Original article

Epileptic Disord 2005; 7 (3): 199-204

Heart rate increase in otherwise subclinical seizures is different in temporal *versus* extratemporal seizure onset: support for temporal lobe autonomic influence

Sabine Weil, Stephan Arnold, Ilonka Eisensehr, Soheyl Noachtar

Department of Neurology, University of Munich, Germany

Received February 16, 2004; Accepted January 21, 2005

ABSTRACT – Ictal heart rate was investigated in otherwise subclinical epileptic seizures to test the hypothesis as to whether ictal tachycardia is physiological and not a physical or psychological stress response. In addition, we aimed to evaluate the localizing significance of pure ictal tachycardia. We included 21 epilepsy patients, who showed an ictal EEG seizure pattern during 22, otherwise subclinical seizures. All patients underwent ictal video-EEG recordings to evaluate the possibility of resective epilepsy surgery. The changes in heart rate in these patients were investigated in order to determine their relationship to localization and duration of EEG seizure patterns. Ictal tachycardia was observed in 41% of the otherwise subclinical seizures (nine out of 22), and significantly more often in seizures arising from the temporal lobe than from extratemporal regions (62% *versus* 11%, $p < 0.0018$). The seizure duration as defined by EEG was significantly positively correlated with an increase of heart rate ($p = 0.043$). Ictal heart rate can increase as a result of epileptic activation of autonomic cortex, reflecting a temporal lobe autonomic influence. Thus, measurement of heart rate should be included in the evaluation of otherwise subclinical epileptic seizures, because of its localizing value.

Key words: vegetative seizures, autonomic seizures, subclinical, EEG-video monitoring, autonomic cortex

Correspondence:
S. Noachtar
Department of Neurology,
Klinikum Großhadern,
University of Munich,
Marchioninistr. 15,
D-81377 Munich,
Germany
Tel.: (+ 00 49) 89 7095 3691
Fax: (+ 00 49) 89 7095 6691
<noa@med.uni-muenchen.de>

Epileptic seizures are often accompanied by tachycardia (Zijlmans *et al.* 2002). Mesiotemporal structures, particularly the amygdala, which play a role in both autonomic control and epileptogenesis have been identified in animal models (Oppenheimer *et al.* 1991). Moreover, a growing number of studies also indicate that the insular cortex and temporal lobe are influential in the control of cardiovascular function in humans (Oppenheimer *et*

al. 1992, Epstein *et al.* 1992, Baumgartner *et al.* 2001). Ictal tachycardia seems to help discriminate between seizures arising from temporal or extratemporal regions (Garcia *et al.* 2001). It has not yet been clarified, whether tachycardia develops because of physical or psychic stress during the seizures or whether it reflects epileptic activation of the autonomic cortex. We therefore investigated changes in heart rate during otherwise subclinical seizures to identify autonomic seizures and to determine their relationship to the localization and duration of EEG seizure patterns.

Patients and methods

A review of the database of the University of Munich Epilepsy Monitoring Unit (552 patients), identified 27 patients who had had subclinical seizures documented by EEG and video. Subclinical seizures were defined as EEG seizure patterns that were not associated with any disturbances of sensory phenomena, motor functions, or consciousness in the awake patient, with any movements during sleep or arousals on EEG. Twenty-one patients with a total of 22 subclinical seizures, in whom ictal EEG files and high-quality video could be retrieved for analysis, were selected. Heart rate before and during the EEG seizure patterns was analyzed in these patients and correlated with the localization and duration of their EEG seizure patterns.

Patients

Twenty-one patients participated in the study (11 men, 10 women; median age = 33 years, range 17-76 years). Ten patients had temporal lobe epilepsy, four patients had frontal lobe, and one patient parieto-occipital lobe epilepsy. Another two patients had left hemispheric epilepsy, two had right hemispheric focal epilepsy, and two had focal epilepsy, which could not be lateralized. All patients were considered candidates for epilepsy surgery and were off anti-epileptic medication during EEG-video monitoring to record seizures.

EEG-video monitoring

All patients underwent continuous EEG-video monitoring with 32-64 channel EEG machines (Vangard, Cleveland, OH, USA). The patients were observed for 24 hours, day and night, by technicians specially trained in EEG video monitoring. The EEG was digitized at a sampling rate of 200 Hz (12 bit), amplified, and stored on hard discs and magneto-optical discs for off-line analysis. All seizures were analyzed off-line on EEG and time-synchronized video.
Recordings were performed with surface electrodes in 13 patients and with subdural electrodes in another 8 patients. The localization or lateralization of seizure origin in these eight patients had been previously hypothesized on the basis of non-invasive EEG-video recordings. Responsiveness was tested systematically during the EEG seizure patterns in 13 patients. EEG seizure patterns occurred in nine patients during non-REMsleep. As direct observation and video recordings of these sleeping patients did not reveal any clinical change in behavior, they were not awakened and tested formally. Electroencephalography revealed no arousal.

Heart rate analysis

Heart rate was calculated from RR distances in the ECG. Measurements started 10 seconds prior to the onset of EEG seizure patterns and were calculated until heart rate remained constant after the seizure had ceased. An increase in heart rate was calculated by dividing the maximum frequency by the minimum frequency. In 12, non-epileptic controls with pseudoseizures and parasomnias (age 4-83 years, median 29 years) the mean increase in heart rate during long-term EEG-video monitoring was 1.6 (+ 0.2 SD). On the basis of this calculation, an increase of 1.8 was considered significant. Heart rate was plotted against time to exclude the impact of extrasystoly on the calculation. The resulting curves were fitted with a third grade polynomial fitting curve to calculate the point of maximum heart rate increase. The slopes of the fitting curves were calculated at this point *(figure 1)*. Mean maximum slopes of heart rate were 30% with a standard deviation of 50% in our controls *(figure 1*, slope line*)*. A maximum increase in slope of at least 100% was considered significant *(figures 2a, b)*.

Results

Thirteen EEG seizure patterns were localized to the temporal region (right n = 8, left n = 5), eight seizure patterns were localized to the frontal area (right n = 4, left n = 4), and one to the right occipital region.
The median duration of the EEG seizure patterns was 57.1 s (range 16.1 s- 178.9 s). Patient data and results of heart rate analyses are summarized in *table 1*.

Median increase of heart rate in all patients was 1.5 fold compared to the heart rate before seizure onset (range 1.1-3.7). Median increase of heart rate was higher in patients with seizures of temporal origin than in those with seizures from an extratemporal origin (1.8 *versus* 1.3, range 1.2-3.7 *versus* 1.2-1.8). A significant ictal increase in heart rate was observed in 9 out of 22 seizures (8 out of 21 patients). Significant ictal tachycardia was seen more often in patients with regional temporal EEG seizure patterns (62%, 8 out of 13) than in those with regional extratemporal seizure patterns (11%, 1 out of 9; $p < 0.0018$). Families of slope lines at the point of maximum increase in heart rate set at zero are shown in *figure 2*.

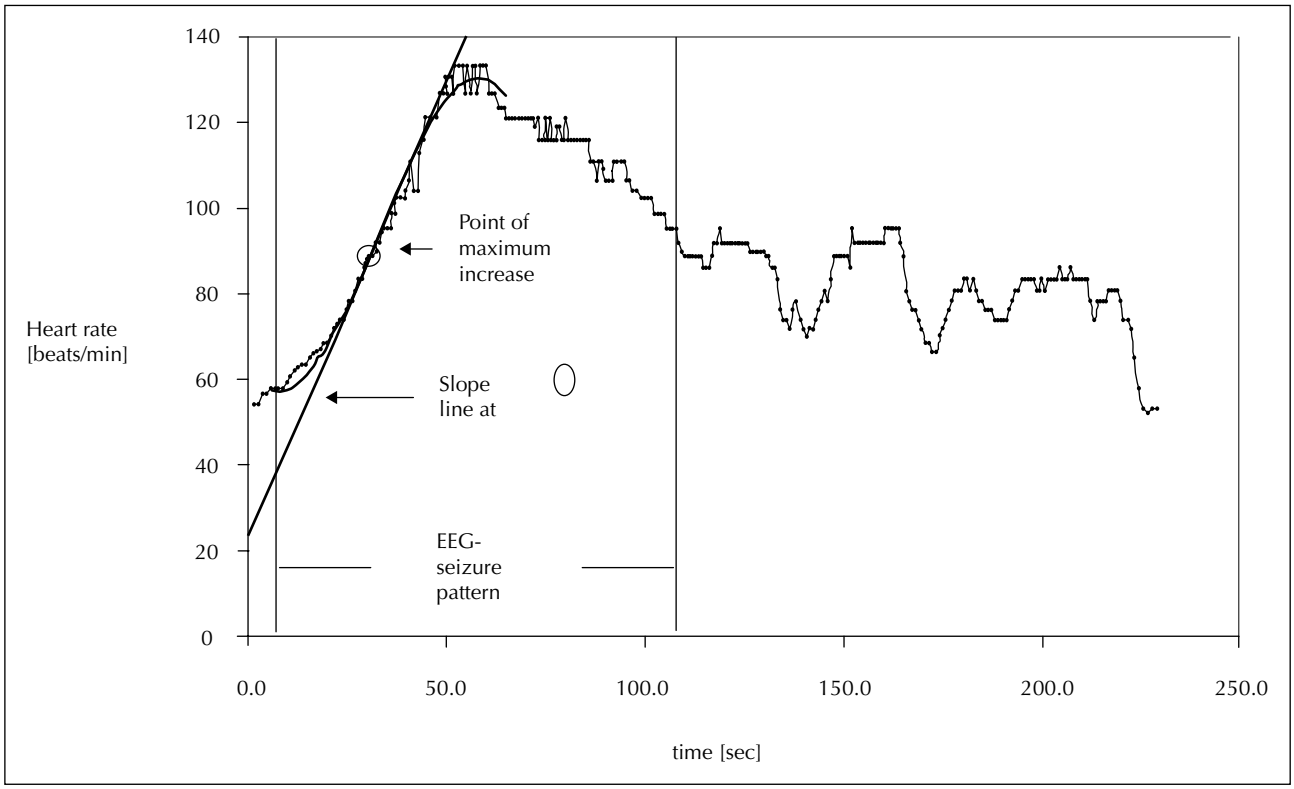

Figure 1. Plot of heart rate for patient no. 4 *versus* time was fitted to a third-grade polynomic curve. The maximum increase in heart rate occurred after 32 seconds. Heart rate increase at this time was 1.9 bpm/sec, corresponding to a 190% slope at this point.

There was a correlation between duration of seizure patterns and tachycardia (Mann-Whitney test, p = 0.043). There was no significant decrease in the heart rate during seizures. Furthermore, there was no correlation between lateralization of the EEG seizure pattern and changes in heart rate (Chi square, p = 0.548).

Discussion

Our study investigated whether ictal tachycardia could be (i) a secondary to psychic or physical stress, or (ii) a result of an epileptic activation of cortical areas responsible for autonomic functions. We found that a significant increase in heart rate in 9 out of 22 seizures was not associated with any subjective (aura) or clinical seizure manifestations other than tachycardia. This makes it extremely unlikely that the ictal tachycardia in our patients was secondary to physical or psychological stress. Sinus tachycardia frequently occurs in various types of epileptic seizure (Nei *et al.* 2000), but it predominates in seizures originating in the temporal lobe (Epstein *et al.* 1992, Galimberti *et al.* 1996, Baumgartner *et al.* 2001, Garcia *et al.* 2001, Zijlmans *et al.* 2002). Our findings in otherwise subclinical seizures support this view: significant tachycardia was seen in 8 out of 13 temporal seizure patterns, but in only 1 out of 9 extratemporal seizure patterns.

Several clinical and experimental studies support the hypothesis that autonomic heart functions are represented in the insular cortex (Zamrini *et al.* 1990, Oppenheimer *et al.* 1991, Epstein *et al.* 1992). Electrical stimulation of the insular cortex in humans is associated with cardiovascular changes (Oppenheimer *et al.* 1992). In a study of six patients, bradycardia was more often elicited during left insular stimulation, whereas tachycardia occurred more often during right insular stimulation (Oppenheimer *et al.* 1992). Twenty six out of 45 patients with ictal bradycardia reported in the literature had seizure localized to the left hemisphere. Nineteen were localized on the right side (Tinuper *et al.* 2001). Tachycardia preceded EEG seizure onset in 75.9% of the seizures in a recent study on focal epilepsies (Leutmezer *et al.* 2003). Heart rate changes preceded EEG onset significantly more often in mesial TLE as compared with extratemporal epilepsy. In this study, it is not mentioned whether the patients were tested at the onset of the tachycardia (Leutmezer *et al.* 2003). Thus, the relation of the ictal tachycardia to clinical seizure onset is not clear. It cannot be excluded that at least some patients had an aura at this time. Auras are frequently not associated with EEG seizure patterns on surface EEG recordings and typically, clinical aura onset precedes the EEG onset.

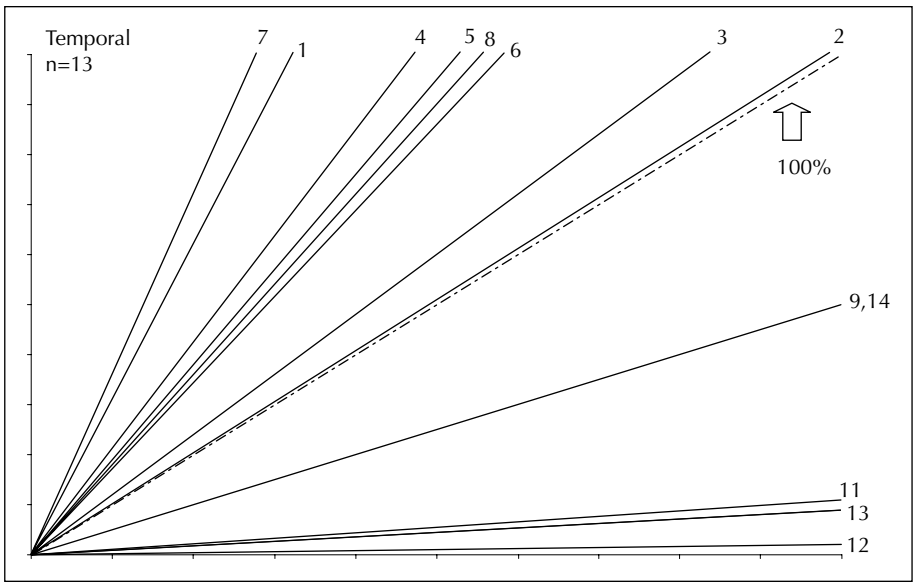

Figure 2a. Family of slope lines indicating maximum increase in heart rate, set at zero, for patients with temporal seizure patterns. A slope line with a slope of 100% is shown with tick bars; values for 8 patients were above the line, and 5, below.

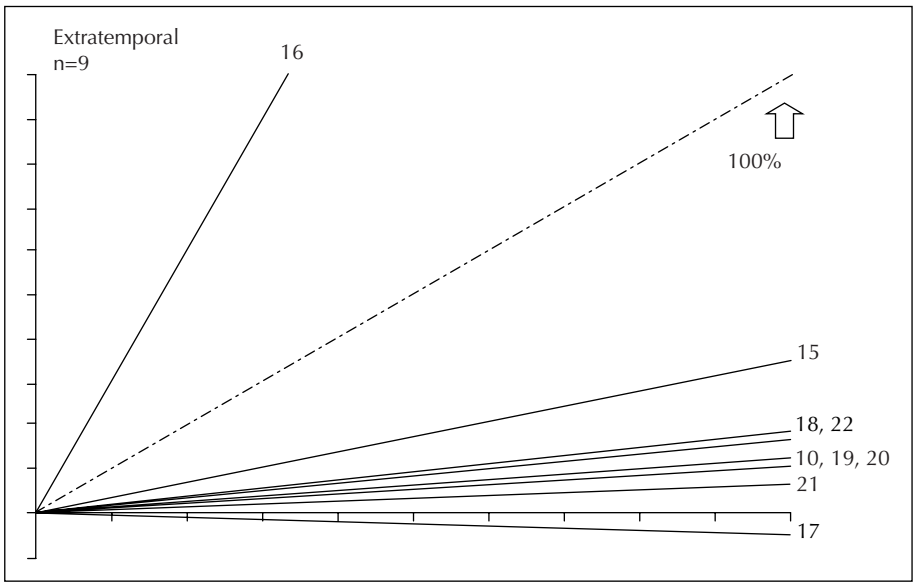

Figure 2b. Family of slope lines, set at zero, for patients with extratemporal seizure patterns.
A slope line with a slope of 100% is shown with tick bars; 1 patient was above the line, and 8 below.

It was concluded that the ictal EEG discharges directly influence areas of the central autonomic network, thus regulating heart rate and rhythm (Leutmezer *et al.* 2003). However, from the data presented in this study it cannot be exclude that tachycardia was secondary to the experience of aura and associated psychological stress in their patients (Leutmezer *et al.* 2003). To overcome this problem it was crucial in our study to exclude patients who did experience auras during ictal tachycardia.

The development of tachycardia usually requires widespread unilateral limbic involvement of the ictal discharges, irrespective of the side of origin (Epstein *et al.* 1992). Our finding of a positive correlation between duration of seizure patterns and significant tachycardia emphasizes this importance of widespread epileptic activity. The subclinical seizure became symptomatic and thereby constituted an autonomic seizure only if it spread to enough of the cortex.

The mechanism by which partial seizures cause autonomic symptoms and signs is thought to involve the spread of ictal epileptic discharges from the cortex to the hypothalamus. The large number of limbic-hypothalamic

Table 1. Patients data and results of ictal EEG and heart rate.

Seizure #	Age (years)	Sex	Syndrome	Ictal EEG						
				Localization of seizure pattern	Duration of seizure pattern	Min HR	Max HR	Max-Min	Max/Min	y
					(sec)	(beats/min)	(beats/min)	(beats/min)		(% slope)
1*	26	m	Foc. E Rt.	Rt. T	105.2	51	190	139	3.7	311
2*				Rt. T	178.9	57	148	91	2.6	102
3	23	m	TLE Rt.	Rt. T	85.5	44	89	44	2.0	120
4	34	m	TLE bilat.	Lt. T	95.6	52	133	81	2.6	212
5	28	w	TLE Lt.	Lt. T	79	63	112	49	1.8	190
6	65	w	TLE bilat.	Lt. T	60	46	86	40	1.9	172
7	44	m	Foc. E bilat.	Rt. T	125.6	51	99	48	1.9	360
8	44	w	TLE Rt.	Rt. T	43.2	52	92	40	1.8	150
9	29	m	TLE Rt.	Rt. T	54.2	43	70	27	1.6	50
10	32	w	FLE Lt	Lt. F	40.6	61	74	13	1.2	11
11	53	m	TLE bilat.	Lt. T	72.9	74	89	15	1.2	11
12	34	w	TLE Rt.	Rt. T	95.2	49	70	21	1.4	2
13	35	w	TLE L	Lt. T	35.2	81	107	26	1.3	9
14	76	w	TLE R/L	Rt. T	75.8	81	116	35	1.4	50
15	28	w	POLE R	Rt. O	51.4	102	121	19	1.2	35
16	59	w	Foc.E bilat.	Rt. F	16.1	57	102	45	1.8	300
17	23	m	Foc. E	Rt. F	53.9	51	63	12	1.2	-5
18	33	w	Foc.E Lt	Lt. F	80	55	83	29	1.5	17
19	28	m	FLE Lt.	Lt. F	44.2	49	63	14	1.3	12
20	26	m	Foc.E Lt.	Lt. F	41.1	49	63	14	1.3	11
21	17	m	FLE Rt.	Rt. F	41.2	89	116	27	1.3	7
22	50	m	FLE Rt.	Rt. F	26	63	67	4	1.1	18
Mean	37				66.9	60	98	38	1.7	97
Median					68.2	53	90	28	1.5	40
Min.	17				16.1	43	63	4	1.1	-5
Max.	76				178.9	102	190	139	3.7	360

Rt. = right, Lt. = left, bilat. = bilateral, FLE = frontal lobe epilepsy, TLE = temporal lobe epilepsy, POLE = parieto-ccipital lobe epilepsy, Foc. E = focal epilepsy, sec. = seconds, Min = minimum, Max = maximum, Mean = mean value.
* Seizures 1 and 2 are in the same patient.

connections probably accounts for the prominence of autonomic symptoms in seizures originating from the temporal lobe (Liporace and Sperling 1997, Cerullo *et al*. 1998).

A subclinical or purely electrographic seizure pattern is defined as an ictal pattern that is identical to EEG patterns during epileptic seizures lacking behavioral symptoms. The documentation of symptoms requires adequate monitoring. Direct observation and video recordings in our study did not show any ictal symptoms during EEG seizure patterns that were defined as subclinical. However, we cannot exclude the possibility that our testing procedure failed to detect subtle motor or neuropsychological symptoms. Autonomic symptoms and signs occurring during epileptic seizures are often missed because of inadequate testing and observation. Ictal tachycardia also occurred during sleep. A retrospective review revealed that ictal tachycardia had not been initially detected in 41% of our patients with "subclinical seizures".

We conclude that purely ictal tachycardia indicates epileptic activity in or close to the temporal cortex. It is not exclusively a phenomenon secondary to physical or psychological stress during seizures. In view of its localizing value, the analysis of heart rate should be included in the evaluation of otherwise subclinical epileptic seizures. □

References

Baumgartner C, Lurger S, Leutmezer F. Autonomic symptoms during epileptic seizures. *Epileptic Disord* 2001; 3: 103-16.

Cerullo A, Tinuper P, Provini F, *et al.* Autonomic and hormonal ictal changes in gelastic seizures from hypothalamic hamartomas. *Electroenceph Clin Neurophysiol* 1998; 107: 17-322.

Epstein MA, Sperling MR, O'Connor MJ. Cardiac rhythm during temporal lobe seizures. *Neurology* 1992; 42: 50-3.

Galimberti CA, Marchioni E, Barzizza F, Manni R, Sartori I, Tartara A. Partial epileptic seizures of different origin variably affect cardiac rhythm. *Epilepsia* 1996; 3: 742-7.

Garcia M, D'Giano C, Estelles S, Leiguarda R, Rabinowicz A. Ictal tachycardia: its discriminating potential between temporal and extratemporal seizure foci. *Seizure* 2001; 10: 415-9.

Leutmezer F, Schernthaner C, Lurger S, Pötzelberger K, Baumgartner C. Electrocardiographic changes at the onset of epileptic seizures. *Epilepsia* 2003; 44: 348-54.

Liporace JD, Sperling MR. Simple autonomic seizures. In: Engel jr J, Pedley TA, eds. *Epilepsy: a comprehensive textbook*. Philadelphia: Lippincott Raven, 1997: 549-55.

Nei M, Ho RT, Sperling MR. EKG abnormalities during partial seizures in refractory epilepsy. *Epilepsia* 2000; 4: 542-8.

Oppenheimer SM, Wilson JX, Guiraudon C, Cechetto DF. Insular cortex stimulation produces lethal cardiac arrhythmias: a mechanism of sudden death? *Brain Res* 1991; 550: 115-21.

Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology* 1992; 42: 1727-32.

Tinuper P, Bisulli F, Cerullo A, *et al.* Ictal bradycardia in partial epileptic seizures. Autonomic investigation in three cases and literature review. *Brain* 2001; 124: 2361-71.

Zamrini EY, Meador KJ, Loring DW, *et al.* Unilateral cerebral inactivation produces differential left/right heart rate responses. *Neurology* 1990; 40: 1408-11.

Zijlmans M, Flanagan D, Gotman J. Heart rate changes and ECG abnormalities during epileptic seizures: prevalence and definition of an objective clinical sign. *Epilepsia* 2002; 43: 847-54.