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Original Article

The diagnostic accuracy of stress myocardial perfusion scintigraphy in patients with end-stage renal disease

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Abstract: Objective: This study examined the diagnostic accuracy of myocardial perfusion scintigraphy (MPS) in end-stage renal disease (ESRD) patients and the incidence and clinical and biochemical predictors of myocardial perfusion abnormalities. Methods: We evaluated 500 asymptomatic ESRD patients on hemodialysis referred for MPS for cardiac risk stratification before renal transplant surgery. Patients with abnormal MPS and an additional few patients without abnormal MPS underwent invasive coronary angiography (ICA). Results: Sixty-nine patients (13%) showed abnormal MPS (reversible or fixed defect). The majority of patients had cardiovascular risk factors. There were statistically significant differences in age, male gender, hypertension, diabetes, hypercholesterolemia, and left ventricular ejection fraction (LVEF) ($P < 0.05$ for each) between patients with normal and abnormal MPS. Multivariate regression analysis showed that age (≥ 62 years) and low LVEF (≤ 47%) were independent predictors for abnormal MPS. ICA was performed in 112 subjects; the sensitivity, specificity, positive predictive value, and negative predictive value of MPA to detect CAD is 72%, 70%, 79%, and 61%, respectively. Conclusions: In ESRD, the incidence of myocardial perfusion defects is 13%. In addition to other traditional CAD risk factors, such as diabetes and hypertension, age, and LVEF are the strongest predictors of MPS abnormalities. Initial risk stratification can be cost-effective for identifying high-risk patients who will benefit from more imaging with CAD risk factors and LVEF. In ESRD patients, MPS diagnostic performance is relatively poor. To further evaluate the utility of MPS in diagnosis and risk stratification in ESRD, more data is therefore required.

Keywords: End-stage renal disease, prevalence, coronary artery disease risk stratification, myocardial perfusion scintigraphy (MPS)

Introduction

End-stage renal disease (ESRD) demonstrates advanced glomerular filtration dysfunction (< 15 ml/min/1.73 m^2), which is largely reversible and warrants renal substitution [1]. ESRD patients are 8 times more likely to die, and 40 of all deaths are caused primarily by coronary heart disease due to cardiovascular causes (CAD). The existence of CAD is several times larger than for age-matched subjects. This high prevalence of CAD without ESRD is attributable to the clustering of typical atherosclerotic risk factors in ESRD [1], and ESRD patients who have developed CAD are frequently asymptomatic due to diabetic or uremic nephropathy or impaired capacity to exercise [2]. Screening for severe CAD may contribute to the identification of patients with a prognosis, and medical and/or coronary revascularization should be improved. Myocardial perfusion single-photon emission computed tomography (MPS) is frequently used in ESRD as a risk-assessment tool, but the application, clinical effects, and prevalence of ESRD MPS perfusion defects are controversial.

Multiple small studies evaluating the diagnostic performance of MPS in ESRD in patients with ESRD for kidney transplantation [3] have shown that the sensitivity of MPS in ESRD is 67 percent, with 77 percent specificity for CAD detection, identified as 70 percent dimeter stenosis [4, 5]. The prognostic value of MPS in patients with ESRD has been demonstrated in many studies. Several studies have shown that renal dysfunction is a significant independent risk predictor for cardiovascular events, and it has

been shown that MPS with exercise or vasodilator stress agents provides an additional prognosis across the whole spectrum of renal dysfunction [6-8]. In one prospective study, 215 patients were allocated to low- and high-risk groups at the start of dialysis using clinical and echocardiographic evidence; high-risk patients subsequently underwent MPS screening, which found that patients with abnormal MPS had a relative risk of 3.3 compared to normal MPS, MPS assigned incremental importance to baseline clinical and echocardiographic findings [9]. Current data on the prevalence of MPS abnormalities in ESRD are limited and controversial and come from small studies with highly variable prevalence rates, which range from 20% to 45% [10]. For example, positive MPS was reported to be 22.5% in one study in patients with initiated chronic peritoneal dialysis [11]. Nonetheless, MPS perfusion abnormalities were reported to be 45% in another small prospective study [12]. The goal of this study was to assess the diagnostic accuracy of MPS and the prevalence and predictors of myocardial perfusion defects in patients undergoing kidney transplantation in ESRD patients who were currently undergoing hemodialysis.

Materials and methods

Study population

Between January 2015 and October 2019, 500 asymptomatic hemodialysis patients with ESRD were referred to myocardial perfusion tension MPS for a routine preoperative screening test prior to kidney transplantation. Prior CAD patients identified as having prior percutaneous coronary intervention, coronary bypass surgery, or prior myocardial infarction were excluded. Non-diagnostic experiments, such as prolonged extracardiac behavior or uncorrected objects of motion and non-gated studies, were also omitted. Data were collected on variables that linked to CAD risk factors, such as hypertension, hypercholesterolemia, diabetes, CAD family history, and smoking. All patients in this study underwent MPS; patients with abnormal MPS were referred for ICA. An additional 46 patients with normal MPS also underwent ICA. A total of 112 patients underwent ICA. There were no specific criteria for additional diagnostic ICA for patients with normal MPS; however, they could have been referred to ICA based on physician preference or CAD-suggestive symptoms such as chest pain or abnormal echocardiography. The study was approved by our institution's research ethics committee, and informed consent was waived by the hospital ethics committee as the study was retrospective and did not interfere with the patients' management.

MPS acquisition and analysis

With either a two separate-day or same-day rest-stress protocol, patients underwent a stress myocardial perfusion study. The dose of either technetium-99 (Tc-99m) sestamibi or tetrofosmin was 1100 megabecqurel (MBq) in patients undergoing a two-day or same-day rest-stress regimen. The stress dose of either (Tc99m) sestamibi or tetrofosmin was 1100 MBq mCi in patients who underwent the rest-stress protocol on the same day. Tc-99m sestamibi or Tc-99m tetrofosmin was injected with adenosine (140 μg/kg/min) or dipyridamole during peak pharmacological vasodilatation. Thirty minutes after pharmacological vasodilatation, single-photon computed tomography (SPECT) imaging was initiated. Rest SPECT images were started approximately 60 minutes after injection. SPECT imaging was performed on a dual-detector gamma camera fitted with attenuation correction and truncation compensation with line source attenuation correction (Cardio MD, Philips Medical System, Milpitas, California). In accordance with the most current ASNC recommendations for nuclear cardiology procedures, the acquisition criteria and post-processing were carried out.

Auto SPECT (Cedars-Sinai Medical Center, Los Angeles, California) was used for visual analysis by experienced nuclear medicine doctors, and all images were reoriented to short, vertical, and horizontal views. Using 17 tomographic segments, which included 6 segments each for the basal and midventricular slices and 4 segments for the apical short-axis slices, stress and rest perfusion images were scored. The final segment is located on the left ventricle's most apical section. Finally, to calculate the ejection fraction, gated short-axis images were processed with quantitative SPECT software. In the visual study, for both the stress and rest images, the 17 segments were rated for perfusion defects on a 4-point scale (0 = normal; 1 =

Table 1. Patient characteristics, total study population (N) 500

Factors	Total Number, %
Gender	
Female	218 (43.6%)
Male	282 (56.4%)
Age, years	53±14
Hypertension	466 (93%)
Diabetes mellitus	325 (65%)
Hypercholesterolemia	176 (35%)
Smoking	93 (19%)
Family history of CAD	61 (12%)
Body mass Index (BMI), kg/m^2	28±5
Abnormal MPS	69 (14%)
EF %	56±11
GFR ml/min/1.73 m^2	8±4

CAD; coronary artery disease, MPS; myocardial perfusion scintigraphy, eGFR; estimated glomerular filtration rate.

mild; 2 = moderate; and 3 = severe). In this study, ischemia was characterized as a change between stress and rest in the segmental score. Segments were graded as nonreversible, with no change between stress and rest. Summary stress and rest scores were determined by summing the 17 segmental scores in each image set. Utilizing the summed difference score (SDS), defect reversibility was calculated from the difference between the summed stress and rest scores. An SDS lower than 4 was considered nonischemic, 4 to 8 was considered mild ischemia, and greater than 8 was considered moderate to severe ischemia. By comparing both the perfusion and functional results, the reader made the final determination of an abnormal SPECT analysis. To shape the interpretation of the MPS tests, the perfusion defects represented by the perfusion scores at stress and rest were used; left ventricular ejection fraction (LVEF) at rest > 50% on gated SPECT images was considered normal.

Invasive coronary angiography

Within three months following the MPS, traditional ICAs were carried out. According to the American Heart Association, the coronary arteries are divided into segments [13]. Two interventional cardiologists who were blinded to the CTCA outcomes analyzed the angiograms, and when the lumen reduction was > 50%, the stenosis was graded as important.

Statistical analyses

All continuous data were expressed as a mean (± standard deviation), and all non-continuous avian data were expressed as percentages. Using the Students' t-test for unpaired samples, continued variables were compared. A chi-square test for independence was applied to assess whether there was a substantial correlation between two categorical variables from a single population. Variance statistical analysis (ANOVA) was conducted for continuous results, and a logistic regression was performed to ascertain the effects of age, gender, left ventricular ejection fraction, diabetes, and hypertension on the likelihood of perfusion defects on MPS.

Results

Patients' characteristics and prevalence of inducible myocardial ischemia

The study population consisted of 500 patients, 282 of whom were male and 218 female (age 53±14 years). The demographic characteristics and risk factors for CAD are summarized in **Table 1**. Sixty-nine patients (13%) showed abnormal MPS (reversible or fixed defect), and the majority of patients had cardiovascular risk factors. The majority of patients (466, or 93%) had hypertension, 325 patients (65%) had diabetes, 176 (35%) had hypercholesterolemia, and only 61 patients (12%) had a positive family history of premature CAD.

Comparison of demographics and biochemical characteristics of patients with normal and abnormal MPS

The clinical and biochemical characteristics of patients with positive and negative MPS are shown in **Table 2**. There were statistically significant differences in age, male gender, hypertension, diabetes, hypercholesterolemia, and LVEF ($P < 0.05$ for each) between these two groups. The presence of smoking, BMI, premature family history of CAD, and GFR were not statistically significant between patients with normal and abnormal MPS.

Multivariate logistic regression analysis of risk factors for abnormal MPS

Based on the factors that were found to be significant in the univariate analysis, we performed

Table 2. Comparison of demographics and biochemical characteristic of patients with normal and abnormal MPS, N = 500

	Overall Number (%) 500	Normal MPS 431 (86%)	Abnormal MPS 69 (14%)	*P*-Value
Age/years	53±14	52±14	62±10	0.000
Male	282 (56)	229 (53)	53 (77)	0.000
Female	218 (44)	202 (47)	16 (23)	
Hypertension	466 (93)	398 (92)	68 (97)	0.037
Diabetes	325 (65)	271 (63)	54 (78)	0.008
Smoking	93(17)	78 (84)	15 (16)	0.284
Family history of CAD	61(12)	56 (13)	5 (7)	0.120
Hypercholesterolemia	176 (35)	141 (32)	35 (51)	0.003
BMI, Kg/m^2	28±5	28±5	28±5	0.608
GFR ml/min/1.73 m^2	8±4	8±3	8±5	0.454
LVEF %	56±11	58±10	47±10	0.000

Abbreviation as in **Table 1**.

Table 3. Multivariate Logistic regression analysis of risk factors for abnormal MPS

Variables	Odds ratio	95% CI	*P*-Value
Age	1.092	1.060-1.125	0.000
LVEF	0.893	0.865-0.921	0.000
Gender	1.832	0.919-3.650	0.085
Diabetes	0.659	0.314-1.382	0.270
Hypertension	0.614	0.073-5.142	0.653
Hypercholesterolemia	0.677	0.359-1.275	0.227

Table 4. Total number of SPECT in comparison with coronary angiography

Parameters	Angiographic Disease ≥ 50 stenosis	NO angiographic Disease ≤ 50 stenosis	Total
SPECT +	50	19	69
SPECT -	13	30	43
Total	63	49	112

multivariate regression analysis, which identified age (≥ 62 years) and LVEF (≤ 47%) as independent factors for abnormal MPS. Other factors, such as diabetes, hypertension, and hypercholesterolemia, did not reach statistical significance, as shown in **Table 3**.

Diagnostic accuracy of MPS in ESRD

Data obtained from 112 subjects who underwent both MPS and ICA were shown in **Table 4**. The sensitivity, specificity, positive predictive value, and negative predictive value of MPA required to detect CAD is 72%, 70%, 79%, and 61%, respectively, are shown in **Table 5**.

Discussion

The study aimed to determine the prevalence of abnormal myocardial perfusion in ESRD. Compared to previous studies, this one involved a higher number of subjects who had relatively different characteristics. Our results show that in patients with ESRD who were referred to MPS as a preoperative assessment, the prevalence of myocardial perfusion disorders was only 13%, which is much lower than presented in previous research. A study by Kim et al., for instance, reported a 45% prevalence of myocardial perfusion abnormalities in ESRD [9], while Moose et al. reported a 27% prevalence [14]. The exact reason for this large difference between the prevalence of myocardial abnormalities compared to previous studies is unclear, but one potential explanation is that the mean age of our study group is significantly lower than that of other studies, and in our study, there is also a lack of history of CAD or angina symptoms, although most of our patients had several risk factors for CAD (e.g., diabetes, hypertension).

Ischemic heart disease in ESRD is correlated with conventional and non-traditional CAD risk factors (e.g., anemia, inflammation, defects of mineral and bone diseases), as well as dialysis-related factors (type and frequency of dialysis) [15]; vascular calcification, including coronary

Table 5. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of MPS in ESRD

Percentage	Angiographic Disease ≥ 50 stenosis
Sensitivity	72
Specificity	70
PPV	79
NPV	61
Accuracy	71

MPS, myocardial perfusion scintigraphy; ESRD, End-stage renal disease; PPV, positive predictive value; NPV, Negative predictive value.

artery calcification, is also well known to increase as GFR decreases [16].

In our univariate study, we found that age, male gender, hypertension, diabetes, hypercholesterolemia, and left ventricular dysfunction were correlated with abnormal MPS, all of which had a *P* value of less than 0.05. However, only age and left ventricular dysfunction was correlated with abnormal MPS in the multivariate study. This is helpful data for clinicians to select high-risk patients using MPS for CAD screening. Initial CAD screening using clinical and echocardiographic information may be more cost-effective with a more appropriate systemic approach. Patients with LV impairment and multiple risk factors for CAD, such as elderly patients with long-term diabetes mellitus and hypertension, may be further refined by MPS imaging, while asymptomatic patients with normal LV function without major risk factors for CAD or long-term diabetes mellitus have a reasonably low risk and will not benefit from additional imaging [17].

A previous analysis of 138 pre-transplant candidates using 50% diameter stenosis showed that MPS had sensitivity and specificity of 53% and 82%, respectively [18]. In our cohort of patients, MPS had a 72% sensitivity, with a 70% specificity for CAD detection, identified as 50% dimeter stenosis. Overall, the pooled results from several small studies examining the accuracy of MPS in ESRD patients undergoing kidney transplantation assessment showed that MPS had a sensitivity and specificity of 67% and 77%, respectively [13]. The results of our research are consistent with many prior studies and consistent with the relatively poor diagnostic accuracy of MPS for ESRD. In this population, the explanation for the comparatively poor diagnostic output of MPS is multifactorial. First, ESRD patients have some hemodynamic and anatomic defects; this could impede diagnostic precision, such as in relation to left ventricular hypertrophy, which could compromise the identification of minor or moderate anomalies of perfusion [10], a large ventricular cavity that may increase the inferior wall's attenuation defect. Second, in the absence of epicardial coronary artery stenosis, a hypertensive reaction to stress may also result in transient ischemic dilation and perfusion abnormalities [19]. Third, in the absence of epicardial coronary artery disease, endothelial dysfunction is a well-known finding in diabetic patients with ESRD [20]. Our findings also indicate that the prevalence of CAD in ESRD is 56%, based on 50% diameter stenosis; this result is consistent with a large study of 3,698 patients who were referred to MPS as part of the assessment of renal transplantation, in which CAD (defined as > 50 dimeter stenosis) was found in 62% of 260 patients who underwent invasive coronary angiography (33% with 3-vessel disease). A similar outcome was reported in a cohort of 222 patients, and there was no difference in survival between angiography patients and non-angiography patients [22]. The indications for invasive coronary angiography and revascularization in general should be close to those for the general population. Performing routine coronary angiography and prophylactic coronary revascularization prior to kidney transplant surgery is not recommended in healthy patients without an existing indication for improving survival.

Study limitations

This was a retrospective study of a large cohort of patients with ESRD and is thus susceptible to biases inherent in retrospective studies. The results of the MPS were not blinded to both the referring doctors and cardiologists; they were free to use the information gathered to assess the therapeutic strategy of the patient. It was also not an event-based outcome study; rather, the study was designed to evaluate the prevalence of MPS abnormalities and the predictors of these abnormalities in this specific group to classify patients who would benefit from additional imaging and preoperative evaluation.

However, a few small studies have been conducted to assess the significance of MPS in ESRD, all of which have reliably demonstrated that myocardial perfusion defect is an independent predictor of serious cardiac adverse events [19, 23].

Conclusions

We find that the incidence of myocardial perfusion defects in ESRD is 13% in MPS, which is comparatively much smaller than in previous studies due to the different characteristics of the patients examined. In addition to other traditional CAD risk factors, such as diabetes and hypertension, age, and left ventricular dysfunction are the strongest predictors of MPS abnormalities. Initial risk stratification by echocardiography with CAD risk factors and left ventricular function may be cost-effective for selecting high-risk patients who would benefit from further imaging. Due to many factors, the diagnostic performance of MPS is relatively poor in ESRD patients for several reasons. More research is therefore required to further assess the utility of MPS in ESRD patients' diagnosis and risk stratification, and whether it can direct decision-making to improve ESRD outcomes. Other non-invasive tests, such as myocardial perfusion positron emission tomography and hybrid imaging with positron emission computed tomography, coronary computed tomography (PET/CTA), and single-photon emission computed tomography/coronary computed tomography angiography (SPECT/CTA) could be excellent alternative tests for this special population and need to be investigated in future studies.

Disclosure of conflict of interest

None.

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