Detecting Myocardial Ischemia With ^{99m}Tc -Tetrofosmin Myocardial Perfusion Imaging in Ischemic Stroke

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Abstract

Background: To assess the myocardial status in patients with stroke, employing myocardial perfusion imaging (MPI) with ^{99m}Tc -tetrofosmin (^{99m}Tc -TF)-single-photon emission computed tomography (SPECT). **Methods:** Fifty-two patients with ischemic stroke were subjected to ^{99m}Tc -TF-SPECT MPI within 1 month after stroke occurrence. None of the patients had any history or symptoms of coronary artery disease or other heart disease. Myocardial perfusion imaging was evaluated visually using a 17-segment polar map. Myocardial ischemia (MIS) was defined as present when the summed stress score (SSS) was >4 ; MIS was defined as mild when SSS was 4 to 8, and moderate/severe with $\text{SSS} \geq 9$. Patients with $\text{SSS} >4$ were compared to patients with $\text{SSS} <4$. Parameters such as age, body mass index, waist perimeter, smoking habits, and medical history (diabetes mellitus, dyslipidemia, etc) were evaluated according to MPI results. **Results:** Myocardial ischemia was present in 32 (62%) of 52 patients with stroke. Among them, 20 (62%) of 32 patients had mild abnormalities and 12 (38%) of 32 had moderate/severe. The age and waist perimeter showed a tendency to relate to severe MIS when patients with $\text{SSS} >9$ were compared to patients with $\text{SSS} <4$. In MPI-positive patients, an age was to be association with SSS, with the oldest age exhibiting the highest SSS ($P = .01$). The association of age with SSS remained statistically significant in the multivariate analysis ($P = .04$). **Conclusion:** The study suggested that more than half of patients with stroke without a history of cardiac disease have MIS. Although most of them have mild MIS, we suggest a thorough cardiological evaluation in this group of patients for future prevention of severe myocardial outcome.

Keywords

myocardial perfusion imaging, MPI, tetrofosmin, SPECT, ischemic stroke, myocardial ischemia, coronary artery disease

Introduction

Atherosclerosis is a common pathway to acute myocardial infarction (MI) and acute ischemic stroke (IS), and proper modification of known risk factors is required for primary and secondary prevention of both conditions.¹⁻³ Symptomatic patients with multi-vessel coronary artery disease are at a high risk of stroke.³⁻⁶ Interestingly, patients who recover from cerebral infarction or transient ischemic attack (TIA) usually die from MI rather than a recurrent stroke or other neurological disease.¹⁻⁷ It is estimated that MI follows a TIA/stroke in 2% to 3% of patients during hospitalization for stroke management. Additionally, it has been reported that patients with TIA/stroke have an increased prevalence, up to 20% to 40%, of asymptomatic coronary artery disease (CAD).²⁻⁷ However, the literature regarding the relationship of stroke to asymptomatic CAD is relatively limited.

Significant angiographically proven CAD can also be accurately imaged utilizing multifocal collimator single-photon emission computed tomography (SPECT)/CT with sensitivity,

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specificity, positive predictive value, negative predictive value, and an accuracy of 85%, 83%, 66%, 94%, and 84%, respectively.⁸ Another study using sestamibi SPECT myocardial perfusion imaging (MPI) in comparison with angiography in 116 patients revealed relative coronary abnormalities with sensitivity of 85%, specificity of 14%, positive predictive value of 45%, and negative predictive value of 53%.⁹ Pharmacologic stress MPI is another method used to detect CAD especially in women with reduced exercise capability with a reported sensitivity and specificity of 85% and 84%, respectively.¹⁰

The purpose of the present study was to estimate the presence of silent CAD in patients hospitalized due to recent IS employing MPI and to evaluate its clinical significance.

Materials and Methods

Patients

Patients diagnosed with first ever IS hospitalized in the department of neurology of our hospital were prospectively recognized and included in this study during a period of 6 months (May 2013 to December 2013). We included only patients less than 70 years of age, since after 70 years of age the prevalence of comorbidity is highly increased.

Ischemic stroke was defined according to the World Health Organization definition and was confirmed by brain imaging, exhibiting a recent brain infarct corresponding to the clinical presentation. Recruitment in the study was performed according to TOAST criteria and included patients with lacunars (small, subcortical, hypodense lesions with a diameter less than 15 mm, and corresponding to lesion clinical lacunar syndrome) and patients with large artery atherosclerosis (hypodense lesions with a diameter >15 mm and >50% stenosis in the appropriate intracranial artery).¹¹ The study protocol was in compliance with the Helsinki Declaration and was approved by the institutional ethics committee (registration number: 295/June 1, 2012). An informed consent was read and signed by all eligible participants.

A detailed medical history was obtained, and a thorough physical examination was performed. Demographic features, body mass index (BMI), waist perimeter, and established atherosclerotic risk factors for IS and ischemic heart disease were recorded. A more detailed evaluation of patients with stroke included color-coded duplex ultrasonography imaging or CT angiography of extracranial or/and intracranial arteries, electrocardiogram, echocardiography (transthoracic or transeophageal), and the assessment of prethrombotic syndromes and autoimmune disorders. In order to evaluate only patients with stroke due to atherosclerosis, strokes that occurred in the course of systemic conditions such as immunological disorders or coagulopathies were excluded in order to ensure the solely atherosclerotic etiology of the stroke. Patients with cryptogenic stroke were excluded as well, as many of these strokes are due to underlying cardioembolism. A history of

coronary heart disease (angina pectoris, unstable angina, myocardial infarction, and heart failure), heart valve disease, and arrhythmias was assessed using a questionnaire and relevant medical confirmation by a cardiologist. To be eligible for inclusion, all patients had to be free from any history of coronary heart disease and heart valve disease, to have never received anticoagulant therapy, and should not have had a cardioembolic stroke. Patients with markers of coronary artery disease such as NSTEMI, TWI, and Q waves on ECG or/and troponin elevation at admission or during their hospitalization were also not included in the study.

Fifty-two patients were finally recruited in the study. All patients underwent MPI Tc-99 mTetrofosmin stress and rest SPECT (MPI-^{99m}Tc-TF-SPECT) within a period of 30 days following the stroke. All study individuals were subjected prior to and after stress to ^{99m}Tc-TF-SPECT using the imaging protocol described in a previous study¹² and according to published guidelines.¹³ The MPI evaluation was assessed by 2 nuclear medicine physicians, using a 17-segment polar map¹⁴ scoring each segment with a scale of 0 to 5, according to the severity of the myocardial perfusion deficit (0 = no decreased myocardial activity; 1 = mild decreased activity; 2 = mild to moderate decreased activity; 3 = moderate to severe decreased activity; 4 = severe decreased activity; and 5 = no tracer activity). The individual scores of perfusion defects in stress and rest MPI, within each segment, were combined providing the summed rest score and summed stress score (SSS).

The primary aim was to study the proportion of patients with stroke with evidence of perfusion deficits on MPI. Patients were considered based on the presence of perfusion deficits on MPI, when SSS was ≥ 4 . Furthermore, MIS was graded as mild when SSS was 4 to 8, moderate when SSS was 9 to 13, and severe when SSS >13 ,¹⁵ and the patients were grouped accordingly. The Modified Rankin Scale (mRS) was also calculated for every patient at the time SPECT MPI was performed.

Statistical Analysis

Binary data were described as percentages, whereas continuous data were expressed as the mean (standard deviation [SD]).

Myocardial perfusion imaging was considered as a categorical variable, and patients were grouped according to their SSS score. Myocardial perfusion imaging-positive patients (SSS ≥ 4) were compared to MPI-negative (SSS <4) patients. Furthermore, the different groups of multiple severities of SSS were compared as a secondary analysis. Statistical comparisons between the groups were performed using the χ^2 test (for any potential association of groups with gender and risk factors such as smoking, arterial hypertension, diabetes mellitus, and dyslipidemia) and *t* test (for any potential association of groups with age, BMI, and waist perimeter). All *P* values were 2 tailed and were considered statistically significant for *P* < .05.

Table 1. Characteristics of the Patients.^a

Characteristics (Total 52)	Patients
Mean age, years	55.6 (7.6); 31-69
Gender	41 M (79%)/11 F (21%)
BMI, kg/m ²	28.3 (4.4); 20.85-40.09
Waist perimeter, cm	105.5 (13.4); 77-138
mRS—median	2 (0-4)
Smoking	33/52 (63%)
Hypertension	29/52 (56%)
Diabetes mellitus	13/52 (25%)
Hyperlipidemia	30/52 (58%)
Alcohol consumption	21/52 (40%)

Abbreviations: BMI, body mass index; mRS, Modified Rankin Scale.

^aValues presented as mean value (standard deviation); min-max.

Univariate and multivariate analyses were performed. In the initial univariate analysis, a threshold of $P < .1$ was used to identify candidate variables for inclusion in the multiple variable logistic regression models. The final multivariate analyses were conducted using a backward selection procedure, and statistical significance was achieved if $P < .05$.

Further linear regression analysis was done in MIS-positive group to examine gender, age, stroke risk factors, age, BMI, and abdominal perimeter association with SSS score. Univariate and multivariate linear regression analyses were performed. In the initial univariate regression analysis, a threshold of $P < .1$ was used to identify candidate variables for inclusion in the multiple variable linear logistic regression model. The final linear multivariate analyses were conducted using a backward selection procedure, and a statistical significance was achieved if $P < .05$.

Results

The mean age of patients included in the study was 55.6 (7.6), with the youngest patient being 31 years old and the oldest patient being 69 years old. The characteristics of patients recruited in the study are shown in Table 1.

Of the 52 patients, 32 had MIS, with SSS ≥ 4 (62%), whereas 20 patients had SSS < 4 (38%). All ^{99m}Tc-TF-SPECT abnormalities were clinically silent. Women had a higher percentage of MIS than men, as 8 (73%) of 11 females had MIS compared to 24 (58%) of 41 male patients, without reaching statistical significance (Table 2). When the MPI-negative (SSS < 4) patient groups were compared with MPI-positive (SSS ≥ 4) patient groups, for parameters including gender, age, BMI, waist perimeter, smoking, hypertension, diabetes mellitus, dyslipidemia, and alcohol consumption, no parameter was found to be statistically related to the presence of perfusion deficits on MPI.

Among 32 patients with MIS, 20 (62%) patients with stroke had mild MIS, 10 (31%) had moderate MIS, and 2(6%) of 32 had severe MIS. However, due to the small number of patients with moderate MIS and severe MIS, they were evaluated together statistically (12 [38%] of 32 patients with stroke

having moderate/severe MIS (SSS ≥ 9). The univariate analysis showed that age and the waist perimeter had a tendency to relate to severe MIS when patients with SSS ≥ 9 were compared to patients with SSS < 4 ($P = .06$), but this tendency was lost in the multivariate analysis.

In MPI-positive patients, univariate linear regression analysis showed age is associated with SSS, with the oldest age having the highest SSS ($P = .01$). No other parameter revealed statistically significant association with SSS. The association of age with SSS remained statistically significant in multivariate linear regression analysis ($P = .04$), without any other parameter showing significant association with SSS.

Furthermore, there was no significant association between the mRS and SSS score in all the patients, both genders.

Discussion

The main finding of the present study is the abnormal MPI in up to 62% of patients after a recent stroke, suggesting preexistence of myocardial ischemia. This is to our knowledge the highest percentage ever recorded. Coexistence of stroke and coronary artery disease in the European population has been previously reported in different studies in approximately 50% of patients with stroke,^{6,16} whereas in the Japanese population, 2 different studies reported 40% and 37.5% of patients with stroke, respectively,^{17,18} and in the Indian population up to 42%,¹⁹ suggesting possible geographical, dietary, and racial differences. No parameter, such as gender, age, BMI, waist perimeter, smoking, hypertension, diabetes mellitus, dyslipidemia, and alcohol consumption, was found to be statistically related to the presence of perfusion deficits on MPI.

The conventional intra-arterial coronary angiography remains the “gold standard” for CAD detection. Similar to our results, in the largest and most recent study to our knowledge regarding the coexistence of stroke and CAD, angiography revealed, regardless of severity, coronary atherosclerotic plaques in 62% of the patients with stroke, while significant coronary stenosis $> 50\%$ was detected in 26% of the patients.⁷ The other study that was consistent with our results was an autopsy study that has shown prevalence of atherosclerotic plaques in 70% and a hemodynamic coronary artery stenosis of $> 50\%$ in 29% of patients with fatal stroke and without coronary heart disease history.²⁰

The majority of the patients with stroke in this study were primarily male and few were female. Interestingly, in our study, in which a relatively young population was included, MIS was at a higher percentage in women than in men, that is, 8 (73%) of 11 females had MIS in contrast to 24 (58%) of 41 male patients but not reaching statistical significance. Additionally, the age and the waist perimeter showed a tendency to relate to severe MPI (SSS ≥ 9) compared to patients with negative MPI ($P = .06$) without reaching statistical significance. Similarly to other studies, multivariate analysis showed association of age with severe CAD, adjusting for other risk factors included in the model ($P = .04$).^{7,16}

Table 2. Characteristics of the Patients in MPI-Negative and -Positive Groups.^a

	SSS <4	Myocardial Perfusion Imaging ^{99m} TF-SPECT	
		SSS ≥ 4	P
No. of patients (%)	20/52 (38%)	32/52 (62%)	
Gender (%)	17/41 (41%) M 3/11 (27%) F	24/41 (58%) M 8/11 (73%) F	
Age	55.1 (8.9)	55.8 (6.7)	NS
BMI, kg/m ²	27.6 (4.8)	28.8 (4.2)	NS
Waist perimeter, cm	101 (13.5)	108.4 (12.8)	NS
Smoking (%)	14/20 (70%)	19/32 (59%)	NS
Hypertension (%)	13/20 (65%)	16/32 (50%)	NS
Diabetes mellitus (%)	5/20 (25%)	8/32 (25%)	NS
Dyslipidemia (%)	13/20 (65%)	17/32 (53%)	NS
Alcohol consumption (%)	4/20 (20%)	7/32 (22%)	NS

Abbreviations: BMI, body mass index; MPI, myocardial perfusion imaging; NS, nonsignificant; SSS, summed stress score; TF-SPECT; tetrofosmin–single-photon emission computed tomography.

^aBinary data were described as percentages, whereas continuous data were expressed as the mean (standard deviation [SD]).

In the present study, we used radionuclide myocardial scanning as an alternative noninvasive study to conventional coronary angiography in order to assess CAD in patients with stroke. We consider cardiac SPECT as an appropriate diagnostic tool to reveal silent CAD. Furthermore, the prognostic value of radionuclide myocardial scanning has been documented in the literature.^{8,14}

Our study suffers from limitations: it was a single-center study and our sample size was small; therefore, moderate and severe MIS were grouped together for statistical evaluation. In addition, we have not obtained conventional coronary angiography data to estimate the true sensitivity and specificity of the MPI. However, with SPECT, the sensitivity and specificity for detecting abnormal MPI reached up to 80% and 86% and for detecting severe infarction 95% and 72%, respectively,²¹ which are considered as acceptable alternative methods to conventional coronary angiography. Finally, another major limitation of the present study was the absence of a long-term follow-up of the patients recruited.

In conclusion, adult patients with IS often have coexisting myocardial ischemia based on abnormal SPECT scans and this is a proof of the systemic nature of atherosclerosis. The necessity to screen patients with stroke for asymptomatic CAD should be tested in large-scale prospective studies.

Author's Note

The author Sotirios Giannopoulos is also the guarantor for this study.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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