

QUANTIFICATION OF RESPIRATORY PARAMETERS IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

*Fulvio Alexandre Scorza¹, Ana Maria Fonseca Abreu²,
Marly de Albuquerque², Julio B Cota Pacheco², Renato Breviglieri²,
Josemir Wanderley Sander⁴, Antônio Carlos da Silva³,
Esper Abrão Cavalheiro¹, Ricardo Mario Arida³*

ABSTRACT - Dysfunction affecting cardiac or pulmonary systems has been postulated as a major factor in sudden death in epilepsy (SUDEP). Whilst the majority of studies of cardiorespiratory function have focused on changes during seizures, here we investigate whether epilepsy influences basal respiratory parameters in patients with temporal lobe epilepsy (TLE) during the interictal period. Spirometry was performed in 10 females and 10 males. Measurements of Vital Capacity (VC), Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1) and ratios of FEV1 to FVC (FEV1/FVC) were obtained, and these values were analyzed as percentages of predicted values. None of the patients had chronic obstructive pulmonary disease and no significant alterations in respiratory function tests were found among these patients. No association between seizure frequency, antiepileptic drugs and SUDEP could be found in this study. Although the study did not identify any specific respiratory abnormality in TLE patients during the interictal period, re-evaluation of clinical data on pulmonary disorders in people with epilepsy should be better investigated.

KEY WORDS: epilepsy, SUDEP, respiratory parameters.

Quantificação de parâmetros respiratórios em pacientes com epilepsia do lobo temporal

RESUMO - Alterações cardíacas e pulmonares têm sido propostas como principais fatores de risco no fenômeno da morte súbita em epilepsia (SUDEP). Enquanto a maioria dos estudos tem verificado as alterações da função cardiorrespiratória durante as crises epilépticas, nosso estudo avaliou a função pulmonar de indivíduos com epilepsia do lobo temporal (ELT) no período interictal. Vinte pacientes com ELT (10 homens e 10 mulheres) participaram de nosso estudo. Nos testes de função pulmonar foram mensurados os seguintes parâmetros: Capacidade Vital Forçada (CVF), Capacidade Vital Lenta (CVL), Volume Expiratório Forçado no primeiro segundo (VEF1) e o Índice VEF1/CVF. Os resultados foram comparados aos valores de normalidade preditos na literatura. Nenhum dos pacientes apresentou doença pulmonar obstrutiva ou restritiva e alterações significativas nos testes de função pulmonar. Não foram encontradas associações entre a frequência de crises, drogas antiepilépticas e SUDEP. Embora nosso estudo não tenha identificado qualquer anormalidade respiratória específica em indivíduos com ELT durante o período interictal, os dados clínicos sobre transtornos pulmonares em indivíduos com epilepsia devem ser melhor avaliados.

PALAVRAS-CHAVE: epilepsia, SUDEP, parâmetros respiratórios.

Sudden unexplained death in epilepsy (SUDEP) is a major cause of mortality in patients with epilepsy^{1,2}. The aetiology of SUDEP remains unclear and may be multifactorial. Autonomic dysfunction affecting cardiac or pulmonary systems has been postulated as a

major factor in SUDEP. Cardiac rate and rhythm disturbances and respiratory abnormalities have been identified during seizures³⁻⁶. Seizures can alter respiratory rate and pattern, producing tachypnoea, hypopnoea or apnoea, and secretions. Apnoea is com-

¹Laboratório de Neurologia Experimental, Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo, Brasil (UNIFESP/EPM); ²Laboratório de Neurociências, Núcleo de Pesquisas Tecnológicas / Universidade de Mogi das Cruzes, São Paulo, Brasil (NPT / UMC); ³Departamento de Fisiologia, Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo, Brasil (UNIFESP/EPM); ⁴Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College of London, London, UK. Research supported by CNPq, FAPESP, CAPES and FAEP. A.M.Abreu is fellowship from CNPq.

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Dr. Fulvio Alexandre Scorza - Rua Botucatu 862 - Laboratório de Neurologia Experimental / Edifício Leal Prado / UNIFESP - 04023-900 São Paulo SP - Brasil. E-mail: scorza.nexp@epm.br

mon during tonic-clonic seizure and brief apnoea occurs during many complex partial seizures⁴. Studies using video-EEG monitoring have shown pulmonary dysfunction in patients with epilepsy when a life-threatening period or death occurs⁷⁻⁹. Pulmonary oedema is the result of an increase in pulmonary vascular pressure from increased sympathetic activity, provoking the combination of pulmonary vasoconstriction and increased left atrial pressure from systemic hypertension. *Status epilepticus* and repetitive seizures can cause pulmonary oedema, which can alter pulmonary function for up to 72 hours¹⁰. Studies have shown that seizure-associated respiratory compromise due to hypoventilation or obstructive apnoea is an important feature in SUDEP^{4,11}. In a series of 15 witnessed SUDEPs, respiratory difficulties were seen in 12¹¹. Although various abnormalities in pulmonary cardiac functions that can cause sudden death during the ictal period in patients with epilepsy have been reported¹²⁻¹⁴, there are only a few reports with respect to the interictal period¹⁵.

We aimed to assess whether patients with epilepsy have higher respiratory co-morbidity than the general population, and whether the prevalence of respiratory co-morbidity differs between people with epilepsy with and without known risk factors for SUDEP. Whereas most available studies of cardiorespiratory function have focused on changes during seizures^{5,13}, here we investigate whether epilepsy influences pulmonary function. We analyzed respiratory parameters in patients with temporal lobe epilepsy (TLE), the most frequent refractory epilepsy, during the interictal period.

METHOD

Adult outpatients with medically proven TLE were invited to participate as study subjects during a routine visit to a specified neurological outpatient clinic (Itapeti Neuroclinic, Mogi das Cruzes, Brazil). Patients were informed about the procedures of the study, and if agreed to take part in the study signed an informed consent form. The study was ethically reviewed and approved by the Institutional Human Research Ethics Committee.

Inclusion criteria were age over 18 years, a reliable diagnosis of TLE, ability to read and comprehend the meaning of the questionnaire and able to provide informed consent to participate in the study. Patients with a clinical diagnosis of asthma, allergic rhinitis, smoking habits, and other respiratory disorders were excluded. All had a multidisciplinary evaluation, including history and physical examination, EEG monitoring and magnetic resonance imaging (MRI). In brief, thirteen patients presented psychic seizures

within complex partial seizures: nine with epigastric aura and four with affective manifestations of fear. These events occurred before anti-epileptic drugs (AED) treatment. EEG analysis with scalp electrodes performed during sleep and wakefulness showed epileptiform activity with spike waves predominantly in the anterior temporal region in nine patients, focal EEG slowness in the temporal regions in two patients and normal EEG in nine patients. MRI showed hippocampal atrophy in nine patients.

Spirometry was performed in 10 females and 10 males. All completed a questionnaire about age, sex and health habits. Body measurements were taken, including standing height and weight. After explanation of the test procedures, every subject attempted to perform spirometric manoeuvres. Forced expiratory manoeuvres were recorded with a pneumotachograph (Koko Spirometer). A minimum of 3 acceptable and reproducible manoeuvres were obtained for each patient, according to the standards recommended by the American Thoracic Society¹⁶. All spirometric examinations were carried out with the subject seated, wearing a nose clip and using a disposable mouthpiece. The technical procedures, acceptable criteria, and reproducibility followed American Thoracic Society guidelines¹⁷. Measurements for Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1) and ratios of FEV1 to FVC (FEV1/FVC) were obtained, and these values were compared with predicted values. Reference values from Crapo¹⁸ and Rodrigues¹⁹ were used.

Statistical analysis – Statistical analysis was done by employing the ANOVA test with Tukey post test. Significance was established at the $p < 0.05$ level.

RESULTS

None of the 20 patients with TLE had chronic obstructive pulmonary disease. Anthropometrics and clinical characteristics of the patients with epilepsy in the study are shown in the Table. The mean age of the patients was 41 ± 12.3 years and the mean duration of epilepsy was 20 ± 9 years. All patients were treated with AEDs, using at least one medication at the time of the study. Carbamazepine (80%) was the most commonly used AED, followed by clobazam (10%). Almost all patients presented with controlled seizures. Pulmonary function of patients with epilepsy showed no significant alterations in respiratory tests: FVC (4.09 ± 1.24), FEV1 (3.33 ± 1.03) and FEV1/FVC (0.81 ± 0.05). No association between seizure frequency, AED and altered pulmonary function was found.

DISCUSSION

Potential mechanisms of SUDEP comprise cardiac arrhythmia, autonomic imbalance, hypoxia, arrhyth-

Table. Anthropometrics and clinical characteristics of the patients with temporal lobe epilepsy.

| | |
|-----------------------------------|------------|
| Sex | |
| Male | 10 |
| Female | 10 |
| Age (years-SD) | 41±12.3 |
| Weight (Kg-SD) | 70.3±16.5 |
| Height (cm-SD) | 167.7±11.6 |
| Mean duration of epilepsy (years) | 20±9 |
| Seizure frequency | |
| Controlled | 13 |
| Weekly | 2 |
| Monthly | 5 |
| Seizure type | |
| SPS | 0 |
| CPS | 18 |
| SPS/CPS | 2 |
| AED | |
| Carbamazepine | 12 (60%) |
| Oxcarbazepine | 4 (20%) |
| Divalproex | 1 (5%) |
| Phenobarbital | 1 (5%) |
| Clobazam | 5 (25%) |
| Clonazepam | 3 (15%) |
| Nitrazepam | 2 (10%) |
| Hidantoine | 1 (5%) |
| Therapy treatment | |
| Monotherapy | 10 |
| Polytherapy | 10 |

SPS, simple partial seizure; CPS, complex partial seizure.

mogenic drugs or central or obstructive apnoea^{4,20-22}. We analyzed respiratory parameters in patients with TLE during the interictal period and found no significant alterations in respiratory function tests.

The exact pathomechanism of SUDEP is unknown. Cardiac mechanisms may play a role, due to repetitive cardiac damage during seizures and to arrhythmia during seizures, possibly triggered by apnoea and/or cerebral autonomic imbalance. Several studies deal with respiratory parameters during seizures^{4,15,23} but information on respiratory function in patients with epilepsy during the interictal period is lacking. One study¹⁵ found vital capacity levels to be significantly lower in patients with generalized epilepsy than in those with partial epilepsy. Respiratory physicians detected no pathology during examinations of patients, so the differences found in vital capacity were evaluated as a lack of coordination in respiratory function tests. Another group also observed that respiratory function tests in the interictal period were no

different from those of a control group¹⁴. Information about the interictal period was also analysed in animals with pilocarpine-induced epilepsy²⁴. In this study rats with epilepsy presented an altered ability to compensate for changes in arterial gas levels with changes in ventilation in response to an increase or decrease in PaCO₂.

Although data from literature have showed seizure control in 10-40% of TLE patients, we observed that 75% of the patients from our study presented controlled seizure under therapy treatment. One explanation for our findings might be that most patients in this study had controlled seizures, and increased seizure frequency is reported to be a strong risk factor for SUDEP. Most of our patients, however, were taking AED polytherapy, another known risk factor for SUDEP.

Several autopsy studies in people with SUDEP have reported pulmonary oedema²⁵ or increased lung weights¹⁴. The post-mortem data in one study²⁶ revealed bronchial fluid or pulmonary oedema in four of six cases, suggesting that the increased autonomic stimulation associated with seizures in SUDEP observed in their study may contribute to pulmonary changes that may be important in SUDEP; pre-existing pulmonary diseases could exacerbate this process.

It might be speculated that ictal as well as interictal ventilatory dysfunction could have a role in some SUDEP cases. Although our study did not identify any specific common respiratory abnormality in TLE patients during the interictal period, re-evaluation of clinical data about pulmonary disorders in people with epilepsy should be better investigated.

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