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Original

Myocardial perfusion imaging single photon emission computed tomography may detect silent myocardial ischemia in patient with epilepsy

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Abstract

Background: The aim of the present study was to compare the myocardial perfusion imaging (MPI) with [^{99}mTc]tetrofosmin stress — rest single-photon emission computer tomography (SPECT) of patients with epilepsy with matched control individuals.

Material and methods: All 29 adult epileptic patients were receiving antiepileptic drugs (AEDs) for epilepsy. Thirty-two individuals matched for gender and age consisted of the control group. MPIs SPECT were performed, and myocardial summed scores were obtained during stress (SSS) and rest (SRS) images. Abnormal MPI was considered when SSS was ≥ 4. In addition, the difference (SDS) between SSS and SRS was also assessed, which represents a rate of reversibility after stress.

Results: Twenty of 29 (68.97%) patients with epilepsy had abnormal MPI and 14/32 (43.75%) of the controls ($p = 0.04$). Among males, 18/23 patients and 11/25 controls had abnormal MPI ($p = 0.01$), with quite a significant difference for mean SSS between male patients and controls ($p = 0.002$). Furthermore, SDS comparison showed that irreversible abnormalities were more common in patients than in control individuals. A difference of inadequately compensated myocardial ischemia between patients treated with enzyme inducing AEDs and patients treated with valproic acid was also detected.

Conclusions: Single-photon emission computer tomography (SPECT) may detect increased risk for coronary artery disease and further cardiovascular events in patients with epilepsy. Our findings favor the conclusion that SPECT could be used for the early identification of cardiovascular comorbidity in epilepsy.

KEY words: cardiovascular disease; epilepsy; myocardial ischemia; myocardial perfusion imaging; seizures

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Introduction

Cardiovascular disease represents a significant contributor to the increased mortality and hospitalized morbidity in people with epilepsy, compared with the general population [1]. Myocardial infarction (MI) following seizures may occur in a variety of epileptic conditions including single or repetitive, convulsive or nonconvulsive seizures [2]. Higher prevalence of cardiovascular risk factors such as hypertension, diabetes, and high cholesterol has been reported in patients with epilepsy compared to the general population [3]. Oxidative stress circulating markers are higher in epileptic patients and may lead to atherosclerosis [4]. In addition, previous scientific reports have indicated that antiepileptic drugs (AEDs) monitor various risk factors linked to atherothrombotic disease [5].

Even though coronary angiography is the first examination performed for the diagnosis of ischemic myocardial disease,

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alternative non-invasive cardiovascular imaging methods may be utilized, especially in cases where the symptoms and findings are controversial and inconsistent. Among them, myocardial perfusion imaging (MPI) with ^{99m}Technetium (^{99m}Tc) tetrofosmin (TF) SPECT, is probably the non-invasive modality of choice to distinguish a silent ischemic myocardial area [6].

The aim of the present study was the comparison of MPI SPECT results in patients with epilepsy to age and gender-matched control individuals and assess whether MPI SPECT could be utilized for diagnosis of early myocardial ischemia in patients with epilepsy exhibiting non-specific cardiac symptoms and having normal ECG and cardiologic examination.

Material and methods

Patients

The study patients with active epilepsy (epilepsy on AEDs or with one or more seizures in the past year or both) were followed in the Epilepsy Outpatient Clinic of our University Hospital from January 2019 to November 2019. For inclusion in the study, patients should suffer from epilepsy for over 5 years. In addition, they should have exhibited transient or persistent atypical cardiac complaints such as non-specific chest wall discomfort or shortness of breath and had normal ECG and cardiologic evaluation. The control group consisted of gender and age-matched individuals that demonstrated similar symptoms. All study participants (patients and control individuals) had no known history of coronary artery disease (CAD). In addition, patients and controls had a medical history and thorough physical examination obtained. Specifically, relevant biochemical parameters and cardiovascular risk factors were recorded (smoking, arterial hypertension, diabetes mellitus, hypercholesterolemia, and cardiovascular disease heredity). The history of family cardiovascular disease (angina pectoris, unstable angina, myocardial infarction) was assessed by questionnaire.

Among the patients with epilepsy, several data were noted such as age at the onset of epilepsy, the duration of epilepsy, and the frequency and the type of epilepsy. Moreover, the type, frequency and number of the AEDs at the time of inclusion and during the study were documented. Patients were also classified according to epilepsy type (focal/generalized and symptomatic/no symptomatic-genetic and of unknown origin), seizures type (focal without and with awareness loss/primary generalized and secondary generalized-focal with bilateral spasms), and whether their therapeutic schema included enzyme-inducing AEDs and/or valproic acid (VPA). The study was approved by the Medical Ethical Committee Section of our University General Hospital.

SPECT MPI

All study individuals, patients and controls, were subjected to ^{99m}Tc-TF-SPECT, before and after stress, according to standard protocols [7]. Single-photon emission computer tomography (SPECT) images were acquired 15–60 minutes post radiopharmaceutical injection. Images were visually evaluated by two nuclear medicine specialists, using a 17-segment polar map as previously reported [8, 9] and scoring each segment with a scale of 0 to 4, in accordance with the severity of the myocardial perfusion deficit. A SSS score ≥ 4 was indicative of myocardial ischemia. Myocardial ischemia was considered mild if the SSS was between 4 and 8, moderate if the SSS was between 9 and 13, and of a high degree when SSS was over 13 [10].

Statistical analysis

All continuous data were stated as mean ± standard deviation (± SD), whereas binary data were noted as percentages. All patients and controls were considered as having 'pathologic' MPI (MPI ≥ 4) or not. Comparisons of traits of interest between patients and controls were quantified by x^2 test for dichotomous outcome pathologic MPI and with t-test for SSS and SDS scores. Logistic regression analysis was performed to detect any potential association of age, gender and cardiovascular risk factors with MPI results between patients and controls. Mean SSS and SDS for patients and controls were also calculated. Linear regression analysis was performed to examine the impact of gender, age, and cardiovascular risk factors associated with SSS score and SDS and compare patients and controls.

In patients was epilepsy, the impact of gender, age, cardiovascular risk factors, age of epilepsy onset, epilepsy duration, epilepsy type, seizures type, AEDs number and AEDs type on the dichotomous outcome pathologic MPI was assessed with logistic regression analysis and on SSS and SDS results with linear regression analysis. All statistical tests were calculated with the SPSSv26 software.

Results

Twenty-nine patients with epilepsy (23 males, 6 females) and 32 control individuals (25 males, 7 females) were recruited for the study. The mean age of the patients was 56.2 ± 10.5 years *vs.* 55.0 ± 9.3 years for control individuals ($p = 0.58$). There were no differences in the cardiovascular risk factors between patients with epilepsy and the control group for both genders. The mean age of epilepsy onset was 30.4 (± 21.0) years, the mean duration of epilepsy was 26.4 (± 18.5) years and the mean number of AEDs receiving was 2.2 (± 1.2). (Tab. 1).

Twenty patients (68.9%) and 14 controls (43.7%) had abnormal MPI with SSS ≥ 4, $p = 0.04$. Among males, 78.2% (18/23) patients and 44% (11/25) controls had abnormal MPI ($p = 0.01$). No statistical difference was found for the female individuals. The mean SSS was 4.5 (± 2.3) for the patients and 3.1 (± 1.8) for the controls, $p = 0.01$. For males, a statistically significant difference was found for SSS scores and for SDS scores between patients and controls with $p = 0.002$ and $p = 0.02$ accordingly (Tab. 1). The logistic regression analysis did not show any association of age and cardiovascular risk factors with MPI results. The linear regression analysis did not disclose any association of gender, age and cardiovascular risk factors with the SSS and SDS scores for patients and controls.

Focusing on patients and controls with pathologic MPI, a statistically significant difference was found between male patients and controls for SDS ($p = 0.04$). The above results on SDS scores were also found by analyzing the impact of age, gender and cardiovascular risk factors with regression models. Besides the effect of gender on SDS, no other association was found (Tab. 2). No difference in the demographics, the risk factors, the characteristics of epilepsy,

Table 1. Characteristics of epilepsy patients and controls

	Patients with epilepsy		
	Total	Males	Females
Number [%]	29	23/29 (71.8)	6/29 (20.7)
Age [y] (± SD)	56.2 (10.5)	56.7 (11.4)	59.3 (7.0)
Hyperlipidemia [%]	20/29 (69)	17/23 (73.9)	3/6 (50)
Hypertension [%]	14/29 (48.3)	12/23 (52.2)	2/6 (33.3)
Smoking (%)	12/29 (41.4)	10/23 (43.5)	2/6 (33.3)
Diabetes mellitus [%]	7/29 (24.1)	5/23 (21.7)	2/6 (33.3)
CV Heredity [%]	10/29 (34.5)	7/23 (30.4)	3/6 (50)
Age of epilepsy onset, [y] (± SD)	30.4 (21.0)	31.0 (20.6)	28.3 (24.7)
Epilepsy duration, [y] (± SD)	26.4 (18.5)	25.3 (18.2)	31 (20.4)
Epilepsy type [F/G]	13/16	12/11	1/5
Epilepsy type [S/non S]	12/17	9/14	3/3
Seizures type [f/g]	4/25	1/22	3/3
Current AEDs, mean (± SD)	2.24 (1.2)	2.3 (1.2)	2.0 (1.0)
Inducers, No.	9	9	0
Inducers (AED, No.)	(CBZ:6, PH:2, PB:1)	(CBZ:6, PH:2, PB:1)	0
VPA, No.	9	7	2
Other AEDS (No.)	LEV(12), LMG (8), LCM(4), TPM(5), ESL(5), BRV(4), ZNS(3), OXC(2), CLB(2), PRP(2), PRG(2), GBP(1)	LEV(10), LMG(5) LCM(3), TPM(4), ESL(4), BRV(3), ZNS(2), OXC(2), CLB(1), PRP(2), PRG (2), GBP (1)	LEV(2), LMG(3), LCM(1), TPM(1), ESL(1), BRV(1), ZNS(1), OXC(0), CLB(1), PRP(0), PRG(0), GBP(0)
Total AEDs, mean (± SD)	3.1 (1.4)	3.1 (1.4)	3.3 (1.6)
Abnormal MPI [%]	20/29 (69)	18/23 (78.3)	2/6 (33.3)
SSS, mean (± SD)	4.5 (2.3)	5.1 (2.2)	2.5 (1.6)
SDS, mean (± SD)	2.2 (1.1)	2.4 (2.3)	1.4 (1.5)
	Control group individuals		
	Total	Males	Females
Number [%]	32	25/32 (78.1)	7/32 (21.8)
Age [y] (± SD)	55.0 (9.3)	55.1 (9.2)	54.7 (10.2)
Hyperlipidemia [%]	18/32 (56.25)	15/25 (60)	3/7 (42.9)
Hypertension [%]	21/32 (65.6)	15/25 (60)	6/7 (85.7)
Smoking (%)	15/32 (46.9)	12/25 (48)	3/7 (42.9)
Diabetes mellitus [%]	7/32 (21.9)	6/25 (24)	1/7 (14.3)
CV Heredity [%]	13/32 (40.6)	9/25 (36)	4/7 (57.1)
Abnormal MPI [%]	14/32 (43.7)	11/25 (44)	3/7 (42.9)
SSS, mean (± SD)	3.1 (1.8)	3.2 (1.6)	2.5 (1.6)
SDS, mean (± SD)	2.4 (1.7)	1.1 (1.7)	1.8 (1.7)
	p-value		
	Total (p1)	Males (p2)	Females (p3)
Number [%]		0.58	
Age [y] (± SD)	0.38	0.60	0.35
Hyperlipidemia [%]	0.22	0.23	0.61
Hypertension [%]	0.13	0.39	0.08
Smoking (%)	0.43	0.49	0.58
Diabetes mellitus [%]	0.53	0.56	0.43
CV Heredity [%]	0.45	0.50	0.61
Abnormal MPI [%]	**0.04***	**0.01***	0.58
SSS, mean (± SD)	**0.01***	**0.002***	0.86
SDS, mean (± SD)	0.06	**0.02***	0.58

*statistically significant; AED — antiepileptic drugs; BRV — brivaracetam; CBZ — carbamazepine; CLB — clobazame; CV — cardiovascular; ESL — eslicarbazepine; f — focal without and/or with loss of awareness; F — focal; g — primary generalized and secondary generalized (focal with bilateral spasms); G — generalized; GBP — gabapentin; LCM — lacosamide; LEV — levetiracetam; LMG — lamotrigine; MPI — myocardial perfusion imaging; No. — number; Non S — no symptomatic = genetic and of unknown origin; OXC — oxcarbamazepine; p(1) — comparison between the total number of patients and controls; p(2) — between the male patients and controls; p(3) — comparison between the female patients and controls; PB — phenobarbital; PH — phenytoin; PRG — pregabaline; PRP — perampanel; S — symptomatic; SD — standard deviation; SDS — summed difference score; SRS — summed rest score; SSS — summed stress score; TPM — topiramate; y — years; ZNS — zonisamide

Table 2. Patients and controls with myocardial perfusion imaging (MPI) ≥ 4

	Patients			Controls			p-value		
	Total	Males	Females	Total	Males	Females	(1)	(2)	(3)
Age [y] (± SD)	56.2 (11.2)	56.1 (11.9)	57 (0)	56.0 (5.5)	55.1 (5.1)	59.3(6.5)	0.95	0.75	0.59
Hyperlipidemia [%]	13/20 (65)	12/18 (66.6)	1/2 (50)	7/14 (50)	7/11 (63.6)	0/3 (0)	0.48	0.58	NA
Hypertension [%]	9/20 (45)	8/18 (44.4)	1/2 (50)	10/14 (71.4)	7/11 (63.6)	3/3 (100)	0.17	0.26	0.40
Smoking [%]	10/20 (50)	9/18 (50)	1/2 (50)	6/14 (42.8)	6/11 (54.5)	0/3 (0)	0.73	0.55	NA
Diabetes mellitus [%]	4/20 (20)	3/18 (16.6)	1/2 (50)	2/14 (14.2)	1/11 (0.1)	1/3 (33.3)	0.51	0.50	0.70
CV Heredity (%)	6/20 (30)	6/18 (33.3)	0/2 (0)	9/14 (64.2)	7/11 (63.6)	2/3 (66.6)	0.08	0.08	NA
SSS, mean (± SD)	5.6 (1.9)	5.8 (1.9)	4 (0)	5.0 (0.7)	4.1 (2.3)	5.3 (6.5)	0.19	0.14	0.18
SDS, mean (± SD)	2.7 (2.6)	2.7 (2.4)	2.5 (2.1)	1.8 (1.9)	1.2 (2.1)	3.6 (1.1)	0.13	**0.04***	0.57

*statistically significant; CV — cardiovascular; MPI — myocardial perfusion imaging; p(1) — comparison between the total number of patients and controls; p(2) — between the male patients and controls; p(3) — comparison between the female patients and controls; SD — standard deviation; SDS — summed difference score; SSS — summed stress score

Table 3. Epilepsy patients with myocardial perfusion imaging (MPI) ≥ 4 and MPI < 4

	MPI ≥ 4	MPI < 4	p-value
Number	20	9	
Age [y] (± SD)	56.2 (11.2)	59.6 (9.1)	0.38
Hyperlipidemia [%]	13/20 (65)	7/9 (77.7)	0.41
Hypertension [%]	9/20 (45)	5/9 (55.5)	0.45
Smoking [%]	10/20 (50)	2/9 (22.2)	0.16
Diabetes mellitus [%]	4/20 (20)	3/9 (33.3)	0.36
CV Heredity [%]	6/20 (30)	4/9 (44.4)	0.40
Age of epilepsy onset [y]	29.4 (20.9)	32.8 (22.4)	0.69
Epilepsy duration [y]	25.3 (19.0)	29 (18.1)	0.62
Epilepsy type (F/G)	7/13	6/3	0.11
Epilepsy type (S/Non S)	7/13	5/4	0.26
Seizures type (f/g)	18/2	7/2	0.36
AEDS, current number (± SD)	2.3 (1.3)	2 (1)	0.43
AEDs, total number (± SD)	3.1 (1.5)	3.2 (1.2)	0.89
nducers [%]	8 (40)	1 (11)	0.13
Valproic acid [%]	4 (20)	5 (55.5)	0.07

AED — antiepileptic drugs; CV — cardiovascular; f — focal without and/or with loss of awareness; F — focal; g — primary generalized and secondary generalized (focal with bilateral spasms); G — generalized; MPI — myocardial perfusion imaging; Non S — no symptomatic = genetic and of unknown origin; S — symptomatic; SD — standard deviation

the AEDs number, and the AEDs type (enzyme inducers and VPA) with MPI results was found between patients with MPI ≥ 4 and patients with MPI < 4 (Tab. 3).

The impact of enzyme inducers and valproic acid was also assessed. No difference was found for the presence of pathologic MPI and for SSS and SDS scores (Tab. 4). Of interest was the finding of the statistically significant difference in SDS scores between patients receiving inducers and patients receiving VPA, which favors inducers (p = 0.05).

Discussion

In the present study, we used radionuclide myocardial scanning to assess early cardiovascular disease in patients with epilepsy. Our findings suggested that patients with epilepsy have higher percentage of early cardiovascular disease compared to age and sex-matched controls. Most of the patients in the study were males and few were females. Male patients had also statistically significant pathologic MPI while the small number of females did not allow any statistical conclusion to be made.

The role of non-invasive imaging techniques in the evaluation of patients with suspected or known CAD has increased exponentially over the past decade [11]. The value of radionuclide MPI has been reported in the literature [11–13] since it represents a reliable non-invasive test for the evaluation of myocardial ischemia in various medical conditions [14–21].

Several studies reported that patients with epilepsy exhibited increased mortality from MI or increased risk of MI. Risk for premature death was three to four times higher in people with epilepsy than in the general Chinese population, much higher in young people with epilepsy, with MI myocardial among the leading putative causes of death [22]. A retrospective open cohort analysis reported that socioeconomically deprived patients with epilepsy experience high mortality and die 17 years prematurely, with cardiovascular diseases, cancer, and unintentional injuries being the most common causes of death [23]. A nationwide Danish population showed that epilepsy was linked to higher risk of MI [24], while another study

Table 4. Antiepileptic drugs (AEDs) type

	AEDs				p-value		
	Inducer	No inducer	VPA	No VPA	(1)	(2)	(3)
Age of patients with MPI ≥ 4 (±SD)	56.2 (14.6)	56.1 (9.1)	55 (20.3)	56.5 (8.8)	0.53	0.81	0.78
SSS, mean (±SD)	5.5 (2.0)	4.1 (2.4)	4.2 (1.9)	4.7 (2.5)	0.12	0.58	0.16
SDS, mean (±SD)	3.4 (2.7)	1.6 (2.1)	1.1 (2.0)	2.7 (2.5)	0.06	0.11	**0.05***

AED — antiepileptic drugs; MPI — myocardial perfusion imaging; p(1) — comparison between patients taking inducers *vs.* patients not on inducer; p(2) — comparison between patients on VPA *vs.* patients not on VPA; p(3) — comparison between patients taking inducers and patients taking VPA; SD — standard deviation; VPA — valproic acid

demonstrated that adult patients with epilepsy but no previous cardiac disease had higher risk for MI compared to patients with fracture of their lower extremity or individuals with migraine [25]. Another population-based case-control study of 1799 cases with first acute MI found that epilepsy was linked to a higher risk for MI and that there was a graded positive relation between number of hospitalizations for epilepsy and risk of MI [26]. Our study offers an alternative perspective, trying to assess patients with early cardiovascular disease using MPI SPECT. We did not manage to show that any of epilepsy characteristics, such as the age of epilepsy onset, epilepsy duration, epilepsy type, or seizures type are associated with the presence of perfusion deficits on MPI, probably due to the small number of the patients.

Several mechanisms may explain why epilepsy and cardiovascular disease tend to coexist including causal associations, shared risk factors, and those resulting from epilepsy or its treatment [1]. In patients with epilepsy, various vascular risk biomarkers that get worse could be attributed to epilepsy itself and/or its antiepileptic medications. Predictors of asymptomatic atherosclerosis in adult patients with epilepsy were assessed in a case-control study of 225 patients with epilepsy showing that the intima-media thickness (IMT) was significantly thickened in various groups of patients with epilepsy and the levels of total homocysteine (tHcy), von Willbrand factor (vWF), malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARs) and Ox-LDL levels were increased [4].

An experimental PTZ-induced model in rats showed increased myocardial injury and increased incidence of vertical tachycardia episodes in myocardial ischemia, implying that seizures in epilepsy may increase ventricular arrhythmia and myocardial injury during heart attack [27]. Patients with epilepsy may have troponin I value as high as 5.5 ng/mL and 6.3 ng/mL after generalized or temporal seizures [28, 29], indicating some degree of ischemic myocardial injury due to sympathetic overactivity elicited by the generalized seizure [30, 31]. An increase in mean serum levels of heart-type fatty acid-binding protein (H-FABP), a sensitive biomarker for myocardial ischemia, has been reported in children with intractable epilepsy either in the ictal or interictal periods [32], while in patients with known CAD myocardial infarction may follow an epileptic convulsive seizure [33].

Sudden unexpected death in epilepsy (SUDEP) is a well-known phenomenon of the ongoing investigation. Sudden death may be more frequent in individuals with epilepsy which is refractory to most medications. A study in 23 patients with epileptic seizures demonstrated that 40% of them had ST-segment depression during active seizures, indicating an increased risk of cardiovascular disease in patients with frequent, not well-controlled seizures [34]. A case-control study of all SUDEP cases in Denmark showed that SUDEP cases had significant fibrosis of the myocardium, possibly related to frequent bouts of myocardial ischemia secondary to repetitive epileptic seizures, which, associated with the ictal sympathetic storm, may lead to lethal arrhythmias causing SUDEP [35].

The literature reports that various AEDs may themselves affect cardiovascular risk in patients with epilepsy [1]. The treatment with some AEDs can increase levels of cholesterol, such as carbamazepine, and lead to MI [5, 36]. VPA may cause weight gain, insulin resistance, and metabolic syndrome [5, 37] and increase the risk for MI [38], although, in comparison with carbamazepine, VPA had a reduced risk of MI [39]. In the present study, we provide some evidence the SDS scores of inadequately compensated myocardial ischemia differed between patients treated with enzyme-inducers and patients treated with VPA.

Apart from the small number of participants, other limitations of the present study include the limited number of females and lack of other information in the databases such as physical activity, alcohol intake, etc. Furthermore, no conventional coronary angiography was performed for comparison with the MPI. However, MPI is considered as acceptable noninvasive method to diagnose myocardial abnormalities compared to conventional coronary angiography [40].

Our findings demonstrate that epilepsy patients, predominantly males, with atypical cardiac symptomatology exhibit increased myocardial silent ischemia compared to control individuals with similar symptoms. In our study there was no difference in the risk factors between patients and controls, to explain the difference in MPI results, suggesting that epilepsy itself may sometimes generate an additional risk factor for cardiovascular diseases, possibly if the seizures are refractory to medications. The early identification and treatment of cardiovascular comorbidity in epilepsy deserves further attention [23].

Single-photon emission computer tomography (SPECT) may detect increased risk for coronary artery disease and further cardiovascular events in patients with epilepsy. Our findings favor the conclusion that SPECT could be used for the early identification of cardiovascular comorbidity in epilepsy. Although many studies have investigated the risk of MI in patients with epilepsy, we believe to the best of our knowledge this is the first attempt to provide some evidence for MPI SPECT use for early myocardial disease in patients with epilepsy.

Conclusions

In conclusion, SPECT MPI in patients with epilepsy may reveal increased myocardial silent ischemia. However, further clinical trials could delineate the role of MPI SPECT in the evaluation of myocardial ischemia in patients with epilepsy.

Conflict of interest

The authors have no conflicts of interest to declare.

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