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"Ictal" bradyarrhythmias in patients with drug-resistant epilepsy: results of long-term heart rhythm monitoring

Aim	To determine the type and incidence of ictal bradyarrhythmias in patients with drug-resistant types of epilepsy by long-term electrocardiogram (ECG) monitoring.
Material and methods	Subcutaneous ECG monitors programed for recording pauses >3 sec and episodes of bradycardia ≤45 bpm were implanted in 193 patients with persistent epileptic seizures without organic pathology of the myocardium. Recording was activated by the patient/family at the onset of epileptic seizure. The follow-up period was 36 months with visits to the clinic every three months.
Results	For 36 months of monitoring, 6494 ECG fragments were recorded. Ictal bradycardia was observed in 6.7% of patients, including ictal asystole in 2.6% of patients. Episodes of bradycardia and asystole during epileptic seizures were transient and developed significantly more frequently in men, patients with long duration of the disease, bilateral tonic-clonic or focal seizures with disorder of consciousness, during sleep, on the background of treatment with several antiepileptic agents, mostly from the group of potassium channel blockers.
Conclusion	Bradyarrhythmias accompanying epileptic seizures are transient and reproducible from seizure to seizure. They reflect functional changes in the myocardium and do not determine the life prediction for patients with epilepsy without organic pathology of the heart.

Keywords	Disorders of heart rhythm and conduction; subcutaneous loop electrocardiogram recorder; bradycardia; asystole; epileptic seizures
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Approximately 70 million people worldwide suffer from epilepsy. Almost 1 million patients have seizures, despite treatment, which reduce daily activity and quality of life. Seizures are also a cause of increased morbidity and mortality [1, 2]. Epilepsy is a complex problem rather than a simple neurological disease characterized by unprovoked seizure attacks and is attracting increased attention from clinicians. The electrophysiological changes in the heart are a natural consequence of the long-term course of epilepsy. Cardiac effects can vary from deviated rhythm variability to bradyarrhythmia, asystole, and other heart rate disorders, showing the unbreakable brain-heart connection and interaction. A range of heart arrhythmias are detected in more than 50% of cases of epileptic seizure attacks [3, 4]. Bradyarrhythmia is not a common reaction to an epileptic seizure attack [5–7]. Ictal bradyarrhythmia syndrome is usually typical of focal attacks with impaired consciousness. They are less frequent in cases of secondary generalization, and are more frequently observed in patients with temporal epilepsy significantly [8–10].

Of particular interest is the role of ictal brady arrhythmias in the pathogenesis of sudden death (SD) in epilepsy and are presumed to be a leading factor of SD.

Current perceptions concerning heart rhythm in the ictal period present fragmented information obtained primarily by video electroencephalogram (EEG) monitoring, including in patients who died suddenly [11].

Aim

To determine the nature and frequency of ictal bradyarrhythmias in patients with pharmacoresistant epilepsy by long-term electrocardiogram (ECG) monitoring.

Material and methods

The study included 193 patients: 102 males, 91 females, with a mean age of 35.4 years (from 18 to 60 years).

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Inclusion criteria: patients diagnosed with focal epilepsy and persistent attacks which occur at least 2 times per year during the anti-epileptic therapy; aged between 18 and 60.

Exclusion criteria: coronary heart disease; organic myocardial pathology (postinfarction cardiosclerosis, cardiomyopathy, myocardial hypertrophy more than 1.3 cm, heart defects); use of drugs affecting heart rhythm (beta-blockers, non-dihydropyridine calcium antagonists); absence of epilepsy seizure attacks during the anti-epileptic therapy; liver and kidney diseases; and dysfunction, endocrine and mental disorders.

The patients were examined after signing the informed consent. The ethics committee approved the trial protocol.

Each included patient underwent EEG video monitoring, brain magnetic resonance imaging (MRI) (1.5 T). The epileptic focus was localized and lateralized based on the clinical characteristics of attacks, EEG video monitoring, and brain MRI. Organic myocardial pathology was excluded during echocardiography, while hidden myocardial ischemia was ruled out based on a stress test. Organic myocardial pathology was excluded in all cases, as was latent coronary insufficiency during stress tests. The 12-lead resting ECG was recorded, and 24-hour ECG monitoring was performed to detect heart rate and conduction disorders. Total blood count and biochemical blood tests were carried out, in order to estimate electrolyte and metabolic parameters.

Loop recorders, capturing the single-channel ECG corresponding to the V2 lead, were implanted in all patients to record the ictal ECG. The ECG recording to detect bradyarrhythmias was automatically activated by two programmable triggers: heart pauses (>3 s); and bradycardia (<45 bpm). Moreover, each patient or his/her relative/guardian could activate the recording using an external device during or immediately after an epileptic seizure attack. The external device was used to activate the recording:

1. Once:

a) in the case of focal attacks with preserved consciousness (immediately after the attack);
b) in the case of focal attacks without impaired consciousness or bilateral tonic-clonic seizures without aurora (immediately after the attack);

2. Twice:

a) in the case of focal attacks with impaired consciousness or bilateral tonic-clonic seizures with aura (first, during aura, and second, immediately after stopping the attack);
b) in the case of epileptic state/series of seizures (first, epileptic state/series of seizures, and second, when consciousness is regained or if there are signs of the ongoing attack).

We developed an original patented technique (RU2665019C1 "Method for detecting rhythm and conduction disturbances in patients with epilepsy using an implanted subcutaneous ECG loop register").

Patients were examined by a cardiologist and neurologist before the device was implanted and subsequently every 3 months. ECG fragments saved in the subcutaneous register were also interpreted every 3 months. The follow-up period was 36 months, at the end of which the devices were explanted.

Statistical analysis was performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). The means and standard deviations were used to express the normally distributed quantitative data.

Results

During the monitoring of 193 patients over a follow-up period of 36 months (mean follow-up period 34.6±6.03 months), 6,494 ECG fragments were recorded using a loop register. The analysis showed that at the time of the epileptic seizure attacks, 13 (6.7%) of 193 patients had bradycardia, and 5 (2,6%) of the 13 patients in combination with asystole.

It should be noted that the heart rate response to epileptic seizure attacks was stereotypical in all cases. Sinus bradycardia was preceded by sinus tachycardia, including in 3 of 5 patients with asystole. Bradyarrhythmias appeared again from one attack to another. Table 1 shows the clinical characteristics of patients with ictal bradyarrhythmias. The mean age of patients was 42 (27–57) years; 8 patients were male; and 5 were female.

The mean duration of the history of epilepsy was 15 (6–45) years. In 9 of 13 patients epileptic seizures occurred during sleep. When the 12 -lead interictal ECGs of patients with bradyarrhythmias were interpreted, only 2 of 13 patients had abnormalities in the form of partial right bundle branch block (Table 2).

Most of the patients with ictal bradycardia received combined anti-epileptic therapy, including two-component therapy in 5 patients and three-component therapy in another 5 patients. 3 of 13 patients received one anticonvulsant agent. The majority of patients (10 of 13) received Na channel blockers.

Table 1. Clinical characteristics of patients with bradyarrhythmias (n=13)

Patient (sex, age)	Duration of epilepsy, years	Number of attacks per year	Number of BTCSs per year	Type of attack	Number of AEDs	Na channel blockers	Psychoactive agents	Alcohol	Sleep	Structured focus	Lesion localization/ lateralization	Bradycardia, bpm	Asystole, sec	Pacemaker
1 (m, 46)	34	25	25	BTCS	3	Yes	No	Yes	Yes	No	Frontal R+L	38	14.5	Yes
2 (m, 32)	13	4	4	BTCS	1	Yes	No	Yes	No	Yes	Multiregional – unknown	35	15	Yes
3 (m, 49)	45	276	0	FSIC	3	Yes	No	Yes	Yes	No	Temporal – L	49	–	–
4 (f, 50)	14	12	0	FSIC	1	No	No	No	Yes	Yes	Temporal – R	43	–	–
5 (m, 27)	29	12	12	FSIC	3	Yes	No	No	Yes	No	Frontal-temporal – R	30	3.6	–
6 (m, 39)	6	48	48	BTCS	1	No	No	Yes	Yes	Yes	Frontal – R	44	–	–
7 (m, 38)	15	36	0	FSIC	3	Yes	Yes	No	Yes	No	Frontal-temporal – L	36	–	–
8 (m, 51)	11	10	10	BTCS	2	Yes	No	No	Yes	Yes	Frontal-unknown	43	–	–
9 (f, 27)	6	36	40	FSIC	2	No	No	No	No	Yes	Temporal – R	41	–	–
10 (f, 38)	29	25	0	FSIC	2	Yes	No	No	No	No	Temporal – L	45	–	–
11 (f, 35)	33	96	25	BTCS	2	Yes	No	No	Yes	No	Frontal R+L	37	–	–
12 (f, 57)	15	14	12	FSIC	2	Yes	No	No	No	Yes	Frontal – L	38	3.6	–
13 (m, 55)	23	384	300	BTCS	3	Yes	No	No	Yes	Yes	Multiregional R+L	31	7.6	Yes

BTCS, bilateral tonic-clonic seizure; FSIC, focal seizures with impaired consciousness; R, right; L, left: AED, anti-epileptic drugs.

The mean heart rate (HR) during ictal bradycardia was 38.9 (30–45) bpm. The mean duration of asystole episodes reached 8.86 (3.6–15) s (Figures 1, 2). In 3 cases, pauses were recorded immediately after the artifacts inherent in the tonic-clonic phase of seizures. They were followed by spontaneous restoration of the sinus rhythm, and occurred during sleep.

Another patient experienced focal attacks with impaired consciousness while awake. These were characterized by sudden atonia and asystole for 3.6 seconds on ECG, followed by sinus bradycardia with HR 38 bpm. In one patient, episodes of ictal asystole were recorded during focal attacks with impaired consciousness manifested by aurora.

All 5 patients who experienced heart pauses during the ictal period also had asystole events lasting for more than 3s during the 24-hour ECG monitoring at night and were not associated with epileptic seizure attacks.

The epileptic foci in all patients with heart pauses were extratemporal. 4 of the 8 patients with bradycardia had temporal foci, while another 4 patients had extratemporal foci.

Focal attacks with impaired consciousness were detected in 5 of the 8 patients with bradycardia. One of these patients had an aura before the attacks, and 5 patients had attacks with typical symptoms. Bilateral tonic-clonic seizures occurred during sleep at night in 3 of 8 patients with bradycardia.

Table 2. Key interictal ECG measurements in patients with bradyarrhythmias (n=13)

Measurement	Value
Heart rate, bpm	81.9 ± 16.9
RR duration, ms	764 ± 179
PQ duration, ms	156.2 ± 19.4
QRS duration, ms	94.7 ± 5.5
QT duration, ms	360.2 ± 44.4
QTc duration, ms	371.2 ± 51.3

Six patients had a family history of epilepsy and SD: epilepsy in relatives (n=1); recurrent episodes of loss of consciousness (n=3); drownings and accidents (n=2); and SD at a young age (n=1).

Of the 13 patients, 3 individuals with heart pauses of more than 6 seconds had implanted pacemakers, and they noted decreased mental confusion after attacks during the follow-up period.

Discussion

According to the literature, ictal bradycardia detected during the registration of bioelectrical activity of

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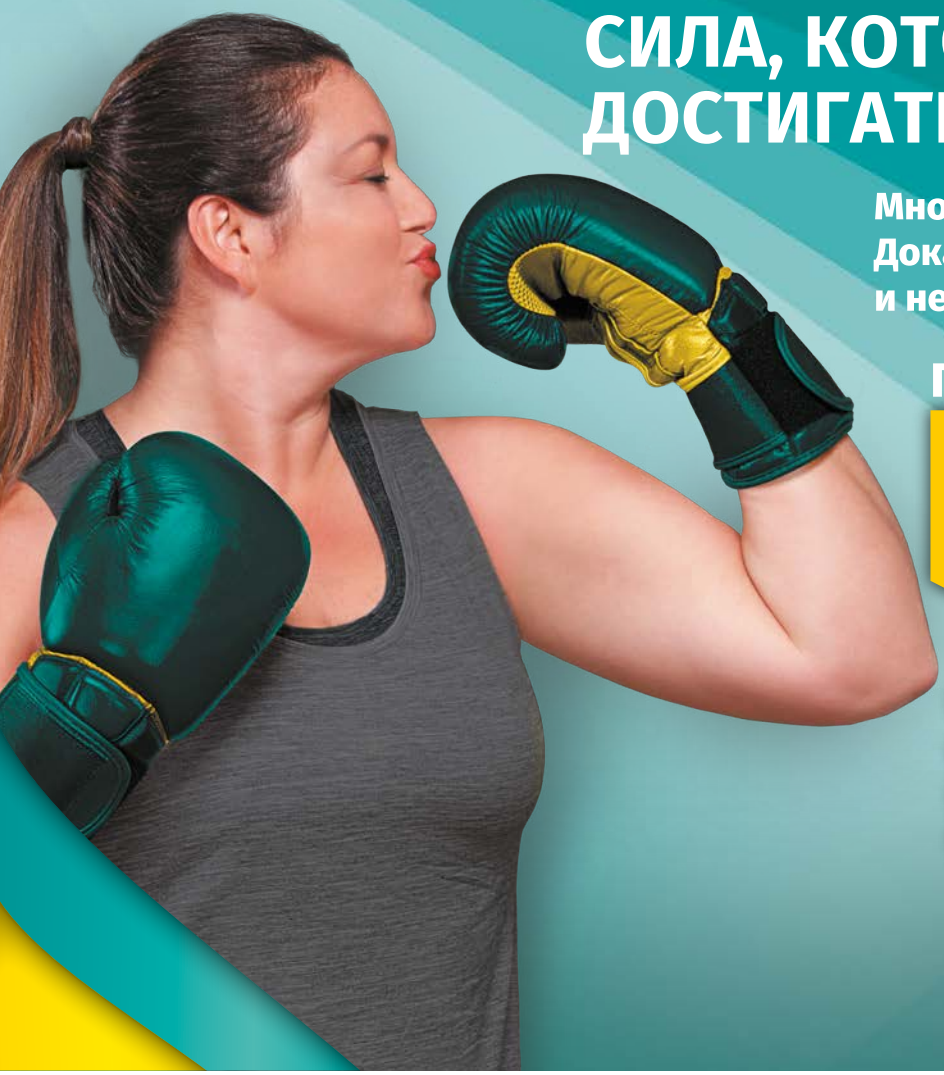

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Регистрационное удостоверение: ЛП-002735. **Торговое наименование:** ДЖАРДИНС. **Международное непатентованное наименование:** эмпаглифлозин. **Лекарственная форма:** таблетки, покрытые пленочной оболочкой. **Состав.** 1 таблетка, покрытая пленочной оболочкой, содержит: *действующее вещество:* эмпаглифлозин – 10,000 мг/25,000 мг. **Фармакотерапевтическая группа.** Гипогликемическое средство для перорального применения – ингибитор натрийзависимого переносчика глюкозы 2 типа. **Код АТХ:** A10BK03. **Показания к применению.** Для терапии сахарного диабета 2 типа у взрослых пациентов с неадекватным гликемическим контролем в дополнение к диетотерапии и физическим упражнениям: в качестве монотерапии; в качестве комбинированной терапии с другими гипогликемическими препаратами, включая инсулин. Препарат показан пациентам с сахарным диабетом 2 типа и высоким сердечно-сосудистым риском* в комбинации со стандартной терапией сердечно-сосудистых заболеваний с целью снижения: общей смертности за счет снижения сердечно-сосудистой смертности; сердечно-сосудистой смертности или госпитализации по поводу сердечной недостаточности. **Высокий сердечно-сосудистый риск определен как наличие хотя бы одного из следующих заболеваний и/или состояний: ИБС (инфаркт миокарда в анамнезе, шунтирование коронарных артерий, ИБС с поражением одного коронарного сосуда, ИБС с поражением нескольких коронарных сосудов); ишемический или геморрагический инсульт в анамнезе; заболевания периферических артерий (с симптоматикой или без).* **Противопоказания.** Гиперчувствительность к эмпаглифлозину и/или любому вспомогательному веществу в составе препарата. Сахарный диабет 1 типа. Диабетический кетоацидоз. 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Низкая секреторная активность бета-клеток поджелудочной железы. **Применение при беременности и в период грудного вскармливания.** Применение эмпаглифлозина во время беременности противопоказано ввиду недостаточности данных по эффективности и безопасности. Данные, полученные в доклинических исследованиях у животных, свидетельствуют о проникновении эмпаглифлозина в грудное молоко. Не исключается риск воздействия на новорожденных и детей при грудном вскармливании. Применение эмпаглифлозина в период грудного вскармливания противопоказано. При необходимости применения эмпаглифлозина в период грудного вскармливания кормление грудью следует прекратить. **Способ применения и дозы.** *Монотерапия или комбинированная терапия.* Рекомендуемая начальная доза составляет 10 мг (1 таблетка дозировкой 10 мг) 1 раз в сутки. Препарат следует принимать внутрь, запивая водой. В случае если суточная доза 10 мг не обеспечивает адекватного гликемического контроля, доза может быть увеличена до 25 мг (1 таблетка дозировкой 25 мг) 1 раз в сутки. Максимальная суточная доза составляет 25 мг. Препарат ДЖАРДИНС может приниматься независимо от приема пищи в любое время дня. При совместном применении препарата ДЖАРДИНС с производным сульфонилмочевины или с инсулином может потребоваться снижение дозы производного сульфонилмочевины/инсулина из-за риска развития гипогликемии. *Действия при пропуске приема одной или нескольких доз лекарственного препарата.* При пропуске дозы пациенту следует принять препарат, как только он об этом вспомнит. Не следует принимать двойную дозу в течение одних суток. *Применение препарата в особых группах пациентов.* Применение препарата у пациентов с почечной недостаточностью при СКФ менее 45 мл/мин/1,73 м² противопоказано. Пациентам с СКФ ≥45 мл/мин/1,73 м² коррекции дозы не требуется. Эмпаглифлозин не должен применяться у пациентов с терминальной стадией почечной недостаточности или у находящихся на гемодиализе. Пациентам с нарушениями функции печени коррекции дозы не требуется. **Побочное действие.** Общая частота нежелательных реакций у пациентов, получавших эмпаглифлозин или плацебо, в клинических исследованиях была сходной. Наиболее частой нежелательной реакцией была гипогликемия, отмечавшаяся при применении эмпаглифлозина в комбинации с производным сульфонилмочевины или инсулина. Нежелательные реакции, наблюдавшиеся у пациентов, получавших эмпаглифлозин в плацебоконтролируемых исследованиях, распределены по системно-органным классам с указанием частоты их возникновения согласно рекомендациям ВОЗ: очень часто (≥1/10), часто (от ≥1/100 до <1/10), нечасто (от ≥1/1000 до <1/100). **Очень часто.** *Нарушения со стороны обмена веществ и питания* – гипогликемия (при совместном применении с производным сульфонилмочевины или инсулином). **Часто.** *Инфекционные и паразитарные заболевания* – вагинальный кандидоз, вульвовагинит, баланит и другие генитальные инфекции, инфекции мочевыводящих путей (в том числе пиелонефрит и уросепсис). *Нарушения со стороны кожи и подкожных тканей* – зуд (генерализованный), сыпь на коже. *Нарушения со стороны почек и мочевыводящих путей* – увеличение мочевыделения. *Общие расстройства и нарушения в месте введения* – жажда. *Лабораторные и инструментальные данные* – повышение концентрации липидов в плазме крови. **Нечасто.** *Нарушения со стороны кожи и подкожных тканей* – крапивница. *Нарушения со стороны сосудов* – гиповолемия. *Нарушения со стороны почек и мочевыводящих путей* – дизурия. *Лабораторные и инструментальные данные* – снижение скорости клубочковой фильтрации, повышение концентрации креатинина в плазме крови, повышение гематокрита. *Полный перечень нежелательных реакций с указанием их абсолютной частоты представлен в инструкции по медицинскому применению.* **Условия хранения.** При температуре не выше 25 °С. Хранить в недоступном для детей месте. **Срок годности.** 3 года. Не следует принимать препарат по истечении срока годности. **Условия отпуска.** По рецепту. ***Полная информация представлена в инструкции по медицинскому применению.***

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Figure 1. Ictal asystole (14.5 s) in the patient with bilateral tonic-clonic seizures detected automatically (recording rate 25 mm/s)

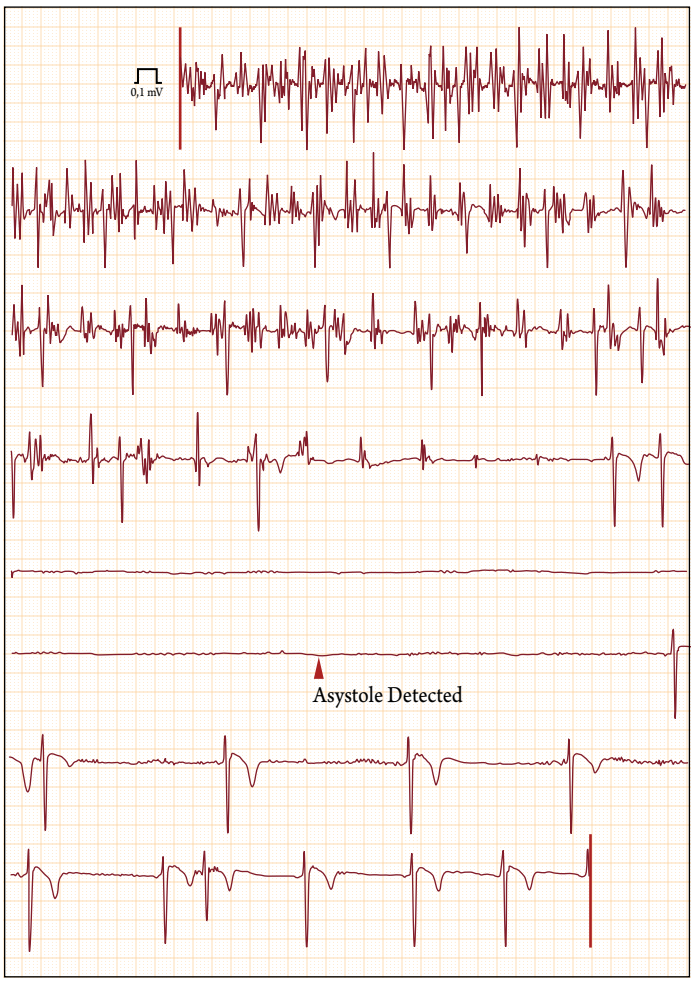
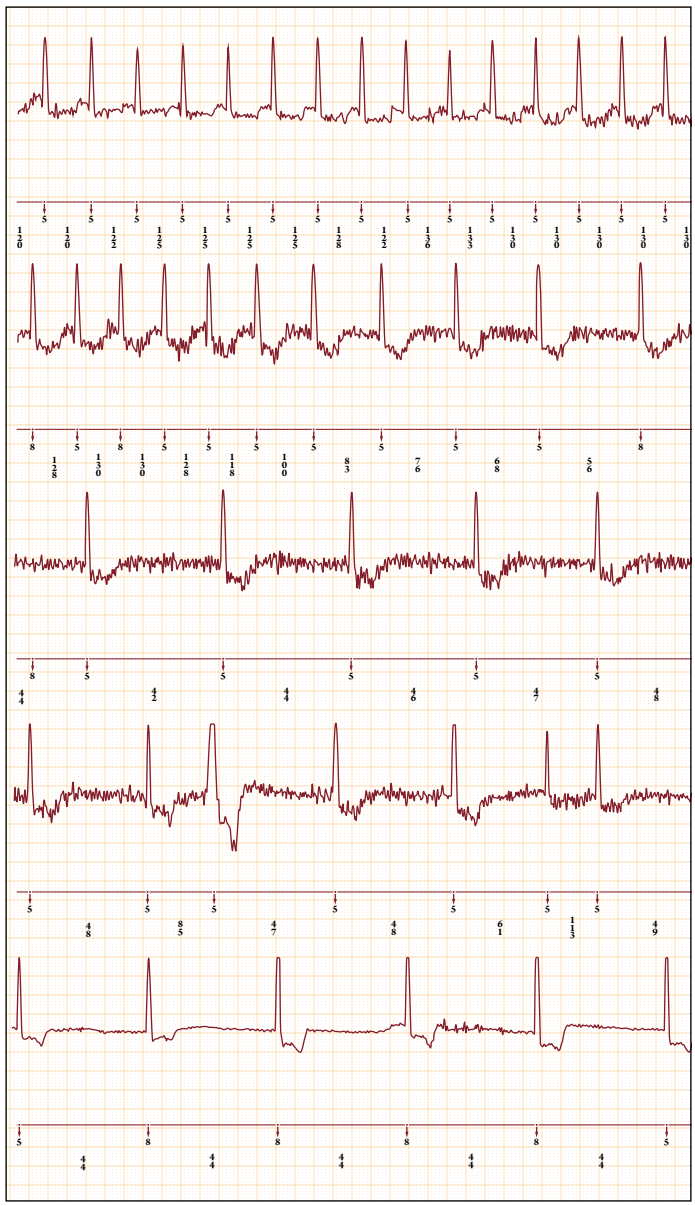


Figure 2. Bradycardia (44 bpm) in a patient with focal epileptic seizures with impaired consciousness registered by patient activated recording (recording rate 25 mm/s)



the brain in the video EEG leads is rare (<5%), while asystole is even rarer (0.3–0.4%) [5, 12]. In our study, patients diagnosed with epilepsy had bradycardia and asystole in 6.7% and 2.1% of cases respectively.This can be attributed to the occurrence of these ECG patterns which do not occur in every epileptic seizure attack, as well as the increased possibilities of long-term heart rhythm recording using a subcutaneous loop register.

Bradyarrhythmias in patients with pharmacoresistant forms of epilepsy are of the most significant interest. This is due to the possible correlation with sudden unexpected epileptic death in which postictal bradyarrhythmias may be associated with a higher risk of SD, since they are the result of tonic muscle contraction and apnea with hypoxia or central apnea [13, 14]. Ictal asystole and bradycardia might be more benign and may occur in the arousal of the parasympathetic nervous system or abrupt cessation of sympathetic activity during an epileptic seizure attack. They may be provoked by a sense of fear when catecholamines are released, causing a vasovagal reaction of cardioinhibition and vasodilation [15].

Unfortunately, our study was limited by the inability to simultaneously record ECG and EEG during epileptic seizure attacks. This prevented us from making conclusions about the correlation between bradycardia and asystole with pathological electrical activity in the brain. However, the use of an external device by a patient or his/her relative/caregiver to activate the ECG recording, depending on the type and symptoms of the epileptic seizure attack and post-attack confusion, enabled us to improve the ECG recording in the ictal period. The assumption that registered bradyarrhythmias are ictal, even based on indirect data in the group of patients examined, was

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significant considering that, according to population studies, the frequency of erroneous diagnosis of epilepsy is as high as 31.8%. This can be ascribed to the high frequency of syncopal states and non-epileptic seizure attacks of psychogenic nature [16].

This study showed no difference in the frequency of bradycardia depending on the location of the epileptic focus or the type of epileptic seizure attacks. Asystole was detected in 3 patients with bilateral tonic-clonic attacks, and 2 patients with focal attacks with impaired consciousness and extratemporal localization of the pathological foci.

The only case of atonia in the patient with focal attacks and impaired consciousness, bradycardia, and asystole may be the result of cerebral hypoperfusion during a sudden decrease in HR or the rapid spread of ictal activity involving the pontine reticular formation, accompanied by a typical clinical picture of the loss of postural tone [17].

Lempert et al. showed that asystoles lasting more than 14s were accompanied by the flattening of the EEG elements at the same time as muscle twitching and tonic spasms. Similar sudden diffuse and generalized slowing of electrical activity in the brain is observed during the tilt test in patients with cardioinhibitory syncopes during their development [18]. Tonic or myoclonic signs associated with brain hypoperfusion are predominantly typical of non-epileptic anoxic phenomena. Only a few typical bilateral tonic-clonic seizures are accompanied by the development of asystole [19].

Three patients with bilateral tonic-clonic seizures had pacemakers implanted as a result of asystole episodes being detected during epileptic seizure attacks. During the follow-up, these patients noted a decrease in post-attack mental confusion, with the same frequency of seizure attacks. This indicates that pathological epileptic activity is the main mechanism of their development.

The epileptic nature of epileptic seizure attacks is also shown by their manifestation by automatisms, visual, olfactory, and auditory aura, and a sense of déjà vu, as experienced in 6 of our patients with episodes of bradycardia and focal motor attacks with impaired consciousness [20].

Moreover, the independent co-existence of mechanisms involved in activating the autonomic nervous system in epileptic seizure attacks involving cardiovascular and cardiorespiratory reflexes cannot be excluded [21]. The interactions of these reflexes with sympathetic and/or parasympathetic effects during attacks can explain the combination of sinus tachycardia and sinus bradycardia.

Conclusion

This study demonstrated the transient nature and reproducibility of the ECG phenomena data. The long history of attacks of loss of consciousness in all patients with bradyarrhythmias/asystole indirectly indicates their benign nature and may exclude the role of such bradyarrhythmias in the origin of sudden epileptic death.

No conflict of interest is reported.

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