrhythmias; they include falls as well as hypoxic changes (ST-segment depression and T wave inversions on electrocardiogram [ECG]) [64]. Aside from their potential role in SUDEP, the prognostic implications of ictal tachycardia, bradycardia and asystole are yet to be fully determined.

Auerbach and colleagues demonstrated that mutant Na channels, which induce expressivity changes in other ion channels provide an important arrhythmogenic substrate leading to SUDEP [27]. Moreover, chronic epilepsy results in ion channelopathy increasing the risk for arrhythmias [10].

The role of genetics cannot be ignored. Mutations in potassium, calcium, and sodium channels confer increased risk for the development of fatal arrhythmias [26,28]. Similar genetic mutations and polymorphisms lower seizure thresholds in certain individuals by increasing neuronal excitability, and in what seems to be a vicious, seizures lead to alterations in gene transcription and expression [29], including matrix metalloproteinase expression [30]. Interestingly, therefore, it can be tacitly assumed that these ion channel dysfunction in both heart and brain creates a double mechanism that leads to an increased propensity to arrhythmias and seizures. Indeed, this concept has been recognized as a plausible mechanism [28,31]. Moreover, the role of matrix metalloproteinases (MMP) in cardiac fibrosis and arrhythmogenesis has been established [32].

Management considerations should thus take into account all factors contributing to arrhythmias. In certain cases, Na channel blocking antiarrhythmics are contraindicated [33]. These contraindications are discussed in a subsection below (iatrogenic contribution to cardiac complications — The role of anticonvulsant drugs).

2.3. Neurogenic stunned myocardium and takotsubo cardiomyopathy

The development of neurogenic stunned myocardium (NSM) has to do with increased cardiac demand in the absence of coronary artery disease. It is a reversible systolic dysfunction with apical ballooning and hypokinesis that occurs due to the ictal/post-ictal hyperadrenergic cardiotoxicity with resultant myocytolysis [34,35]. With a prevalence approaching 50% among patients with SE, contraction band myocyte necrosis seen in post-mortem studies support the etiology of neurogenic stress cardiomyopathy [3,36]. Age and the simplified acute physiology (SAPS) II score are risk factors for the development of NSM [36]. Management involves positive inotropes to improve cardiac output — intra-aortic balloon pumps may be used for refractory cases [3].

Takotsubo cardiomyopathy (TCM) has also been reported in the postictal state. In a national study conducted by Desai and colleagues, the in-hospital incidence of TCM was found to be 0.1% among patients hospitalized for epilepsy [59]. Other studies report a prevalence of about 1.8% in patients admitted for cerebral seizures [60] and 56% in intensive care admitted patients [36]. The underlying pathomechanism of TCM is similar to NSM, i.e., catecholamine-induced myocardial injury [35,37,38].

Autonomic innervation to the myocardium is accomplished via terminal adrenoceptors, which are coupled to G proteins. Hyperadrenergic discharge results in cyclic AMP-mediated calcium overload (beta-1 receptor), oxygen-derived free radicals, and coronary vascular spasm (alpha-1 receptor) [18,35]. Sinus tachycardia might be the only presenting sign in the setting of decreased cardiac output [39].

2.4. Iatrogenic contribution to cardiac complications — the role of anticonvulsant drugs

It is reasonable to briefly describe the mechanisms involved in seizure initiation and propagation as it relates to current pharmacotherapeutic trends in epilepsy.

Depressed gamma-aminobutyric acid (GABA)–mediated inhibitory neurotransmission together with increased glutaminergic activity, calcium, and sodium channel currents are responsible for increased excitability in epilepsy [40]. For termination of status epilepticus seizures, targeted therapy against sodium channels is achieved with carbamazepine, phenytoin, fosphenytoin, and lacosamide [11]. Na channel blockade is associated with various arrhythmias. In addition, the pharmacokinetic properties of anticonvulsant drugs affect the metabolism of cardiovascular drugs leading to toxicity or requiring dosage adjustments. Some notable interactions are presented in Table 1. This highlights the need for cardiac and neurological assessment in patients with seizures as drug interactions may exacerbate cardiac arrhythmias or provoke seizures (See Tables 2 and 3).

2.4.1. Na channel blockers

Carbamazepine works by blocking Na channels thus slowing depolarization and prolonging the QRS complex (on electrocardiogram) duration. Based on this mechanism, it may act as a proarrhythmic drug [41,42] thus contributing to the risk of SUDEP [42]. In healthy subjects, long-term carbamazepine monotherapy is not associated with rhythm disturbances [42], although sinus tachycardia has been observed in young patients with no history of cardiovascular disease (CVD) [41]. Disorders of conduction are more commonly observed in patients with CVD risk factors and/or taking concomitant negative chronotropic drugs, i.e., beta-blockers, calcium channel blockers [41–43]. Ironically,
Carbamazepine is thought to induce dyslipidemia by inducing cytochrome enzymes albeit with an unclear risk of subsequent CVD [30]. Like carbamazepine, phenytoin may exert proarrhythmic effects as well as increase the incidence of dyslipidemia. Equally concerning is the interaction observed with statin medications. Phenytoin has been shown to decrease the efficacy of statin medications [30]. The overall CVD risk of this interaction remains to be elucidated.

Both phenytoin and carbamazepine portend similar pleiotropic effects by virtue of increased atherosclerotic mechanisms, i.e., carotid intima-media thickness (cIMT), serum uric acid levels, oxidant stress [30]. Carbamazepine and phenytoin harbor clinically relevant pharmacokinetic interactions. As potent inducers of cytochrome p450 enzymes [43,44], they decrease serum concentrations of cardiovascular drugs (antiarrhythmics, such as, amiodarone, mexiletine, disopyramide, antiarrhythmics) [45] thereby requiring dosage adjustment. Phenytoin also decreases serum digoxin concentration by cytochrome enzyme-inducing mechanism [45,46]. It appears that there is no increase in the overall risk of major adverse cardiovascular events (MACE) due to these interactions [44].

Pharmacodynamic interactions between certain antiarrhythmic drugs and anticonvulsant drugs explain the increase in efficacy of anticonvulsants observed when both drug classes are used concomitantly. Propafenone and mexiletine act additively/synergistically to increase the anticonvulsant activity of carbamazepine, valproate, phenobarbital, and phenytoin [47].

There is lack of literature data confirming the effect of oxcarbazepine, ethosuximide, and zonisamide on ECG.

3. Diagnoses

Elevations of cTn (TnI and TnT) usually provide clues to the diagnosis of postictal cardiac pathology. Its absence, however, does not preclude the diagnosis of cardiac dysfunction. Electrocardiographic changes may help establish a diagnosis; thus, telemetry is an important component of postictal cardiac workup [18]. Structural myocardial changes with a decline in ejection fraction are detectable in echocardiographic studies [3].

4. Clinical features

Presenting signs of cardiac dysfunction in postictal SE may not include the usual anginal chest pain or dyspnea [35], rather cardiac arrest or sudden unexpected death may follow convulsive or nonconvulsive status epilepticus.

### Table 1

| Anticonvulsant | Mechanism | Cardiovascular drugs | Effect of Interaction on cardiovascular drug |
|---------------|-----------|----------------------|---------------------------------------------|
| Carbamazepine | Potent CYP450 Inducer | Antianginals: Ivabradine | A decrease in serum concentration of cardiovascular drugs |
|               |           | Antiarrhythmics: amiodarone, mexiletine, disopyramide, quinidine, | |
|               |           | Antihypertensives: alprenolol, metoprolol, propranolol, nifedipine, nisoldipine, felodipine, per os verapamil | |
|               |           | Antihyperlipidemic drugs: atorvastatin, simvastatin | |
| Phenytoin     | CYP 450 Inducer CYP450 Inducer | Losartan Digoxin | No change |
|               |           | Antiarrhythmics: amiodarone, mexiletine, disopyramide, quinidine | |
|               |           | Antihypertensives: alprenolol, metoprolol, propranolol, nifedipine, nisoldipine, felodipine, per os verapamil | |
|               |           | Antihyperlipidemic drugs: atorvastatin, lovastatin, simvastatin | |
| Phenobarbital | CYP 450 Inducer | Quinidine Nimodipine | Increased then decreased Warfarin activity |
| Valproate     | CYP 450 Inhibitor | | Decreased serum concentration |
| Levetiracetam | CYP 450 Inhibitor | | Increased serum concentration |

| Channel blockers | Antiarrhythmic drug | AED |
|------------------|---------------------|-----|
| Na               | Lidocaine, Mexiletine, Quinidine, Disopyramide, Flecainide | Phenytoin, Carbamazepine, Lamotrigine, Oxcarbazepine, Lacosamide, Valproic acid, Zonisamid, Topiramate, Felbamate Retigabine |
| K                | Amiodarone, d-Sotalol, Dronaderone | |
| Ca               | Verapamil, Nifedipine, Dilatazem | Ethosuximide, Valproic acid, Zonisamid |

[56,57].
seizure disorders \[4,52\]. Other findings include hypotension and pulmonary edema due to decreased cardiac output \[3\].

5. Conclusion

It is clear that the neuro-cardiogenic axis is an important mediator of cardiovascular complications in chronic epilepsy/SE. However, the role of neurocardiogenic axis synergism with other factors cannot be overlooked. There are no large studies investigating the total burden of major adverse cardiovascular events due to isolated chronic epilepsy and/or SE as well as iatrogenic factors. Future work in this field will increase awareness of short- and long-term debilitating cardiac complications as well as facilitate informed clinical decision making and timely introduction of appropriate risk-reducing therapies.

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Declaration of competing interest

The authors declare no conflict of interest.

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