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Ictal bradycardia in partial epileptic seizures
Autonomic investigation in three cases and literature review

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Summary
Ictal bradycardia is a rare, probably underestimated, manifestation of epileptic seizures whose pathophysiology is still debated. Autonomic modifications may result either from a sympathetic inhibition or from a parasympathetic activation probably due to the ictal discharge arising from or spreading to the structures of the central autonomic network. We review 60 cases of ictal bradycardia from the available literature and present three additional cases associated with left temporal lobe seizures studied by autonomic polygraphic ictal monitoring. Only 47 of the 63 reported cases were documented by simultaneous EEG and ECG recordings during an attack. About 76% of patients in whom well-localized ictal discharges were recorded had temporal or frontotemporal lobe seizures. Forty-five cases included information allowing confident localization of the side of ictal onset, and a 26 : 19 ratio of the left versus right side was evident. Simultaneous monitoring of ECG and other autonomic parameters during EEG recording in partial seizures should be performed to gain more insight into ictal semiology. Correlation of the symptoms referred to by patients with changes in autonomic parameters could avoid erroneous diagnosis of non-epileptic attacks and disclose a potentially lethal condition. Our cases confirm the preferential role of the left hemisphere in the genesis of ictal bradycardia and shed light on the relationship between suprabulbar control of autonomic function and partial epileptic seizures.

Keywords: partial seizures; arrhythmogenic seizures; bradycardia; vegetative ictal symptoms; autonomic system

Abbreviations: BP = blood pressure; HR = heart rate

Introduction
Ictal epileptic discharges can often cause changes in cardiac rhythm. Increased heart rate is the most frequent finding: ictal tachycardia occurs in 64–100% of temporal lobe seizures (Marshall *et al.*, 1983; Blumhardt *et al.*, 1986; Smith *et al.*, 1989).

Almost a century ago, decades before the introduction of EEG or polygraphic monitoring, Russell clinically observed the cessation of the pulse during a seizure in a young man (Russell *et al.*, 1906). Since then, 60 anecdotal cases have been reported in which ictal episodes were accompanied by slowing of the heart rate or asystole. Bradycardia during complex partial seizures has been labelled ictal bradycardia syndrome (Reeves *et al.*, 1996). The true incidence of this rare, potentially life-threatening, condition is probably underestimated. Diagnosis of ictal bradycardia is based on documentation of bradycardia/asystole clearly produced by a concomitant ictal discharge documented on EEG. Misdiagnosis is common because patients with paroxysmal bradyarrhythmias are usually admitted to coronary care units or to cardiology services where simultaneous EEG–ECG monitoring is not routine, and cardiologists consider abnormal heart rhythm only from a cardiac perspective (Jacome and Serropian, 1995; Van Rijckevorsel *et al.*, 1995). On the other hand, neurologists rarely include polygraphic recordings in patients undergoing intensive monitoring for partial seizures, and ictal autonomic modifications are therefore missed. Also for these reasons, ictal bradycardia has been reported in $<6\%$ of complex partial seizures (Smith *et al.*, 1989; Schernthaner *et al.*, 1999; Nei *et al.*, 2000). Approximately one-quarter of patients with ictal bradycardia for whom age is reported were at least 60 years old. This is precisely the age group in which the incidence of partial epilepsy rises significantly. Therefore, we would expect the prevalence of ictal bradycardia to increase either due to the rapid expansion of the elderly portion of our population, or as a result of increased recognition (Reeves *et al.*, 1996).

Getting the diagnosis right is essential because appropriate treatment could prevent sudden unexpected death in epileptic

patients, which, on the evidence of many experimental and clinical studies, is thought to be related to potentially lethal arrhythmias, such as asystole, induced by epileptic seizures (Lathers and Schraeder 1982; Schraeder and Lathers 1989; Oppenheimer *et al.*, 1990; Mameli *et al.*, 1993).

We describe three patients with temporal lobe epilepsy in whom a left temporal lobe seizure was associated with ictal bradycardia. In addition, we review the available literature for similar cases.

Patients and methods

Electrophysiology

In the last 3 years we have studied three patients presenting with partial seizures in which video-polygraphic recordings revealed bradycardia during focal epileptic seizures. Video-EEG documents were reviewed to define seizure semiology and the topographic localization of the ictal discharges. Electrodes were placed according to the 10–20 International System. Bipolar montage and zygomatic leads were used in Case 2 with electrodes placed over the zygomatic notch in the posterior portion of the cheek, 2 cm beyond the tragus (Sindrup *et al.*, 1981). In a separate session we explored the autonomic nervous system changes associated with the seizures. Together with EEG we monitored ECG, plethysmogram, oronasal and abdominal breathing, blood pressure (BP) continuously and non-invasively by means of Portapress-model II (TNO, Biomedical Instrumentation, Amsterdam, The Netherlands). An algorithm (finger to brachial level correct), utilized by the Beatfast computer program, was applied to correct the mean pressure to avoid erroneous estimation of absolute values. We also performed interictal autonomic investigations: patients were studied in a temperature controlled (23 ± 1°C) room with continuous monitoring of systemic BP, heart rate (HR) and respiratory rate. After 30 min of supine rest, head-up tilt, Valsalva manoeuvre and deep breathing were performed using standard procedures (Matthias and Bannister, 1999). The results of testing procedures during the interictal period were compared with the reference range obtained in our control subjects (mean ± 2 SD). The control group consisted of 18 healthy volunteers. Each patient underwent MRI of the brain and cardiological investigations.

We carried out a retrospective analysis of previously reported cases of ictal bradycardia with respect to age, sex, site of ictal onset, ictal recording, neuroradiological features and possible supporting data. Other reported cases, mentioned in abstract form with scant clinical and electrophysiological data were not included in our analysis (Radtke, 1989; Volpi *et al.*, 1995). Moreover, we excluded cases in which bradycardia appeared during apnoeic seizures in children (Coulter, 1984; Hewertson *et al.*, 1996), or followed a precocious phase of tachycardia (Nousiainen *et al.*, 1989*)*. Finally, we excluded reports of bradycardia, thought to be epileptic but in which the electrophysiological data did not support such a hypothesis, in particular, the case described by Ossentjuk (Ossentjuk *et al.*, 1966) and previously reported in another review (Constantin *et al.*, 1990) in which the relationship between bradycardia and ictal discharge was not certain.

Results

Case 1

A 30-year-old left-handed man with an unremarkable family and personal history, presented at 17 years of age with

Table 1 *Results of interictal autonomic function tests in our patients compared with 18 healthy controls (mean ± 2 SD)*

Test	Controls n = 18 (51 ± 7 years)	Patient 1 (30 years)	Patient 2 (42 years)	Patient 3 (81 years)
Tilt test				
Supine				
MAP (mmHg)	78 ± 11	84	91	71
HR (beats/min)	61 ± 7	61	82	62
10 min at 65°				
ΔMAP (mmHg)	+8 ± 6	14	17	16
ΔHR (beats/min)	+10 ± 6	16	26	25
Valsalva manoeuvre				
Phase II_L				
DBP (mmHg)	83 ± 7	95	120	75
Phase IV				
SBP (mmHg)	170 ± 20	160	222	153
VR	1.62 ± 0.3	1.779	2.091	1.209
Deep breathing				
ΔHR (beats/min)	+16 ± 7	21	13	8

MAP = mean arterial pressure; DBP = diastolic BP; SBP = systolic BP; Δ = change with respect to the basal value; Phase II_L = late phase II of Valsalva; Phase IV = overshoot; VR = Valsalva ratio = HR phase II/HR phase IV; Deep breathing ΔHR = maximum – minimum change of HR.

seizures characterized by loss of contact without warning, pallor, staring, gestural automatisms and sometimes unintelligible speech. Seizure duration was ~5–15 s, without post-ictal confusion or aphasia. At our first observation, seizure frequency was one every 2–3 months, despite antiepileptic drug treatment with carbamazepine 1200 mg/day. We tapered carbamazepine adding lamotrigine 200 mg/day, which failed to reduce the frequency of seizures in 18 months of follow-up.

Neurological examination was normal. Interictal EEG showed left frontotemporal theta activity and diffuse sharp waves, prevalent over the left temporo-parieto-occipital region. Interictal autonomic investigations and 24-h ECG monitoring were normal (Table 1). MRI of the brain was normal. Ictal EEG showed, after a diffuse desynchronization of background rhythm, paroxysmal rhythmic theta activity more evident in the left region, followed by paroxysmal sharp waves in both hemispheres with anterior prevalence. During the ictal discharge, a progressive bradycardia occurred without significant modification of the respirogram.

During supine polygraphic autonomic monitoring another identical seizure was recorded. Ten seconds after the clinical onset of the seizure, the patient's BP decreased progressively to a minimum of 60/40 mmHg and sudden bradycardia (46 beats/min) occurred. A plethysmogram showed a signal of increased amplitude. The respiratory rate did not change significantly (Fig. 1).

Case 2

A 42-year-old right-handed woman, suffering from migraine without aura, and with an unremarkable family history, began having seizures at 38 years of age, characterized by a gastric aura and a warm feeling in the chest, rising to her face, with facial flushing followed sometimes by oro-alimentary automatisms. After this she would lose consciousness and, if standing up, fall to the ground. Enuresis sometimes occurred. Seizures lasted <1 min and occurred in perimenstrual clusters. Antiepileptic drug treatment with phenytoin 350 mg/day progressively reduced seizure frequency in three years of follow-up. Neurological examination and 24-h ECG monitoring showed normal results. Interictal EEG showed focal spikes over the left temporal region. Interictal autonomic investigations showed a higher HR at rest and a hyper-sympathetic response to the Valsalva manoeuvre and tilt test with respect to the reference range obtained from our control subjects (Table 1). MRI of the brain disclosed a left mesiotemporal lesion, not enhanced by gadolinium contrast, with a diameter of 5 mm causing a minimal dislocation of the left temporal horn.

Ictal EEG showed disappearance of the interictal abnormalities on the left temporal region followed by a slow amplitude fast activity, subsequently replaced by a prolonged sharp wave discharge that remained confined to the left temporal area (Fig. 2). From the beginning of the discharge there was a progressive slowing of HR and peak bradycardia that coincided with the patient's facial flushing. Normal HR was regained at the end of the seizure.

During polygraphic autonomic recording in the supine condition, another identical seizure was recorded. Eight seconds after seizure onset, a sudden bradycardia (30 beats/min) occurred and persisted for 30 s. BP concomitantly decreased to a minimum of 75/44 mmHg 39 s after seizure onset. BP normalized 3 min after seizure onset. A plethysmogram showed a signal of increased amplitude. The respiratory rate did not show significant changes (Fig. 3).

Case 3

An 81-year-old right-handed man with an unremarkable family history had long-standing hypertension and chronic liver disease after HCV (hepatitis C virus) infection. At 78 years of age, episodes with loss of consciousness began, which were first diagnosed as syncopes. He underwent prolonged ECG monitoring (Holter ECG) that gave normal results. Afterwards, a tonic–clonic seizure diagnosis of epilepsy was made and antiepileptic treatment started. According to our observations 2 years after seizure onset, attacks were characterized by loss of contact, swallowing and pallor without warning. If standing up, he fell down unconscious, staring and unresponsive; in addition some right hand movements might occur. Seizure duration was <1 min, followed by confusion with amnesia and tiredness for 10 min. He had five seizures in 3 years. Phenytoin at a dose of 300 mg completely controlled the seizures.

Neurological examination showed slight extrapyramidal signs in the upper limbs. Interictal autonomic investigations (Table 1) and EEG were normal. Brain CT and MRI scans revealed a mild cortical and subcortical cerebral atrophy and small ischaemic lesions in the periventricular white matter and basal nuclei. Ultrasonography of blood flow in the cerebral vessels showed 35–40% left internal carotid stenosis at the origin, and mild external and internal left carotid and left subclavian artery stenosis. An electrophysiological intracavitary heart study showed normal functioning of the sinoatrial node and normal conduction under the bundle of His. Twenty-four hour ECG monitoring was normal. Ictal EEG and ECG recording, with the patient lying down, showed, at seizure onset, a rhythmic theta activity on the left frontotemporal region after muscle artefacts had been observed (Fig. 4). At the same time, HR progressively decreased until the end of the seizures (from 63 to 36 beats/min). Coincident with the start of the EEG discharge the patient turned pale, lost consciousness and started swallowing and then remained unresponsive for 1 min. At the end of the seizures he could not remember objects shown to him during the attack. No other episode recurred during autonomic recording.

Literature cases

Tables 2 and 3 list the clinical features of the cases previously described in the literature in chronological order. Table 2

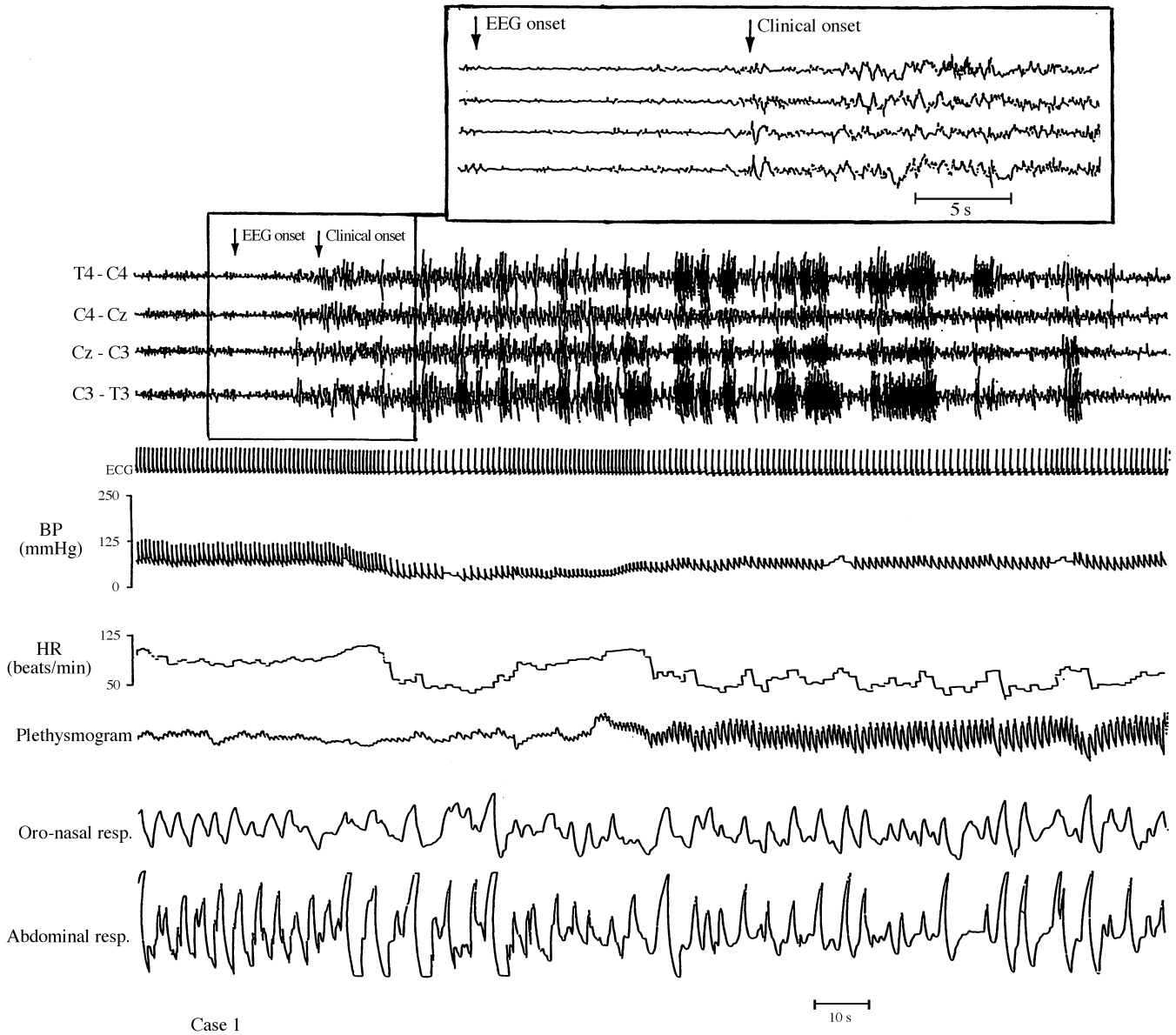

Fig. 1 Case 1: ictal polygraphic recording on a compressed time scale. EEG of seizure onset was characterized by a slow amplitude fast activity (enlarged detail on the top of the figure) followed by a high amplitude spike and wave complex on the left derivations. This was subsequently replaced by a prolonged sharp wave discharge more evident on the left temporal area. After seizure onset there was a sudden and sustained BP fall associated with bradycardia. A plethysmogram showed a signal of increased amplitude. The respiratory rate did not show significant changes. Resp. = respiration.

lists those cases (Katz *et al.*, 1983; Gilchrist, 1985; Blumhardt *et al.*, 1986; Rabending and Fisher, 1986; Bertholds *et al.*, 1988; Jacome and Serropian, 1988; Howell and Blumhardt, 1989; Tamara *et al.*, 1989; Lucas *et al.*, 1991; Fincham *et al.*, 1992; Liedholm and Gudjonsson, 1992; Wilder-Smith, 1992; Munari *et al.*, 1995; Van Rijckevorsel *et al.*, 1995; Nashef *et al.*, 1996; Reeves *et al.*, 1996; Devinsky *et al.*, 1997; Jallon, 1997*b*; Iani *et al.*, 1997; Kowalik *et al.*, 1998; Manitius-Robeck *et al.*, 1998; Saussu *et al.*, 1998; Kahane *et al.*, 1999; Nei *et al.*, 2000) in which simultaneous ictal EEG–ECG recording was available, including our cases. Table 3 lists those observations in which only EEG or ECG (Phizackerley *et al.*, 1954; Pritchett *et al.*, 1980; Devinsky *et al.*, 1986; Kiok *et al.*, 1986; Smaje *et al.*, 1987; Constantin *et al.*, 1990; Joske and Davis, 1991; Jallon, 1997*a*), or neither (Constantin *et al.*, 1990; Smaje *et al.*, 1987) were available during the seizures. Data reported by the authors to support the diagnosis of ictal bradycardia are added.

Discussion

A number of studies have been performed both in man and different animal models to identify the components of the central autonomic network involved in the functional relationships between cortical and subcortical centres in

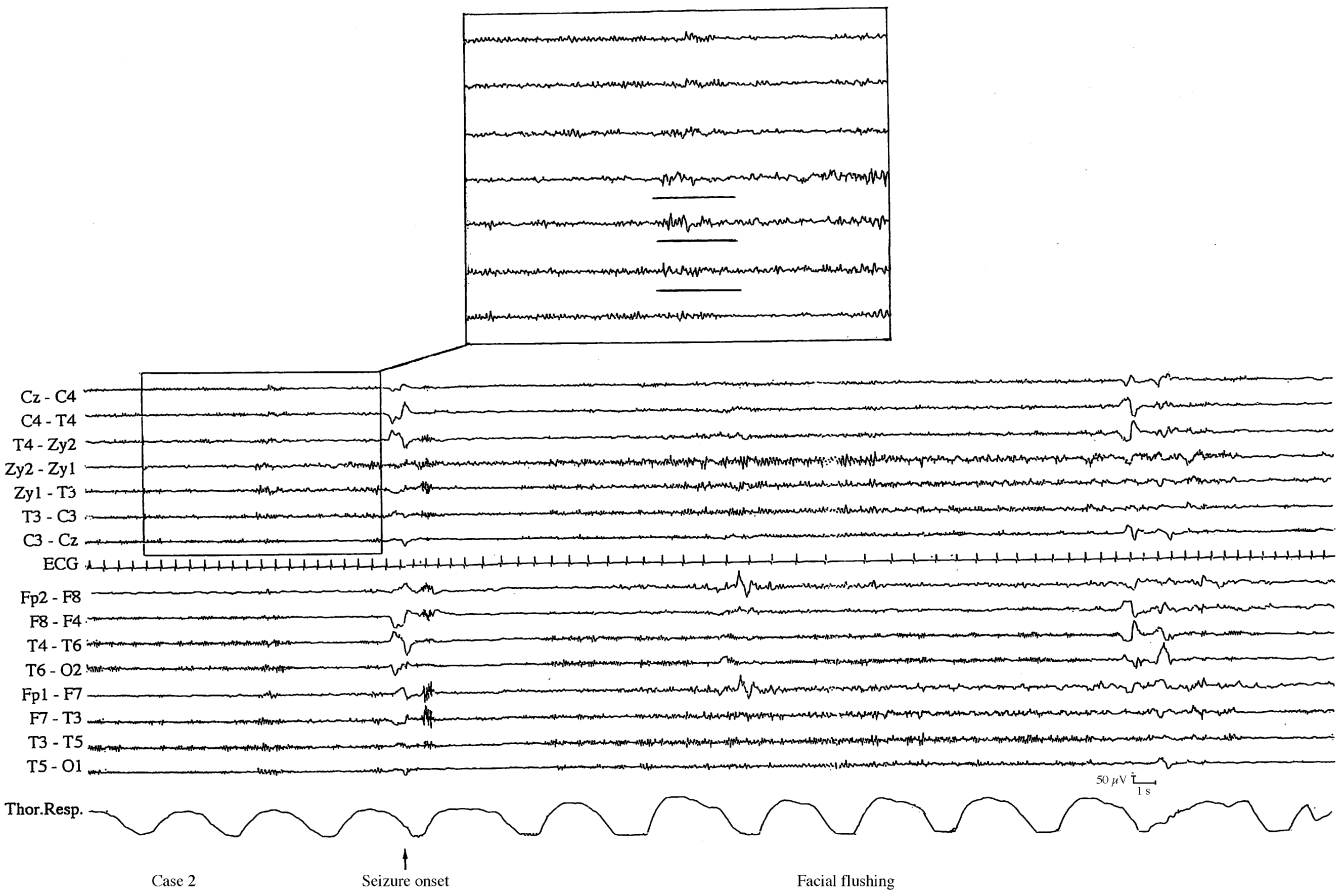

Fig. 2 Case 2: ictal EEG. EEG seizure onset is characterized by the disappearance of the interictal abnormalities on the left temporal region with the onset of a slow amplitude fast activity (enlarged detail on the top of the figure) subsequently replaced by a prolonged sharp wave discharge that remained confined to the left temporal area. From the beginning of the discharge there was a progressive slowing of heart rate, peak bradycardia coinciding with the patient's facial flushing. Normal heart rate was regained at the end of the seizure. Clinical onset (↑). Thor.Resp. = thoracic respiration.

cardiovascular control (Lathers *et al.*, 1987; Bennaroch, 1997).

Early studies on simultaneous recording of autonomic functions during spontaneous and pentylenetetrazole-induced temporal lobe seizures described a stereotyped response consisting of hypertension, tachycardia, decreased skin resistance and plethysmogram, swallowing, inhibition of respiration and gastric motility (Van Buren, 1958; Van Buren and Ajmone-Marsan, 1960; Van Buren *et al.*, 1961).

Since then, both stimulation and ablation experiments have demonstrated that limbic structures modulate hypothalamic functions (Van Buren *et al.*, 1961; Gloor, 1975; Wannamaker, 1985). Electrical stimulation of limbic structures (especially the amygdala and periamygdaloid pyriform cortex) can produce autonomic changes, including cardiovascular responses, mediated by either sympathetic or parasympathetic pathways, which change the excitatory state at lower levels of the central representation of the autonomic system (Gloor, 1975). Electrical stimulation of the cingulate gyrus and orbitofrontal cortex has also produced changes in HR (Pool and Ransohoff, 1949; Kaada, 1951; Wall and Davis, 1951; Van Buren *et al.*, 1961; Oppenheimer *et al.*, 1990) and cases of ictal bradycardia related to orbitofrontal lobe seizures have been reported (Munari *et al.*, 1995). The insular cortex, the central nucleus of the amygdala and some structures of the hypothalamus (paraventricular nucleus, lateral hypothalamic area and dorsomedial nucleus) belong to the central autonomic network (Benarroch, 1997), which controls pre-ganglionic sympathetic and parasympathetic viscero-motor outputs. Mesial temporal and frontal areas are inter-connected to the central autonomic network so that ictal discharges arising from or spreading to these regions are more likely to induce autonomic changes. Within the temporal lobe, the insula might be the cortical area involved in the genesis of changes in cardiac rhythm during partial seizures.

A left/right asymmetry in suprabulbar control of autonomic function is supported by experimental studies (Critchley *et al.*, 2000, 2001). Intraoperative stimulation of the left insular cortex produces bradycardia and hypotension, while stimulation of the same structures on the right side produces tachycardia and hypertension (Oppenheimer *et al.*, 1992). On the other hand, unilateral hemispheric inactivation with

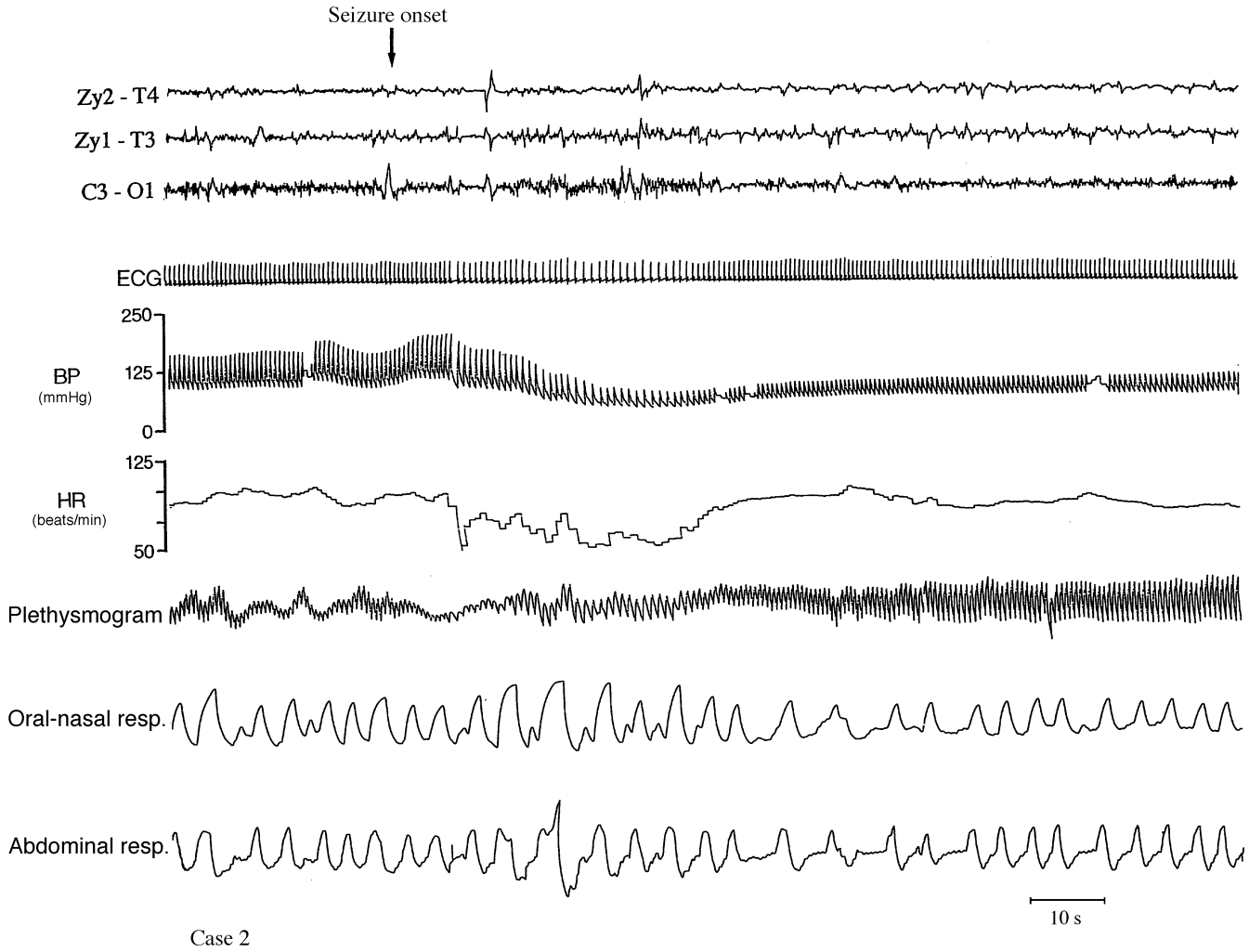

Fig. 3 Case 2: ictal polygraphic recording on a compressed time scale. Eight seconds after seizure onset a sudden bradycardia, 30 beats/min, lasting 30 s with a concomitant BP decrease to a minimum of 75/44 mmHg 39 s after seizure onset occurred. BP normalized 3 min after seizure onset. The plethysmogram showed a signal of increased amplitude. The respiratory rate did not show significant changes. Resp. = respiration.

intracarotid amobarbital infusion produces tachycardia when performed on the left side and bradychardia when applied on the right side (Zamrini *et al.*, 1990). It seems, therefore, that a cerebral lesion or a focal seizure may disrupt the hemispheric influence on autonomic centres of the brainstem. Recent PET studies have described significant changes in regional blood flow of different cerebral areas during peripheral sympathetic or parasympathetic activities: the right anterior cingulate gyrus, right insula, cerebellum and brainstem were activated during peripheral cardiovascular arousal, whereas the amygdala, hippocampus, prefrontal cortex, left insula and regions of the cingulate gyrus, cerebellum and brainstem showed decreased cardiovascular arousal, corresponding perhaps to parasympathetic autonomic activity (Critchley *et al.*, 2000). In contrast, the cardiac effects of the amytal test in a larger population of patients with complex partial epilepsy have suggested that the right hemisphere may have preferential access to vagal systems affecting HR (Ahern *et al.*, 2001). Eleven cases of ictal bradycardia with intracranial monitoring have been described (Munari *et al.*, 1995; Devinsky *et al.*, 1997; Manitius-Robeck *et al.*, 1998; Kahane *et al.*, 1999; Altenmüller *et al.*, 2000), but only two of them reported ictal EEG and its correlation with the onset of bradycardia. In the first case (Devinsky *et al.*, 1997), that of a right-handed man, the seizure onset was localized in the left temporal lobe, but the cardiac changes occurred after the seizure had spread to the right mesial temporal lobe. However, the authors did not record directly from the insula and the sinus arrest may have resulted from the seizure spread to the left insula. In the second case, that of a left-handed woman, bradycardia occurred during seizures originating in the right frontocentral and temporal neocortical areas (Kahane *et al.*, 1999).

Reviewing the cases of ictal bradycardia described in the literature and our personal observations, only 47 (for references, see Table 2) out of the 63 reported cases were

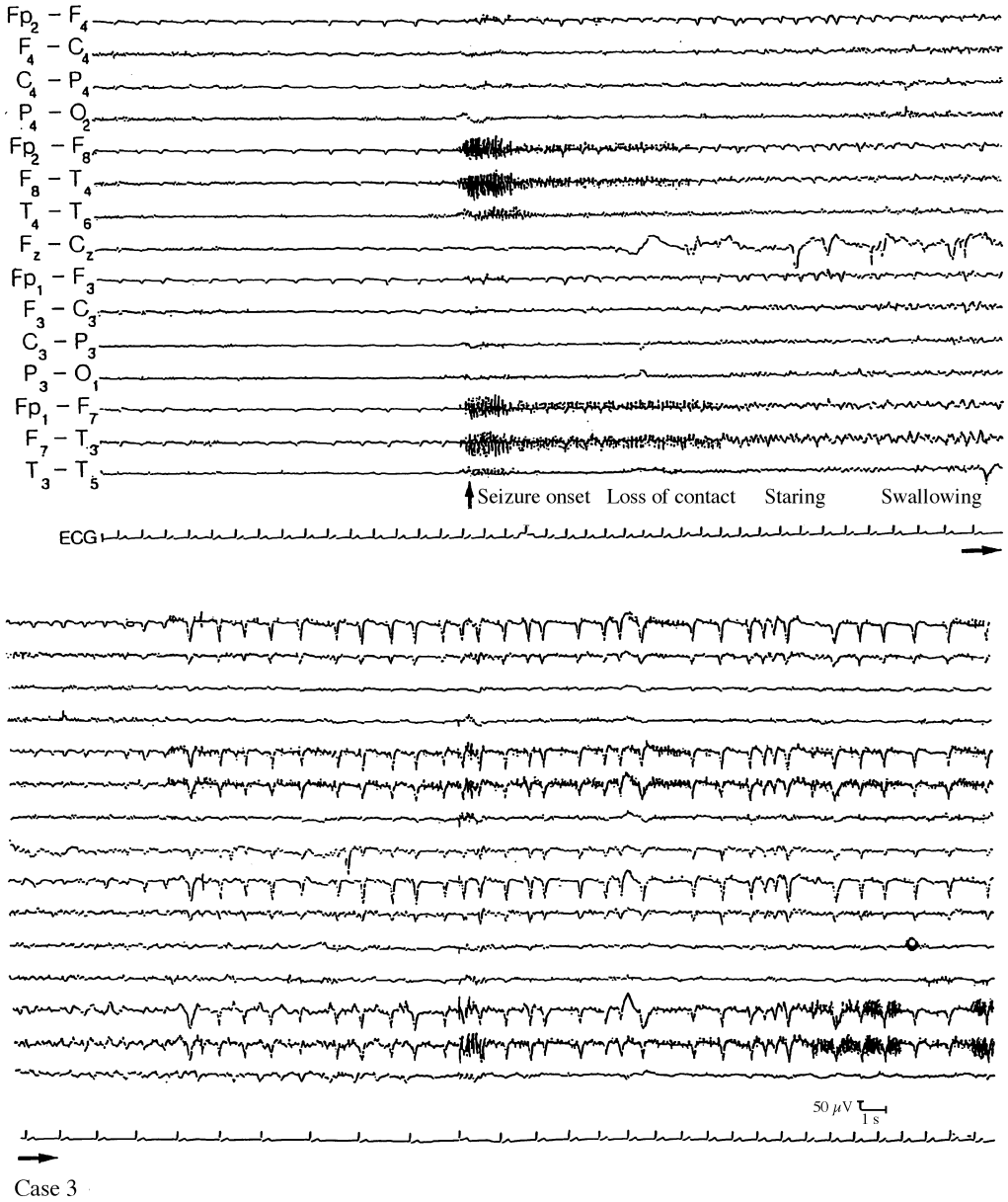

Fig. 4 Case 3: ictal EEG and ECG. The onset of the electrographic seizure was partially masked by a muscle artefact. A few seconds later a paroxysmal discharge appeared over the left temporal region accompanied by a progressive slowing of HR. Normal rhythm was regained at the end of the seizure.

documented by simultaneous EEG and ECG recordings during an attack, and 46 out of 63 cases (Katz *et al.*, 1983; Gilchrist, 1985; Blumhardt *et al.*, 1986; Kiok *et al.*, 1986; Rabending and Fisher, 1986; Bertholds *et al.*, 1988; Jacome and Serropian, 1988; Howell and Blumhardt, 1989; DiLuzio and Rutecki, 1989; Lucas *et al.*, 1991; Fincham *et al.*, 1992; Liedholm and Gudjonsson, 1992; Wilder-Smith, 1992; Munari *et al.*, 1995; Van Rijckevorsel *et al.*, 1995; Reeves *et al.*, 1996; Devinsky *et al.*, 1997; Iani *et al.*, 1997; Jallon, 1997*a*, *b*; Kowalik *et al.*, 1998; Manitius-Robeck *et al.*, 1998; Saussu *et al.*, 1998; Kahane *et al.*, 1999; Nei *et al.*, 2000) included information that allowed confident localization of ictal onset.

The majority (31 out of 46) of these patients had seizures originating from the temporal lobes. The frontal lobe was involved in 13 cases, and in four of these cases the temporal lobe was involved as well. A seizure onset from the orbital portion has been documented in six patients. In one case, EEG recording montages were limited to two channels that did not allow an exact localization, although the visual aura suggested an initial involvement of the occipital lobe (Fincham *et al.*, 1992). In another case, the lateralization of

Table 2 *Data from the literature (our data added) of cases with simultaneous ictal recordings of EEG and ECG*

Age (years)/ sex/D. H.	Loc.	Ictal recording	Rhythm	NMR/CT/path	Authors
NA	RT	EEG + ECG	As	–	Katz *et al*., 1983
NA	RT	EEG + ECG	As	–	Katz *et al*., 1983
22/M	LT	EEG + ECG	Br/As/Tc	CT nn	Gilchrist, 1985
35/F	RT	EEG + ECG	Br/As	–	Rabending and Fisher, 1986
NA	T	EEG + ECG	Br	NA	Blumhardt *et al*., 1986
69/M	RT	EEG + ECG	Br	CT nn	Jacome and Serropian, 1988
62/M	LT	EEG + ECG	As	–	Bertholds *et al*., 1988
56/F	RT	EEG + ECG	As	–	DiLuzio and Rutecki, 1989
55/M	LH	EEG + ECG	As	–	Howell and Blumhardt, 1989
62/M	LT	EEG + ECG	Br	MR nn	Lucas *et al*., 1991
68/M	RO	EEG + ECG	Br/As	CT nn	Fincham *et al*., 1992
38/F/R	LT	EEG + ECG	As	CT nn	Liedholm and Gudjonsson, 1992
56/F	LT	EEG + ECG	Br	CT nn	Wilder-Smith, 1992
25/M	LT	EEG + ECG	Br	CT nn	Van Rijckevorsel *et al*., 1995
4m/M	LT	EEG + ECG + RESP	Br	–	Van Rijckevorsel *et al*., 1995
Six patients	F	SteEEG + ECG	Br	NA	Munari *et al*., 1995
Four patients	NA	EEG + ECG + RESP	Br/As	NA	Nashef *et al*., 1996
44/M	LT	EEG + ECG	Br	MR nn	Reeves *et al*., 1996
60/M	RT	EEG + ECG	Br/As	MR nn	Reeves *et al*., 1996
17/M	BiT	EEG + ECG	Br/As	CT nn	Reeves *et al*., 1996
72/F	LT	EEG + ECG	Br	MR nn	Reeves *et al*., 1996
71/M	RT	EEG + ECG	As	MR RT aneurysm	Jallon, 1997*b*
42/M/R	LT	SubEEG + ECG	As	MR R hippocampal atrophy	Devinsky *et al*., 1997
39/M	RT	EEG + ECG	Br	Path RT astrocytoma	Iani *et al*., 1997
36/M/R	LFT	EEG + ECG	Br	MR LF atrophy	Saussu *et al*., 1998
36/F	RT	SubEEG + ECG	As	Path RT neocor. Haematoma	Manitius-Robeck *et al*., 1998
29/M	RT	EEG + ECG	As	Path RT ganglioglioma	Manitius-Robeck *et al*., 1998
38/M	LT	SubEEG + ECG	As	Path LT hippocampal gliosis	Manitius-Robeck *et al*., 1998
50/M	LT	EEG + ECG	Br/As	MR: nn	Kowalik *et al*., 1998
27/F	LT	EEG + ECG	As	MR LF venous malformation	Kowalik *et al*., 1998
20/F/L	RFT	SteEEG + ECG	Br	MR hypothalamic haematoma	Kahane *et al*., 1999
Three patients	FT	EEG + ECG	Br	NA	Schernthaner *et al*., 1999
NA	LT	EEG + ECG	As	NA	Nei *et al*., 2000
46/F	LT	SubEEG + ECG	AVblock	NA	Altenmüller *et al*., 2000
30/M/L	LFT	EEG + ECG + RESP	Br	MR nn	Present study
42/F/R	LT	EEG + ECG + RESP	Br	MR LT non-specific lesion	Present study
81/M/R	LFT	EEG + ECG	Br	MR cortical atrophy	Present study

D. H. = dominant hand; Loc. = location; NMR = nuclear magnetic resonance; Path = pathology; NA = not available; m = months; M = male; F = female; L = left; R = right; Bi = bilateral; T = temporal lobe; F = frontal lobe; O = occipital lobe; H = hemispheric; EEG + ECG = simultaneous; RESP = respirogram; SteEEG = stereo-EEG; subEEG = subdural-EEG; Br = bradycardia; As = asystole; Tc = tachydysrhythmia; AV = atrioventricular block; nn = normal; – = not performed.

the discharge was determined without a precise localization (Howell and Blumhardt, 1989). Other reported cases either had specific EEG data omitted (Russell *et al.*, 1906; Joske and Davis, 1991), or had no recordings of any ictal disharges (Phizackerley *et al.*, 1954; Pritchett *et al.*, 1980; Devinsky *et al.*, 1986; Smaje *et al.*, 1987; Constantin *et al.*, 1990). Among the 47 cases documented by simultaneous EEG–ECG monitoring, the side of ictal onset discharge was only clearly evident in 32: left in 20 patients and right in 12. Considering also those cases of ictal bradycardia in which ictal onset was assumed solely on the basis of interictal EEG, a 26 : 19 ratio of the left versus right side was evident. In our three cases we recorded a paroxysmal discharge clearly confined to the left temporal areas concomitant with the beginning of the bradycardia.

Therefore, our data and the literature cases weigh against the idea that the right hemisphere has a preferential role in producing the ictal bradycardia, even if we cannot rule out that the left focal discharge, inhibiting the left tachy-arrhythmogenic hemisphere, releases the bradycardic influence of the contralateral hemisphere. However, this is speculation and the preferential role of the left hemisphere seems the most likely explanation of ictal bradycardia in agreement with the above experimental and clinical studies. Another hypothesis is that there is a relationship between dominancy and lateralization of seizures producing

Table 3 *Data from literature of cases without simultaneous ictal recording of EEG and ECG*

Age (years)/ sex/D. H.	Loc.	Ictal recording	Supporting data	Rhythm	NMR/CT/ pathology	Authors
21/M	NA	Pulse monitoring	Clinical history	As	–	Russell, 1906
71/F	RT	ECG	EEG	As	–	Phizackerley *et al*., 1954
21/M	RT	ECG	EEG; resp to CBZ	Br/Var	–	Pritchett *et al*., 1980
15/M	LT	ECG	EEG; resp to PHT	Br/Var	–	Pritchett *et al*., 1980
23/M/R	RT	EEG/ECG	NA	As	CT RT atrophy	Kiok *et al*., 1986
62/M	NA	Pulse monitoring	Resp to PRM Br	CT nn		Devinsky *et al*., 1986
19/M	BiF	ECG	EEG; resp to CBZ	Br/As	CT nn	Devinsky *et al*., 1986
35/M	LT	Pulse monitoring	EEG	Br/As	CT craniopharyng.	Smaje *et al*., 1987
47/M	LT	ECG	EEG; resp to PHT	Br	CT nn	Constantin *et al*., 1990
59/M	LT	–	EEG/ECG resp to CBZ	Br	CT nn	Constantin *et al*., 1990
43/M	L > RFT	ECG	EEG; resp to PHT	Br	MR not significant	Constantin *et al*., 1990
37/M	LT	ECG	EEG; resp to PHT	Br	MRI nn	Constantin *et al*., 1990
39/M	R > LT	ECG	EEG; resp to PHT	Br	MR RT lobe atrophy	Constantin *et al*., 1990
44/M	RT	ECG	Clin his resp to CBZ	As	Path RT glioblastoma	Joske and Davis, 1991
32/F	RT	EEG	NA	As	-	Jallon *et al*., 1997
22/M	RT	EEG	NA	Br	Tumour	Jallon *et al*., 1997

In the tables the sex and age of the patients have been reported when available from the cited papers. Supporting data = data supporting the diagnosis of ictal bradychardia; clin his = clinical history; resp = responsive; PHT = phenytoin; CBZ = carbamazepine; PRM = primidone; Var = various arrhythmias present. For other abbreviations see Table 1.

bradycardia but, as hand preference has been reported in few patients with ictal bradycardia (nine out of 63), this hypothesis remains speculative.

Nashef described four cases in which transient bradycardia or sinus arrest always occurred with a change in respiratory pattern and suggested that bradycardia may be enhanced by cardiorespiratory reflexes, with apnoea playing a central part and hypoxia providing an additional contributory factor (Nashef *et al.*, 1996). He concluded that the interpretation of bradyarrhythmias is incomplete without simultaneous recording of respiration, which has been reported in the literature in only one case (Van Rijckevorsel *et al.*, 1995). We only monitored the respiratory rate in Cases 1 and 2. They presented minor breathing changes during the seizures, affecting amplitude but not frequency, and no apnoeic or anoxic events were recorded. Therefore, we believe that, in our cases, the possibility that bradycardia was enhanced by cardiorespiratory reflexes is unlikely. A more likely interpretation of the breathing changes associated with ictal bradycardia is that the ictal discharge could activate central regions, causing both bradycardia and apnoea; in fact, the electrical stimulation of the frontotemporal lobe in man gave results that seem to support this hypothesis (Bailey and Sweet, 1940; Van Buren *et al.*, 1960).

Documenting ictal bradyarrhythmias during epileptic seizures is relevant in patient management for two main reasons: to avoid undesirable cardiac side-effects of antiepileptic treatment and to prevent potentially life-threatening events such as sudden unexpected death in epileptic patients. Ictal bradycardia *per se* is not a particular concern, but it could reflect more dangerous events such as heart block and asystole. These life-threatening situations have been disclosed in studies on cat models of ictal bradyarrhythmias leading to complete heart block in cats (Lathers and Schraeder, 1982). The preferential choice of a specific antiepileptic drug in patients with ictal arrhythmia has not been studied (Devinsky *et al.*, 1986). Carbamazepine can lengthen the ECG Q–T interval and increase the arrhythmic effects of epileptic seizures, and was present in chronic therapy in some series of epileptic patients presenting with sudden unexpected death (Timmings *et al.*, 1998). Moreover, carbamazepine has been implicated in the development of asystole, sinoatrial, atrioventricular block and decreased Purkinje automaticity in elderly patients with trigeminal neuralgia (Hamilton, 1978). On the other hand, phenytoin, on the basis of experimental studies, acts by centrally depressing hyperactivity in cardiac sympathetic nerves and abolishing arrhythmias (Gillis *et al.*, 1971; Evans and Gillis, 1974; Evans and Gillis, 1975). Therefore, this drug, already known to be effective in the treatment of tachyarrhythmias (Epstein *et al.*, 1987; Rizzon *et al.*, 1987; Callaham *et al.*, 1988; Fogoros *et al.*, 1988), could be particularly useful in cases of ictal tachycardia, but not in patients with ictal bradycardia. For these reasons, in Patient 1 we changed carbamazepine to lamotrigine, while in Patients 2 and 3 we did not change the phenytoin treatment as the seizures were completely controlled by this drug. The choice of a specific antiepileptic drug in patients with proven arrhythmogenic seizures should be tailored to the specific ictal pattern of the patient and the possible pre-existing heart disease. When antiepileptic drug treatment fails to control arrhythmogenic seizures, insertion of a cardiac pacemaker should be considered.

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