Original
Nuclear Medicine Review 2020, 23, 2: 58–62
DOI: 10.5603/NMR.a2020.0014

ISSN 1506–9680

VIA MEDICA

The impact of depression and anxiety in prognosis of patients undergoing myocardial perfusion imaging with ^{99m}Tc tetrofosmin SPECT for evaluation of possible myocardial ischemia

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[Received 13 XII 2019; Accepted 22 IV 2020]

Abstract

BACKGROUND: The goal of this study was to evaluate the prevalence of depression and anxiety in patients subjected to myocardial perfusion imaging (MPI) with ^{99m}Tc tetrofosmin stress-rest single-photon emission computer tomography (SPECT), and their impact on their cardiological events or disease.

MATERIAL AND METHODS: Patients referred to the Nuclear Medicine Department for ^{99m}Tc tetrofosmin myocardial MPI-SPECT were asked to fulfill the Zung Self-Rating Depression Scale (ZDS) and Hamilton anxiety questionnaire (HAQ). Among 213 patients who completed the ZDS and HAQ, 80 patients (59 males and 21 females) were selected for this study because they had no known psychological disease, other disease that could influence psychological status, or use of narcotic drugs. Collected data from MPI and psychological status were subsequently analyzed.

RESULTS: Among all 80 patients, 52 patients (65%) had abnormal MPI of whom 28/52 (53.8%) exhibited either depression, anxiety or both, and 28 (35%) patients had normal MPI of whom 10/28 (35.7%) had abnormal psychological status. The higher number of patients with abnormal psychological status in association with abnormal MPI was noted predominantly in patients with previously established coronary artery disease. A correlation was also noted between obesity, cardiac heredity and depression or anxiety in patients with abnormal MPI.

CONCLUSIONS: Patients that exhibit depression, anxiety, or both, have high rates of myocardial ischemia, and thus are at risk for subsequent cardiological events.

KEY words: myocardial perfusion imaging; myocardial ischemia; depression; anxiety; psychological status; MPI; SPECT

Nucl Med Rev 2020; 23, 2: 58–62

Introduction

Anxiety and depression are frequently manifested in patients with cardiovascular diseases. Prevalence may vary between 15 and 50%, according to diagnostic criteria used and demographic characteristics of the patients [1]. Depression may be associated with coronary artery disease (CAD) and its consequences such as cardiac arrhythmias, myocardial infarction (MI) and heart failure. Although the exact physiological mechanisms for this association remain unclear, it may be due to hypothalamic – pituitary dysregulation, altered immune function or existence of common unknown risk factors for both medical conditions [2, 3]. Scientific evidence over the last few years reported significant association between anxiety or depression and various organic conditions including cardiac

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diseases [1, 4]. Furthermore, patients with cardiac diseases and depression tend to exhibit poor risk factor control resulting into further deterioration of their cardiac disease and prognosis [1]. Anxiety has been also linked to increased mortality in patients with CAD but this association was reported less strong than that of depression [5]. It is interesting that anxiety seems to improve in patients that have detailed imaging studies concerning their disease and good communication with their physician about the status of their medical condition [6].

Myocardial perfusion imaging (MPI) SPECT may be used to assess the myocardial condition either in patients with known MI, or post either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting(CABG)[7], or with silent myocardial ischemia due to non-specific cardiac complaints [8–10]. The MPI grading may be able to provide an excellent tool to monitor response to treatment, follow-up status and long term prognosis [11, 12].

Women overall appear to display more nonspecific cardiac complaints than men. However, these symptoms by themselves have unknown clinical significance not necessarily linked to myocardial ischemia in the absence of other relative clinical manifestations [10]. However, MPI may be able to identify myocardial ischemia in elderly women with angina or in asymptomatic women with concomitant diabetes mellitus or hypertension [13]. Female patients with CAD demonstrate positive MPI [14] with sensitivity of 87.16% and specificity of 97% [15]. In such cases, a summed stress score (SSS) ≥ 14 denoted an increased risk for cardiac events and an SSS ≥ 22 for subsequent significant cardiac events such as acute MI and cardiac death [16].

In the present retrospective study, we evaluated the rate of myocardial ischemia in patients who were subjected to MPI with ^{99m}Tc-TF-SPECT, due to non-specific cardiac complaints of various types, or in patients that had known myocardial disease for follow up after CABG or PTCA. Furthermore, in all patients we evaluated the association of anxiety and/or depression with the known cardiovascular risk factors such as age, smoking, obesity, diabetes mellitus (DM), arterial hypertension, dyslipidemia and cardiac heredity.

Material and methods

Patients

In the present study there were 80 patients, 59 men and 21 women, that had MPI either for non-specific cardiac symptoms (workup to rule out CAD), or patients with known CAD and previous PTCA or/and CABG for follow up of their myocardial status. Cardiac risk factors were noted in each patient's medical history (obesity, smoking, arterial hypertension, diabetes mellitus, dyslipidemia, and cardiac heredity). Patients were considered as smokers when smoking habits were active or stopped during the last 3 months. Females under anti-hypertensive drugs or with systolic blood pressure (BP) ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg were noted as having hypertension as risk factor. Diabetes mellitus as risk factor was noted in females under antidiabetic medication and fasting glucose > 126 mg/dL. Finally, dyslipidemia was considered in patients receiving therapy with statins or exhibiting fasting cholesterol level > 220 mg/dL.

SPECT MPI

All study participants had been subjected to ^{99m}Tc-TF-SPECT before and after stress using a 1-day imaging protocol according to published guidelines [17]. Stress protocol was consisted either of a dynamic exercise (Bruce protocol treadmill exercise test) or a pharmacological test with either dipyridamole or dobutamine. The electrocardiography was continuously monitored during stress. All patients were first injected with 8 mCi Tc-99m tetrofosmin after stress or 20 mCi at rest followed by acquisition of images 40 minutes later via a 90°-angled dual-head camera, employing a collimator with 64 stops and 25 s per projection over a 180° arc. Reconstruction of images was consisted of filter back projection without attenuation correction [18].

MPI was visually evaluated by two nuclear medicine specialists, using a 17 scoring each segment on a scale of 0 to 4 according to the severity of the myocardial perfusion deficit [18].Thus, score 0 was designated when there was no decreased myocardial activity, score 1with mildly decreased activity, score 2 for moderate decreased activity, score 3 for severely decreased activity and score 4 for absent tracer activity. All individuals scores at rest and stress were combined and produced the summed rest score (SRS) and summed stress score (SSS). The difference of the two scores (S-RSS) was also calculated and evaluated. A summed difference score (SDS) was obtained by subtracting the rest score from the stress score; in the presence of a reversible defect (or ischemia) the score was positive. Myocardial ischemia (MIS) was graded as mild when SSS was 4 to 8, moderate from 9 to 13, and severe when SSS over 13 [19].

Evaluation of psychological status

Patients who were subjected to ^{99m}Tc-TF-SPECT- MPI in the Department of Nuclear Medicine were asked to fulfill the Zung Self-Rating Depression Scale (ZDS) and Hamilton anxiety questionnaire (HAQ). The ZDS consists of 20 items that quantify the depressive symptoms of a patient. Each item is scored on a range from 1 to 4. Total score lower than 50 is considered as normal, between 50 and 59 as mild depression, between 60 to 69 as moderate depression, while score over 70 as severe depression [20]. The HAQ consists of 14 items and is widely used to assess both psychic and somatic anxiety. Each item is scored on a range of 0 (not present) to 4 (severe anxiety), with a total score ranging from 0 to 56 [21].

Among the patients who agreed to participate to the study, those with known disease such as cancer, multiple sclerosis, chronic kidney disease or any other condition that could influence psychological status were excluded from the study. Furthermore, those with known psychological disease, use of narcotic drugs were also excluded. ZDS and HAQ results were evaluated by a psychiatrist.

Statistical analysis

The evaluation of the myocardial perfusion studies were analyzed utilizing the statistical software SPSS version 20 for windows (SPSS, Chicago, IL). Several groups of patients were developed based on the gender, the degree of abnormality and their correlation with the specific characteristics of depression, anxiety, obesity, cardiac heredity, smoking and hypertension.

Baseline characteristics were described using, median and frequencies for categorical variables. For the verification of correlation

Table 1. Characteristics of the patients [mean value ± standard deviation (min-max)]

Characteristics	All 80 patients	Male 59 patients	Females 21 patients
Diagnostic MPI	45/80 (56%)	28/45 (62%)	17/45 (38%)
PTCA &CABG MPI	31/80 (39%)	27/31 (87%)	4/31 (13%)
Mean age [years]	66.69 ± 11.61	66.72 ± 11.15	66.57 ± 13.10
Myocardial infarction	20/80 (25%)	17/80 (85%)	3/80 (15%)
Smoking	25/80 (11%)	19/25 (76%)	6/25 (24%)
Hypertension	59/80 (74%)	43/59 (73%)	16/59 (27%)
Diabetes mellitus	35/80 (44%)	28/35 (80%)	7/35 (20%)
Hyperlipidemia	54/80 (67%)	42/54 (78%)	12/54 (22%)
Obesity	26/80 (33%)	20/26 (77%)	6/26 (23%)
Heart heredity	27/80 (34%)	20/27 (74%)	7/27 (26%)

MPI — myocardial perfusion imaging; PTCA — percutaneous transluminal coronary angioplasty; CABG — coronary artery bypass grafting

"N-1" Chi-squared test has been utilized to determine the significant difference between the means of two groups, which may be related in certain features. The alpha of 0.05 was used as the cutoff for significance and thus if the p-value was less than 0.05, the difference of the two groups was significant. Additionally, a Spearman's rho methodology applied for the identification of the correlation among the different characteristics and features. A Spearman's rank-order correlation between the groups of features provides a degree of correlation regarding the level of the r_s score. Thus, r_s of 0.2 to 0.39 describe as weak correlation and 0.4 to 0.59 as moderate correlation, respectively.

Results

The patients' age, medical history of myocardial infarction and cardiac risk factors are shown in Table 1. Abnormal MPI was found in 52 of 80 patients (65%), and normal MPI in 28/80 (35%) patients. Among all study participants with abnormal MPI 53.8% exhibited depression, anxiety or combination of both (Tab. 2). However, patients with normal MPI demonstrated lower rate of psychological abnormalities at 35.7%. Statistical analysis did not reveal any statistical significance possibly due to the small number of patients studied; however, a statistical trend was noted (p = 0.1244). Patients that had previously established CAG and had abnormal MPI performed for follow-up after PTCA or CABG had significantly higher rates of depression or anxiety (57.1%) compared to those that had normal MPI (28.6%). However, such a difference was less pronounced in patients that were undergoing MPI as an initial evaluation of myocardial status for suspected CAD (Tab. 2).

Furthermore, evaluation of the results according to sex demonstrated that men had much higher percentage of abnormal MPI (47/59, 80%) compared to women (5/21, 24%) p < 0.0001 (Tab. 3). In addition, our results suggested that women had a higher rate of anxiety than men; however, due to the small numbers of female patients it was not able to document it statistically, even though a trend of statistical significance was noted, p = 0.1363.

In addition, a Spearman's rank-order correlation was run to determine the relationship between the depression and anxiety with several cardiological risk factors. In patients with abnormal MPI, depression and anxiety found to have a moderate correlation

Table 2. Rates of abnormal MPI, depression, anxiety, or both in patients subjected to myocardial scintigraphy either for diagnostic reasons or after cardiologic intervention (follow-up)

Psychological status	MPI (+) 52/80 (65%)	MPI (–) 28/80 (35%)	p
All patients that had MPI (N = 80)			
Depression	10/52 (19.2%)	3/28 (10.7%)	0.3284
Anxiety	13/52 (23.1%)	4/28 (14.3%)	0.3512
Both	5/52 (9.6%)	3/28 (10.7%)	0.8764
Total	28/52 (53.8)	10/28 (35.7%)	0.1244 *
MPI performed for diagnostic reasons (N = 45)			
Depression	3/24 (12.5%)	2/21 (9.5%)	0.7520
Anxiety	6/24 (25%)	3/21 (14.3%)	0.3761
Both	3/24 (12.5%)	4/21 (19%)	0.5526
Total	12/24 (50%)	9/21 (42.9%)	0.7471
MPI performed after cardiologic intervention (PTCA, CABG or both) (N = 35)			
Depression	7/28 (25%)	1/7 (14.3%)	0.5523
Anxiety	7/28 (25%)	1/7 (14.3%)	0.5523
Both	2/28 (7.1%)	0/7 (0.0 %)	0.4743
Total	16/28 (57.1%)	2/7 (28.6%)	0.1835 *

MPI (–) — Normal myocardial perfusion imaging; MPI (+) — Abnormal myocardial perfusion imaging; PTCA — Percutaneous transluminal coronary angioplasty; CABG — Coronary artery bypass grafting; * — a trend of statistical significance

Table 3. Patients with abnormal MPI and depression, anxiety, or both

Sex	No	MPI (+)	Depression	Anxiety	Both
Male	59	47/59 (80%) p < 0.0001**	9/47 (19%) p = 0.921	11/47 (23%) p = 0.1363*	4/47 (9%) p = 0.5631
Female	21	5/21 (24%)	1/5 (20%)	2/5 (40%)	1/21 (5%)
Total	80	52/80 (65%)	10/52 (19%)	13/52 (25%)	5/52 (8%)

MPI — Myocardial perfusion imaging; MPI(+) — Abnormal myocardial perfusion imaging; PTCA — Percutaneous transluminal coronary angioplasty; CABG — Coronary artery bypass grafting; p* — trend of statistical significance; p** — statistical significance

(r_s = 0.411, p = 0.001) and weak correlation (r_s = 0.369, p = 0.001), retrospectively, with obesity. On the other hand, in normal MPI group, the obesity was only correlated weakly with the anxiety (r_s = 0.351, p = 0.001). Another feature that appears correlation with the MPI patient's condition is the cardiac heredity. Thus, weak correlation (r_s = 0.231, p = 0.001) appeared for abnormal MPI patients between the cardiac heredity and the depression.

Discussion

Depression and anxiety are frequently observed in patients with cardiovascular disease and linked with increased morbidity and poor prognosis. Apart from a possible direct effect on several cardiovascular risk factors such as blood pressure, they lead the patient into neglecting the physician-directed therapeutic interventions and further deterioration of their cardiovascular status [22, 23].

In the present study, 80 patients were subjected to MPI in order to assess their myocardial status either as an initial evaluation of possible CAD or as a follow-up of known CAD. Among all patients examined, 52 patients (65%) had abnormal MPI and 28 (35%) normal examination. In the group with the abnormal

MPI, 53% exhibited depression (19.2%), anxiety (23.1%) or both (9.6%). In contrast only 35.7% ($p = 0.1244$/indicating a trend of statistical significance) of patients with negative MPI exhibited any psychological abnormality (depression 10.7%, anxiety 14.3%, both 10.7%) (Tab. 2). This trend towards statistical significance of increased frequency of psychological abnormalities in patients with positive MPI, but not definite statistical significance, may be due to the relative small number of patients. It suggests though that psychological abnormalities may predispose to the development of CAD, independently of the other well established risk factors. Interestingly, in our study, these differences were more pronounced in the group of patients with known CAD, undergoing the MPI for follow up rather than the group that test for diagnostic purposes, supporting the same conclusion. Definitely, larger studies are needed to verify these findings. A prospective cross-sectional study of 314 patients presented with chest pain showed a significant association between degree of depression and CAD in female patients [24]. Similar results of female predominance of depressive symptoms as well as higher incidence of anxiety and CAD were reported in a Chinese study [25]. Another large study in 514 German CAD patients, evaluated by the Mini International Neuropsychiatric Interview and the Global Assessment of Functioning (GAF) scale demonstrated comorbidity of depression with CAD and treatment of the depression resulted in improvement of this condition [26]. Interestingly, patients undergoing CABG operation, depression and anxiety were increased after the operation compared to the pre-operative period [27].

Evaluation of our results according to sex, demonstrated predominance of men rather than women as having abnormal MPI and thus CAD (Tab. 3). In addition, although our findings suggested that women had a higher rate of anxiety than men, the numbers of female patients were too small to establish any significance; however, with caution we noted a trend of statistical significance. A previous study in patients undergoing MPI for assessing myocardial status in patients with known or unknown CAD was consisted with our findings showing high level of anxiety mostly in women prior to the examination [28]. Other studies in women reported positive MPI findings in 32% [29], and a sensitivity of 91% and specificity of 70% when SSS was > 8 [30]. In general, patients with anxiety disorders or co-existence of anxiety/depression are associated with increased prevalence of coronary heart disease [31]. Although in some studies depression seems to be the most important factor associated with CAD [32, 32], other studies indicate anxiety as the predominant psychological factor contributing to CAD [31]. Nevertheless, co-existence of both psychological factors appears to have added validity towards this regard. A study on 118 men without history of psychological disturbances demonstrated that after CABG, 16–39.8% of them developed depression and 27.1% anxiety independent of CAD severity [33]. However, female patients demonstrate further reduced quality of life after a cardiac event compared to men. This quality of life refers to appearance anxiety, depression and low self-esteem among other things and may last for over one year [34]. In another study, the reported rates of CAD in female veterans' patients were 4.16%, reaching up to 36% when patients were smokers. Furthermore, those with depression had 60% higher chance of CAD [35].

The mechanisms that the described psychological parameters contribute to the development of CAD are not very well defined and could be multi sequential. Some investigators suggest that somatic-vegetative features of depression may be linked at an early stage to the development of coronary artery disease [36]. In our study, obesity and cardiac heredity were also associated with depression and anxiety. Previous studies have described an association between hypertension and anxiety, and both depression and anxiety have been linked to diabetes mellitus [37] and hypercholesterolemia [38].

Conclusions

In conclusion, our results showed that patients with myocardial dysfunction, as evident by abnormal MPI, have increased frequency of coexisting depression, anxiety or both, suggesting that these factors may be contributing risk factors. In addition, both males and females were at higher risk for CAD if depression and anxiety were combined with obesity or cardiac heredity. Further larger studies are needed to verify these findings.

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