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Maximal/exhaustive treadmill test features in patients with temporal lobe epilepsy: Search for sudden unexpected death biomarkers

Guilherme L. Fialho[a,b,*], Arthur G. Pagani[c], Roger Walz[b,d,e], Peter Wolf[b,d,f], Katia Lin[b,d,e]

[a] Cardiology Division, Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil
[b] Medical Sciences Post-graduate Program, Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil
[c] School of Medicine, Graduation Program, Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil
[d] Neurology Division, Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil
[e] Applied Neurosciences Center (CeNAp), Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil
[f] Danish Epilepsy Centre, Dianalund, Denmark

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ABSTRACT

Autonomic dysfunction may account for sudden unexpected death in patients with epilepsy (PWE). On the other hand, low cardiovascular fitness, which may affect autonomic function, is a risk factor for sudden death and all-cause mortality in the general population. Little is known about autonomic variables and cardiovascular response to exercise in PWE. We submitted thirty consecutive PWE with no known cardiovascular diseases to maximal treadmill test, comparing them with matched controls. All individuals were submitted to clinical assessment, 12-lead electrocardiogram (ECG) and echocardiogram to exclude cardiovascular disease. Maximal/exhaustive treadmill test using the Bruce protocol was then performed. Clinical-epidemiological features were similar in both groups, regarding age, sex, body mass index and traditional cardiovascular risk factors. PWE achieved a lower peak heart rate (163.8 ± 21.28 bpm × 180.9 ± 12.52 bpm; $p = 0.002$), lower duration of exercise (673.6 ± 148.27 s × 784.4 ± 155.72 s; $p = 0.004$), lower Duke Score (11.8 ± 2.48 × 13.4 ± 2.28; $p = 0.02$) and lower achieved metabolic equivalent of task (MET) (12.8 ± 2.49 × 14.5 ± 2.46; $p = 0.006$). Chronotropic incompetence was more frequent in PWE. Female gender, age of epilepsy onset, number of secondarily generalized seizures and polytherapy were associated to lower cardiovascular fitness in multiple linear regression. Increased risk for SUDEP in PWE may be associated with autonomic disturbances of the cardiovascular system secondary to low cardiovascular fitness.

1. Introduction

Epilepsy is one of the most important neurological diseases in clinical practice, being the second most common neurological disease in primary care. All over the world, around 65 million individuals suffer from epilepsy (Thurman et al., 2011) and patients with epilepsy (PWE) have a 20–40-fold increased risk for sudden death (Ficker et al., 1998; Mohanraj et al., 2006). In fact, Sudden Unexpected Death in Epilepsy (SUDEP) is responsible for 17–38% of deaths in PWE. SUDEP has been defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in PWE, with or without evidence for a seizure, with exclusion of documented status epilepticus, and when post-mortem examination does not reveal a structural or toxicological cause for death (Nashef, 1997; Nashef et al., 2012).

The exact mechanisms of SUDEP are unknown. Its definition per se, includes ignorance of causative factors and demonstrates the lack of a comprehensive explanation for its occurrence (Tomson et al., 2008). Possible mechanistic explanations include seizure-related autonomic abnormalities associated with respiratory and cardiac dysfunction (Ravindran et al., 2016; Devinsky et al., 2016). However, the precise factors involved and the ability to predict which patients will ultimately die from sudden death remain elusive.

Cardiovascular autonomic response can be assessed by many tools, including heart rate variability (at rest or exercise) and cardiac response to exercise (peak heart rate, heart rate recovery, blood pressure response) (Freeman et al., 2006).

Exercise tests have been used in cardiology for a long time, not only for diagnostic purposes, but recently also for prognosis of sudden death and death from all causes. Clinical, hemodynamic, electrocardiographic and autonomic variables can be assessed by exercise tests to determine

* Corresponding author at: Departamento de Clínica Médica, 3o andar, Hospital Universitário Polydoro Ernani de São Thiago, Rua Prof. Maria Flora Pausewang S/No, Caixa Postal 5199, Campus Universitário, Universidade Federal de Santa Catarina, Trindade, 88040-900 Florianópolis, SC, Brazil.
E-mail addresses: fialhog@gmail.com (G.L. Fialho), arthurgpag@hotmail.com (A.G. Pagani), rogerwalz@hotmail.com (R. Walz), wolfcph@gmail.com (P. Wolf), linkatia@uol.com.br (K. Lin).

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prognosis (Fletcher et al., 2013).

Few studies analyzed systematically exercise test variables in epilepsy patients. Therefore, the present study aimed to evaluate maximal exercise stress test variables in PWE without known cardiovascular disease and compare them with an otherwise healthy population, without epilepsy.

2. Material and methods

2.1. Patients and controls

We conducted a case–control study between July 2015 and July 2016. Cases were diagnosed with epilepsy according to International League Against Epilepsy (ILAE) criteria (Fisher et al., 2014), endorsed by electroencephalography and neuroimaging (brain CT or MRI). Individuals with evidence of progressive structural lesions in the central nervous system or progressive encephalopathy were not included. All patients were temporal lobe epilepsy patients. They were clinically categorized as having focal seizures (with impairment of awareness) or secondarily generalized seizures; and according to etiology (Fisher et al., 2014). Antiepileptic drug (AED) treatment was assessed according to dosage and number of AEDs taken. They were followed at the Comprehensive Epilepsy Center, University Hospital of Federal University of Santa Catarina for at least one year.

Epilepsy patients with any known cardiovascular disease, including ischemic heart disease, prior coronary angioplasty or revascularization surgery, structural heart disease [(myocardial, valve (moderate or severe stenosis or insufficiency), congenital or arrhythmic] were excluded. Patients with moderate to severe hypertension (Malachias et al., 2016), neurovascular or peripheral artery disease were also excluded.

The control group was composed of healthy individuals, matched with cases by sex, age and body mass index (BMI) who were seeking medical advice to get a health certificate for gymnastics, work, or routine, excluding cardiovascular, neurovascular or peripheral artery disease.

2.2. Test procedures

All individuals were interviewed using a standard protocol, which included data on medical conditions and medications, first-degree cardiovascular family history, smoking status (active or previous), alcohol use, social economic status and physical activity. Anthropometric data were collected and a complete physical exam was performed.

All individuals were submitted to a 12-lead electrocardiogram (ECG - Cardiette ar600view – Cardioline S.p.A. Via De Zinis, 6 38011 Cavareno (TN) Italy info@cardioline.it; www.cardioline.it), transthoracic echocardiogram (General Electric Medical Systems, Vivid S6, Tirat, Carmel, Israel) and a treadmill test (Super ATL, Imbramed, Porto Alegre, RS, Brazil) using the Bruce protocol until exhaustion (Fletcher et al., 2013), followed by a 2-minute walking cool down period and further analysis for 3 more minutes. During the treadmill test, all individuals were verbally encouraged to exercise as long as possible. Individuals were asked to stay in exam laboratory for 1-hour after the end of the treadmill test. Recordings were all obtained between 8 a.m. and 4 p.m. and patients were investigated in an interictal period (without generalized tonic–clonic seizures at least 24 h within the date of the test). All exams were performed by a board-certified cardiologist (G.L.F.), member of the Brazilian Cardiology Society, according to current guidelines (Fletcher et al., 2013). This investigator was blinded to any clinical and demographic data of the subjects.

Treadmill test variables associated with prognosis in general population (Fletcher et al., 2013; Mark et al., 1987) were observed, including:

- Clinical variables during exercise and until 5 min in the recovery period such as chest pain, syncope, dizziness and cyanosis.
- Electrocardiographic variables such as ventricular or atrial arrhythmia, atrioventricular or bundle branch block, ST deviation.
- Autonomic/hemodynamic variables such as blood pressure response during and after exercise; heart rate at rest, at peak effort, and after one minute in the recovery period; duration of exercise; and metabolic equivalent of task (MET) achieved. The Duke score was calculated using the formula: {Exercise time – (5 × maximal ECG ST segment deviation) − (4 × angina index)} (Mark et al., 1987). Chronotropic incompetence, defined as the inability of the heart to increase its rate in response to activity, was also analyzed. Chronotropic incompetence is assumed when there is failure to achieve 85% of maximal heart rate predicted by age, calculated as 220 – age (Karnoven's formula) (Karvonen et al., 1957) or 208 − (0.7 × age) (Tanaka's formula) (Tanaka et al., 2001) or 80% of the chronotropic index {(peak heart rate − rest heart rate)/(220 − age − rest heart rate)}. We also calculated the chronotropic index replacing Karnoven's formula by Tanaka's formula on the denominator of the equation {(peak heart rate − rest heart rate)/(208 − (0.7 × age) − rest heart rate)}.

2.3. Statistical analysis

A sample size of 56 individuals (28 patients and 28 controls) was considered necessary to detect a significant difference (effect size, Cohen's $d = 0.84$) on treadmill parameters (based on the article of Yerdelen et al., 2012) between groups with a power of 80% and a two-sided test significance level of 5%. Statistical analysis was performed using IBM® SPSS® software package for Mac, standard version 21.0, and Microsoft Excel® software package for Windows, 2014. Descriptive analysis was made to characterize the sample. Quantitative variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as percentage values. The normality of the data distribution was assessed by Kolmogorov–Smirnoff test. Student's *t* test was used to compare continuous variables, while Fisher's exact test (2 × 2 contingency tables) or Pearson's Chi square analysis (3 × 2 contingency tables) was used to compare categorical variables and frequencies of occurrence.

Multiple linear regression analysis was done to identify the independent predictors among the clinical–epidemiological data for the altered maximal exercise stress test findings. For this analysis, variables were identified by the previous univariate analysis with a *p* value lower than 0.20 (Appendix A). For the final model, we retained those variables that had a significant ($p \leq 0.05$) association with the dependent variable.

A p value < 0.05 was considered statistically significant. Considering the clinical and biological plausibility of all the studied variables, no adjustments for the "*p*" level of significance due to multiple comparisons were applied to avoid an increased possibility of type II error (Perneger, 1998).

2.4. Ethical approval

This study was carried out in accordance with the Code of Ethics of the World Medical Association and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (WMA Declaration of Helsinki, 2014). Institutional review boards and local ethics committees (CEPSH/UFSC) approved the study protocol and informed consents. All subjects signed an informed consent form and voluntarily agreed to participate.

3. Results

Sixty subjects (30 PWE and 30 controls) were consecutively enrolled. Clinical–epidemiological features of PWE are described in