Ictal Asystole and Ictal Syncope: Insights into Clinical Management

Running title: Bestawros et al.; Ictal Aystole & Ictal Syncope

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Abstract:

Background - Ictal asystole is a rare, serious, and often treatable cause of syncope. There are currently limited data to guide management. Characterization of ictal syncope predictors may aid in the selection of high-risk patients for treatments such as pacemakers.

Methods and Results - We searched our epilepsy monitoring unit database from October 2003 through July 2013 for all patients with ictal asystole events. Clinical, EEG, and ECG data for each of their seizures were examined for their relationships with ictal syncope events. In 10 patients with ictal asystole, we observed 76 clinical seizures with 26 ictal asystole episodes, 15 of which led to syncope. No seizure with asystole duration ≤6 seconds led to syncope, while 94% (15/16) of seizures with asystole duration >6 seconds led to syncope (P=0.02). During ictal asystole events, 4 patients had left temporal seizure onset, 4 patients had right temporal seizure onset, and 2 patients had both. Syncope was more common with left temporal (40%) than right temporal seizures (10%; P=0.002). Treatment options included anti-epileptic drug changes, epilepsy surgery, and/or pacemaker implantation. Eight patients received pacemakers. During follow-up of 72±95 months, all patients remained syncope-free.

Conclusions - Ictal asystole >6 seconds is strongly associated with ictal syncope. Ictal syncope is more common in left than right temporal seizures. A permanent pacemaker should be considered in patients with ictal syncope if they are not considered good candidates for epilepsy surgery.

Key words: syncope (fainting), cerebrovascular circulation, autonomic nervous system, pacemaker, seizures
Introduction

Determining the etiology of a transient loss of consciousness (TLOC) spell can be quite challenging for a clinician. These patients often present to a cardiologist with a diagnosis of syncope, which is defined by the European Society of Cardiology as a TLOC due to transient global cerebral hypoperfusion with “rapid onset, short duration, and spontaneous recovery.” However, a concurrent diagnosis of epilepsy expands the differential diagnosis. In such patients, clinical uncertainty may persist as to whether their TLOC is due to seizures, syncope, or both.

Ictal asystole, or seizure-induced asystole, is a rare but potentially serious and treatable cause of TLOC. Ictal asystole can lead to traumatic falls and is hypothesized as one of several potential mechanisms of sudden unexpected death in epilepsy (SUDEP), which is the most common cause of death in longstanding uncontrolled epilepsy. Due to the presentation of syncope or asystole, patients with ictal asystole will often be seen by a cardiologist for evaluation and management.

Ictal asystole can be difficult to diagnose, due to both its under-recognition and its appearance only during seizures. Although the optimal treatment is not currently known, the cardiologist must still determine whether a pacemaker will prevent syncope. In this retrospective study, we examined whether clinical data collected during inpatient video EEG/ECG monitoring in an epilepsy monitoring unit may identify patients at higher risk for syncope who may benefit from a pacemaker.

Methods

We searched our epilepsy monitoring unit (EMU) database from October 2003 through July 2013 using the terms: syncope, bradycardia, and asystole. All results were reviewed to identify episodes of ictal asystole. Asystole was defined as RR interval >3 sec and >2-fold lengthening...
over the prior RR interval. Syncope was identified on video monitoring as loss of tone and collapse that followed shortly after the onset of asystole. Patient characteristics, seizure descriptions, video EEG data, ECG data, treatment plan, and follow-up data were assessed.

Video EEG/ECG data included seizure latency (years from diagnosis with seizures to onset of ictal asystole episodes), number of subclinical and clinical seizures while in the EMU, seizure duration, time from seizure onset to onset of asystole (asystole latency), time from seizure onset to onset of syncope (syncope latency), asystole duration, syncope duration, and lateralization of seizure onset (Figure 1).

Treatments included changes in antiepileptic drugs, epilepsy surgery, and/or pacemaker implantation.

This retrospective protocol was approved by the Vanderbilt Institutional Review Board with a waiver of consent.

Inpatient Video EEG/ECG Monitoring

All patients were evaluated with complete clinical assessment, and continuous scalp video-EEG recording using the international 10–20 system for electrode placement including supplementary sphenoidal electrodes (inferomesial temporal electrodes) and T1-T2 electrodes (true anterior temporal electrodes). An ECG record was made systematically, and oximetry was monitored when possible. All antiepileptic drugs (AEDs) were withdrawn on the day of admission except carbamazepine and oxcarbazepine that were slowly tapered during investigation. The seizure-onset zone was defined by multimodal information including the initial symptoms and scalp EEG. Lateralization was predominantly determined by EEG ictal discharge.

Statistical Methods

Generalized estimating equation models were used to model the multiple seizures of study
subjects. The Hubert-White sandwich estimator was used for all models. For continuous response measures we used the identity link function and a Gaussian random component. For dichotomous response measures we used a logit link function and a binomial random component. Our model of the effect of syncope on seizures of short duration among seizures with asystole failed to converge due to perfect agreement between lack of syncope and short duration. A sensitivity analysis was performed to obtain an upper bound of the P value associated with this analysis. The relationship between continuous video EEG/ECG variables was assessed by first calculating the mean value for each variable among the seizures of each individual patient then deriving Pearson correlation coefficients for the relationships between these mean values.

Values are reported as mean ± SD unless otherwise noted. Probability values <0.05 were considered statistically significant, and all tests were 2-tailed. Statistical analyses were performed using Stata (version 13, StataCorp LP; College Station, TX). Prism for Windows (version 5.02, GraphPad Software Inc; La Jolla, CA) was used for graphical presentation.

Results

Baseline Patient, ECG, and Seizure Characteristics

We identified 10 patients with a diagnosis of ictal asystole out of 5312 video EEG/ECG studies between October 2003 and July 2013. The cohort was followed for 72 ± 95 months following the diagnosis of ictal asystole. At diagnosis, the patients were 46 ± 18 years old, and 60% were men with a height of 171 ± 12 cm, a weight of 77 ± 7 kg, and a body mass index (BMI) of 26 ± 6 kg/m². Seizure latency was 11 ± 13 years since seizure diagnosis (Table 1). The systolic blood pressure (130±13 mmHg), diastolic blood pressure (75±7 mmHg) and heart rate (72±14 bpm) were normal.

These 10 patients suffered a total of 76 seizures during 3 ± 1 days of video EEG/ECG
monitoring. Most of these seizures (n=56) were clinically apparent, including 26 ictal asystole episodes, of which 15 led to syncope (Table 1). All episodes of asystole were due to sinus arrest. The seizures associated with ictal asystole were all complex partial except for two that were secondarily generalized (one without syncope). Ictal asystole was associated with suppression of EEG activity, whereas generalized seizure activity is associated with ictal discharge. The ictal asystole in association with secondarily generalized seizures was after generalization. Two female patients had ictal asystole without ictal syncope (Table 1). Baseline ECGs were normal with the exception of patient 3, who had an ectopic atrial rhythm at a rate of 61 bpm prior to pacemaker implantation.

The duration of seizures with asystole was 48±35 sec. From the time of seizure onset, asystole latency was 40±52 sec. In the subgroup with syncope, syncope latency was 35±23 sec (Table 1). Asystole duration was 11±9 sec and syncope duration was 23±19 sec (Table 1).

**Seizure Duration Correlations**

Seizure duration positively correlated with asystole latency (r=0.98; P<0.0001), syncope latency (r=0.97, P=0.0001), and syncope duration (r=0.79; P=0.02). Seizure duration was significantly shorter for ictal syncope episodes (35 ± 14 sec) than for all other seizures (61±42 sec; P = 0.005). Among seizures with asystole, seizure duration was shorter with syncope than without  P=0.02). The average duration of seizure in patients with asystole but without syncope was (71±45 sec).

**Asystole Correlations**

Asystole duration was significantly correlated with syncope duration (r=0.94; P=0.0005).

Asystole duration was significantly longer during seizures with syncope (15 ± 11 sec) than during those without (5.0 ± 1.7 sec; P < 0.0005). Of the 16 episodes with asystole duration >6 seconds, 15 (94%) had syncope (Figure 2). The only asystole episode that lasted >6 seconds and
did not result in syncope occurred in a patient who had another ictal asystole episode that lasted one second longer and resulted in syncope. There were 16 seizures with asystole, 10 of which lasted ≤ 6 sec. No syncope occurred in these 10 seizures (P<0.0005; Figure 2).

Among patients with syncope, asystole latency correlated with syncope latency (r=0.96; P=0.0003) and syncope duration (r=0.87; P=0.005). There was a non-significant trend to shorter asystole latency during ictal syncope episodes (26±16 sec) than in episodes without syncope (60±75 sec; P=0.16).

**Lateralization Correlations**

Most seizures were right-sided (51/76; 67%). However, laterality did not significantly affect the occurrence of asystole or syncope events. Left-sided seizure onset was slightly more common in ictal asystole events (14/26; 54%, P = 0.09) and ictal syncope events (10/15; 67%, P = 0.19). Left vs. right lateralization was not related with asystole duration (10.4 vs. 10.7 sec; P=0.74) or syncope duration (19 vs. 29 sec; P=0.49).

**Therapy and Follow-Up (Figure 3)**

Individual patient follow-up data is presented in Table 2, with a summary schematic in Figure 3. Ictal syncope occurred in 8 of our 10 patients with ictal asystole. Both patients who had ictal asystole without syncope had maximal asystole duration of 4 sec. One had changes made to her antiepileptic drugs and a dual-chamber pacemaker implanted, and at follow-up, she had further seizures without syncope. The other has had no treatment changes because she is awaiting epilepsy surgery. During 3 months of follow-up, she has not had any seizures or syncope.

Of the remaining 8 patients, 7 had a dual-chamber pacemaker implanted. The other had epilepsy surgery and antiepileptic medication changes, and he has not had any further seizures or syncope. One of the other 7 that received a dual-chamber pacemaker also had epilepsy surgery.
without antiepileptic medication changes, and he has had continued seizures without syncope.

The other 6 patients all received a pacemaker and did not have surgery. None of these had further syncope at follow-up. Four patients had antiepileptic medication changes, and 2 of these 4 had further seizures without syncope. The 2 patients without antiepileptic medication changes remain both seizure-free and syncope-free.

Regarding pacemaker therapy, 8 of our 10 patients received pacemakers. Of the 2 patients who did not receive a pacemaker, 1 patient has undergone successful epilepsy surgery, and the other patient is awaiting surgery and only had a single ictal asystole event without syncope in follow-up.

During a follow-up of 72 ± 95 months, none of our patients have had further syncope, although 4 patients have had recurrent seizures.

Discussion

In this study, we retrospectively examined clinical characteristics in patients with ictal asystole that may help predict clinical outcomes and aid in therapeutic decision-making. Our results show that asystole duration ≥6 seconds is strongly associated with syncope. Additionally, while most seizures in our patients were right-sided, the left-sided seizures were 4-fold more likely to result in syncope than the right-sided seizures.

Prevalence

Not only is ictal asystole uncommon, but due to its brief and intermittent nature, it is also difficult to diagnose. Of the 5312 patients admitted to our epilepsy monitoring unit, only 10 (0.19%) were diagnosed with ictal asystole. Four large retrospective studies in EEG/ECG-monitored epilepsy patients have similarly found the prevalence of ictal asystole to be 0.25%-0.40% in over 11,000 epilepsy patients, although these retrospective analyses likely
underestimate the true prevalence.\textsuperscript{5-8} Longer term monitoring may lead to increased detection of ictal asystole. In a study of 19 patients with refractory partial seizures who underwent ILR implantation, 7 had ictal bradyarrhythmia.\textsuperscript{9}

Of the 76 seizures observed in our ictal asystole patients, only 26 of these seizures were associated with ictal asystole. Many patients with ictal asystole have recurrent asystolic episodes, but it is important that most seizures in these patients do not appear to result in ictal asystole. Rugg-Gunn et al. similarly found that in ictal syncope patients, 93-95\% of individual seizure episodes will not demonstrate bradyarrhythmia.\textsuperscript{9}

**Patient Characteristics and Presentation**

All of our patients had a long history of epilepsy (11±13 years) and had failed at least 2 antiepileptic medications. Classically, patients with ictal asystole tend to be young with a history of severe and longstanding epilepsy, and patients have typically failed at least 2 antiepileptic medications.\textsuperscript{7,10}

Ghearing et al. have described a “common presentation” of ictal asystole as a sudden loss of tone often associated with brief and non-rhythmic bilateral upper extremity myoclonus or posturing.\textsuperscript{11} This sudden loss of tone was seen in all of our patients. Another series of 16 episodes of ictal asystole noted that 8 episodes demonstrated sudden atonia, 6 were the same as previous seizures, and 2 were associated with generalized tonic-clonic seizures.\textsuperscript{7} Both these studies, and our experience, emphasize that the diagnosis of ictal asystole cannot be made based on a detailed history alone.

**ECG and Seizure Characteristics**

Our patients’ ECGs at baseline showed no significant bradycardia and were of no predictive value. Holter monitoring might have provided a longer window, but these data were not reliably
available. During their ictal asystole episodes, all of our patients demonstrated temporal lobe ictal discharge followed by a gradual sinus rate slowing with eventual sinus pause, suggestive of an increase in vagal tone after seizure onset (Figure 4). This common pattern has partially led mechanistic hypotheses that include direct vagal stimulation of the conduction system versus an uncoordinated autonomic surge.\textsuperscript{12}

In our patients, all episodes could be localized to the temporal lobes, but roughly half of ictal asystole events and two-thirds of ictal syncope events were left-sided. Historically, ictal asystole was thought to occur due to left-sided temporal lobe seizures that led to increased vagal tone, but this left-sided lateralization hypothesis is not supported by a prior published series.\textsuperscript{13} In our patients with ictal syncope, left-sided seizures were four times more likely to result in syncope than right-sided ones, suggesting that lateralization may have some prognostic significance.

In our search for predictors of syncope in ictal asystole patients, we examined the relationship between syncope and seizure duration, asystole latency, and asystole duration. Seizure duration and asystole latency were not useful in predicting outcomes between ictal asystole episodes with and without syncope.

**Asystole Duration and Syncope**

Asystole duration was highly correlated with syncope during asystolic episodes. Of the 26 ictal asystole episodes in our 10 patients, syncope was not observed when asystole duration was $\leq$6 seconds. In contrast, 94\% of asystolic episodes $>$6 seconds led to syncope. These data are consistent with the Red Wing Study, which found that the “average time from arrest of cerebral circulation to loss of consciousness” was 6.8 seconds, with all of their subjects requiring at least 5 sec of loss of cerebral blood flow prior to TLOC.\textsuperscript{14} Nguyen-Michel et al. similarly reported
that ictal asystole duration was longer in patients with hypoperfusion changes on EEG.15

Treatment of Ictal Asystole

Many therapeutic approaches to ictal asystole exist, including adjustment of antiepileptic medications, epilepsy surgery for medically refractory patients, and pacemaker implantation. Our data suggest that pacemaker therapy is an effective treatment for ictal syncope. Of the 8 patients who received a pacemaker, 4 continued to have seizures, but none have had further syncope.

Ictal asystole without syncope may not require a pacemaker, especially if epilepsy surgery is planned. Given that ictal syncope is associated with longer duration of asystole, patients without an asystole episode >6 seconds may not require a pacemaker. Two of our patients did not receive a pacemaker and have not had recurrent syncope. One had epilepsy surgery, and the other is awaiting epilepsy surgery. Antiepileptic medication changes without surgery did not prevent further seizures in 3 of the 5 ictal syncope patients that were treated this way, suggesting that antiepileptic medication changes alone may not be adequate therapy to prevent seizures and possible syncope.

Several investigators have described their approaches to pacemaker therapy. Although no follow-up data was presented, 4 case series describe a total of 18 ictal asystole patients, of which 14 received a pacemaker, 1 refused a pacemaker, and the others were followed by cardiology.6-8,12 Another series of 7 ictal asystole patients with falls reported that 6 were fall-free after pacemaker implantation.11 In a study of 16 ictal bradyarrhythmia patients (10 with seizure-related falls or injuries), 7 became fall-free with either changes in their medications or with epilepsy surgery, 7 patients required a pacemaker to achieve the same results, and 2 patients refused both surgery and pacemaker implantation and continued to have seizures and falls.5
Recommendations

The diagnosis of ictal asystole can be challenging unless the clinician suspects it or it is captured on video-EEG/ECG monitoring. In drug-refractory epilepsy patients with multiple risk factors for SUDEP and/or a history of traumatic falls, the diagnosis of ictal asystole should be considered. If these patients have a negative video-EEG/ECG, the longer monitoring window of an implantable loop recorder can make it a useful tool in the diagnosis of ictal asystole. Thus long-term implantable loop recorder implantation or insertable cardiac monitoring to capture asystole following seizure-related motion artifact may be considered.

Upon diagnosis of ictal asystole, evidence suggests that some patients benefit from pacemaker implantation, while others will remain seizure- and fall-free with further epilepsy treatment. Epilepsy surgery may be more effective in preventing further seizures than antiepileptic medication changes alone.

It is our clinical recommendation that asystole duration be used to guide pacemaker implantation decisions when epilepsy surgery is not a therapeutic option. In all situations, if the condition continues, is severe, or is associated with marked asystole, then pacemaker implantation should be strongly considered.

Limitations

Our study had several limitations. First, as a retrospective study, the investigators have less control over measurements and increased risks for confounding variables. While we made every attempt to identify every ictal asystole patient during our study period, it is possible that there were other ictal systole patients that were not uncovered with our search algorithm. Second, our estimates of prevalence are based on this single-center study in a tertiary care referral center with all diagnoses made by video EEG/ECG. Although as noted above, our prevalence estimates are
similar to results from other centers using video EEG/ECG. More prolonged monitoring or using ILR monitoring might lead to higher estimates, while monitoring in a different clinical setting may lead to lower estimates. Finally, the sample size is small (10 patients). Stronger conclusions could be made from a larger study.

Conclusion

Syncope almost always results in patients with ictal asystole greater than 6 seconds in duration. Pacemaker implantation should be strongly considered in patients for whom epilepsy surgery is not a therapeutic option and whose asystolic duration is $\geq$6 seconds.

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Conflict of Interest Disclosures - None

References:


Table 1: Ictal Asystole Episodes

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<td>Mean</td>
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<td>8±7</td>
<td>6±4</td>
<td></td>
<td>48±35</td>
<td>40±52</td>
<td>11±9</td>
<td>35±23</td>
<td>23±19</td>
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</table>

*See text in Methods section for definition
† N/A refer to spells that did not result in syncope
Table 2: Therapies and Results at Follow-Up

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<th>ID</th>
<th>Change in AEDs</th>
<th>Pacemaker</th>
<th>Epilepsy surgery within 6 months of diagnosis</th>
<th>Further Seizures</th>
<th>Further syncope</th>
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Figure Legends:

Figure 1: Definitions - Asystole latency and syncope latency is the time from seizure onset to the onset of asystole and syncope, respectively. Black bar: seizure duration. Gray bar: asystole duration. White bar: syncope duration.

Figure 2: Asystole Duration - Percentage of asystole events (upper panel) and syncope events
(lower panel) broken down by asystole duration.

**Figure 3:** Patient Treatments - See text in Results section for full explanation.

AED = Anti-epileptic drug, PPM = permanent pacemaker

**Figure 4:** Ictal Asystole - EEG from left and right mesial-basal temporal electrodes (Sp1 and Sp2) and vertex (Cz) and ECG. Preceding bradycardia, one can see focal seizure activity developing at Sp2. After the onset of asystole (1), the ictal discharge propagated to Sp1 (2). Onset of asystole precedes onset of slow EEG activity (3) then attenuation (4) at Cz, while the ictal discharge continues at Sp1 and Sp2.
Ictal Asystole (n=10)

- Syncope (n=8)
  - No PPM, AED changes & Epilepsy Surgery (n=1)
  - PPM (n=7)
    - Epilepsy Surgery & AED changes (n=1)
    - No Epilepsy Surgery (n=6)
      - AED changes (n=4)
      - No AED changes (n=2)

- No Syncope (n=2)
  - AED changes and PPM (n=1)
  - Awaiting Epilepsy Surgery (n=1)
Ictal Asystole and Ictal Syncope: Insights into Clinical Management
Michael Bestawros, Dawood Darbar, Amir Arain, Bassel Abou-Khalil, W. Dale Plummer, William D. Dupont and Satish R. Raj

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Iktální asystolie a iktální synkopa
Náhled do klinické léčby

Michael Bestawros, MD, MPH; Dawood Darbar, MD, PhD; Amir Arain, MD; Bassel Abou-Khalil, MD; Dale Plummer, BS; William D. Dupont, PhD; Satish R. Raj, MD, MSCI

Úvod—Iktální asystolie je vzácná, závažná a často léčitelná příčina synkop. V současné době máme pro její léčbu k dispoziční omezené informace. Charakteristika prediktorů iktální synkopy nám může pomoci vybrat vysoce rizikové pacienty pro léčbu kardiostimulátorem.

Metody a výsledky—V naší databázi monitorovací jednotky pro epileptiky od října 2003 do července 2013 jsme vyhledali všechy pacienty s příhodami iktální asystolie. Informace o klinickém stavu, z vyšetření elektroencefalogramem a EKG každého jejich záchvatu byly zkoumány z hlediska jejich vztahu k příhodě iktální asystolie. U 10 pacientů s iktální asystolií jsme zaznamenali 76 klinických záchvatů s 26 epizodami iktální asystolie, z nichž 15 vedlo k synkopě. Žádný záchvat s asystolií ≤ 6 sekund k synkopě nevedl, zatímco 94% (15/16) záchvatů s asystolií > 6 sekund synkopu zapříčinilo (p = 0,02). Během příhod iktální asystolie vycházel záchvat u 4 pacientů z levého temporálního laloku, u 4 z pravého temporálního laloku a u 2 z obou laloků. Synkopa se častěji vyskytla u záchvatů vycházejících z levého (40%) než z pravého temporálního laloku (10%; p = 0,002). Mezi možnosti léčby patřila změna antiepileptické medikace, chirurgická léčba epilepsie a implantace kardiostimulátoru. Osmi pacientům byl implantován kardiostimulátor. Během následného sledování trvajícího 72 ± 95 měsíců neprodělal synkopu žádný z pacientů.

Závěry—Iktální asystolie > 6 sekund má úzký vztah k iktální synkopě. Iktální synkopa je častější u záchvatů vycházejících z levého než z pravého temporálního laloku. O trvalém kardiostimulátoru by se mělo uvažovat u pacientů, kteří prodělali iktální synkopu, není-li u nich vážně zvažována chirurgická léčba epilepsie. (Circ Arrhythm Electrophysiol. 2015;8:159-164. DOI: 10.1161/CIRCEP.114.001667.)

Klíčová slova: autonomní nervový systém ■ cerebrovaskulární cirkulace ■ srdeční zástava ■ záchvaty ■ synkopa

Editorial k tomuto abstraktu článku naleznete na straně 14