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The role of temporal lobe epilepsy in cardiac structure and function

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Summary

Cardiac autonomic and structural changes may occur in temporal lobe epilepsy (TLE) patients and may contribute to the risk of sudden unexpected death in epilepsy patients (SUDEP). The purpose of this investigation was to evaluate whether the presence of TLE and lifetime seizure activity in TLE patients correlates with changes in left ventricle (LV) dimensions, ejection fraction (EF), and LV mass. We reviewed clinical charts to obtain patients' demographics, lifetime seizure count, antiepileptic drug (AED) use, and history of heart disease. A transthoracic echocardiogram machine was used to calculate LV dimensions, EF, and LV mass. By comparing TLE patients to control subjects, we found that TLE patients had thinner LV walls, smaller EF, and no significant difference in LV mass. Analysis of TLE patients with high or low number of lifetime seizures suggested that the two groups had no significant differences in LV wall thickness, EF, or LV mass. TLE does correlate with changes in the LV and EF, but the number of lifetime seizures does not. Future investigations should address the effects of different combinations of AEDs used by patients in this study on epileptic rats' LV wall thickness and EF. Applications of this work include early diagnosis of TLE through the use of echocardiography data and reducing risk of patients dying of SUDEP.

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Introduction

Epilepsy is a brain disorder characterized predominantly by recurrent and unpredictable seizures, or interruptions of normal brain function caused by hypersynchronization of neuronal firing. Epilepsy affects more than 50 million people worldwide (1), and the most common type of epilepsy in adults is temporal lobe epilepsy (TLE). Seizures confined to the temporal lobe and those that propagate throughout the brain can both affect autonomic nervous system function (2). The autonomic effects of seizures, such as increased heart rate, are thought to play an important role in Sudden Unexpected Death in Epilepsy Patients (SUDEP), a major cause of death in epilepsy patients (3). SUDEP is defined as an unforeseen death of patients with epilepsy, in which postmortem examination does not reveal a structural or toxicologic cause for death (4).

Cardiac functional and structural changes may occur in epilepsy patients that contribute to the risk of SUDEP. For example, previous studies have shown increased ventricular tachycardia, an abnormal increase in heart rate, during seizures as a possible cause of SUDEP (5). The non-uniform recovery of excitability in ventricular muscle may result in long term damage to cardiac myocytes (6), which potentially decreases the thickness of the ventricular walls. Additional studies have also shown a significant decrease in ejection fraction (EF), the amount of blood pumped per contraction, in patients with high risk of SUDEP (7). Since SUDEP is a major cause of death in epilepsy patients, these cardiac alterations may occur in TLE patients. The cumulative impact of these cardiac alterations in TLE patients has not been studied in depth. Because SUDEP patients commonly display damaged cardiac myocytes and decreased ejection fraction, this study examined septal and posterior wall thickness (SWT and PWT, respectively) and ejection fraction (EF). We targeted our investigations to the left ventricle because it is the chamber responsible for pumping blood to the brain and body.

Another factor that may contribute to SUDEP is the frequency of seizures a patient experiences. Previous studies indicate that increases in generalized seizures are strongly associated with an increased risk for SUDEP (8). Seizures adversely affect the autonomic nervous system over time, and this can lead to a deterioration of cardiac muscle tissue with each epileptic episode. Thus, as the frequency and duration of seizures increases, the potential damage to cardiac structure and function also increases. However, many studies assess seizure frequency over a relatively short duration of time, not over a patient's lifetime. Thus, we assessed the effect of the number of seizures over a lifetime in TLE patients on cardiac measurements.

The purpose of this investigation was to evaluate

whether temporal lobe epilepsy (TLE) and lifetime seizure count correlate with changes in left ventricle (LV) wall thicknesses and ejection fraction (EF). Based on the cardiac measurements from this investigation, TLE patients can be assessed as either high or low risk for cardiac disorders and SUDEP. It was hypothesized that SWT, PWT, and EF would be significantly lower in TLE patients compared to healthy controls, and that SWT, PWT, and EF would also be significantly reduced in patients with a higher number of lifetime seizures compared to patients with fewer seizures.

Results

The rationale for this investigation was to evaluate the claim that the presence of TLE correlates with significant changes in left ventricle (LV) dimensions, ejection fraction (EF), and LV mass, and that lifetime seizure activity in TLE patients correlates with changes in the same cardiac measurements. All subjects were given a Transthoracic Echocardiogram (TTE) where septal wall thickness (SWT), posterior wall thickness (PWT), and ejection fraction were measured using standard procedures. Additional measurements on LV mass that are routinely obtained in TTE studies were recorded. TLE subjects were grouped based on whether they had a high or low incidence of lifetime seizures, using 100 seizures as the cutoff. The two groups were analyzed for LV dimensions, EF, and LV mass.

We found that the presence of TLE correlated with changes in cardiac structure and function, specifically SWT, PWT, and EF. TLE patients were found to have thinner septal walls than controls (Figure 1A; $p < 0.001$). TLE patients also had thinner posterior walls than controls (Figure 1B; $p < 0.001$). A thinner LV wall may indicate a larger LV volume, leading to cardiac hypertrophy (9). Cardiac hypertrophy may lead to arrhythmia, which may increase the risk for tachycardia (10). The EF of controls were not found to be significantly different from those of

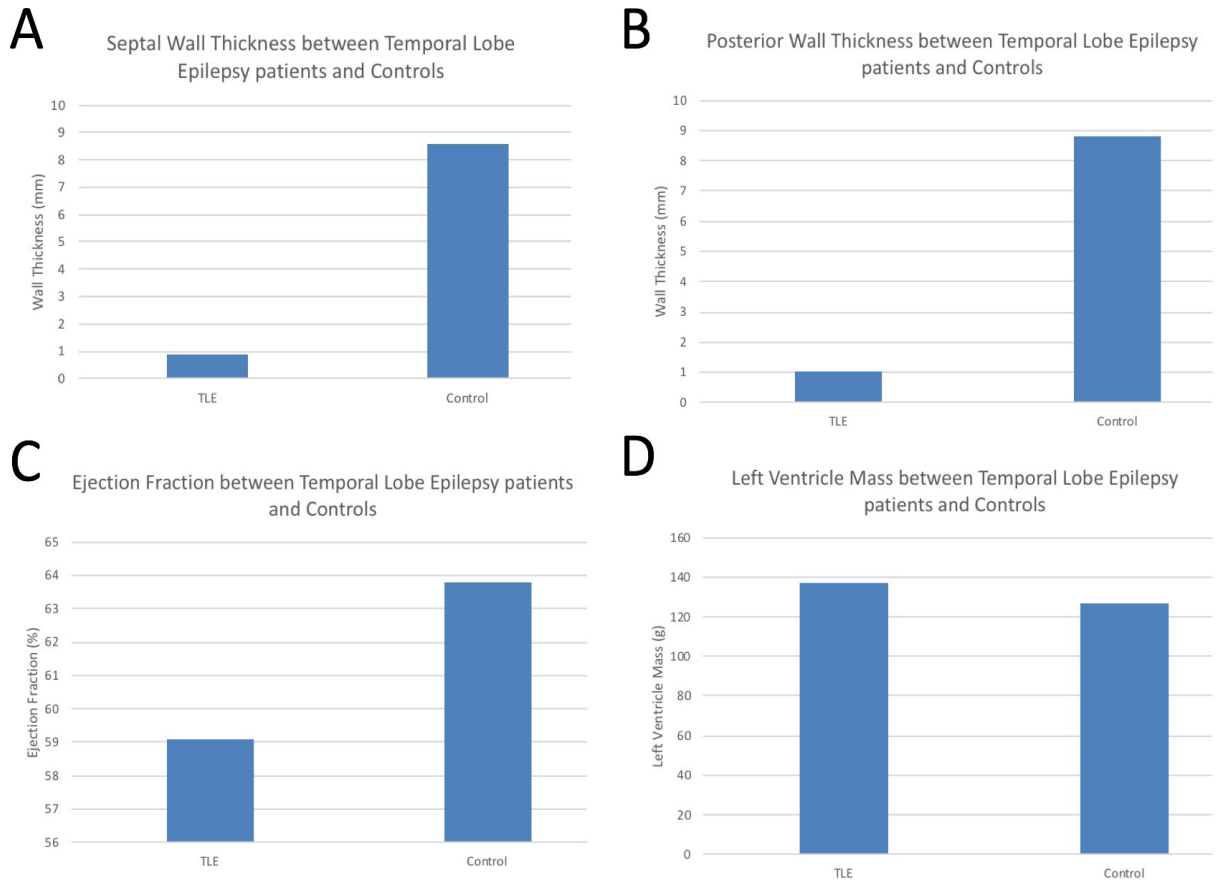

Figure 1. Difference in cardiac measurements between temporal lobe epilepsy and control subjects. A) Difference in septal wall thickness between temporal lobe epilepsy and control subjects. Temporal lobe epilepsy patients (n = 50) had thinner septal walls than controls (n = 734; $p < 0.001$). B) Difference in posterior wall thickness between temporal lobe epilepsy and control subjects. Temporal lobe epilepsy patients (n = 50) have a thinner posterior wall than controls (n = 734; $p < 0.001$). C) Difference in ejection fraction between temporal lobe epilepsy and control subjects. Temporal lobe epilepsy patients (n = 50) have a smaller ejection fraction than controls (n = 734; $p = 0.001$). D) Difference in left ventricle mass between temporal lobe epilepsy and control subjects. Temporal lobe epilepsy patients (n = 50) did not have statistically significant differences in left ventricle mass compared to controls (n = 734; $p = 0.172$).

TLE patients (Figure 1C; p = 0.231). The LV mass was not significantly different between the TLE and control subjects (Figure 1D; p = 0.174).

Patients with more than 100 lifetime seizures did not have a significantly different septal wall thickness compared to patients with less than 100 lifetime seizures (Figure 2A; p = 0.827). Patients with high seizure incidence also lacked a significantly different posterior wall thickness compared to patients with a low incidence (Figure 2B; p = 0.332), nor did they have a significantly different EF from patients with low incidence (Figure 2C; p = 0.697). Patients with a high incidence of lifetime seizures also did not have a significantly different LV mass compared to patients in the low incidence group (Figure 2D; p = 0.795).

Discussion

Patients with TLE displayed changes in cardiac structure and function, specifically in the SWT, PWT, and EF. Changes in SWT and PWT may be due to heart chambers having to become enlarged to pump greater volumes of blood (ejection fraction) in a short amount of time. Decreased wall thickness may indicate a risk for ventricular fibrillation, a life-threatening heart rhythm, which has shown to result in cardiac arrest and death without treatment (11). EF may not have been significantly different between TLE patients and controls due to the AEDs the patients were taking at the time of the investigations. A previous study that used AEDs, including valproic acid and carbamazepine, did not result in significantly different EF compared to controls (12).

LV mass was not found to be significantly different between TLE patients and healthy controls. This may

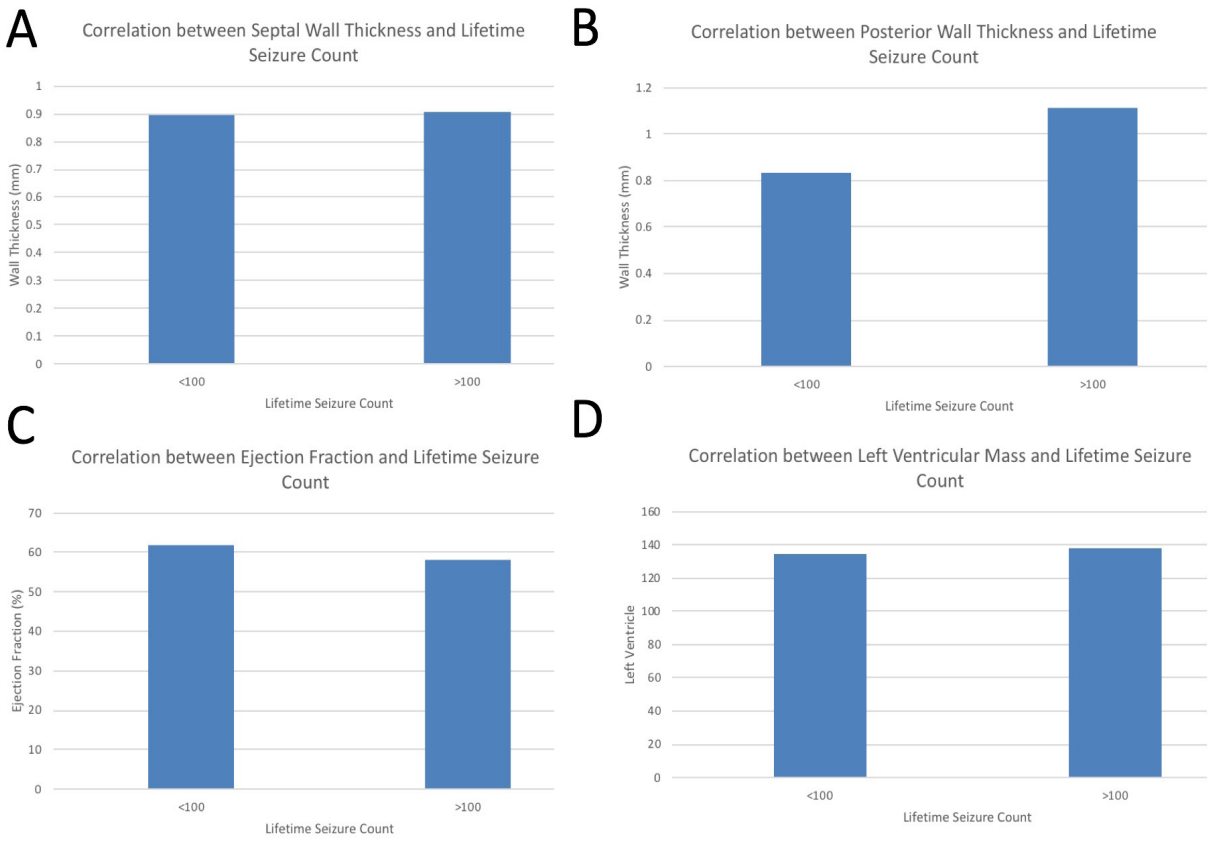

Figure 2. Difference in cardiac measurements between temporal lobe epilepsy patients with high and low number of lifetime seizures. A) Difference in septal wall thickness between temporal lobe epilepsy patients with high and low number of lifetime seizures. Patients with greater than 100 lifetime seizures (n = 38) did not have significantly different septal wall thicknesses compared to patients with less than 100 lifetime seizures (n = 12; p = 0.827). B) Difference in posterior wall thickness between temporal lobe epilepsy patients with high and low number of lifetime seizures. Patients with greater than 100 lifetime seizures (n = 38) did not have significantly different posterior wall thicknesses compared to patients with less than 100 lifetime seizures (n = 12; p = 0.332). C) Difference in ejection fraction between temporal lobe epilepsy patients with high and low number of lifetime seizures. Patients with greater than 100 lifetime seizures (n = 38) did not have a significantly different ejection fractions compared to patients with less than 100 lifetime seizures (n = 12; p = 0.697). D) Difference in left ventricle mass between temporal lobe epilepsy patients with high and low number of lifetime seizures. Patients with greater than 100 lifetime seizures (n = 38) did not have significantly different left ventricular masses compared to patients with less than 100 lifetime seizures (n = 12; p = 0.795).

be because although the LV volumes may increase, the mass would not increase significantly due to the LV walls thinning, thereby decreasing the mass. Previous studies have reported increases in LV mass in TLE patients (13). The discrepancy in this study may be attributed to AED usage. For example, Tegretol has been correlated with a decrease in cardiac mass (14). Patients that took Tegretol may have lowered the average LV mass for the TLE patients.

The number of lifetime seizures did not correlate with a difference in LV dimensions, EF, or mass. A thinner LV wall observed in TLE patients (Figure 1A & Figure 1B) indicates a larger LV volume; however, similar to the wall thickness, a decrease in thickness over time may be a short-term effect, and examination of the effects of the seizure frequency over a lifetime may make the changes too small to notice (15). Previous studies have reported decreased SWT and PWT with greater seizure frequencies in TLE subjects (16). The difference observed in this study may be because in a short period of time, overexertion of cardiac muscle during high frequency of seizures leads to the left ventricular walls slowly wearing away and decreasing in thickness over time (17). However, the frequency of seizures over a lifetime may erode the walls to a steady-state minimum thickness, contributing to no significant difference.

Differences in EF may not have been found because changes in EF due to seizures may occur gradually over time. Regarding LV mass, although previous studies have observed increases in LV mass in TLE patients (18), the mass may not have increased significantly because thinning of the LV walls (Figure 1A & Figure 1B) would decrease the LV mass. In addition, because thinning of the left ventricular walls may produce short-term effects (19), examination of the effects of the frequency of seizures over a long period of time may make the effects minimal over a lifetime.

Future studies should improve upon this investigation by using a larger sample size to yield a wider range of more reliable data. In addition, follow-up investigations should explore EF readings before, during, and after seizures to get a more in-depth look at the functional changes of the heart during an epileptic episode. Future investigations include observing effects of different combinations of AEDs used by patients in this study on epileptic rats' LV wall thickness and EF. This would enable more accurate interpretations of changes in cardiac data of TLE patients, as many patients take AEDs to help treat epilepsy. Applications of this research can be used in early diagnosis of TLE through the use of echocardiography data. This would benefit TLE patients and also prepare them for seizures, which may help reduce the risk of patients dying from SUDEP.

Materials and Methods

Ethics Statement

This study was approved by the Institutional Review Board at SUNY Downstate and adheres to the Declaration of Helsinki (1964, 2008). All subjects gave written consent before participating in the study. Study data was kept confidential in a secure location and used only for research purposes.

Patient Selection

50 TLE patients (33 male, 18 female), 18 years or older, were selected for this study, with an average age of 46.5 years. Groups with prior diagnosis of certain heart conditions, including atrial fibrillation, heart valve disorders, and myocardial infarction, were excluded from the study.

Human control values for echocardiogram measures were taken from a previous study (20). The controls were matched with the study subjects based on age, race, height, and weight.

Echocardiography

All subjects were given a Transthoracic Echocardiogram (TTE) performed using a Phillips SONOS 5500 echocardiography machine equipped with a 3.5-MHz probe. Septal wall thickness (SWT), posterior wall thickness (PWT), and ejection fraction were determined using standard procedures. Additional measurements on LV mass that are routinely obtained in TTE studies were recorded. Because some of these derived measurements required simultaneous electrocardiogram (ECG), all subjects underwent a three-lead ECG with electrodes attached to both arms and the left leg.

Medical Record Review

Past medical records of all the TLE patients were reviewed to extract data, including their demographics, age of seizure onset, TLE type, history of epilepsy surgery, and frequency of seizures. In addition, neurological data was extracted, including data obtained by Magnetic Resonance Imaging (MRI), Electroencephalography (EEG), and Video Electroencephalography (VEEG). Lastly, a record of all antiepileptic drugs (AEDs), past AEDs, and medications that the patients were prescribed was analyzed for this study. The following AEDs were factored in during the data analysis of this investigation: Zonegran, Tegretol, Topamax, Lamictal, Trileptal, Neurontin, Gabitril, Phenobarbital, Phenytoin, Keppra, Depakote, Vimpat, Onfi, Dilantin, Klonopin, Banzel, and Aptiom.

Patient Selection

Patients who have an average of 2-3 seizures per year were considered to have a low frequency of seizures and

patients who have more than 8 seizures per year were considered to have a high frequency of seizures. The average age of the patients was 46.5 years old, and the average age of seizure onset was 26.6 years old. Based on these estimates, the average TLE patient of this study had epilepsy for 20 years, with 60 or fewer seizures being a low number of lifetime seizures and 160 or more being a high number of lifetime seizures; thus 100 was set as the cutoff between the high and low number of lifetime seizures.

Statistical Analysis

Statistical analysis was performed to find any significant differences in LV dimensions and EF between the TLE patients and healthy controls. A one-sample Student's T-test was used to analyze group differences in the LV wall thickness and EF. If a *p*-value was less than 0.05, the difference was deemed significant.

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