ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 6, Issue, 5, pp.3887-3892, May, 2015

International Journal of Recent Scientific Research

RESEARCH ARTICLE

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

Ghchime R[1,2], Benjelloun H[2], Kiai H[3], Lahjouji F[1], Belaidi H[1] and Ouazzani R[1]

[1]Clinical Neurophysiology Department, Specialties Hospital, CHIS Rabat-Salé, University of Souissi, Rabat, Morocco
[2]Unit of Cardiology A, Ibn Sina University Hospital, Rabat, Morocco
[3]Food Sciences Laboratory, Department of Biology, Faculty of Sciences – Semlalia, Prince Moulay Abdellah Avenue, Marrakesh, Morocco

ARTICLE INFO

Article History:

Received 2nd, April, 2015
Received in revised form 10th, April, 2015
Accepted 4th, May, 2015
Published online 28th, May, 2015

Key words:

Postural orthostatic tachycardia syndrome; orthostatic intolerance; cardiac dysautonomia; temporal lobe epilepsy; orthostatic test; heart rate.

ABSTRACT

The temporal epilepsy is generally associated to cardiac dysautonomia. Thus recognition of such syndrome in epileptic patients is a crucial step for offering the appropriate therapy. The aim of this study was to focused, on the one hand, on the determination of the orthostatic intolerance prevalence, especially the postural orthostatic tachycardia syndrome (POTS) in temporal epileptic patients compared to control group, and on the other hand, to evaluate the variation of heart rate (HR) from supine to standing position during orthostatic test for refractory and well-controlled temporal lobe epilepsy (TLE).The Orthostatic test was performed on 30 TLE patients and 30 control subjects. Orthostatic heart rate (ortho HR) was recorded and compared to supine pre-orthostatic heart rate (preortho HR). To determine the prevalence of the POTS, three subgroups were admitted for the trial, as follow: Subgroup A (POTS): ortho HR-preortho HR ≥ 30 beat/min, Subgroup B (orthostatic tachycardia): 20 beat/min ≤ ortho HR-preortho HR< 30 beat/min and Subgroup C (normal): 10 beat/min ≤ ortho HR-preortho HR< 20 beat/min.

Our data have shown a significant enhanced occurrence of intolerance orthostatic that was 46.66 % in TLE versus 16.66 % in healthy subjects. The present study has brought evidence a higher POTS prevalence in TLE than in control subjects.

INTRODUCTION

Epileptic seizures may be associated to autonomic dysregulation manifesting, such as heart rate (HR) and blood pressure (BP) changes (Isojärvi *et al*., 1998; Ansakorpi *et al*., 2000). Moreover, there is increasing evidence of interictal autonomic nervous system dysfunction in the TLE patients (Opherk *et al*., 2002; Ronkainen *et al*., 2005). Temporal epilepsy is related to dysfunction of central autonomic structures as well as the epileptogenic discharges are likely to interfere with cardiovascular modulation in centers of autonomic control such as the insular, the amygdale, the hippocampal and the paraventricular regions (Oppenheimer *et al*., 1992; Hilz *et al*., 2002). The TLE is frequently associated with ictal and interictal cardiovascular autonomic dysfunctions in particular the POTS which can be considered as a risk factor for sudden unexplained death (SUDEP). The mortality rate among people with epilepsy is 2-3 times higher and the risk of sudden death is 24 times greater than in the general population. Moreover, the SUDEP in epilepsy subjects accounts for deaths in about 2% of population based cohorts with epilepsy and in 18-25% subjects with more severe intractable epilepsy (Mukherjee *et al*., 2009). The POTS is defined as a disorder of orthostatic intolerance characterized by excessive tachycardia. The common diagnostic criteria for POTS is a heart rate (HR) increases of 30 beats per minute (bpm) or more, or over 120 bpm within the first 10 min of sustained orthostasis (Parry *et al*., 2008; McDonald *et al*., 2009), associated with a diverse range of symptoms including palpitations, syncope and profound fatigue (Carew *et al*., 2009; Haensch *et al*., 2010). The aim of the present study is to evaluate the prevalence of the orthostatic intolerance, particularly POTS for temporal epileptic patients and healthy subjects, and to investigate the changes of heart rate from supine to standing position during orthostatic test for refractory and well-controlled TLE.

MATERIALS AND METHODS

Patients and control subjects

The present study was carried out at the outpatient department of neurology in the university hospital (UHC) Ibn Sina, Rabat,

Corresponding author:* **Ghchime R
Clinical Neurophysiology Department, Specialties Hospital, CHIS Rabat-Salé, University of Souissi, Rabat, Morocco

Morocco, with the approval of the ethics committee of the local medical faculty.

Thirty patients with TLE who were followed up in the outpatient clinic participated in the study after giving their informed consent. Nineteen subjects suffered from recurrent TLE seizures despite adequate AED treatment, whereas 11 patients had well controlled TLE (seizure-free on AEDs or < 2 seizures /year) (Mukherjee *et al*., 2009).

The control group consisted of 30 healthy age and sex matched subjects who were either hospital staff or recruited by the staff. The subjects were eligible for the study if they did not have a disease or medication known to affect the autonomic nervous system (ANS) in their medical history and if the complete physical examination finding were normal.

The demographics of the studied patients and control subjects are given in table 1.

Two patients with well-controlled TLE have received CBZ as monotherapy. Whereas, twenty eight patients with nineteen refractory TLE and nine patients who had well-controlled TLE were on polytherapy as a combination of two or three of the followers antiepileptic drugs (AEDs): CBZ, VPA, LTG, CPZ, CLB, PB.

Interictal electroencephalography (EEG) recording was obtained from all patients. Left temporal focal slow waves or irritation or both were detected in 18 patients. Whereas, right temporal focal disturbances were seen in 11 patients. One patient had bilateral temporal focal irritation (Table 2).

All patients were carefully interviewed and clinically examined. The epilepsy type was classified according to the recommendations of the international league against epilepsy (Ansakorpi *et al*., 2011). None of the patients showed any symptoms or signs of illness other than epilepsy known to affect the ANS.

Table 1 The demographics of the study patients and control subjects

Parameters	Patients with refractory TLE	Patients with well-controlled TLE	All patients	Control subjects	p
	(n=19)	(n=11)	(n=30)	(n=30)	
Age (year)	34.2 ± 9.9	29 ± 11	32.3 ± 10.4	43± 12.2	0.001
Gender (F/M)	12/7	6/5	18/12	21/9	0.140
Duration of epilepsy (years)	27.3 ± 11.4	20.18 ± 10.1	24.67 ± 11.32	_	_
Basal SBP (mmHg)	111 ± 12	113.36 ± 8.4	111.86 ± 10.75	110.08 ± 12.38	0.554
Basal HR (beats/min)	63.26 ± 7.6	67. 73 ± 8.3	64.9 ± 8.03	68.41 ± 8.9	0.116

SBP: systolic blood pressure.
HR: heart rate.
Values expressed as mean± SE. p significant if < 0.05 (Student's t-test).

Table 2 Clinical characterization of patients with temporal epilepsy

	Patients N°	Age (year)	Gender	Seizure focus in the interictal or ictal EEG	Antiepileptic medication
Patients with refractory TLE	1	20	F	Left-temporal	CLB, LTG
	2	36	M	Left-temporal	CBZ,CLB
	3	25	F	Left-temporal	VPA,CBZ,CZP
	4	28	F	Bilateral-temporal	CBZ, CLB
	5	40	F	Right-temporal	CBZ,VPA
	6	24	F	Left-temporal	CBZ,CLB
	7	19	F	Left-temporal	CBZ, CLB,VPA
	8	38	F	Left-temporal	CLB,CBZ
	9	27	F	Left-temporal	CBZ,CLB
	10	42	M	Right-temporal	CBZ,CLB,PB
	11	46	F	Left-temporal	CBZ,CLB,PB
	12	29	M	Right-temporal	CBZ,CLB
	13	38	F	Left-temporal	CBZ,CLB,PB
	14	40	M	Left-temporal	LTG,CBZ
	15	51	F	Left-temporal	CBZ,CLB,PB
	16	28	F	Left-temporal	CBZ,CLB,PB
	17	50	M	Left-temporal	CBZ,CLB,PB
Patients with well-controlled TLE	18	26	M	Left-temporal	CBZ, CLB
	19	43	M	Right-temporal	CBZ, CLB
	20	40	F	Left-temporal	CBZ,VPA
	21	22	M	Left-temporal	VPA, PB
	22	25	F	Left-temporal	CBZ, CLB
	23	38	F	Right-temporal	CBZ
	24	16	M	Right-temporal	CBZ, VPA
	25	19	F	Right-temporal	CBZ
	26	34	F	Left-temporal	CBZ, CLB,VPA
	27	40	M	Right-temporal	CBZ, PB
	28	44	M	Right-temporal	CBZ, CLB
	29	29	F	Right-temporal	CBZ, CLB
	30	12	M	Right-temporal	CBZ, CLB

TLE: Temporal lobe epilepsy; EEG: Electroencephalography; VPA: Sodium Valproate; CBZ: Carbamazepine; LTG : Lamotrigine; CLB: Clobazam; CZP: Clonazepam and PB: Phenobarbital.

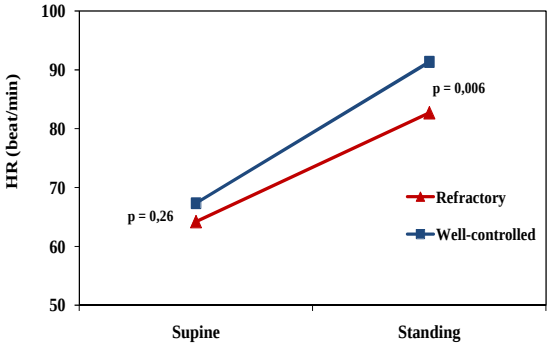
Orthostatic test

All patients recruited at the Department of Clinical Neurophysiology underwent an orthostatic test (OT) in the center of cardiac autonomic studies at the department of cardiology A of the University Hospital Center (UHC) Ibn Sina, Rabat, Morocco.

Table 3 Variations in preortho and orthostatic values of the heart rate (ΔHR) in TLE patients and in control subjects during the orthostatic test.

Sub-group	TLE		Control subjects	
	Preortho HR	Ortho HR	Preortho HR	Ortho HR
A	67.9 ± 8.15 (54-82)*	102.8 ± 11.23 (86-122)*	80	123
B	67.8 ± 9.6 (59-82)*	90.4 ± 10.3 (79-103)*	66.5 ± 8 (59-77)*	90.62 ± 9.14 (82.5-102)*
C	63.2 ± 6.6 (49-74)*	75 ± 6.2 (61-88)*	67.6 ± 10.2 (50-93)*	81.6 ± 10 (62-105)*

Values expressed as mean± SE (Student's t-test). Subgroups are defined in the Methods section.
* Results are given with extremes.



Patients with well-controlled TLE:
- Supine: 67.36 beat/min ± 6.6
- Standing: 91.36 beat/min ± 16.7

Patients with refractory TLE:
- Supine: 64.21beat/min ± 8.1
- Standing: 82.74 beat/min ± 13.5

Figure 3 Variation of heart rate from supine to standing position during orthostatic test in patients with refractory and well-controlled temporal lobe epilepsy. The values are estimated as means ± SE (Student's t-test). The p value describes the significance of the difference of the change from supine to standing position between the patient groups.

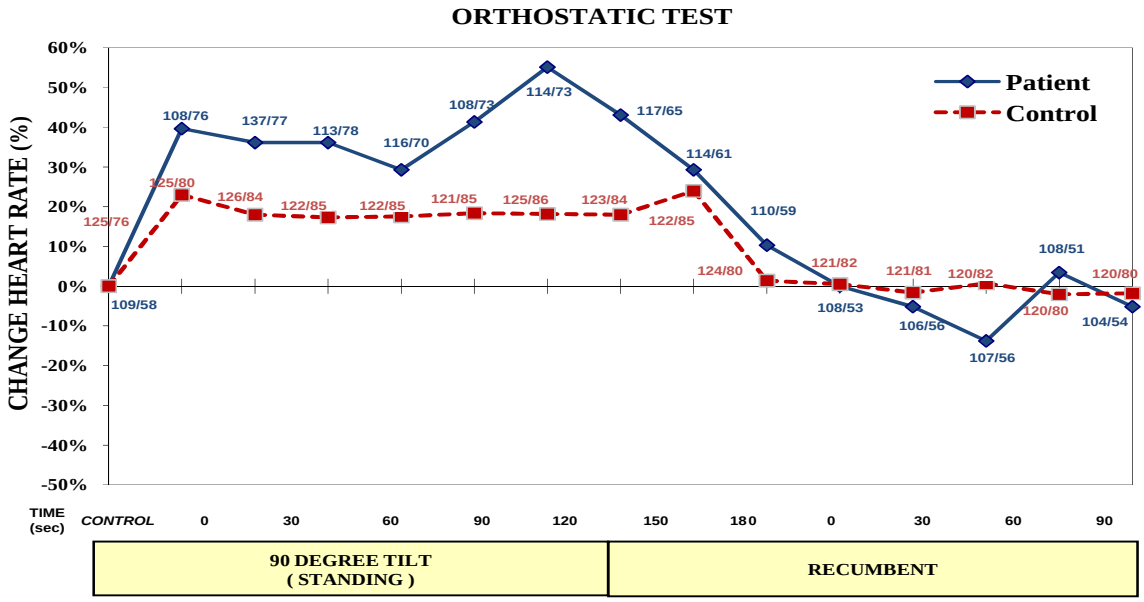


Figure 1 Graph showing comparison of the kinetic of HR and BP changes during orthostatic test. The POTS was characterized by increase of HR with 40 % during the first 5 min of orthostatic test.

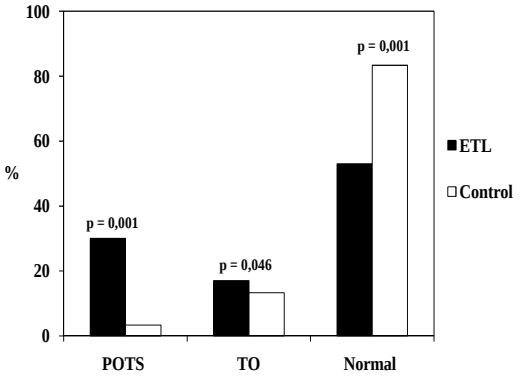


Figure 2 The prevalence of the patients according to the degree of variation in the HR (ΔHR) in the temporal epileptic patients (TLE) and in the control subjects during the orthostatic test (OT). The value expressed as mean± SE. p significant if < 0.05 (Student's t-test).

The OT is a simple, noninvasive and reproducible test included among the cardiovascular ANS tests, it is allows the stimulation of the peripheral beta- sympathetic system by increasing the HR and then the measurement of the Blood Pressure (BP) and the Heart Rate (HR) variation during the upright posture (Fig 1) (Low and Pfeifer, 2007).

The test was performed in the morning, under standardized conditions, in a silent room (20 - 23°C). The studied subjects were defended smoking or drinking coffee within two hours and using alcohol and under no treatment during at least 48 hours except anti-epileptic treatment. The patient initially lied on a table of examination in a quiet room for at least 10 minutes. The monitoring of BP and HR was performed using a Dynamap (CRITIKON, 1846SXP) and a screen of posting (LCDCS503E; HELLIGE. EK512E), respectively.

The baseline HR and systolic BP were measured in both arms after a rest of at least 30 minutes. Then we proceeded to the orthostatic test.

The orthostatic test was performed in 30 TLE patients (19 intractable and 11 well-controlled) and 30 control subjects. Orthostatic heart rate (ortho HR) was recorded for 10 minutes at the rhythm of three measurements per minute and compared with the values of pre-orthostatic heart rate (preortho HR).
To determine the prevalence of POTS, three subgroups were selected from the patients with temporal epilepsy and healthy volunteers classified as follow:

- Subgroup A (POTS) : ortho HR-preortho HR ≥ 30 beat/min;
- Subgroup C (normal) : 10 beat/min ≤ ortho HR-preortho HR< 20 beat/min;
- Subgroup B (orthostatic tachycardia): 20 beat/min ≤ ortho HR-preortho HR< 30 beat/min.

Besides comparing the prevalence of POTS in the two groups, we also compared the variation of heart rate from supine to standing position between patients with refractory and well-controlled TLE.

Statistics analysis

Descriptive statistics included the range mean and standard deviation for interval variables and the frequency and percentage for categorical variables. Group comparisons were carried out by independent samples Student's t-test for interval variables and the $\chi 2$ test for categorical variables, with the odds ratio (ORs) and 95% confidence intervals (CIs) calculated where appropriate. P values were considered statistically significant if it is less than 0.05. All analyses were performed using SPSS, version 15.0 (SPSS Inc. Chicago. IL).

RESULTS

The mean age was 32.3 ± 10.4 years in TLE (with extremes ranging from 12 to 51 years) and 43 ± 12.2 years in the control group (with extremes ranging from 20 to 63 years). (p = 0.001)
Mean basal HR did not differ significantly between the two groups (64. 9 ± 8.03 beats/min in TLE versus 68.41 ± 8.9 beats/min in control subjects; p = 0.116).

Mean basal SBP did not differ significantly between the two groups (111.86 ± 10.75 mmHg in TLE versus 110.08 ± 12.38 mmHg in control group; p = 0.554).

The duration of TLE was 24.67 years ± 11.32 (with extremes ranging from 7 to 48 years).

The occurrence of intolerance orthostatic was significantly higher in TLE than in healthy subjects (46.66 % versus 16.66 %; p= 0.001).

In sub-group A: the preortho-HR mean was respectively 67.9 ± 8.15 beat/min in TLE versus 80 beat/min in control subjects, while the orthostatic-HR mean was 102.8 ±11.23 beat/min in TLE and 123 beat/min in control subjects (Table 3). The prevalence of POTS in TLE was highly significant than control subjects (30 % versus 3.30%; p = 0.001) (Fig 2).

In sub-group B: the preortho-HR means were 67.8 ± 9.6 and 66.5 ± 8 beat/min in TLE and control subjects respectively. Whereas, the orthostatic-HR mean was 90.4 ± 10.3 beat/min in TLE versus 90.62 ± 9.14 beat/min in control subjects (Table 3). The prevalence of OT was then 17 % in TLE versus 13.3 % in control subjects. p = 0.046 (Table 3).

In sub-group C: The preortho-HR mean was 63.2 ± 6.6 beat/min in TLE versus 67.6 ± 10.2 beat/min in control subject. However, the orthostatic-HR mean was of 75± 6.2 beat/min in TLE versus 81.6 ± 10 beat/min in control subjects (Table 3).
The prevalence of no significant variation in orthostatic HR was 53% in TLE versus 83.4% in control subjects. p = 0.001(Fig 2)

DISCUSSION

The present investigation was conducted to evaluate the prevalence of POTS and TO as types of orthostatic intolerance in two groups: TLE and control subjects. For that purpose, it was interesting to compare the peripheral sympathetic nervous system (SNS) response of the two groups to stimulation using a cardiovascular autonomic test.

Our data have shown a significant enhancement of orthostatic intolerance occurrence in TLE compared to healthy subjects. The percentage of OT in TLE was significantly higher than in the control group. Furthermore, the POTS was found in 9/30 patients in TLE. However, only one case of this orthostatic intolerance was found in control group.

The pathogenesis of postural tachycardia syndrome (POTS) is not so clear. Several hypothesis have been raised to elucidate the underlying mechanisms of POTS including partial sympathetic denervation in the legs, excessive venous pooling, beta-receptor hypersensitivity, alpha-receptor hyper-or hyposensitivity, and altered sympathetic–parasympathetic balance (Low and Pfeifer, 1997; Seeck *et al*., 2002). Brainstem dysfunction has also been suspected. A previous study demonstrated a shift in burst frequency and amplitude of sympathetic nerve activity in patients with POTS compared to controls, consistent with increased sympathetic activity (Seeck *et al*., 2002).

The occurrence of the POTS in TLE could be explained by affecting the beta peripheral sympathetic system caused by the impact of the association of dysfunction centers of autonomic control, especially in temporal lobe such as the insular, the amygdale, the hippocampal and the paraventricular regions. Whereas, these finding are in agreement with several previous studies which demonstrate that TLE affects autonomic cardiac regulation (Massetani *et al*., 1997; Isojärvi *et al*., 1998; Tomson *et al*., 1998; Druschky *et al*., 2001; Hennessy *et al*., 2001; Persson *et al*., 2003; Mukherjee *et al*., 2009).

The possible contribution of AEDs to ANS dysfunction in patients with temporal epilepsy has not been clearly established. Previous studies have shown that CBZ alters autonomic functions in epileptic patients (Hennessy *et al*., 2001; Persson *et al*., 2003). However, in the current study most patients were under polytherapy. Thus, it was not possible to study the effects of different AEDs on HR variability. Nevertheless, it is possible that AEDs contributed to the detected alterations in the cardioregulation, and studies designed to analyze the effects of different AED regimens on autonomic cardiac function are needed.

The assessment of HR variation during orthostatic test in refractory and well-controlled TLE was also assessed. The obtained results showed that the HR values of refractory TLE in supping and standing positions were lower than those found for well-controlled TLE patients.

In fact, the change from supine to standing position revealed mainly a breakdown of the sympathovagal balance in these patients. Although, a high significant difference ($p = 0.006$) were detected between the two patient groups, there was a consistent trend towards lower values of the test parameters in the refractory TLE group, indicating a more disrupted cardioregulatory function compared to well-controlled TLE patients.

CONCLUSION

To the best of our knowledge, there is one main point that the present study adds to existing literature. Autonomic dysfunction in the form of POTS can occur in TLE patients. The mechanisms of ANS impairment in patients with TLE patients are likely associated with dysfunction centers of autonomic control especially in temporal lobe increasing the inadequate beta-peripheral sympathetic response in orthostatism. It would be interesting to conduct a further studies focusing on a direct comparison including all the cardiovascular ANS tests between TLE and other types of epilepsy.

In addition, the recognition of such syndrome in epileptic patients is important in order to offer appropriate therapy, especially the POTS which is a severe degree of heart rate variation compared to the OT. In that focus, earlier diagnosis is very important to prevent epileptic risk factors of SUDEP.

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How to cite this article:

Ghchime R et al., Postural Orthostatic Tachycardia Syndrome in Patients With Temporal Lobe Epilepsy. *International Journal of Recent Scientific Research Vol. 6, Issue, 5, pp.3887-3892, May, 2015*

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