

Arrhythmogenic epilepsy and pacing need: A matter of controversy

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Abstract

There is increasing awareness among the cardiology community regarding ictal bradyarrhythmias as a cause of loss of consciousness. A high degree of suspicion is necessary when diagnosing ictal bradyarrhythmias, and delay in diagnosing this condition may lead to morbidity associated with falls and trauma. Ictal bradyarrhythmias

have also been suggested to be associated with sudden unexplained death in epilepsy, although evidence related to this association is limited. There is no guideline-directed therapy for symptomatic ictal bradyarrhythmias due to a lack of randomized, controlled trials. Cardiac pacemaker therapy is commonly used for these patients; however, currently, there is no universal agreement on the pacing indications for these patients. In this review, we focus on the pathophysiology and clinical presentation of ictal bradyarrhythmias and then discuss the pacing need based on the available literature data.

Key words: Arrhythmogenic epilepsy; Syncope; Ictal bradyarrhythmia; Pacemaker; Anticonvulsive therapy

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Core tip: There is increasing awareness among the cardiology community regarding ictal bradyarrhythmias as a cause of loss of consciousness. Pacing is commonly used therapy for symptomatic ictal bradyarrhythmias. However, currently, there is no universal agreement on the pacing indications for these patients due to lack of randomized, controlled trials. In this review we will first focus on pathophysiology and clinical presentation of ictal bradyarrhythmias and then try to discuss the pacing need based on the available literature data.

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INTRODUCTION

Epileptic seizures have been associated with a variety of systemic and autonomic manifestations.

Cardiovascular autonomic manifestations include alterations in heart rate and rhythm, blood pressure and electrocardiography (ECG)^[1].

Sinus tachycardia is the most frequently observed arrhythmia in patients with epilepsy, with a reported a frequency of 60%-100%^[1-3]. Heart rate acceleration has been shown to precede, follow or coincide with seizure^[1]. Bradyarrhythmias are rarely observed, occurring in less than 5% of all seizures^[1,4]. Sinus bradycardia, AV block and prolonged asystole have been reported in a variety of case reports and case studies^[1]. Most episodes have been shown to occur in the ictal state by simultaneous electroencephalography (EEG) and ECG monitoring systems. Ictal asystole (IA) has been reported to be observed in 0.27%-0.4% of patients during prolonged video EEG telemetry^[5,6]. Although rare, ictal bradyarrhythmias have substantial morbidity because they are related with sudden loss of consciousness (LOC), which may lead to falls and traumatic injuries. Ictal bradycardia (IB) and IA have also been suggested to be associated with sudden unexplained death in epilepsy (SUDEP), although evidence of association is limited^[7-9].

This review will focus on the pathophysiology and clinical presentation of ictal bradyarrhythmias and discuss the pacing need based on the available literature.

PATHOPHYSIOLOGY

The pathophysiology of ictal bradyarrhythmias is not entirely clear, and complex pathways have been believed to be involved in the central nervous system. Most seizure-related bradyarrhythmias have been observed in individuals with temporal lobe epilepsy and appear to be less frequent in patients with seizures originating from the frontal lobes and other brain regions^[8]. It has been hypothesized that seizure-related stimulation of certain brain regions, such as insular cortex, cingulate cortex, amygdala and hypothalamus, interferes with autonomic control of the heart *via* connections with autonomic nuclei of the brain stem and spinal cord^[10]. Seizure-induced stimulation of the central nervous system has been suggested to directly affect postganglionic discharges on the heart^[11]. A recent comprehensive review of literature data on seizure-related cardiac arrhythmias reported that ictal bradyarrhythmias have been observed during focal dyscognitive seizures and that they were mostly commonly observed in individuals with temporal lobe epilepsy^[12]. Some studies have suggested lateralization of foci related to ictal arrhythmias; *i.e.*, seizures originating from the right hemisphere have been suggested to be more frequently associated with ictal tachycardia and seizures originating from left hemisphere with ictal bradyarrhythmias^[5,13,14]. However, there are inconsistent data in the literature on this lateralization hypothesis^[15,16].

CLINICAL PRESENTATION

Sudden LOC is the major manifestation of prolonged IA

related to complex partial seizures. Clinical presentation with sudden LOC and related falls, as well as subsequent trauma, may be similar in clinical presentation to vasovagal syncope. Schuele *et al.*^[17] described similar heart rate patterns during asystolic events in patients with IA and vasovagal asystole, with a tendency for tachycardia preceding the asystolic event, which then evolved into progressive bradycardia and asystole. Based on these observations, the authors suggested that both IA and vasovagal asystole might be mediated through a similar mechanism, leading to increase in vagal tone. Cerebral hypoperfusion related to prolonged asystole appears to be responsible for sudden LOC in patients with IA rather than seizure-induced activation of cortical or subcortical regions. However, absence epilepsy should also be considered in patients with sudden impairments of consciousness. Absence epilepsy is primarily observed in children and adolescent patients and is characterized by sudden cessation of movement without convulsions, impairment of consciousness, fixation of gaze and sudden termination of the epileptic episode without postictal depression^[18]. Absence seizures are typically accompanied by bilateral 3-4 Hz spike-wave discharges on EEG^[18].

Arrhythmogenic epilepsy should be considered in the differential diagnosis of patients with syncope^[10,19]. Ictal bradyarrhythmias should particularly be suspected in patients with epilepsy and syncopal episodes^[10]. IA and symptomatic IB are commonly associated with complex partial seizures. Patients commonly present with seizure-related symptoms, such as staring, unresponsiveness, epigastric aura and oroalimentary and manual automatisms, preceding the syncope^[20]. Thus, patients with atypical signs and symptoms before a syncopal episode should also be evaluated for the presence of arrhythmogenic epilepsy. IA or symptomatic IB may also be the first ictal manifestation of new onset epilepsy, and a high degree of suspicion is necessary for diagnosis. Recently, Giovannini *et al.*^[21] published a literature review on IA cases (31 patients from 21 articles) in the context of new-onset/newly diagnosed epilepsy. They reported that symptoms suggestive of partial seizures preceding syncope were absent for most patients. Only 7 patients have been reported to display symptoms such as visual illusion, hallucinations, jamais vu, fear, psychic aura and epigastric aura prior to syncope. Four patients have been reported to display seizure-related motor activities, such as tonic-clonic contractions and automatisms. Simultaneous long-term video EEG and ECG recording appears to be the key diagnostic modality for arrhythmogenic epilepsy^[21]. Long-term subcutaneous implantable loop recorders have also been useful in selected cases^[22,23].

LITERATURE DISCUSSION

There is no guideline-directed therapy for IA or symptomatic IB due to the lack of randomized controlled trials^[24]. Therapeutic options for symptomatic ictal

bradyarrhythmias include anticonvulsive medications, epileptic surgery and/or cardiac pacemaker implantation. Currently, there is no universal agreement on the pacing indications for these patients. Some authors have suggested that IA is a benign phenomenon, and long-term data regarding the effectiveness of pacemaker therapy for IA are missing due to low recurrence rates^[17]. Schuele *et al.*^[25] and Moseley *et al.*^[26] suggested that IA promotes seizure termination by causing cerebral ischemia/anoxia. However, case studies have indicated that pacemaker implantation may reduce seizure-related falls and injuries^[24,27-29]. Giovannini *et al.*^[21] reported that most patients (21 of 31 patients) with IA in the context of new-onset/newly diagnosed epilepsy had undergone pacemaker implantation at the time of case report publications, although outcome data for these patients are unknown. Other studies have reported some discordant outcome findings after pacemaker implantation in patients with ictal bradyarrhythmias. Ghearing *et al.*^[27,28] reported outcome data for 7 patients with IA who had falls and LOC prior to pacemaker implantation. Only one patient experienced seizure-related falls after pacemaker implantation at a mean follow-up duration of 27 mo. Schuele *et al.*^[6] performed a database search for 6825 patients undergoing long-term video EEG monitoring for episodes of IA and found that IA was recorded in 10 patients (0.27% of all patients with epilepsy). Pacemaker implantation had been performed in 6 of these patients, and none of these patients reported recurrent IA or significant bradycardia leading to pacemaker activation. However, 4 patients had been reported to have recurrent and multiple seizures after pacemaker implantation. Moseley *et al.*^[29] reported the outcome data of seven patients with IA who had a pacemaker implanted in their institution between 1990 and 2004. The authors stated that the mean fall rate was significantly reduced from 3.28 to 0.005 falls/month after pacemaker implantation. Seizure-related fractures and motor vehicle accidents were also reduced following pacemaker implantation.

Strzelczyk *et al.*^[24] reviewed 16 patients with IA or IB from 4 epilepsy centers who had been evaluated between 2002 and 2009. They reported that pacemaker implantation had been performed in 7 of these patients (43.8%). Outcome data were available for 43 patient-years. Accordingly, 5 patients (31.3%) were seizure-free in the follow-up period; 2 of these patients had experienced epilepsy surgery, 2 had received anticonvulsive therapy, and 1 had received pacemaker implantation. Nine patients (56.3%) had persisting seizures but without seizure-associated falls; 3 of these patients had received anticonvulsive therapy, and 6 had received pacemaker implantation. Two patients (12.5%) who denied epileptic surgery and did not receive pacemaker implantation had persisting seizures and continuous falls. Based on these observations, the authors proposed a clinical algorithm for treating patients with symptomatic ictal bradyarrhythmias. They recommend that cardiac pacemaker should be

considered for symptomatic patients after optimizing antiepileptic therapy and discontinuing any coexisting arrhythmogenic medications. Recently, Bestawros *et al.*^[30] reported outcome data of 8 patients with IA who received pacemaker therapy. The authors stated that all patients remained free of syncope during a follow-up of 72 ± 95 mo.

Although most patients continued to have seizures after pacemaker implantation in the above-mentioned studies, some papers have suggested decreases in the number of seizures and in seizure intensity after pacemaker implantation^[31,32]. The mechanism of this unexpected finding is unclear; however, it has been suggested to be related to the effect of cardiac pacing on cardiac vagal afferents and their connections to the brain^[29]. However, in our opinion, a placebo effect of cardiac pacemaker implantation cannot be excluded, similar to the suggestion for vasovagal syncope^[33].

CONCLUSION

There is increasing awareness for ictal bradyarrhythmias as a cause of LOC in the cardiology community. A high degree of suspicion is necessary for diagnosing ictal bradyarrhythmias, and a delay in diagnosing this condition may lead to substantial morbidity for the patient. Based on the available data, a cardiac pacemaker might be related to decreased morbidity associated with falls and trauma. However, literature data also suggest that optimization of anticonvulsive therapy might be effective in preventing ictal bradyarrhythmias. In our opinion, pacemaker therapy should be reserved for patients who remain symptomatic after optimizing anticonvulsive therapy. Currently, no data are available related to any effect of cardiac pacemaker implantation on preventing SUDEP. Such evidence would be very useful for a potential indication of pacemaker therapy. The results of a randomized controlled study are urgently needed to clarify the pacemaker need in patients with ictal bradyarrhythmias.

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