



Case Report

Ictal asystole during long-term video-EEG; semiology, localization, and intervention



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ABSTRACT

Ictal arrhythmias are disturbances of cardiac conduction that occur during clinical or electrographic seizures. Ictal asystole (IA) is rare, and its incidence can range from 0.3–0.4% in patients with epilepsy who were monitored by video-EEG (van der Lende et al., 2015).

We report on ten patients (six males and four females) with an age ranging from 31 to 70 years old who were monitored in our video-EEG (VEEG) unit over the last eight years. These patients were selected based on the history of documented ictal asystole during inpatient VEEG monitoring. In our series the mean latency from the seizure onset to the onset of ictal asystole was 22 seconds and the mean duration of the IA was 15.8 seconds. During the asystolic phase the seizures may clinically continue or syncopal signs may supervene.

In our case series all the patients had either left or right temporal lobe epilepsy, six of which were lesional. We found two patterns of ictal semiology in our series. The first group of patients included five patients who experienced a rapid onset of IA in their seizure and the second group where the latency of ictal asystole was relatively late. All our cohort had a permanent pacemaker following the diagnosis, six of these patients have been event free since placement.

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1. Introduction

Ictal arrhythmias are cardiac conduction defects that occur in relation to electrographic seizures. These include ictal tachycardia, ictal bradycardia, and ictal asystole (IA). Ictal tachycardia is the most common, occurring in about 80% of patients with epilepsy. Ictal bradycardia is less common (5% of the patients) and ictal asystole is rare amongst epilepsy patients who were monitored by VEEG (0.3–0.4% of the patients) [53].

Widespread use of VEEG has increased awareness of peri-ictal arrhythmias and most cases of IA are diagnosed using VEEG. Often the diagnosis is made incidentally as many patients with habitual seizures may not report symptoms such as syncope, and in some cases may even be asymptomatic. Rarely IA is diagnosed de novo in patients after their first or second seizure. Also, the diagnosis needs to be considered in patients with recurrent syncope and mild ictal symptoms [39].

IA is defined as the absence of a heartbeat for a minimum of three seconds during a recorded seizure [11]. In addition, IA has

been defined as the absence of ventricular complexes for more than 4 seconds associated with electrographic seizure onset [7]. Ictal tachycardia can precede seizure onset and is a useful marker in VEEG recordings. Ictal bradycardia typically occurs after the onset of electrographic seizures and can evolve into IA [11]. Other arrhythmias that have been reported to occur with seizures include ictal bigeminy [38].

There is no clear link between ictal asystole and SUDEP. IA is usually self-terminating and may not increase the risk of SUDEP. Studies are on-going to clarify this risk further [44].

In this case series, we present a retrospective analysis of ten elective vEEG monitoring patients with ictal asystole at our Epilepsy Monitoring Unit (EMU) in Beaumont Hospital.

1.1. Cases

We report ten patients who were monitored in our EMU between 2011 and 2019. During this period the prevalence of IA amongst our cases was 0.6%. The average length of monitoring

was 102 hours. Patient selection was based on the presence of IA reported in Beaumont hospital video EEG databases. We collected patient demographics, seizure semiology, scalp EEG data, and imaging data. Table 2 shows patient demographics and investigation findings. Table 3 shows the semiology of recorded seizures and ictal EEG.

1.2. Clinical features of included patients

Four of our patients were females and six were males. The age of patients ranged from 31 to 70 years old. The earliest age of onset of epilepsy was 11 years and the oldest was 59 years of age. Three of our patients had a family history of epilepsy. Five patients had imaging-negative epilepsy. Of those that had lesions, two patients had mesial-temporal sclerosis; other etiologies of seizures included frontal cavernoma, encephalomalacia from previous head trauma, and postoperative change from a previously resected glioma. All but one patient had a baseline normal electrocardiogram, showing incomplete right bundle branch block (normal variant).

1.3. Seizure semiology

We collected descriptions of seizure from the video record. Descriptions included details of the seizure semiology at onset and progression, lateralizing signs, and postictal state. Ten patients experienced IA. Seizure duration ranged from 25 seconds to 140 seconds with a mean electrographic seizure duration of 65 seconds. The duration of IA ranged from 7 seconds to 25 seconds with a mean of 16 seconds. The latency of IA from the onset of the electrographic seizure ranged from 3 seconds to 63 seconds with a mean latency of 22 seconds. Eight of our ten patients had clinical syncope.

We found two patterns in ictal semiology, dichotomized by the latency between ictal onset and asystole. Five patients experienced a rapid onset of ictal asystole (<30 seconds). The latency of ictal asystole was relatively late (>30 seconds) in the other patients. Both groups of patients had temporal lobe epilepsy.

In the rapid-onset group, the first patient reported a focal aware emotional seizure followed by a focal impaired awareness seizure with motor onset progressed to bilateral tonic-clonic with asymmetric tonic limb posturing “figure of four”. The second patient with early IA had a right temporal onset, characterized by **focal aware seizure - non-motor** (autonomic aura). The third patient had a focal impaired awareness seizure with motor symptoms (left hand automatisms), our fourth patient developed focal impaired awareness seizure with motor symptoms starting with pallor and then slumping to the left with tonic posturing followed by a terminal myoclonic jerk. The last patient in this group also had a focal impaired awareness seizure with motor symptoms starting with clonic jerks of his right shoulder followed by non-verse head turning to the left and right arm extension. Except for the previously mentioned patient, the ictal EEG for all this group’s patients showed a left temporal origin. Two patients with early-onset IA experienced clinical syncope (7 and 8 seconds in duration). The other patients had ictal asystole of 8, 22 and 7 seconds respectively but they did not experience clinical syncope. Patient one with early-onset IA had a right bundle branch block (normal variant) on ECG with otherwise normal cardiac investigations.

Five patients had late-onset of IA defined by asystole that occurs 30 seconds after an electrographic change [30]. All five patients experience clinical syncope as part of their semiology. Patients experienced focal aware seizures with nonmotor symptoms in the form of either autonomic or cognitive auras. One patient had myoclonic jerks after the syncopal phase and three patients had further bilateral tonic-clonic seizures after the syncopal phase.

All patients with IA had a short phase of ictal bradycardia (30 to 40 bpm) before the onset.

Regarding further management all our IA patients had permanent pacemaker following the diagnosis, six of whom have been event free since.

1.4. EEG findings

Interictal epileptiform discharges were recorded in the left temporal region in four patients, right temporal in three patients and bitemporally in the remaining three patients. However, the ictal EEG was more lateralized and localized showing unequivocally ictal discharges over the left temporal region in six patients and four patients had right temporal seizures. EEG suppression was observed during the asystolic phase in six patients.

2. Discussion

We reported ten patients (six males and four females) with an age ranging from 31 to 70 years old who were monitored in our EMU over the last eight years. Patients were selected based on the history of documented IA during inpatient VEEG monitoring.

In our series the mean latency to asystole was 22 seconds and the mean duration of the IA was 15.8 seconds. During the asystolic phase the seizures may clinically continue or syncopal signs may supervene.

IA, in a similar fashion to syncope, may present with falls or drop attacks. The main differentiating features are discussed in (Table 1). A behavioral arrest may occur during the ictus and patients are confused postictally. Cardiac syncope also presents with falls and drop attacks usually preceded by nonspecific symptoms such as nausea, dizziness, palpitations, and confusion [3].

Table 1 showing the main differentiating features between symptoms of IA and cardiac syncope.

In our patients, signs of clinical syncope included loss of awareness, decreased blood pressure, and pallor. Falls resulting in injuries occurred in some of our patients. Syncope invariably had a self-terminating effect on seizure activity in all except one patient.

IA can be classified as early or late-onset. Late-onset IA is defined as asystole that occurs within 30 seconds after the onset of the electrographic seizure [30]. Latency of IA may have lateralizing value, early onset IA was associated with temporal lobe epilepsy; four out of five of our patients with early onset had left temporal

Table 1
Clinical differences between Ictal Asystole and Cardiac Syncope.

	Ictal Asystole	Cardiac Syncope
Sudden drop attacks	Possible	Almost always
Behavioural arrest preceding event	Common	Usually none
Epileptic aura	Frequently	Usually none
Post ictal confusion	Present	Unexpected
Response to Pacemaker insertion	Variable	Favourable outcome
Motor features: A) Tonic-clonic B) Myoclonus C) Tonic Posturing	Usually rhythmic and generalized. Rhythmic, synchronous and may precede loss of consciousness. Common feature.	Arrhythmic, multifocal or generalized but shorter in duration. Usually asynchronous, follow loss of consciousness. Usually none.
Tongue biting	Lateral with tonic-clonic seizures	Rare
Recovery post event	Delayed with postictal confusion	Rapid
EEG	Characteristic ictal features	Normal

Table 2
Characteristics of patients.

Patient	Age	Gender	Age of onset of seizures	Past medical history	ECG	MRI findings
1	70	Female	59	Squamous cell lung cancer and limbic encephalitis	Incomplete right bundle branch block (Normal variant)	Right mesial temporal sclerosis
2	31	Male	18	Undescended testicle repair	Normal	Normal
3	38	Male	55	Non-contributory	Normal	Left frontal cavernoma
4	42	Male	11	Non-contributory	Normal	Left mesial temporal sclerosis
5	38	Female	23	Mayer-Rokitansky-Kuster-Hauser syndrome	Normal	Normal
6	43	Male	30	Tonsillectomy	Normal	Normal
7	37	Female	25	Non-contributory	Normal	Normal
8	44	Male	30	Non-contributory	Normal	Normal
9	39	Male	26	Right temporal lobe glioma	Normal	Post operative changes right temporal lobe
10	60	Female	28	Migraine	Normal	Right encephalomalacia from head trauma

Table 3
Seizures semiology.

Patient	Ictal Semiology	Lateralising signs	Post Ictal symptoms	Syncope	Final localization
1	Focal aware autonomic seizure to bilateral tonic-clonic	Left head version	None	No	Right temporal
2	Focal impaired aware seizure with behavioral arrest evolving to bilateral tonic-clonic	None	Agitation	Yes	Left anterior temporal
3	Focal impaired awareness seizure with automatisms evolving to bilateral tonic-clonic seizure	Post-ictal aphasia	Aphasia	Yes	Left anterior temporal
4	Focal impaired awareness seizure with automatisms evolving to bilateral tonic-clonic seizure	None	Postictal confusion	Yes	Left anterior temporal
5	Focal impaired awareness autonomic seizure	None	Myoclonic Jerks	Yes	Left temporal
6	Focal aware emotional seizure evolving to focal impaired aware seizure with behavior arrest to bilateral tonic-clonic seizure	Figure of four	Postictal confusion	No	Left temporal
7	Focal aware cognitive seizure evolving to focal impaired aware seizure with behavior arrest	None	Postictal confusion	Yes	Left temporal
8	Focal aware emotional seizure evolving to focal impaired awareness motor seizure	None	None	Yes	Right temporal
9	Focal impaired awareness seizure with behavior arrest evolved to bilateral tonic-clonic	Eye version to left	None	Yes	Right temporal
10	Focal impaired awareness seizure with behavioral arrest and automatisms evolving to bilateral tonic-clonic	None	None	No	Right temporal

lobe seizure while the fifth had a right temporal onset. In our study, three patients had ultra-short latency to IA between three and six seconds, and two additional patients had a latency less than 30 seconds. The duration of IA may have localizing value; a longer duration of asystole was found in extra-temporal seizures [10] which was not demonstrated in our cohort.

Monté et al. described the clinical features of ictal bradycardia and IA in a literature review of 174 cases. Patients with IA rather than bradycardia were more likely to have an attenuation of the EEG during the asystolic phase. The duration of IA in most of their cases was not life-threatening (3 seconds to 20 seconds). In another series, the mean duration of time from seizure onset to the onset of IA was 24 seconds, consistent with our series (van der Lende, 2016).

Patients with IA experience loss of muscle tone and myoclonic jerks, and these should not be interpreted as being epileptic phenomena. The EEG typically shows diffuse slowing and attenuation during the asystolic event, due to cerebral hypoperfusion. The mean duration of asystole in a review by Li et al. was 15 seconds and was strongly associated with loss of consciousness while the onset of IA was at least one year from the onset of seizures, and often several years later [22].

In our case series all the patients had either left or right temporal lobe epilepsy, six of which were lesional. We found two pat-

terns of ictal semiology in our series. The first group of patients included five patients who experienced a rapid onset of IA in their seizures and the second group where the latency of ictal asystole was relatively late. Both groups of patients have temporal lobe epilepsy. All our cohort had a permanent pacemaker following the diagnosis, six of these patients have been free from IA events since, which might support the role of permanent pacemaker insertion in patients with IA.

2.1. Risk factors for ictal asystole

Left-sided or frequent focal seizures [37] may be a risk factor for ictal bradyarrhythmias. Other authors have found that right-sided lateralization is more related to ictal tachycardia [35]. New onset of IA was associated with female gender and underlying cardiac comorbidity [10].

2.2. Pathophysiology

Currently, the pathophysiology of ictal bradyarrhythmias is undetermined. There is evidence that patients with epilepsy have dysregulation of autonomic function. Patients with temporal lobe epilepsy, have a faster inter ictal heart rate [51]. Other studies have found abnormalities in heart rate variability (HRV) in patients with

epilepsy [12]. Autonomic dysfunction is more common in patients with right-sided lesional epilepsy compared to left-sided [19]. Cardiac arrhythmias that occur in patients with epilepsy include supraventricular tachycardia, sinus tachycardia, and atrioventricular block [26]. EEG correlation with cardiac electrocorticography has allowed us to localize regions of the brain that regulate the cardiac conduction system [6]. Vagal nerve stimulation (VNS) studies show that stimulation of the vagus nerve has a central effect on reducing seizure frequency [46].

As in our series, ictal asystole is most commonly a feature of temporal lobe epilepsy. Frontal lobe epilepsy is also associated with IA. Autonomic networks for the CNS are diffusely spread and include the amygdala, insular cortex, cingulate gyrus, brainstem and pre-frontal cortex. Subcortical structures that cause bradycardia include the thalamus [36]. What is still unclear is how these autonomic centres integrate together and the role they play in IA. The orbito-insular cortex, amygdala, and hippocampal structures project to the medulla oblongata which controls cardiac function causing bradycardia and asystole. These centres can either be diffusely triggered during the ictus or can be selectively involved. Chronic epilepsy over time can alter how seizures spread to other areas of the brain and these may include autonomic centres resulting in pathologic activity [46].

Human cortical studies have shown that a decrease in the heart rate occurs with electrical stimulation of the left insular cortex [37] and cingulate cortex [18]. Stimulation of the right insula caused bradycardia as compared to the left [37]. Current knowledge indicates that ictal asystole and bradycardia are not a reliable lateralizing sign in epilepsy [49].

In one report of ictal asystole, the authors used stereo-EEG to localize the epileptogenic zone. Depth electrodes were inserted in the left hippocampus, left insula, and left frontal and temporal lobes. Seizures were shown to start at the temporal lobe with rapid propagation to the insula. Stimulation of the left hippocampus resulted in IA lasting 11 seconds after the EEG onset. This was the first study to show that stimulation-induced seizures in humans could cause ictal asystole [15]. Stimulation of the posterior long gyrus of the insula on the left also caused bradycardia.

2.3. Diagnosing ictal asystole

IA should not be diagnosed on clinical grounds alone; it is a clinical-electrophysiological diagnosis [25]. The key to diagnosing IA is to have a high index of suspicion and refer for VEEG monitoring and/or cardiac monitoring. Two scenarios of ictal asystole need to be kept in mind. The first is a cardiac patient with syncope with focal seizures at the onset of syncope. The second is a patient with epilepsy with focal seizures whose syncope is missed as this is thought to be part of the seizure. In both cases, cardiologists and neurologists need to be familiar with these syndromes. One must also be aware of the long QT syndrome and all patients must have a routine ECG.

2.4. Treatment

The treatment of IA needs to be individualized to the patient. Questions that need to be answered are as follows: does ictal asystole pose a significant risk to the patient? If there is drug-resistant epilepsy is epilepsy surgery indicated? The most widely held opinion is that control of seizures is the most important factor. Ten of our cohort had a permanent pacemaker inserted following the diagnosis. This evidence comes from patients who have had a long duration of treated IA with pacemakers and who respond dramatically when antiseizure medication (ASM) is commenced [41].

Many of these patients have tried several ASMs and are presurgical candidates. There is no consensus on which ASM to consider for the treatment of IA. Drugs that have known interaction with the heart include phenytoin, lacosamide, and pregabalin. Lacosamide can induce ventricular tachycardia [50].

ASMs which prolong the QT interval such as lacosamide should be discontinued if IA is diagnosed [33]. Rarely lamotrigine has caused Brugada syndrome if levels reach toxic concentrations [40]. Lamotrigine can also cause a complete heart block in toxic doses [20]. Pregabalin has been reported to cause complete AV block [2]. AEDs that rarely cause bradycardia include clonazepam [16].

There are no guidelines on how long the duration of asystole should be before treatment is considered but most clinicians insert cardiac pacemaker if the duration of IA is six seconds or longer. A meta-analysis calculated the risk of recurrence of ictal asystole as 40% with a confidence interval of 32% to 50% [25], suggesting that the risk of ictal asystole is high and may sway clinicians towards pacemaker insertion. Cardio-neuroablation with parasympathetic denervation of the sinus node can be a new option for these patients and avoids the need for pacemaker insertion [6]. Cardio-neuroablation in one patient resulted in remission of the syncopal episodes and fewer injuries [6]. The authors hypothesized that the asystole was due to cardiac inhibition from central neural circuits and ablating the parasympathetic system would resolve the asystole. A follow-up VEEG with a similar episode of postictal slowing was not accompanied by clinical events. In contrast to a pacemaker insertion, cardio-neuro ablation seeks to diminish the effect of the parasympathetic system on the cardiac conduction system.

There are risks associated with pacemaker insertion, including pneumothorax and infection [54]. Pacemakers prevent the asystole, but the treatment of epilepsy must continue [13]. Pacemakers can prevent injury that occurs during syncope related falls (s).

3. Conclusion

Our case series report identified a similar incidence of IA to what has been previously reported in the literature, 0.3–0.4 % in patients with epilepsy who were monitored by video EEG [53]. All the patients had either left or right temporal lobe epilepsy, six of which were lesional. We did not identify any specific lateralizing distinction with IA. We however, observed two distinctive patterns in ictal semiology. The first group included five patients who experienced a rapid onset of IA in their seizure and the second group where the latency of ictal asystole was relatively late. Both groups of patients have temporal lobe epilepsy with rapid onset more likely to be left sided (four out of five). The manifestation of syncope was more likely present in the late onset group. All our cohort had a permanent pacemaker following the diagnosis, six of these patients reported no further syncope to date reducing the risk of falls and injuries which were prominent features in two of our patients.

Ethical approval

Ethical approval was not needed for this study as it is a retrospective study, and no patient information were included. This study was waived from the ethical issues.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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