

Asystole induced by electrical stimulation of the left cingulate gyrus

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ABSTRACT – The cortical control of the autonomic system may account for the clinical phenomenon of ictal asystole which, in turn, has been speculated to be a potential mechanism for sudden unexpected death in epilepsy (SUDEP). We report an 18-year-old patient with frontal lobe epilepsy who had intracranial electrode placement showing bifrontal seizure-onset. This patient received electrical stimulation to the left cingulate gyrus and developed cardiac asystole within 3 seconds of electrical stimulation. Intracranial monitoring showed epileptiform discharges in the left frontal polar, frontal lateral and interhemispheric electrodes. We suggest that the left cingulate gyrus, as part of the central autonomic network, may mediate bradyarrhythmia through the vagal pathway. There remains the possibility that other brain regions were also involved due to the time lag between asystole and epileptiform discharges, and the lack of intracranial exploration in the mesial temporal and insular regions.

[Published with video sequences]

Key words: cardiac asystole, cingulate gyrus, SUDEP, frontal lobe epilepsy

The cortical representation of the autonomic system has long been investigated through animal and human studies. The limbic structures are thought to be the principal mediators of this function. Penfield and Jasper carried out experiments in humans in the 1950s and showed that stimulation of the cingulate gyrus produced apnoea (Penfield and Jasper 1954). Later on, variation in heart rates elicited by bilateral stimulation of cingulate gyrus was reported (Pool *et al.* 1949). Despite the many electrical stimulation studies in the past (Penfield and Jasper 1954, Pool *et al.* 1949, Oppenheimer *et al.* 1992, van Buren *et al.* 1961, Altenmüller *et al.* 2004),

direct evidence about stimulation of the cingulate cortex remains in short supply. We report a case of asystole during electrical stimulation of the left cingulate gyrus as part of the pre-surgical evaluation of a patient with refractory epilepsy.

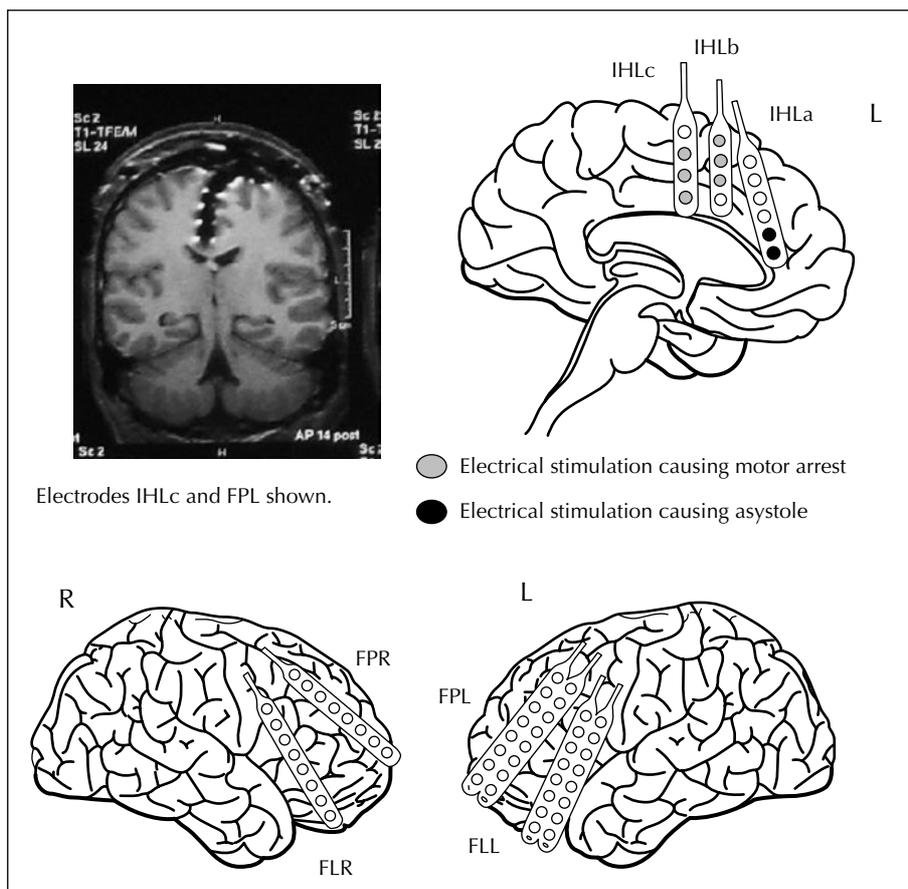
Case report

An 18-year-old man with a history of complex partial seizures since the age of seven was referred to our center for pre-surgical evaluation. During his usual attack, which may occur on a daily basis, he may experience an aura of an “indescribable feeling”, fol-



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Electrodes IHLc and FPL shown.

- Electrical stimulation causing motor arrest
- Electrical stimulation causing asystole

Figure 1. Schematic diagram showing the array of intracranial electrode placement and the stimulation points. On the MRI, interhemispheric electrode IHLc and a small part of FPL was shown.

lowed by staring and motor arrest. In addition, drop attacks occurred about once a month. Secondly generalized seizures also took place between once a month and once every two months. His prenatal history and developmental milestones were unremarkable. There was no history of head trauma, febrile convulsions and family history was unremarkable. He also had no history of any cardiac condition. His baseline electrocardiogram (ECG) and thyroid function were normal. Despite combination antiepileptic drug therapy with lamotrigine, carbamazepine and levetiracetam, his seizure frequency remained unchanged. He was not on any other medication. Scalp electroencephalogram (EEG) showed focal slow waves and interictal discharges in bifrontal regions. Video EEG showed only bifrontal onset of epileptiform discharges during an epileptic event. High resolution magnetic resonance imaging (MRI) of the brain did not reveal a definite lesion, although the question of cortical dysplasia over the left frontolateral area was raised. A Wada test showed left hemisphere language lateralisation. Due to the non-concordant EEG results, subdural electrodes were inserted at the left frontal polar (FPL), left frontal lateral

(FLL), right frontal polar (FPR), right frontal lateral (FLR) areas. In addition, left interhemispheric electrodes (IHLa-c) covering the superior frontal gyrus, paracentral lobule and cingulate gyrus were implanted (*figure 1*). Monitoring with intracranial electrodes captured nine seizures originating simultaneously from the bilateral frontal polar and lateral electrodes, five seizures from the left frontal polar or lateral electrodes, two seizures from the right frontal polar or lateral electrodes and two seizures from the left interhemispheric electrodes. During the monitoring period, carbamazepine was withheld. No definite arrhythmia was observed during the interictal periods.

Event description (*figures 2, 3*)

On the seventh day of recording, electrical stimulation of the left cingulate gyrus was carried out. Electrical stimulation of electrodes IHLb2-3, 3-4, IHLc 1-2, 2-3 produced motor arrest, suggesting that these areas may correspond to the pre-supplementary motor areas. Electrical stimulation of IHLa 1-2 using 1.0mV 50Hz (pulse width 15ms) for two seconds was given in two trials. In the first trial, no

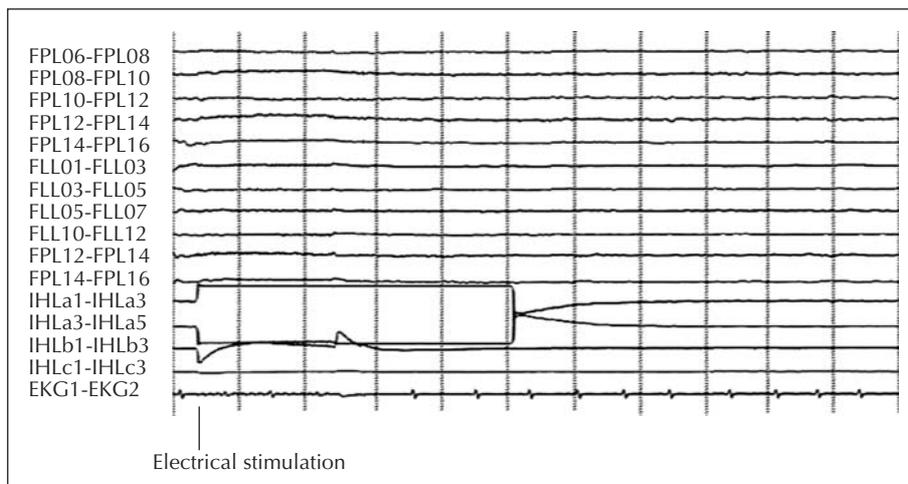


Figure 2. Intracranial EEG recording showing the first trial of electrical stimulation of left cingulate cortex. No electrically-induced seizure was present and the patient remained well.

specific change in clinical or electrical parameters was observed. In the second trial, the patient experienced a typical aura, followed by bradycardia (defined as heart rate < 50 beats per minute or RR interval > 1.2sec) and cardiac asystole (with RR interval up to 4.9 sec). The patient also developed convulsive syncope (see video sequence). The onset of bradycardia was less than three seconds from the moment of stimulation. Epileptiform discharges were later registered at FPL6-8, FPL8-10, FPL10-12, FPL12-14, FPL14-16, FLL1-3, FLL3-5, FLL5-7, FLL10-12, FLL12-14, FLL14-16 and IHLa1-3. The patient recovered consciousness rapidly. The ECG returned to baseline rate after 10 seconds and no other abnormality on the ECG was registered thereafter.

Discussion

The limbic system is often seen as a structure that ties together higher functions with autonomic and motor control to generate integrated behaviour. This cortical control of the heart rate has been shown by many electrical stimulation studies in the past (Penfield and Jasper, 1954, Pool *et al.* 1949, Oppenheimer *et al.* 1992, van Buren *et al.* 1961, Altenmüller *et al.* 2004) with putative roles given to the operculo-insulo-mesiotemporal-orbital pathway (Mufson and Mesulam 1982) and the cingulate cortex (Devinsky *et al.* 1995). According to one study, stimulation of cingulate cortex may produce either tachycardia or bradycardia (Pool *et al.* 1949). Functional MRI studies

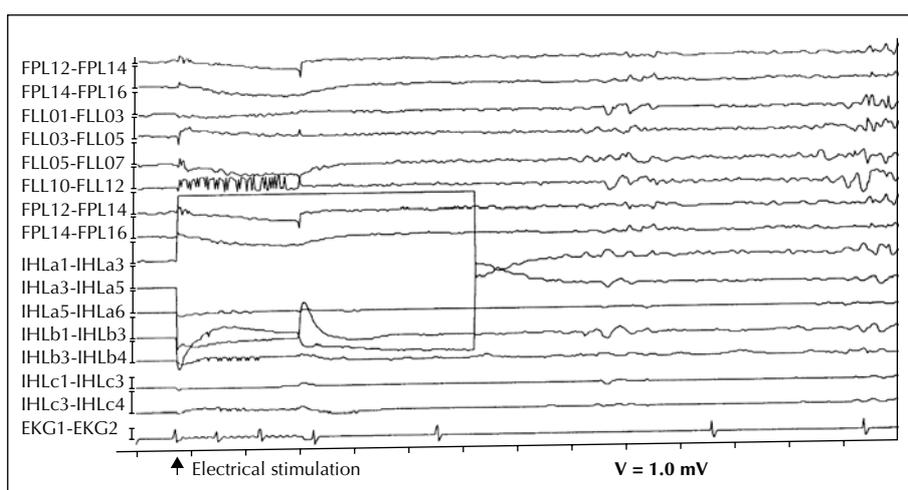


Figure 3. Intracranial EEG recording showing the second trial of electrical stimulation of left cingulate cortex. Stimulation artifacts were seen at FLL10-12, IHLb3-4. Amplifier saturation was seen at IHLa1-5 as these electrodes were switched to the stimulation mode rather than recording mode. Onset of bradycardia (RR > 1.2 sec) occurred approximately three seconds from onset of stimulation. Some epileptiform discharges may be observed later at FLL1-3 on this trace.

demonstrated a relationship between the cingulate gyrus activation and changes in sympathetic activities (Critchley *et al.* 2003) and parasympathetic activities (Matthews *et al.* 2004) respectively.

One review of ictal bradyarrhythmia reported over 60 cases from the literature, although ictal asystole was rarer and only featured in 27 cases (Tinuper *et al.* 2001). A hospital record review of 1244 patient files yielded only five cases of ictal asystole (Rocamora *et al.* 2003). In the largest case series of ictal bradycardia, 13 patients may be identified, once again showing the rarity of such events (Britton 2006). In a prospective study of 20 refractory epilepsy patients, seven patients had ictal bradycardia, and four patients had periods of ictal asystole sufficient to warrant cardiac pacemaker insertion (Rugg-Gunn *et al.* 2004).

There remains the clinical question about the seizure mechanism that underlies such aberrant cardiac manifestation during a seizure. Using data on reviews of ictal bradyarrhythmia, temporal epilepsy is seen more often than frontal epilepsy (Tinuper *et al.* 2001, Mondon *et al.* 2002, Rocamora *et al.* 2003, Britton *et al.* 2006). Using data from available intracranial EEG (Altenmüller *et al.* 2004, Devinsky *et al.* 1997, Rossetti *et al.* 2005, Kahane *et al.* 1999), temporal epilepsy still has a slight preponderance over other types, although very often seizure spreading (such as to the contralateral mesial structure) is observed prior to the bradyarrhythmic episode. Such observations may not reflect the mechanisms of ictal asystole, as temporal epilepsy is usually over-represented in tertiary referral centres. Ictal spread to other mesial regions such as the insular cortex or cingulate cortex, cannot be excluded in those cases, as intracranial electrodes did not cover these areas in most cases.

In our clinical case, we demonstrated the association of cardiac asystole with electrical stimulation of left cingulate cortex. The ictal asystole only occurred in one out of two trials and it was not reproduced afterwards. The fact that some epileptiform discharges were observed in the second trial suggested that the event can be seizure-mediated. We are still far from establishing causality, as there was a time-lag between the onset of asystole and observation of epileptiform discharges and we did not perform intracranial exploration of mesial temporal and insular regions at the time of stimulation or asystole. The observation that a second stimulation within a short time of the first stimulation may produce seizures is in keeping with a previous study (Schindler *et al.* 2006).

Laterality has been a main issue discussed in previous literature (Tinuper *et al.* 2001). Left-sided-onset seizures were more often reported with ictal bradyarrhythmia. Cases with intracranial EEG data also supported this view (Altenmüller *et al.* 2004, Devinsky *et al.* 1997, Rossetti *et al.* 2005), although the cerebral dominance may also need to be taken into account (Kahane *et al.* 1999). The laterality observation prompted investigators to associate the

parasympathetic system activation with the left (or dominant) hemisphere, and indeed this hypothesis can be predicted in one electrical stimulation study (Oppenheimer *et al.* 1992). Oppenheimer found that bradyarrhythmia can be induced by stimulation of the left insular cortex but not the right insular cortex. Our current report is in keeping with the left-right paradigm and the suggestion of the parasympathetic system as the underlying control mechanism.

In our patient, carbamazepine was stopped seven days prior to stimulation and this may help exclude the possibility of a potential cardiac side effect brought about by the drug. However, the evidence for carbamazepine causing arrhythmia is not consistent in the literature (Tomson *et al.* 1998, Kenneback *et al.* 1992). We can find no concomitant cardiac condition in our patient to explain the sudden asystole, although some authors may view an underlying channelopathy as a cause of both the epilepsy and an underlying cardiac condition (Kaneko, *et al.* 2002). There was also no symptom suggesting a vasovagal reaction preceding the onset of stimulation or asystole.

Research focusing on sudden unexpected death in epilepsy (SUDEP) stratified many risk factors (Tomson *et al.* 2005, Tellez-Zenteno *et al.* 2005), and also speculated ictal bradyarrhythmia as one of the possible mechanisms, along with pulmonary oedema and apnoea. Our current report gives evidence towards the cortical control of heart rate on a physiological basis. There remains knowledge gap in the causal inference between these entities. Comparison of the physiological seizure mechanisms in SUDEP patients and in epilepsy patients with ictal bradyarrhythmia may serve as an avenue for more intensive research.

Conclusion

Stimulation of left cingulate gyrus leading to asystole may help confirm the role of the limbic system in causing bradyarrhythmia. A parasympathetic-mediated pathway was thought to be at work. There may be implications for the mechanism of SUDEP, as ictal bradyarrhythmia is also a proposed cause of SUDEP. □

Legend for video sequence

This video segment constituted part of the clinical testing of speech and language functions during electrical stimulation. At onset, the patient was asked to read aloud from a book while electrical stimulation was applied. The first trial was uneventful, but the second trial resulted in the occurrence of a typical aura, followed by asystole and the convulsive syncope described in this report.

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