Ictal Asystole and Ictal Syncope
Insights Into Clinical Management

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

**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 to July 2013 for all patients with ictal asystole events. Clinical, electroencephalogram, 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 s led to syncope, whereas 94% (15/16) of seizures with asystole duration >6 s 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 with right temporal seizures (10%; P=0.002). Treatment options included antiepileptic drug changes, epilepsy surgery, and pacemaker implantation. Eight patients received pacemakers. During follow-up of 72±95 months, all patients remained syncope free.

**Conclusions**—Ictal asystole >6 s is strongly associated with ictal syncope. Ictal syncope is more common in left than in right temporal seizures. A permanent pacemaker should be considered in patients with ictal syncope if they are not considered good candidates for epilepsy surgery. *(Circ Arrhythm Electrophysiol. 2015;8:159-164. DOI: 10.1161/CIRCEP.114.001667.)*

**Key Words:** autonomic nervous system ■ cerebrovascular circulation ■ heart arrest ■ seizures ▪ syncope

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Determining the cause of a transient loss of consciousness (TLOC) spell can be 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 because of transient global cerebral hypoperfusion with rapid onset, short duration, and spontaneous recovery.1 However, a concurrent diagnosis of epilepsy expands the differential diagnosis. In such patients, clinical uncertainty may persist as to whether their TLOC is caused by seizures, syncope, or both.

**Editorial see p 11**

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,2 which is the most common cause of death in long-standing uncontrolled epilepsy.3 Because of 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 because of 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-electroencephalogram/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 database from October 2003 to 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 s 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-electroencephalogram data, ECG data, treatment plan, and follow-up data were assessed.

Video-electroencephalogram/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 epilepsy monitoring unit, 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).
WHAT IS KNOWN

- Ictal asystole, or seizure-induced syncope, is a rare and potentially serious cause of transient loss of consciousness that is most frequently seen in drug-refractory epilepsy.
- The ictal focus usually originates in a temporal lobe and occasionally in a frontal lobe.
- Pacemaker implantation is a potentially effective treatment for these patients’ asystolic episodes.

WHAT THE STUDY ADDS

- Asystole duration with a cutoff of 6 s is a predictor of syncope occurrence.
- Left temporal lobe seizures were 4x more likely to lead to syncope than right temporal lobe seizures.
- In patients with a history of ictal syncope, no further episodes of syncope occurred after pacemaker implantation.

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

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

Inpatient Video-Electroencephalogram/ECG Monitoring

All patients were evaluated with complete clinical assessment, and continuous scalp video-electroencephalogram recording using the international 10 to 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 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 electroencephalogram. Lateralization was predominantly determined by electroencephalogram 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. Our model of the effect of syncope on seizures of short duration among seizures with asystole failed to converge because of 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-electroencephalogram/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. P 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 of 5312 video-electroencephalogram/ECG studies between October 2003 and July 2013. The cohort was followed for 72±95 months after the diagnosis of ictal asystole. At diagnosis, the patients were aged 46±18 years, and 60% were men with a height of 171±12 cm, a weight of 77±7 kg, and a body mass index of 26±6 kg/m². Seizure latency was 11±13 years since seizure diagnosis (Table 1). The systolic blood pressure (130±13 mm Hg), diastolic blood pressure (75±7 mm Hg), and heart rate (72±14 beats per minute) were normal.

These 10 patients had total of 76 seizures during 3±1 days of video-electroencephalogram/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 because of sinus arrest. The seizures associated with ictal asystole were all complex partial except for 2 that were secondarily generalized (1 without syncope). Ictal asystole was associated with suppression of electroencephalogram 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 beats per minute before pacemaker implantation.

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

Figure 1. Asystole latency and syncope latency are the time from seizure onset to the onset of asystole and syncope, respectively. Black bar, seizure duration; gray bar, asystole duration; and white bar, syncope duration.
all other seizures (61±42 s; 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 s.

**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 s) than during those without (5.0±1.7 s; P<0.0005). Of the 16 episodes with asystole duration >6 s, 15 (94%) had syncope (Figure 2). The only asystole episode that lasted >6 s and did not result in syncope occurred in a patient who had another ictal asystole episode that lasted 1 s longer and resulted in syncope. There were 16 seizures with asystole, 10 of which lasted ≤6 s. 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 nonsignificant trend to shorter asystole latency during ictal syncope episodes (26±16 s) than in episodes without syncope (60±75 s; 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 versus right lateralization was not related with asystole duration (10.4 versus 10.7 s; P=0.74) or syncope duration (19 versus 29 s; P=0.49).

**Therapy and Follow-Up**

Individual patient follow-up data are presented in Table 2, with a summary schematic shown 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 s. 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 had no treatment changes because she is awaiting epilepsy surgery. During 3 months

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**Table 1. Ictal Asystole Episodes**

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<th>Clinical Seizures in EMU</th>
<th>Seizure Event</th>
<th>Lateralization*</th>
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EMU indicates epilepsy monitoring unit.

*See Methods section of this article for definition.

†N/A refers to spells that did not result in syncope.
of follow-up, she has not had any seizures or syncope (Figure 3).

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 who 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 and syncope free.

### Table 2. Therapies and Results at Follow-Up

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AEDs indicate antiepileptic drugs.

About 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 s is strongly associated with syncope. In addition, although 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 also because of 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 electroencephalogram/ECG-monitored epilepsy patients have similarly found the prevalence of ictal asystole to be 0.25% to 0.40% in >11 000 patients with epilepsy although these retrospective analyses likely underestimate the true prevalence.\(^4\)\(^-\)\(^6\) Long term monitoring may lead to increased detection of ictal asystole. In a study of 19 patients with refractory partial seizures who underwent implantable loop recorder implantation, 7 had ictal bradyarrhythmia.\(^9\)

Of the 76 seizures observed in our patients with ictal asystole, 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 seem to result in ictal asystole. Rugg-Gunn et al\(^9\) similarly found that in patients with ictal syncope, 93%
to 95% of individual seizure episodes will not demonstrate bradyarrhythmia.

**Patient Characteristics and Presentation**

All of our patients had a long history of epilepsy (11±13 years) and had failed ≥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 ≥2 antiepileptic medications.\(^7,^{10}\)

Ghearing et al\(^{11}\) have described a common presentation of ictal asystole as a sudden loss of tone often associated with brief and nonrhythmic bilateral upper extremity myoclonus or posturing. 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.\(^7\) 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.\(^{12}\)

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 because of left-sided temporal lobe seizures that led to increased vagal tone, but this left-sided lateralization hypothesis is not supported by a previous published series.\(^{13}\) In our patients with ictal syncope, left-sided seizures were 4× 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 patients with ictal asystole, 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 ≤6 s. In contrast, 94% of asystolic episodes >6 s 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 s, with all of their subjects requiring ≥5 s of loss of cerebral blood flow before TLOC.\(^{14}\) Nguyen-Michel et al\(^{15}\) similarly reported that ictal asystole duration was longer in patients with hypoperfusion changes on electroencephalogram.

**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 s 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

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**Figure 4.** Ictal asystole: electroencephalogram (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, whereas the ictal discharge continues at Sp1 and Sp2.
other is awaiting epilepsy surgery. Antiepileptic medication changes without surgery did not prevent further seizures in 3 of the 5 ictal syncpe patients who were treated this way, suggesting that antiepileptic medication changes alone may not be adequate therapy to prevent seizures and possible syncpe.

Several investigators have described their approaches to pacemaker therapy. Although no follow-up data were presented, 4 case series describe a total of 18 patients with ictal asystole, of which 14 received a pacemaker, 1 refused a pacemaker, and the others were followed by cardiology.6–8,12 Another series of 7 patients with ictal asystole with falls reported that 6 were fall free after pacemaker implantation.11 In a study of 16 patients with ictal bradyarrhythmia (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-electroencephalogram/ECG monitoring. In patients with drug-refractory epilepsy and multiple risk factors for sudden unexpected death in epilepsy and a history of traumatic falls, the diagnosis of ictal asystole should be considered. If these patients have a negative video-electroencephalogram/ECG, the longer monitoring window of an implantable loop recorder can make it a useful tool in the diagnosis of ictal asystole.15 Thus long-term implantable loop recorder implantation or insertable cardiac monitoring to capture asystole after seizure-related motion artifact may be considered.

On diagnosis of ictal asystole, evidence suggests that some patients benefit from pacemaker implantation, whereas 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.17 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. Although we made every attempt to identify every patient with ictal asystole during our study period, it is possible that there were other patients with ictal systole who 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-electroencephalogram/ECG. Although as noted above, our prevalence estimates are similar to results from other centers using video-electroencephalogram/ECG. More prolonged monitoring or using implantable loop recorder 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.

Conclusions

Syncpe almost always results in patients with ictal asystole >6 s in duration. Pacemaker implantation should be strongly considered in patients for whom epilepsy surgery is not a therapeutic option and whose asystolic duration is ≥6 s.

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Disclosures

None.

References

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Michael Bestawros, Dawood Darbar, Amir Arain, Bassel Abou-Khalil, Dale Plummer, William D. Dupont and Satish R. Raj

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Iktální asystolie a ichtální 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 synkopa. V současné době máme pro její léčbu k dispozici omezené informace. Charakteristika prediktorů ichtální 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 všechny pacienty s příhodami ichtální asystolie. Informace o klinickém stavu, z vyšetření elektroencefalogramem a EKG každého jejich záchvatu byly zkoumány z hlediska jejich vztahu k příhodě ichtální asystolie. U 10 pacientů s ichtální asystolií jsme zaznamenali 76 klinických záchvatů s 26 epizodami ichtální 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 synkopou zapříčinilo (p = 0,02). Během příhod ichtální 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 ichtální synkopě. Iktální synkopa je častěji u záchvatů vycházejících z levého než z pravého temporálního laloku. O trvalém kardiostimulátoru by se mělo uvažovat u pacientů, kteří prodělali ichtální 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