Review article

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The insula lobe and sudden unexpected death in epilepsy: a hypothesis

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ABSTRACT – Sudden unexpected death in epilepsy (SUDEP) is a major cause of death in patients with refractory epilepsy, particularly those with chronic epilepsy. The physiopathological mechanisms underlying SUDEP have not been elucidated. Autonomic dysregulation of cardiac or respiratory function is thought to underlie SUDEP. Here, we present a summary of available evidence on the involvement of the insular lobe in the regulation of cardiorespiratory function. Ictal discharge that originates in the cortex can, primarily or secondarily, involve the insula lobe through epileptogenic signal networks, leading to cardiorespiratory dysfunction, central apnoea, arrhythmias, and sudden death in patients with epilepsy. Thus, the insula lobe appears to be instrumental in the causation of SUDEP.

Key words: sudden unexpected death, SUDEP, epilepsy, insula lobe

Sudden unexpected death in epilepsy (SUDEP) is a major cause of death in patients with refractory epilepsy, particularly those with chronic cases (Devinsky, 2011). Over 17% of all patients with epilepsy and about 50% of all patients with chronic refractory epilepsy are known to succumb to SUDEP (Sowers *et al*., 2013). As a major hazard for patients with epilepsy (Xu *et al*., 2015), SUDEP has evoked considerable interest in recent years (Beran, 2015). Most of the time, the patient is likely to be healthy and is reported to have unexpectedly died in bed, frequently in a prone position, with a history of recent seizure onset (Sowers *et al*., 2013). The pathophysiology of SUDEP has remained obscure (Miller *et al*., 2014). Autonomic nervous dysfunction and peri-ictal cardiac or respiratory abnormalities have all been postulated as causes of SUDEP (Sowers *et al*., 2013; Malik *et al*., 2015). Certain brain regions are known to regulate respiratory and cardiac function. Anatomical projections that connect the brainstem respiratory and cardiac centres to the temporal lobe have been linked to respiratory arrest and/or cardiac dysfunction (Kaada and Jasper, 1952; Chapman *et al*., 1949). The anatomical and functional evidence of the importance of the insular lobe in regulating autonomic nervous function, including cardiac and respiratory function,

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is well documented (Oppenheimer *et al*., 1992; Cui *et al*., 2012; Oppenheimer, 2006). In this brief review, we summarise the possible mechanisms of involvement of the insular lobe in SUDEP.

Pathophysiology

The following risk factors for SUDEP have been proposed:
– potential genetic susceptibility;
– male gender;
– early age at onset of seizure;
– frequent attacks of epilepsy;
– lying in bed at onset;
– treatment with multiple drugs (Beran, 2015).

More risk factors have increasingly been claimed with the expansion of SUDEP research. Although the evidence base for many of these risk factors is not well-substantiated in the published literature, sudden cardiac arrest and respiratory apnoea are generally considered to be two direct causes of SUDEP (Tomson and Ryvlin, 2008; Surges *et al*., 2010; Nashef *et al*., 2012). Similar findings were also shown in a recent summary by Pansani *et al*. who outlined different experimental models of SUDEP in search of the underlying mechanisms. They reported that respiratory and cardiovascular impairment is more widespread based on animal models of SUDEP (Pansani *et al*., 2016).

Patients with epilepsy often present with arrhythmia and other coexisting cardiovascular rhythm abnormalities, including prolonged QT interval during the seizure attack and shortened QT interval in the postictal phase. In a study involving 26 patients with epilepsy, sudden arrhythmia at the end of the seizure was documented in 42% patients (Duncan and Brodie, 2011). Evidence of sudden asystole in 0.1-0.4% of patients with epilepsy was found by video-EEG monitoring (Rugg-Gunn *et al*., 2004; Schuele, 2009; Devinsky, 2011).

Occurrence of respiratory suppression during a seizure was first reported by Hughlings Jackson in 1899 (Jackson, 1899); the observed phenomenon has since been well-documented (Jackson, 1899; Watanabe *et al*., 1982). For instance, respiratory apnoea occurring at the onset of a seizure episode was documented by concomitant EEG and respiratory monitoring in patients with epilepsy (Nashef *et al*., 1996). These aforementioned studies support cardiac asystole and respiratory apnoea as potential direct causes of SUDEP.

The autonomic nervous dysfunction probably plays an important role in SUDEP. Drastic seizure episodes have been shown to cause autonomic dysfunction leading to respiratory apnoea and cardiac dysfunction, resulting in SUDEP (Devinsky, 2011). In addition to cardiac and respiratory dysfunction, as two major direct causes of SUDEP, central nervous system disorders are likely to be the basic cause of SUDEP due to the regulatory control over cardiac and respiratory function (Terra *et al*., 2013).

The nerve fibres originating from the amygdala and the temporal lobe project into the hypothalamus, parabrachial nuclei, locus coeruleus, ventral median pons, and solitary nucleus. Theoretically, a seizure triggered by an ictal discharge in the temporal lobe and insular lobe can potentially impact on the autonomic nervous system. For example, Lathers *et al*. (Lathers *et al*., 1987) identified the lockstep phenomenon in an animal model, with time synchronisation in relation to: discharge from the cerebral cortex, heart anomalies, sympathetic and parasympathetic nerve discharge, changes in cardiac rhythm and heart rate, atrioventricular conduction, and blood pressure changes during interictal phase (Duncan and Brodie, 2011). This phenomenon is thought to be associated with the causation of SUDEP. The proposed underlying mechanisms include:
– an excessive surge in catecholamine levels induced by excessive sympathetic stimulation that may impair cardiac function;
– irregular postganglionic autonomic nerve discharge that causes alteration in heart rate and blood pressure;
– sudden and acute fluctuations in blood pressure that could precipitate cardiac arrhythmias (Lathers *et al*., 2008).

Shorvon and Tomson found evidence of central apnoea occurring frequently in patients with epilepsy, and autonomic disorder can potentially exacerbate this phenomenon (Shorvon and Tomson, 2011). A seizure episode is liable to cause damage to the respiratory centre in the brain stem (Devinsky, 2011). In a mouse model of SUDEP, 5-hydroxytryptamine (5-HT) appeared to be involved in causing apnoea, triggered by the onset of an epileptic episode (Uteshev *et al*., 2010). A subtype of 5-HT receptor in the respiratory centre region appeared to be involved in the regulation of respiratory function. Expression of this subtype receptor was shown to be significantly decreased in an epilepsy mouse model (Uteshev *et al*., 2010).

Nashef *et al*. documented a total of 20 episodes of central apnoea that occurred during a total of 47 seizure episodes (including partial and generalized tonic-clonic seizures) by video-EEG monitoring in a clinical study involving 17 patients with epilepsy (Nashef *et al*., 1996). These experimental and clinical findings appear to implicate central apnoea as another potential mechanism leading to SUDEP, and serve to link cerebral depression and autonomic dysfunction with SUDEP via another mechanism.

Cardiorespiratory regulation by the insula lobe

The insula lobe is an integral part of the limbic system, both structurally and functionally. Anatomically, the insula lobe is deeply located within the cerebral cortex, within the lateral fissure, under the frontal lobe, in the front of the parietal lobe, and on the inner side of the temporal lobe. The insular cortex is widely connected. Its anterior part is connected to the amygdala, orbitofrontal cortex, temporal pole, entorhinal cortex, and anterior cingulate gyrus. Moreover, its posterior part is connected to premotor cortex, first and second somatosensory cortices, superior temporal sulcus, and posterior cingulate gyrus (Almashaikhi *et al*., 2014). Thus, the insula lobe serves as a virtual nerve centre of the brain owing to its complex interlinkage with the surrounding cortex, autonomic nervous system, as well as with the limbic system. The insula lobe performs multiple physiological functions including those involved in body condition monitoring, interoception, integration of thought and emotion, appetite, taste, internal memory, pain mediation, empathy, and language. Additionally, anatomical and functional evidence suggests that the insular lobe is an important cortical region that modulates functioning of the autonomic nervous system (Oppenheimer *et al*., 1992). Its role in regulating respiratory and cardiac function is also well documented (Oppenheimer, 2006; Cui *et al*., 2012).

In the rat, apnoea lasting for 2 to 10 seconds was induced 10 to 30 minutes after electrical stimulation of the insular cortex, which suggests involvement of the insula lobe in respiratory regulation (Cui *et al*., 2012). The association of disorders of the insula lobe with autonomic dysfunction is well-documented. In rats, periodic minor stimulation of the left insula lobe was shown to lead to prolonged QT interval and decreased ST segment concurrent with bradycardia, complete atrioventricular block, ventricular escape rhythm, and asystole (Cui *et al*., 2012). However, when the lesion is confined to the right side of the insula lobe an increase in blood pressure and heart rate, without any alteration in baroreceptor sensitivity, was demonstrated (Cui *et al*., 2012).

In humans, spontaneous breathing is controlled by the corticospinal and corticobulbar tracts. In parallel with corticospinal and corticobulbar tracts, the downward fibre bundles of the insula lobe are also believed to be involved in the control of respiratory activity, especially tension breathing, and this was shown to be affected by the interoception system and autonomic nervous system in the insula lobe (Cui *et al*., 2012; Sun, 2013). In a clinical study, Oppenheimer *et al*. documented frequent bradycardia and decrease in blood pressure after stimulation of the front caudal left insula lobe in patients with refractory epilepsy. Furthermore, stimulation of the same region on the right side caused an increase in heart rate and blood pressure (Oppenheimer, 2006). This strongly suggests the involvement of the right side of the insula lobe in the control of the cardiovascular sympathetic nervous system, and that of the left side in the control of the cardiovascular parasympathetic nervous system.

The role of the insula lobe in SUDEP

Respiratory depression and cardiac arrhythmias are considered as the major direct causes of SUDEP (Sowers *et al*., 2013) and the insula lobe is known to regulate respiratory and cardiac activities. Thus, it is proposed that the insula lobe plays a vital role in SUDEP. Due to its anatomical and functional characteristics, insula lobe-related epilepsy is liable to be misdiagnosed or completely missed in clinical settings. The epilepsy originating from the insula lobe generally transmits to other brain regions through epileptogenic signal networks, with symptoms that are not only similar to those of temporal lobe-related epilepsy but also tend to be easily confused with those of frontal lobe or parietal lobe-related epilepsy (Cukiert *et al.,* 1998; Kriegel *et al*., 2012). Thus, in clinical practice, insula lobe-related epilepsy is often misdiagnosed as temporal or frontal lobe-related epilepsy (Cukiert *et al*., 1998). Conversely, epilepsy originating from the temporal or frontal lobe can also involve the insula lobe.

Silfvenius *et al*. found that in patients with temporal lobe epilepsy, the dissatisfaction rate for surgical outcome was 42.6% after initial temporal cortectomy and subsequent insular cortectomy, whereas the dissatisfaction rate increased to 83.3% after a temporal cortectomy sparing the insular cortex (Silfvenius *et al*., 1964; Isnard *et al*., 2000). About 60% of patients with temporal lobe epilepsy are reported to be resistant to temporal lobectomy, but their seizures were controlled after insula lobectomy (Isnard *et al*., 2000). These results indicate that in patients with temporal lobe epilepsy, the true epileptogenic lesion may lie in the insula lobe, rather than in the temporal lobe. Moreover, in another study, seizure activity in insula lobe epilepsy showed no improvement after temporal lobectomy (Isnard *et al*., 2000). The three-dimensional EEG recording also showed continued propagation of the temporal epilepsy seizure discharge to one or several regions in the insula lobe. Thus, the symptoms of seizure, though often attributed to temporal ictal discharge, may actually relate to the insula lobe (Isnard *et al*., 2000). Studies have shown evidence of structural damage in most patients with insula lobe epilepsy (Ryvlin, 2006; Malak *et al*., 2009; Lacuey *et al*., 2016).

Thus, the insula lobe may play a central role in epileptic seizures.

Isnard *et al*. (2000) summarized the common features of insula lobe epilepsy based on data obtained from direct stimulation of the insula lobe in patients with epilepsy:

– preserved consciousness;

– preictal premonitory symptoms (usually feelings of electrical current and burning limited to the boundary of the mouth);

– paresthesias, abnormal retrosternal pain, abdominal distension, nausea and vomiting, breathing difficulty, oppressed feeling during or prior to the onset of seizures, as well as dysarthria;

– abnormal pharyngeal motor and sensory symptoms, accompanied by the contralateral hand, or hands, scratching the neck at the onset of seizure;

– accompanying contralateral or ipsilateral motor symptoms, such as facial or upper limb spasm, rotation of the head and eyes, and generalized myodystonia (Cui *et al*., 2012; Sun, 2013).

Thus, in patients with insula lobe epilepsy, autonomous nervous dysfunction is remarkable and the signs and symptoms correlate with the anatomical and functional characteristics of the insula lobe. One study confirmed that elimination of coordinate activities in the cardiovascular system and respiratory depression due to insula lobe epilepsy could be deadly (Dasheiff and Dickinson, 1986; Oppenheimer, 2001). As mentioned earlier, autonomic nervous dysfunction and peri-ictal cardiac or respiratory abnormalities appear to be clear causes of SUDEP. Thus, the insula lobe is potentially associated with SUDEP.

In summary, the insula lobe is probably an important part of the brain involved in SUDEP. Ictal discharge originating in the cortex can involve the insula lobe through epileptogenic signal networks, primarily or secondarily leading to cardiac and respiratory dysfunction, central respiratory inhibition and apnoea, arrhythmias, and even sudden death in patients with epilepsy.

Perspectives on SUDEP

The scope of the present study is limited to the influence of the insula lobe on the respiratory and circulatory system. The epilepsies affecting the temporal lobe and frontal lobe may spread to the insula lobe. However, no definitive evidence of involvement of the insula lobe or other brain lobes in the causation of SUDEP is available. Further studies are required to explore the theoretical basis for the prevention and treatment of SUDEP. In addition, clinical monitoring of cardiovascular and respiratory function in patients with intractable temporal lobe epilepsy, frontal lobe epilepsy, and insula lobe epilepsy is likely to help in the early detection of SUDEP. This will facilitate the development of monitoring devices and help improve our understanding of the mechanism underlying SUDEP.

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TEST YOURSELF

(1) In general, which two factors are deemed to be direct causes of SUDEP?

(2) How does the insula lobe function as a nerve centre of the brain, anatomically?

(3) The insula lobe performs multiple physiological functions; which role does it play in relation to SUDEP?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".