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# Sudden unexplained death in epilepsy: The role of the heart

**S**udden unexplained death in epilepsy (SUDEP) is defined as the sudden, unexpected death of an otherwise healthy person with epilepsy without apparent cause. Death occurs during normal activities and under benign circumstances; it does not arise from trauma, aspiration, or intractable status epilepticus.<sup>1</sup>

SUDEP is most commonly attributed to one of three mechanisms: seizure-induced central apnea, cardiac arrhythmia, and neurogenic pulmonary edema. This review will focus on the potential cardiac causes of SUDEP after providing a brief overview of SUDEP and its other proposed mechanisms.

## ■ RISK FACTORS AND MECHANISMS OF SUDEP

Sudden unexplained death is 24 times more common in patients with epilepsy than in the general population. SUDEP is responsible for 7.5% to 17% of all deaths in epilepsy and has an incidence among adults between 1:500 and 1:1,000.<sup>2,3</sup>

### Factors associated with SUDEP

Because SUDEP is relatively infrequent, research to identify risk factors has focused on cohort and case-control studies. A number of clear associations exist that provide insight into the potential mechanism of SUDEP.

Almost all witnessed cases of SUDEP have occurred in the context of a generalized convulsive seizure.<sup>4</sup> The relative risk of SUDEP is increased in patients with a history of recent generalized tonic-clonic seizures.<sup>5–7</sup> Evidence of uncontrolled epilepsy, demonstrated by continuing convulsive seizures and polytherapy with antiepileptic drugs, is a consistent risk factor for SUDEP in most studies.<sup>7–9</sup> Patients with

epilepsy who are not receiving antiepileptic drugs are at an increased risk of SUDEP.<sup>7</sup> Cessation of seizures after successful epilepsy surgery for drug-resistant epilepsy can normalize or at least significantly reduce the risk of SUDEP.<sup>10–12</sup> Associations have been identified between SUDEP and sleeping or living alone<sup>4,13,14</sup> and having seizures that arise from sleep.<sup>6</sup>

### Pulmonary causes of SUDEP

The majority of seizures, of course, do not result in death. Other cardiorespiratory factors associated with epilepsy or induced by a convulsive seizure must exist to explain the phenomenon of SUDEP. As noted above, pulmonary conditions—central apnea and neurogenic pulmonary edema—are among the mechanisms most frequently implicated in SUDEP cases.

**Central apnea** induced by epileptic activity or occurring in the postictal phase is thought to be the most common cause of SUDEP. In the only animal model of SUDEP, one third of cases died from hypoventilation and had associated pulmonary edema on autopsy.<sup>15,16</sup> In a prospective study of patients in an epilepsy monitoring unit, central apnea lasting at least 10 seconds occurred postictally in 40% of the recorded seizures.<sup>17</sup> Respiratory arrest has been reported in the immediate postictal phase of a complex partial seizure in a healthy 20-year-old woman.<sup>18</sup> The mechanism of seizure-induced apnea may be the inhibition of the brainstem by the brain's own endogenous GABA-ergic seizure-terminating mechanism.<sup>13</sup>

**Acute neurogenic pulmonary edema** can follow severe head injury, subarachnoid hemorrhage, or epileptic seizures. Pulmonary edema is found in many cases of SUDEP at autopsy.<sup>19</sup> A proposed mechanism for seizure-induced neurogenic pulmonary edema is the intense generalized vasoconstriction from the massive seizure-related outpouring of central sympathetic activity, which leads to an increase in pulmonary vascular resistance.<sup>20,21</sup>

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## CARDIAC SUDEP

Fatal arrhythmias are thought to be the mechanism underlying cardiac causes of SUDEP. A prevailing hypothesis is that a lethal cardiac arrhythmia is caused by epilepsy-induced autonomic discharges to the heart.<sup>22</sup> These might occur in a normal heart with no evidence of structural or conduction abnormalities or in a heart with existing myocyte injury secondary to catecholamine excess from prior seizures. The two main potentially lethal arrhythmias implicated in SUDEP are ictal ventricular tachyarrhythmias and ictal bradycardia/asystole.

### Mechanisms of fatal cardiac arrhythmias

Ventricular arrhythmias can be provoked by reentry, abnormal automaticity, and triggered activity due to changes in after-depolarization.<sup>23</sup> These can be seen in patients with left ventricular dysfunction and occur at the border of normal and scarred myocardium.<sup>24,25</sup> Increased sympathetic tone and wall stress, combined with electrolyte disturbances, enhance cardiac arrhythmogenicity.<sup>26</sup>

Ventricular tachyarrhythmias are the cause of sudden cardiac death, and primary prevention of sudden cardiac death has been advocated for patients with ischemic left ventricular dysfunction.<sup>23</sup> Only 5% to 10% of cases of sudden cardiac death occur in patients with no definable structural heart disease.<sup>27</sup> These deaths often can be attributed to primary electrophysiologic abnormalities (eg, Brugada syndrome, long QT syndrome, congenital short QT syndrome, preexcitation syndrome).<sup>28</sup> In children, a familial form of catecholamine-induced ventricular arrhythmia has been described that is caused by a mutation in the cardiac ryanodine receptor gene.<sup>29,30</sup>

Syncopal events may be benign or may be the only warning before an episode causing sudden (cardiac) death.<sup>31</sup> Potentially fatal bradycardic and tachycardic arrhythmias may lead to transient cerebral hypoperfusion and present clinically as syncopal events. Patients with underlying heart disease or an electrophysiologic abnormality associated with ventricular arrhythmias may receive potentially life-saving therapy with an implantable cardioverter defibrillator.<sup>32</sup> Patients with bradycardic syncopal events secondary to sick sinus syndrome or intermittent atrioventricular block may profit from implantation of a pacemaker. However, the most common cause of bradycardia associated with symptomatic cerebral hypoperfusion, vasovagal syncope, has a benign prognosis, and recent studies showed no benefit of pacemaker therapy in patients with vasovagal syn-

cope in terms of event frequency or time to first recurrence.<sup>33–35</sup>

### Anatomy of the cardiovascular autonomic system

The cardiovascular autonomic system consists of an interconnected network throughout the neuraxis (**Figure 1**). At the cortical level, the insula represents the primary viscerosensory cortex, whereas the anterior cingulate gyrus and ventromedial prefrontal cortex constitute the premotor autonomic regions.<sup>36</sup> The central nucleus of the amygdala is involved in mediating the autonomic response to emotions, and the hypothalamus triggers the autonomic response to endocrine stimuli to maintain homeostasis.

**Figure 1** depicts the efferent pathways in detail.<sup>37</sup> The parasympathetic influence on the heart arises primarily from the nucleus ambiguus, decreasing the heart rate predominantly via the right vagus nerve and decreasing atrioventricular conduction and ventricular excitability via the left vagus nerve.<sup>38</sup> As shown in the figure, the sympathetic output receives tonic excitation from the ventrolateral medulla and projects from the intermediolateral cell columns to the cardiac conduction system and ventricle, leading to increased automatism of the sinus node, atrioventricular conduction, and ventricular excitability and contractility.<sup>39</sup>

The figure also depicts the afferent loop of the cardiac autonomic system.<sup>40,41</sup> Visceral sensations are projected to the nucleus tractus solitarius, mediating a variety of medullary reflexes, including the baroreflex. From the nucleus tractus solitarius, the viscerosensory information is relayed via the parabrachial region, either directly or indirectly through the ventrobasal thalamus, to the primary viscerosensitive cortex in the insula.

The balance between cardiac vagal and sympathetic modulation is regulated by two main influences:<sup>42</sup>

- Medullary reflexes triggered by activation of baroreceptors, cardiac receptors, and chemoreceptors
- Descending influences from the cerebral cortex, amygdala, hypothalamus, and periaqueductal gray matter mediating integrated responses to internal and external stressors, in part by affecting the gain of medullary reflexes.

Hughlings Jackson first recognized the unique value of epileptic seizures in localizing brain function and discussed the visceral manifestations of epilepsy.<sup>43</sup> Visceral phenomena are present in most epileptic attacks but are often overshadowed by motor phenomena and loss of awareness.<sup>44</sup> Penfield was able to confirm that such symptoms may result from localized irritation of the cortex and may be precipitated by electrical stimulation of specific regions of the cortex.<sup>45</sup> Seizures that arise from

or spread to areas in the central autonomic network (mainly the insula, cingulate gyrus, amygdala, hypothalamus, and brainstem autonomic centers) can mimic stimulation of autonomic afferents or modify autonomic expression. Central cardiovascular responses related to motivated behavior and emotion may be inappropriately activated during a seizure.<sup>37</sup> Sympathetic responses predominate during most seizures, but any combinations of sympathetic and parasympathetic activation and inhibition may occur simultaneously or sequentially during individual seizures.<sup>46</sup>

### Cardiovascular effects of electrical stimulation

Insight into central localization of autonomic brain function comes largely from lesional and electrical stimulation studies.<sup>47,48</sup> More recently, noninvasive techniques (eg, functional magnetic resonance imaging and positron-emission tomography) have been introduced in the mapping of central autonomic control.<sup>49–52</sup>

In many species the insular cortex seems to play a pivotal role in the integration of interoceptive information and may exert a lateralized influence on cardiovascular autonomic control. Intraoperative stimulation of the left posterior insula elicits a cardioinhibitory response and hypotension, whereas stimulation of the right anterior insula elicits tachycardia and hypertension. Lateralization of parasympathetic activity to the left insula and sympathetic activity to the right insula is supported by some studies of cerebral inactivation during intracarotid amobarbital injection, but results have been controversial.<sup>53–55</sup> Using phasic electrical microstimulation synchronized to the R wave of the electrocardiogram (ECG), a cardiac chronotropic organization was identified in the rat posterior insular cortex.<sup>56</sup> ECG-triggered phasic microstimulation of the rat left posterior insular cortex results in bradyarrhythmia, complete heart block, and asystolic death.<sup>57</sup>

Evidence exists from animal experiments for a synchronization of the cardiac autonomic (sympathetic and vagal) neural discharges with epileptogenic activity. This “lock-step” phenomenon may contribute to the development of cardiac arrhythmias during seizures in epilepsy patients.<sup>58</sup> This is consistent with a study in patients with focal epilepsy that showed that left-sided interictal epileptiform discharges seem to shorten the R-R interval, whereas right-sided discharges seem to prolong the R-R interval, suggesting that interictal epileptiform discharges may influence autonomic control over the cardiac cycle.<sup>59</sup>

### Potential mechanisms of cardiac SUDEP

SUDEP may be related to mechanisms similar to those of sudden cardiac death. During sleep, the heart

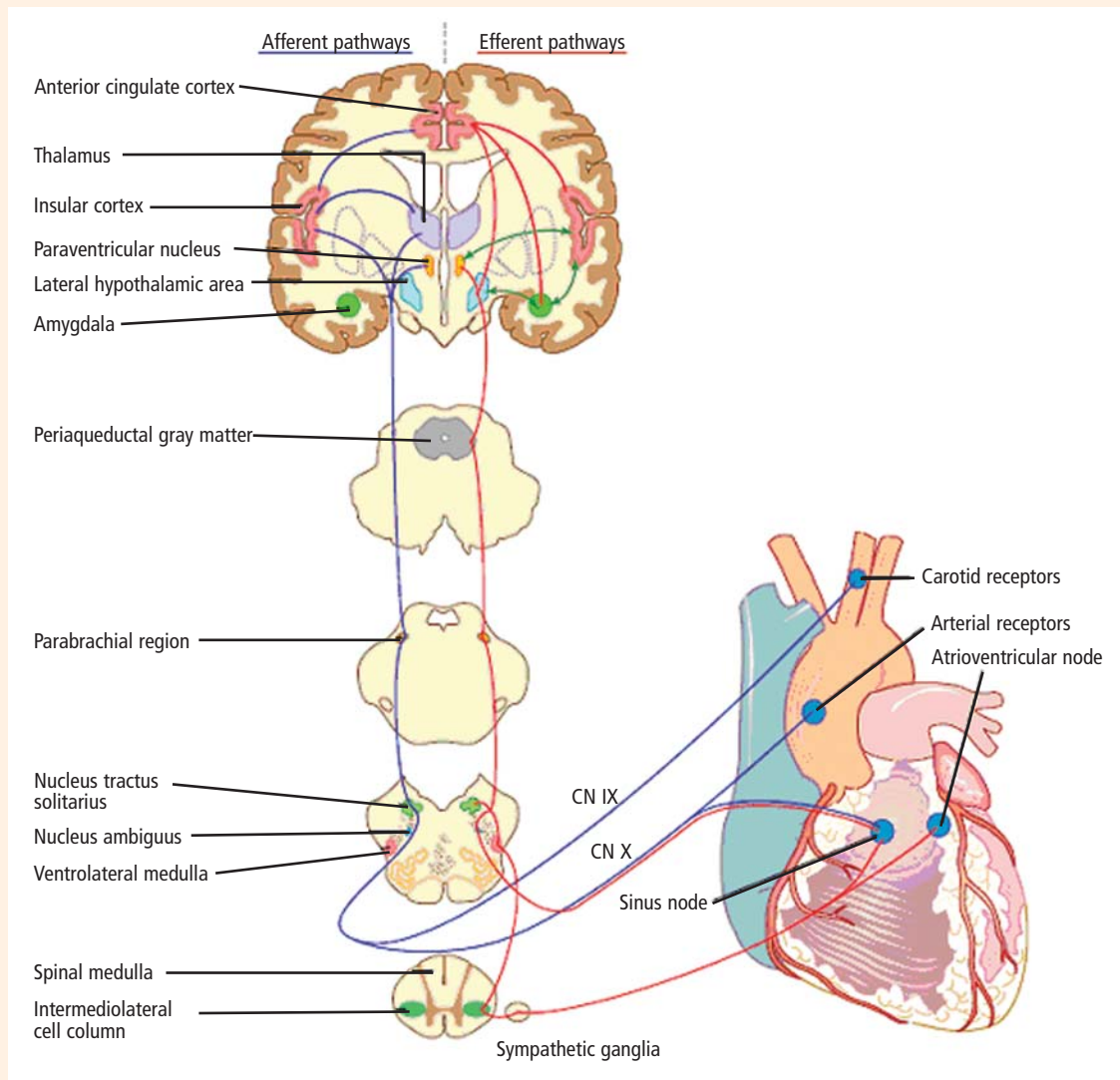
is more susceptible to catecholamines. SUDEP and sudden cardiac death are both associated with a peak incidence in the morning. Vagal tone is increased in sleep; the addition of a massive sympathetic outpouring related to a seizure from sleep in a patient with epilepsy or awakening in a patient with heart disease may precipitate a lethal cardiac arrhythmia.

This view is congruent with a number of studies suggesting that sympathetic-parasympathetic nervous system imbalance may play a role in the generation of ventricular arrhythmias and sudden cardiac death.<sup>26,60,61</sup> Removal of the epileptic focus through epilepsy surgery can reduce the excess sympathetic response<sup>22</sup> and may reduce mortality.<sup>12</sup> However, most of the evidence linking SUDEP with cardiac etiology is indirect, and the one monitored patient who died in intractable ventricular fibrillation during a seizure possibly suffered a coincident myocardial infarction.<sup>62</sup>

Autonomic modulation is altered in patients with epilepsy, with parasympathetic and sympathetic cardiovascular responses being diminished and more variable.<sup>63–65</sup> Abnormal heart rate variability is more pronounced during sleep and during interictal discharges.<sup>59,66</sup> Patients with refractory temporal lobe epilepsy show greater cardiovascular dysfunction than do those with well-controlled temporal lobe epilepsy,<sup>67,68</sup> which parallels the relative risk for SUDEP (ie, greater cardiovascular dysfunction in refractory epilepsy). A short-term (< 2 years) cohort study of the incidence of SUDEP in patients treated with vagal nerve stimulation found no evidence for a significant effect of vagal nerve stimulation on SUDEP.<sup>69,70</sup>

Increased QT intervals have been reported during epileptic discharges on electroencephalography (EEG) in animal models and in recordings of epilepsy patients with SUDEP compared with those without SUDEP.<sup>71,72</sup> Anecdotal evidence suggests that electrophysiologic abnormalities such as Brugada syndrome may play a role in patients with SUDEP.<sup>73</sup> ST-segment depression during or just after a seizure was described in 40% of patients in one series.<sup>74</sup> However, the incidence of ST changes was not increased in patients who later died of SUDEP compared with control patients who had similar seizures,<sup>75</sup> and cardiac troponin levels were not elevated after monitored epileptic seizures.<sup>76</sup>

Evidence for autonomic dysfunction in patients with SUDEP was provided by a study of ECG and EEG data from monitoring unit evaluations of SUDEP patients compared with non-SUDEP epilepsy controls.<sup>75</sup> Patients who had died of SUDEP displayed a significantly higher maximal ictal heart rate change.



**FIGURE 1.** The cardiovascular autonomic system. **Afferent pathways (violet):** The afferent loop of the cardiac autonomic system receives input from chemoreceptors and baroreceptors in the carotid sinus (cranial nerve [CN] IX) and the aortic arch (CN X). The incoming visceral sensations are projected via lamina I of the spinal cord to the nucleus tractus solitarius and from there via the parabrachial region to the primary viscerosensitive cortex located in the insula. **Efferent pathways (red):** The anterior cingulate and orbitofrontal cortex send projections to the hypothalamus and amygdala, but also to the autonomic centers within the brainstem: the periaqueductal gray matter, parabrachial nucleus, nucleus tractus solitarius, nucleus ambiguus, and rostral ventrolateral medulla. The parasympathetic influence on the heart arises primarily from the nucleus ambiguus. The sympathetic output receives tonic excitation from the ventrolateral medulla and projects from the intermediolateral cell columns to the cardiac conduction system and ventricle. **Integrated response to emotion and stress (green):** The amygdala has reciprocal connections with the cerebral cortex and mediates autonomic response to emotions via projections to the hypothalamus and brainstem. The paraventricular nucleus of the hypothalamus controls internal homeostasis and innervates the autonomic relay centers in the rostral ventrolateral medulla, nucleus tractus solitarius, parabrachial nucleus, and preganglionic vagal and sympathetic neurons. Modified from reference 37.

The heart rate increase was most pronounced in seizures that arose from sleep. However, ictal cardiac repolarization and rhythm abnormalities occurred at a similar frequency in the two groups (56% vs 39%,  $P = .39$ ).

Ictal cardiac bradycardia and ictal asystole occur infrequently with seizures, and the possibility that they may be related to SUDEP has been proposed.<sup>77</sup> Ictal bradycardia occurs in fewer than 2% of seizures,

mostly those of temporal and occasional frontal lobe origin.<sup>78–83</sup> Rocamora et al reported ictal cardiac asystole, lasting as long as 60 seconds, in 5 of 1,244 monitored patients.<sup>84</sup> Ictal bradycardia and asystole can occur as a primary ictal event or secondary to apnea.<sup>17,18,84</sup> Ictal bradycardia seems to be of localizing rather than lateralizing value, suggesting temporal lobe onset in patients with partial epilepsy.<sup>83</sup> Ictal bradycardia is probably underdiagnosed, as diagnosis

requires the fortuitous occurrence of a clinical event during a combined EEG/ECG recording. In a recent study in which patients were monitored with long-loop ECG over several months, significant bradycardia/asystole (prompting cardiac pacemaker insertion) was noted in 4 (21%) of 19 epilepsy patients.<sup>85</sup>

Various electrophysiologic mechanisms seem to be related to bradycardic arrhythmias during epileptic seizures: the majority of case reports describe a progressive deceleration of heart rate leading into asystole. A few cases of high-grade atrioventricular block have been described, and in one case the atrioventricular block was triggered by epileptic seizure activity limited to the left temporal lobe.<sup>80,86</sup> However, direct evidence linking bradycardic arrhythmias to SUDEP is still lacking.<sup>87</sup>

In an autopsy study, increased levels of deep and subendocardial fibrosis were observed in SUDEP patients compared with controls, which may reflect the result of repetitive sympathetic activation or recurrent hypoxemia from seizures.<sup>88</sup> Subsequent scarring and interstitial fibrosis may lead to discontinuous propagation and dispersion of cardiac conduction, and may predispose to malignant tachyarrhythmias.<sup>88</sup> Other studies have demonstrated microscopic evidence of cardiac disease in SUDEP patients.<sup>89,90</sup> However, cardiac troponin levels are not elevated after seizures, and it has not been proven directly that myocardial damage occurs during seizures.<sup>91</sup>

## ■ PREVENTION OF SUDEP

Optimal control of seizures through compliance with antiepileptic drug therapy or epilepsy surgery is of paramount importance in preventing SUDEP. Early and successful epilepsy surgery for drug-resistant epilepsy may significantly reduce the risk of SUDEP.<sup>10-12</sup> In patients with refractory epilepsy, noncardiac causes for SUDEP remain difficult to prevent, and measures are currently limited to optimizing positioning and supervision during the ictal event to ensure adequate respiration. For patients at risk, observation or sound monitoring during the night might detect nocturnal seizures and reduce the risk of SUDEP.

There is increasing hope that cardiac cases of SUDEP may be preventable, at least in part, through the use of medical therapy to block the massive central sympathetic surge during ictal events. Alternatively, implantable loop recorders offer the possibility of detecting patients with ictal bradycardia/asystole, who might then benefit from insertion of a permanent pacemaker. However, so far there is only circumstantial evidence linking

ictal bradycardia and asystole to SUDEP, and there is also no proof that the implantation of pacemakers will prevent SUDEP.

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