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Evaluation of left ventricular diastolic function by tissue Doppler imaging in patients with newly diagnosed and untreated primary generalized epilepsy

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ABSTRACT

Purpose: The effects of epilepsy and seizures on cardiac functions have been documented, and this association has drawn attention in recent years. The aim of this study was to investigate left ventricle (LV) diastolic function by tissue Doppler imaging (TDI) in patients with newly diagnosed and untreated primary generalized epilepsy (PGE).

Method: Thirty newly diagnosed and untreated PGE patients (14 females, mean age 27.60 ± 9.64 years) and 30 healthy age- and gender-matched control subjects (14 females, mean age 29.47 ± 6.89 years) were included in the study. The LV functions of the study cohort were evaluated using conventional echocardiography and TDI.

Results: There were no significant differences found between the two groups regarding the left atrium diameter, left atrium volume index, interventricular septum and posterior wall thickness, LV end diastolic diameter, and LV end diastolic volume ($p > 0.05$ for each parameter). PGE patients exhibited a higher LV end systolic diameter and LV end systolic volume compared to the controls ($p < 0.001$ for each parameter). Thus, the fractional shortening and ejection fraction were lower in the PGE patients ($p < 0.001$ for each parameter). The E to average e' ratio, the most important noninvasive indicator of LV filling pressure, was significantly higher in patients with PGE (8.31 ± 2.78 vs. 6.95 ± 1.26, $p = 0.018$).

Conclusion: The present study reports the systolic and diastolic dysfunction of LV in newly diagnosed PGE patients compared to control subjects. Taken together, the screening of epileptic patients using conventional echocardiography and TDI may be useful to evaluate the effects of epilepsy on cardiac functions.

1. Introduction

Epilepsy and seizures may have a profound effect on cardiac function. In patients with seizures, epileptic discharges are thought to propagate to the central autonomic network and change or disturb the normal autonomic control of vital cardiac functions. Typical cardiovascular manifestations of epilepsy include alterations in heart rate and rhythm, blood pressure, and electrocardiogram.[1]

It is well known that patients with epilepsy have an increased risk for sudden unexpected death (SUDEP). The risk of SUDEP is increased 24[2]- to 40[3]-fold in the epileptic population compared to the general population. The exact mechanism of SUDEP is not completely understood however, it is most likely multifactorial. The most important risk factor for SUDEP is the frequency of generalized tonic-clonic seizures.[4] Seizure-related cardiac dysfunction is thought to be one important mechanism of SUDEP. Thus, alterations in cardiac functions in epileptic patients have become an issue of increasing interest.

Left ventricular diastolic dysfunction (LVDD) is common in cardiac disease and contributes to the development of heart failure. Approximately half of the patients with newly diagnosed heart failure have normal or near normal global ejection fractions. These patients have been identified to have diastolic heart failure or heart failure with preserved ejection fraction (HFPEF).[5] LVDD is one of the principal causes of HFPEF.[6] A recent review reported a LVDD prevalence of 27.3% in the general population.[7] The "gold standard" in evaluating LV diastolic functions is the measurement of LV filling pressures. However, this method is invasive and not practical. Echocardiography may be used to noninvasively evaluate both systolic and diastolic cardiac functions.[8] Doppler studies are

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the preferred method to evaluate LVDD. The parameters measured by traditional mitral flow Doppler studies include *E* wave velocity, *A* wave velocity, *E* wave deceleration time (DT), isovolumetric relaxation time (IVRT), and the *E*/*A* ratio. The data obtained using this method are preload dependent and exhibit a lower accuracy. Within the last two decades, tissue Doppler imaging (TDI) has been developed to enhance the accuracy of diastolic heart function analyses.[9] TDI measures the diastolic and systolic velocities of the ventricular walls and mitral annulus, and is less affected by loading conditions.[10] The mitral annulus velocity as determined by TDI is a relatively preload independent variable and is superior to conventional mitral Doppler indices.[11] These parameters may be used to estimate the LV filling pressures.[12] Thus, TDI is currently used worldwide to evaluate LV diastolic function.[13] The ratio of the pulsed Doppler mitral *E* wave velocity to tissue-Doppler-derived peak early diastolic velocity of the mitral annulus movement (E/e') correlates with the LV filling pressures.[8] The European Society of Cardiology recommends using the Doppler echocardiographic index as a first step in the diagnosis of HFPEF.[5]

The aim of this study was to investigate LV diastolic function using TDI in patients with newly diagnosed and untreated primary generalized epilepsy (PGE).

2. Material and methods

2.1. Patients

In this single-center prospective study, patients with electroclinical or only clinical diagnosis of idiopathic generalized epilepsy (IGE), who had at least one electroencephalogram (EEG) available, were recruited consecutively among those who presented to the outpatient epilepsy clinic at Medical Faculty of Baskent University from 2007 through 2011. Thirty newly diagnosed and untreated PGE patients (14 females, mean age 27.60 ± 9.64 years) and 30 healthy age- and gender-matched control subjects (14 females, mean age 29.47 ± 6.89 years) were included in this study. The patient's medical history was obtained, and the physical and neurological examinations were performed by the same neurologist. Similarly, the same cardiologist performed cardiac examinations on the patients and interpreted their electrocardiograms.

The exclusion criteria included pregnancy, known coronary artery disease, impaired liver or renal function, hypertension, moderate or severe valvular heart disease, impaired left ventricular systolic function (ejection fraction $< 50\%$), restrictive, hypertrophic, or dilated cardiomyopathies, congenital heart disease, respiratory diseases, diabetes mellitus, malignancy, smoking, excessive alcohol consumption, hyperlipidemia, history of previous cardiac surgery, severe mitral annular calcification, atrial fibrillation or other severe arrhythmias, the presence of permanent pacemakers or implantable defibrillators, any medication usage, and poor echocardiographic images.

The type of epilepsy was determined according to the guidelines of the International League Against Epilepsy and was based on a detailed medical history obtained from the patients and/or witnesses, physical and neurological examinations, EEGs, and neuroradiological findings.[14] The diagnosis of epilepsy was newly established in the PGE patient group in which anti-epileptic drugs had not been previously used. The epileptic subtypes were determined as follows: 20 patients with primary generalized tonic clonic (GTC) seizures, 4 patients with primary GTC, absence and myoclonic seizures, 4 patients with primary GTC and myoclonic seizures, and 2 patients with only myoclonic seizures. The average age of seizure onset was 23.5 ± 10.5 years. The duration of the seizures ranged from one day to 30 years [9 patients: 3–14 years (average 7.4 ± 3.97 years), 9 patients: 1 year, 6 patients: 1–6 months (average 3.7 ± 2.3 months), 5 patients: 1–7 days, 1 patient: two seizures in the last 30 years]. The frequency of the seizures was 15 or more per year in 36.7% of the patients and between 1 and 6 per year in 63.3% of the patients. The reasons for the delayed visit to a physician were documented as due to low socioeconomic status and the patients' and their families' disaffirmation of the disease due to sociocultural factors. Any etiology for epilepsy was not identified. Six of the patients had a history of epilepsy in their second and third degree relatives. Neurological examination was normal in all of the patients. Cerebral magnetic resonance imaging was performed according to epileptic protocol and was evaluated by a radiologist trained in epileptic imaging. The patients did not have any structural pathologies. For each patient, we obtained a 15-min EEG recording with 5-min hyperventilation and intermittent photic stimulation (IPS) at 2, 6, 10, 14 and 18 Hz (10 s IPS and 10 s rest) using a 14-channel EEG recorder. We used the international 10–20 system for electrode placement. All recordings were obtained in the interictal state without sleep deprivation. The interictal EEG was normal in 17 of the 30 patients. In the remaining 13 patients, 6 patients had a bilateral diffuse epileptic activity disorder, 6 patients had bilateral diffuse paroxysmal discharges of theta and sharp waves, and one patient exhibited background rhythm irregularity formed by beta waves.

2.2. Echocardiography

All of the patients were examined during a seizure-free period of at least 24 h prior to the recordings, and none of the patients reported seizures during the recording periods. All of the included patients underwent an echocardiography with a commercially available standard ultrasound diagnostic system (Vivid 7, GE Vingmed, Horten, Norway) equipped with a 2.5-MHz phased-array transducer. The images were obtained in the left lateral decubitus position after 10 min of rest. All of the patients were evaluated by M-mode, two-dimensional, pulse-wave Doppler and TDI echocardiography. The diameters of the LV and left atrium, and the thicknesses of the interventricular septum and LV posterior wall were measured by the M-mode technique according to the recommendations of the American Society of Echocardiography.[15] The peak velocities of the early (*E*) and late (*A*) diastolic filling, DT, and IVRT were derived from Doppler recordings of the mitral valve inflow and aortic valve outflow.[16] For TDI, the filter setting was lowered, and the Nyquist limit was adjusted (range, 15–20 cm/s). The gain was minimized to allow for a clear tissue signal with minimal background noise. For TDI recordings from the apical window, a 5-mm sample volume was located at the septal and lateral sides of the mitral valve annulus in the 4-chamber view and at the anterobasal and inferior sites in the 2-chamber view.[16] Measurements were recorded with simultaneous electrocardiography at a sweep speed of 50–100 mm/s. The peak systolic velocity (s'), early (e') and late (a') diastolic velocities, and e'/a' ratio were measured. The *E*/average e' ratio was calculated by dividing the transmitral *E* peak by the e' average from the 4 acquisition sites. The LVDD diagnosis and staging were performed according to the recommendations of the European Association of Echocardiography.[17] The LVDD was identified if the mitral annular septal e' velocity was lower than 8 cm/s, if the mitral annular lateral e' velocity was lower than 10 cm/s, and if the left atrium volume index was higher than 34 mL/m^2. LVDD has three grades (I, II, and III). When the LVDD was detected, the grade was estimated using Doppler parameters, including the *E*/*A* ratio, DT, IVRT, and the *E*/average e' ratio as well as ancillary techniques, if necessary.[17] The ejection fraction was calculated according to the Teicholz formula.[18] All of the echocardiographic studies were digitally recorded for off-line analysis. All of the measurements were averaged from three cardiac cycles to minimize the respiratory variability and were blindly performed by a single independent