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Echocardiographic risk markers of sudden death in patients with temporal lobe epilepsy

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ABSTRACT

Patients with epilepsy (PWE) have an increased risk for sudden unexpected death compared to the general population. Echocardiography can analyze structural and functional heart changes that have impact on outcomes, including sudden cardiac and all-cause death. Our hypothesis is that subtle heart abnormalities occur in PWE. Thirty patients with temporal lobe epilepsy without any known cardiovascular disease, followed for at least 1 year, were enrolled between July 2015 and July 2016 and submitted to a 12-lead electrocardiogram, treadmill test and transthoracic echocardiogram. PWE were matched with individuals without epilepsy by sex, age and body mass index. A literature review of studies comparing echocardiographic findings in PWE and individuals without epilepsy was performed. PWE had a higher left ventricle stiffness ($\beta = 5.97 \pm 0.05 \times 5.94 \pm 0.03$; $p = 0.02$), left ventricle filling pressures (9.7 ± 1.3 mmHg $\times 9 \pm 0.8$; $p = 0.02$) and a greater left atrial volume (44.7 ± 13.6 ml $\times 34.1 \pm 9.6$ ml; $p = 0.003$). Seventeen (56.6%) PWE had a total of 22 of six known echocardiographic markers related to increased risk for sudden death in the general population, versus 11 (36.7%) controls with 12 markers ($p = 0.07$). Stiffness is related to fibrosis through extracellular matrix deposition, which promotes systolic and diastolic dysfunction and arrhythmogenesis. Subtle echocardiographic findings in PWE could help to explain why this population has an increased risk to die suddenly.

1. Introduction

It is well known that patients with epilepsy (PWE) have an increased risk for sudden unexpected death compared to the general population (Ficker et al., 1998; Mohanraj et al., 2006). Sudden Unexpected Death in Epilepsy, or SUDEP, accounts for as many as 15% of all epilepsy related deaths, and PWE have a 7%–35% lifetime risk for this tragic outcome (Shorvon and Tomson, 2011; Thurman, 2013).

The mechanisms explaining this increased risk are not fully understood, but probably involve interactions between seizure activity and heart and lung function (Massey et al., 2014; Tomson et al., 2008). Nevertheless, it is still unclear why of many seizure events one can be fatal.

Echocardiography has become an important tool in cardiology to analyze structural and functional heart changes that may have impact on outcomes, including sudden cardiac and all-cause death (Konety et al., 2016; Bayés de Luna and Elosua, 2012). Among others, systolic and diastolic function, myocardial ischemia or certain phenotypes (such as hypertrophy) are associated with increased risk of sudden death (Konety et al., 2016; Bayés de Luna and Elosua, 2012).

Few studies comprehensively analyzed heart function and structure in PWE, looking for clues or risk markers for sudden death. Therefore, the present study aimed to evaluate functional and structural heart alterations in PWE compared to healthy controls. Our hypothesis is that subtle heart abnormalities occur in PWE.

Abbreviations: EDP, end-diastolic pressure; EDV, end-diastolic volume; LVEDV, left ventricular end-diastolic volume; LVEDPVR, left ventricular end-diastolic pressure-volume relationship; TAPSE, tricuspid annular plane systolic excursion

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2. Material and methods

2.1. Patients and controls

Patients with a definite diagnosis of temporal lobe epilepsy not previously submitted to epilepsy surgery, and followed for at least one year at the Comprehensive Epilepsy Center at the University Hospital of Santa Catarina, Brazil, were enrolled between July 2015 and July 2016 (Fialho et al., 2017). Epilepsy was diagnosed according to International League against Epilepsy (ILAE) criteria and endorsed by electroencephalography and neuroimaging (brain CT or MRI) (Fisher et al., 2017). All patients had focal seizures with impairment of awareness, and five had additionally focal seizures evolving to bilateral tonic-clonic seizures (Fisher et al., 2017). The antiepileptic drug (AED) regimens were assessed.

The control group was composed of healthy individuals matched with cases by sex, age and body mass index (BMI).

Individuals (cases and controls) were excluded if they had any known cardiovascular disease, such as ischemic heart disease (including prior revascularization or coronary angioplasty), moderate or severe valve stenosis or insufficiency, congenital or arrhythmic heart disease or greater than mild hypertension (Malachias et al., 2016). Patients with peripheral artery disease or neurovascular disease were also excluded.

Data about medical conditions, medications, first degree family history of cardiovascular disease, smoking status (former or active), alcohol use, physical activity and social economic conditions were obtained in all individuals.

2.2. Test procedures

Cases and controls were submitted to a 12-lead electrocardiogram (EKG – Cardiette ar600view – Cardioline S.p.A, Via de Zinis, 6 38011 Cavareno (TN) Italy info@cardioline.it; www.cardioline.it), treadmill test (Super ATL, Imbramed, Porto Alegre, RS, Brasil) and transthoracic echocardiogram (General Electric Medical Systems, Vivid S6, Tirat, Carmel, Israel), equipped with a M4S-RS 1.5–3.6 MHz Matrix Array transducer.

2.2.1. Echocardiography

Echocardiographic images were obtained in all patients in the left lateral position. Two-dimensional, M-mode, color, pulse or continuous wave Doppler and tissue Doppler images were obtained according to internationally validated guidelines (Lang et al., 2015).

The cavity size was measured as follows: left ventricle diameter by two-dimensional imaging and volume using Simpson's rule (a method in which the ventricle area is measured in two orthogonal planes and then reconstructed as a three-dimensional structure); left atrium diameter by M-mode and volume, and volume indexed to body size; right ventricle using base and mid-cavity diameter; and right atrium volume.

Left ventricle systolic function was measured by Simpson's rule ({end diastolic volume – end systolic volume}/end diastolic volume). Tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode and tricuspid lateral annular systolic velocity wave (s') was measured by tissue Doppler to quantify right ventricle systolic function. Interventricular septum and posterior wall thickness were measured and left ventricle mass was calculated according to previously validated guidelines (Lang et al., 2015). Left ventricle mass was indexed to body size. Aortic root and ascending aortic diameter were also measured.

Tissue Doppler imaging was used in the apical four-chamber view to measure peak systolic (s'), early (e') and late (a') diastolic waves of mitral lateral and septal annular excursion. Average e' was calculated ({septal e' + lateral e'}/2). Ejection time (ET), isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) were measured to calculate global performance (Tei) index (Tei Index = (IVRT + IVCT)/ET), a marker of systolic and diastolic performance of left and right ventricles. Pulse wave Doppler was used to measure the peak velocities of early (E) and late (A) waves of mitral inflow. IVRT was derived from Doppler recordings of mitral valve inflow and aortic valve outflow. E/A ratio and E/(average e') ratio, important indices of diastolic function and filling pressure, were calculated.

Echocardiogram was performed during an interictal period of at least 24 h since the last seizure episode. Exams were performed by a board-certified cardiologist (G.L.F.), member of the Brazilian Cardiology Society, blinded to all clinical and demographic data, according to current guidelines (Lang et al., 2015; Nagueh et al., 2016).

2.2.2. Non-invasive estimation of the left ventricular end-diastolic pressure-volume relationship (LVEDPVR)

We used the method described by Klotz et al. (2006) to assess LVEDPVR and stiffness constant, β (Klotz et al., 2006; Ten Brinke et al., 2010). Briefly, LVEDPVR can be predicted by calculating the left ventricle end diastolic volume (LVEDV) at which pressure is 0 mmHg $\{V_0 = LVEDV \times [0.6\text{-}(0.006x\ DP)]\}$ and volume at which pressure is equal to 30 mmHg $[V_{30} = V_0 + (LVEDV\text{-}V_0)/(DP/27.28)^{(1/2.76)}]$. DP (left ventricle diastolic filling pressure) can be estimated as 4.4 + (0.85 × E/e') (Kasner et al., 2007). LVEDPVR can be estimated as $EDP = \alpha \times EDV^{\beta}$ and $\beta = \log(DP/30)/\log(LVEDV/V_{30})$, where EDP is end diastolic pressure and EDV is end diastolic volume.

2.3. Literature search strategy and selection criteria

A review of studies comparing echocardiographic findings in PWE and individuals without epilepsy was performed. The search strategy and selection criteria were based on articles identified in PubMed, Medline for all original research with human subjects written in English without time limit, with a combination of the words "echocardiography", "ECHO", "epilepsy", "seizure" and "SUDEP". The selection of material was based on its quality, originality, and relevance to the subject. All relevant citations identified in the selected articles, which did not appear in the initial survey, were also selected.

2.4. Statistical analysis

Statistical analysis was performed using IBM® SPSS® software package for Windows, version 20, and Microsoft Excel® software package for Windows, 2014. The sample was characterized by descriptive analysis. Quantitative variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as percentage of the total group. Normality of distribution was assessed by Kolmogorov-Smirnoff test. Two- tailed Student's *t* test was used to compare quantitative variables and Fisher's exact test (2 × 2 contingency tables) or Pearson's Chi square (3 × 2 contingency tables) were used to compare categorical variables and occurrence frequency. A *p* value of ≤ 0.05 was considered statistically significant.

2.5. Ethical approval

This study was conducted in accordance to the Code of Ethics of the World Medical Association and the Uniform Requirements for Manuscripts Submitted to Biomedical Journal (WMA Declaration of Helsinki, 2014). Institutional review boards and local ethics committees (CEPSH/UFSC) approved the study protocol and informed consent, which was signed by all subjects that voluntarily agreed to participate in the study.

3. Results

We consecutively enrolled 60 subjects (30 PWE and 30 controls). Table 1 shows clinical and epidemiological data of PWE. AEDs (dose and type) are described in Supplementary material Appendix A. Both groups were paired for age, gender and BMI and they had similar low