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Review

# Epileptic seizures associated with syncope: Ictal bradycardia and ictal asystole

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ABSTRACT

*Introduction:* Heart rate decrease during epileptic seizures is rare and should be considered in patients with unusual or refractory episodes of syncope or in patients with a history suggestive of both epilepsy and syncope. We systematically reviewed the literature to better understand the clinical signs and risk factors of ictal heart rate decreases.

*Material and methods:* We performed a literature-search on "ictal bradycardia" and "ictal asystole" in Pubmed and added papers from the references and personal archives. Articles relating to animal studies, seizures without ictal decrease of heart rate, cases without simultaneous electroencephalography (EEG) and electrocardiography (ECG), convulsive syncopes, or cases with bradycardia before seizure onset and articles written in other languages than English, Dutch, German, French, or Spanish were excluded. Full texts of the remaining articles were screened for cases of ictal bradycardia or ictal asystole. Cases were selected on the basis of a self-designed quality score. The relationship of RR wave interval of at least 5 s, signs of syncope, and EEG signs of ischemia were analyzed with chi-square test and identifying 95% confidence intervals.

*Results:* Ictal bradycardia and ictal asystole predominantly occurred during focal seizures with loss of awareness (proportion in the combined group of bradycardia and asystole ($p1 + 2$) = 0.85) in people with mainly left lateralized ($p1 + 2 = 0.64$; $p = 0.001$) temporal lobe seizures ($p1 + 2 = 0.91$). Seizures with ictal asystole typically started with a heart rate decrease. During ictal asystole in the majority of cases, not only the clinical signs of syncope occurred (change of proportion ($\Delta p$) = 0.67; 95% CI: 0.48–0.86; $p < 0.0001$), i.e., interrupting the seizure semiology, but also the characteristic EEG signs of ischemia ($\Delta p = 0.50$; 95% CI: 0.26–0.74; $p < 0.001$). We found a statistically significant relation between signs of syncope and EEG signs of ischemia ($\Delta p = -0.37$; 95% CI: $(-0.64)$–$(-0.10)$; $p < 0.01$) but not between duration of asystole (5 s) and either signs of syncope ($\Delta p = -0.36$; 95% CI: $(-0.77)$–0.05; $p = 0.03$) or EEG signs of ischemia ($\Delta p = -0.37$; 95% CI: $(-1.07)$–0.33; $p = 0.16$).

*Conclusion:* In the ictal bradycardia syndrome, signs of syncope disrupt the semiology of ongoing seizures and are associated with EEG signs of brain ischemia and the duration of the cardiac arrhythmia.



## 1. Introduction

In 1906, before the introduction of electroencephalography (EEG), Russell described the cessation of the pulse during a seizure in a young man [1]. Since then, different anecdotal cases have been reported in which ictal episodes were accompanied by a decrease of the heart rate or even asystole. In 1996, Reeves described the ictal bradycardia syndrome as "a syndrome that occurs when epileptic discharges profoundly disrupt normal cardiac rhythm, resulting in cardiogenic syncope during the ictal event" [2].

Although ictal tachycardia is very frequent (70–90%), ictal bradycardia is considered a rare event, which affects <5% of patients with epilepsy [3,4]. Asystolic episodes following ictal bradycardia seem to occur even less frequent (0.3-0.4%) [5,6]. Since these studies were typically based on relatively short-term monitoring, the incidence of ictal asystole could have been underestimated.

The recognition of ictal bradycardia is important. Documenting ictal arrhythmias during epileptic seizures is relevant in patient management to avoid undesirable complications. Insertion of a cardiac pacemaker should be considered in case of asystoles. Different authors argued that ictal bradycardia and subsequent asystole are potentially

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life-threatening and might be a possible explanation for sudden unexpected death in epilepsy (SUDEP). The mortality in epilepsy monitoring units study (MORTEMUS), however, showed that in cases of witnessed SUDEP, the asystole is a terminal event after a long period of central apnea [7].

Reeves concluded that the ictal bradycardia syndrome should be considered in patients with unusual or refractory episodes of syncope or in patients with a history suggestive of both epilepsy and syncope. He found an association between seizure onset in the temporal lobe and male gender [2]. Tinuper found that in the majority (31 out of 46) of patients, the epileptic seizures originated from the temporal lobe and the left hemisphere (20 versus 12, 15 unknown). Furthermore, a male/female ratio of 20:10 was found [8].

The pathophysiology of ictal bradycardia is not known. Seizure discharges may activate sympathetic or parasympathetic centers, which result in ictal tachycardia or ictal bradycardia [4]. Parasympathetic activation may exert a strong influence on the atrioventricular (AV) node.

We systematically reviewed the literature to better understand the clinical signs and risk factors of ictal bradycardia.

## 2. Material and methods

### 2.1. Literature search

We performed a systematic review from the first date available to February 2018 and searched Pubmed by queries containing the terms "ictal bradycardia" and "ictal asystole". We also checked the references of these papers we added from our personal archives. One author (CM) screened all full texts.

Articles relating to animal studies, seizures without ictal decrease of heart rate, cases without simultaneous EEG and electrocardiography (ECG), convulsive syncopes, or cases with bradycardia before seizure onset and articles written in other languages than English, Dutch, German, French, or Spanish were excluded.

### 2.2. Selection of cases

Full texts of the remaining articles were screened for cases of ictal bradycardia or ictal asystole. Cases were selected on the basis of a self-designed quality score. This score was based on the availability of sufficient information on the 10 following items: sex, age, antiepileptic drugs, cardiac history, seizure type, seizure onset zone, semiology of seizures, the time relation between the heart rate decrease and the seizure onset, definition of heart rate decrease (in beats per minute/pacemaker activation/asystole), and description of EEG during the seizure. Each approved item resulted in 1 point with a maximum score of 10. Only cases with a score of at least 5 were retained.

We also took care to ensure that identical cases that had been published in different articles were included only once.

### 2.3. Clinical signs and risk factors

For each individually included case, we recorded the 10 items mentioned above, the duration of the asystole, the presence of signs of syncope, and the presence of EEG characteristics of ischemia (slow waves followed by a generalized decrease of amplitude) [9] following the heart rate decrease.

All cases were first subdivided into 2 groups: those with seizures with only ictal bradycardia in the absence of ictal asystole ("ictal bradycardia") and those with at least one seizure with ictal asystole ("ictal asystole", RR interval at least 3 s). The second group was subdivided into 3 subgroups based on the chronology of the asystole into the seizure: within 30 s after seizure onset, after 30 s of seizure onset, and unknown chronology.

We also selected all the cases with a clearly defined heart rate decrease (absence of asystole, presence of asystole with known duration), information on the presence or absence of signs of syncope, and EEG signs of ischemia. The relationship of the RR interval of at least 5 s, signs of syncope, and EEG signs of ischemia were analyzed with a chi-square test including identifying the confidence intervals.

### 2.4. Statistical analysis

For all items, proportions were calculated, and differences in proportions were indicated as Δp. Ninety-five percent confidence intervals based on the (differences in) proportions are given. All tests were two-tailed and considered statistically significant when alpha ≤ 0.05.

## 3. Results

### 3.1. Included cases

Based on our queries containing the terms "ictal bradycardia" and "ictal asystole", we found 218 different papers (Supplement 1). One paper was missing, and 114 were excluded resulting in 75 case reports and 28 case series for further analysis.

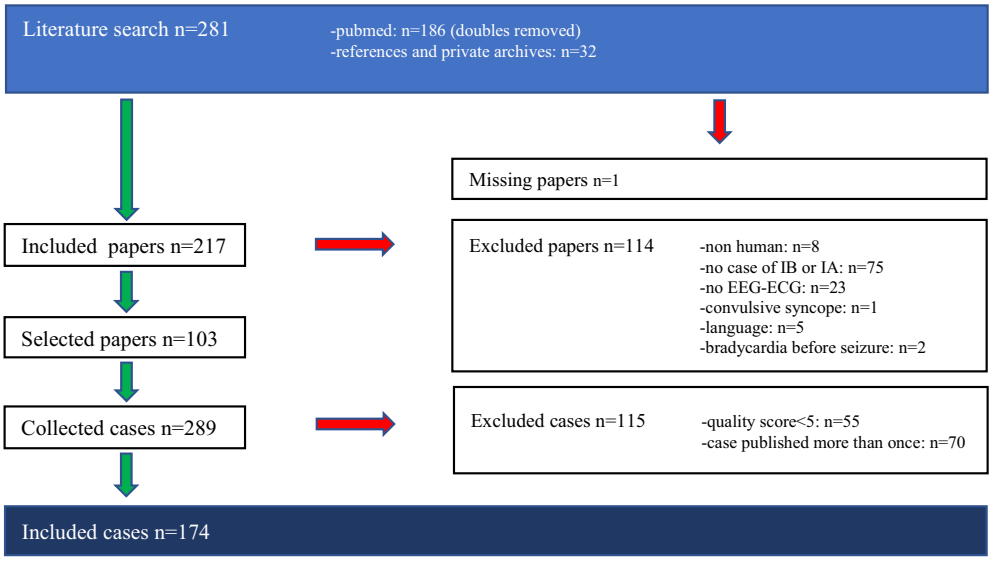


**Fig. 1.** Flowchart literature search to inclusion case: IB, ictal bradycardia; IA, ictal asystole.

**Table 1**
Summary of characteristics of cases: Bradycardia, cases without asystole; Asystole, cases with at least one seizure with asystole; loc, loss of consciousness; HR, heart rate; p1 + 2, proportion in combined group of bradycardia and asystole; Δp = p1 − p2 (change of proportion).

| Summary characteristics of cases: | | Bradycardia | | Asystole | | Bradycardia vs asystole | | | Bradycardia and asystole |
|---|---|---|---|---|---|---|---|---|---|
| | | n | p1 | n | p2 | Δp | 95% CI | p | |
| Signs of syncope (1) | One of loc, atonia, fall | 6 | 0.94 | 85 | 0.27 | 0.67 | 0.48–0.86 | p < 0.0001 | |
| EEG during HR decrease (2) | Cerebral hypoxia | 6 | 0.83 | 48 | 0.33 | 0.50 | 0.26–0.74 | p < 0.001 | |
| (1) and/or (2) | Cerebral hypoxia | 10 | 0.92 | 96 | 0.37 | 0.55 | 0.37–0.74 | p < 0.001 | |
| Seizure type | Focal | 13 | 0.83 | 47 | 0.93 | −0.09 | −0.26 to −0.07 | p = 0.35 | p1 + 2 = 0.85, mainly focal |
| EEG seizure onset | Temporal/extratemporal | 28/5 | 0.93 | 118/9 | 0.85 | 0.08 | −0.05–0.21 | p = 0.14 | p1 + 2 = 0.91, mainly temporal |
| | Left/right temporal | 18/10 | 0.64 | 69/38 | 0.64 | 0.00 | −0.20–0.20 | p = 0.98 | p1 + 2 = 0.64, p = 0.001 |
| Demographics | Male/female | 22/13 | 0.52 | 65/60 | 0.63 | −0.11 | −0.29–0.07 | p = 0.25 | p = 0.268 |

We collected 289 cases and excluded 70 cases who were reported more than once and 55 cases not fitting our quality score which resulted in 174 different cases for this analysis (Fig. 1).

### 3.2. "Ictal bradycardia" vs "ictal asystole"

Between the groups "ictal bradycardia" and "ictal asystole", statistically significant differences were found for the presence of signs of syncope (Δp = 0.67; 95% CI: 0.48–0.86; p < 0.0001), EEG signs of ischemia (Δp = 0.50; 95% CI: 0.26–0.74; p < 0.001), and either one or both of them (Δp = 0.55; 95% CI: 0.37–0.74; p < 0.001) (see Table 1). Age, sex, seizure type, and onset zone were not statistically different between both groups. Ictal bradycardia and ictal asystole predominantly occurred during focal seizures with loss of awareness in people with mainly left lateralized (p = 0.001) temporal lobe epilepsy and were not associated with a statistically significant sex difference.

### 3.3. "Early ictal asystole" vs "late ictal asystole"

We divided the group of ictal asystole into early or late ictal asystole based on the occurrence of the asystole before or after 30 s from seizure onset. In the majority, this distinction was not possible because of the lack of information on chronology. Despite the small number of included patients, there was a significant association between early ictal asystole and left lateralized temporal lobe epilepsy (Supplement 2).

### 3.4. Signs of syncope, EEG signs of ischemia, and the duration of asystole

In Table 2, we analyzed the importance of signs of syncope, EEG signs of ischemia, and the duration of asystole (RR interval > 5 s). We found a clear, statistically significant relation between signs of syncope and EEG signs of ischemia (Δp = −0.37; 95% CI: (−0.64)–(−0.10); p < 0.01) but not between duration of asystole (5 s) and either signs of syncope (Δp = −0.36; 95% CI: (−0.77)–0.05; p = 0.03) or EEG signs of ischemia (Δp = −0.37; 95% CI: (−1.07)–0.33; p = 0.16).

### 3.5. Other risk factors

Ictal heart rate decrease was not associated with a history of cardiac disease. The mean age of the patients with ictal bradycardia and ictal asystole at the time of diagnosis was similar to that reported in other series [6,8,10,11] suggesting that ictal bradycardia and ictal asystole are a midlife pathology and unlike most cardiac complications that are associated with old age.

**Table 2**
Occurrence of EEG signs of ischemia in cases of bradycardia versus syncope and proportions in signs of syncope, EEG signs of ischemia, and duration of asystole (RR interval > 5 s); Δp = p1 − p2 (change of proportion).

| p1 | | p2 | Δp | 95% CI | p |
|---|---|---|---|---|---|
| EEG ischemia | vs | Syncope | | | |
| 0.44 | | 0.80 | −0.37 | −0.64 to −0.10 | p < 0.01 |
| Duration asystole (>5 s) | vs | Syncope | | | |
| 0.50 | | 0.86 | −0.36 | −0.77–0.05 | p = 0.03 |
| Duration asystole (>5 s) | vs | EEG ischemia | | | |
| 0.50 | | 0.87 | −0.37 | −1.07–0.33 | p = 0.16 |

## 4. Discussion

### 4.1. General

Ictal bradycardia and ictal asystole predominantly occurred during focal seizures with loss of awareness in people with mainly left lateralized temporal lobe epilepsy. Seizures with ictal asystole typically started with a heart rate decrease. During ictal asystole in the majority of cases, not only the clinical signs of syncope occurred, which interrupted the seizure semiology, but also the characteristic EEG signs. Occurrence of signs of syncope was statistically associated with the presence of EEG signs of ischemia and the duration of asystole. No deaths were reported in patients with ictal asystole suggesting that ictal asystoles are self-limiting (but the comorbidity due to falls might be considerable). Signs of ictal bradycardia at the time of diagnosis are relevant because they may be associated with ictal asystole during other seizures at home.

### 4.2. Advantages and limitations

The cases were selected based on a self-designed quality score. The limitation of such a score is that it is not validated, but in other papers, similar procedures were performed and the items used for the score seem self-evident.

The diagnosis of ictal bradycardia is based on documentation of bradycardia/asystole associated with epileptic seizures recorded in an epilepsy monitoring unit. Such patients are a highly selected group, often candidates for epilepsy surgery. This might result in a higher number of cases at young age, having focal seizures predominantly from the temporal lobe. Since we analyzed data collected from retrospective studies, other sources of bias (selection, publication, classification, etc.) may also occur.

A clear definition of the decrease of heart rate is an important methodological issue. The reported heart rate complications ranged from a limited bradycardia to a long asystole of 77 s [12] with varying definitions. Muscle artifacts and limitations of EEG registration may have led to proper recognition of seizure onset zone and may have obscured the detection of ictal arrhythmias with a single lead ECG channel.

### 4.3. Clinical signs of ictal bradycardia and ictal asystole

The course of events is typical: an initial sinus tachycardia is followed by a progressive decrease of heart rate sometimes ending into asystole of variable duration. The duration of most documented pauses are not life-threatening (RR interval range: 3–20 s), but longer pauses have been accidentally observed. The decrease may or may not be present in the beginning of the seizure. During this asystole, seizure signs may continue or the seizures are interrupted by one or more signs related to a syncope (complete loss of consciousness, atonia, fall,

and myoclonic jerks). The loss of consciousness might be difficult to distinguish from the signs of a focal seizure with loss of awareness. In focal seizures with loss of awareness, the altered consciousness takes the form of decreased awareness and motor arrest, during which the patient is motionless and inaccessible. The period of impairment of awareness may or may not be preceded by other symptoms or signs of a focal seizure. This distinction of loss of consciousness vs awareness is, however, somewhat arbitrary. In fact, in the 2017 seizure classification, if awareness of the event is impaired for any proportion of the seizure, then the seizure is classified as a focal seizure with impaired awareness [13]. The ictal asystole during the seizure may also induce a sudden loss of muscle tone. This loss of muscle tone also may be confined to only a group of muscles and then even leading to a fall on the ground. This fall should be distinguished from falls at the start of a seizure caused by a myoclonic–atonic mechanism. Myoclonic–atonic seizures most often begin during childhood as a part of different epilepsy syndromes than those that are associated with ictal asystole. Syncope-related myoclonic or tonic movements may be confounded with epileptic seizure signs. They may appear during the asystole or after the return of cardiac activity. The accompanying loss of brain blood flow because of the asystole is probably facilitating termination of the epileptic event. In 1994, Gambardella et al. described 6 cases with temporal lobe drop attacks defined as abrupt falls, sometimes preceded by a warning and usually followed by impairment of consciousness lasting 1 to 2 min or by confusion [14]. Comparison is difficult because of the lack of information on cardiac rhythm. Furthermore, all of these cases previously underwent temporal resection, and the drop attacks followed the onset of epilepsy after a long delay. In 16 cases, seizure type was classified as "focal to bilateral tonic–clonic" [5,6,15–22]. In the majority, the presence of this sign was unclear because of the lack of information.

We found a clear, statistically significant relation between signs of syncope and EEG signs of ischemia but not between duration of asystole (at least 5 s) and either signs of syncope or EEG signs of ischemia. This means that the duration of the asystole is less important than the presence of EEG signs of ischemia in terms of the presence of signs of syncope. In none of the cases, ictal blood pressure was mentioned. Hypotension might be an important factor resulting from heartrate decrease (both bradycardia and asystole) or even cortical involvement. Lacuey et al. suggested that Brodmann area 25 has a role in lowering systolic blood pressure in humans. It is a potential symptomatogenic zone for peri-ictal hypotension in patients with epilepsy [23]. Future research is needed.

### 4.4. Lateralization and seizure onset zone

We found a consistent left hemispheric lateralization in the large group of ictal bradycardia and ictal asystole cases. Other authors previously have suggested that a seizure onset in the left hemisphere results in bradycardia and that a right-sided onset results in tachycardia. Ictal bradycardia and ictal asystole were clearly associated with temporal lobe epilepsy. Because of the "epilepsy monitoring unit bias" mentioned above, people with temporal lobe epilepsy may have been overrepresented. Ictal asystole could be a direct consequence of epileptic activity modulating the central autonomic network. Focal stimulation of parts of the limbic system, such as the cingulate gyrus, amygdala, and insular and orbitofrontal cortex, may provoke asystole.

### 4.5. Diagnosis

The clinical events of an ictal asystole are not unique because the same events are observed in vasovagal and situational reflex faints. For the nonneurologist clinician, particularly the emergency room practitioner, the difficulty in differentiating seizure disorders from syncope is great, especially when one attempts to distinguish ictal-induced asystole from transient loss of consciousness because of neurally mediated reflex faints. A carefully documented medical history and, if possible, a detailed eyewitness account of the episode in the hands of an experienced clinician is the crucial diagnostic step. Historical findings of automatisms; visual, olfactory, auditory, or gustatory hallucinations; or the "déjà vu" or "jamais vu" sensations are suggestive of an epileptic origin. These signs are not observed with reflex faints.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.10.027.

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