Original Article

Diagnostic accuracy of ^{13}N-ammonia myocardial perfusion imaging with PET-CT in the detection of coronary artery disease

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Background: ^{13}N-ammonia positron emission tomography-computed tomography (PET-CT) is being increasingly used as a non-invasive imaging modality for evaluating patients with known or suspected coronary artery disease (CAD), but information about the diagnostic accuracy of PET-MPI is sparse. Objectives: Our objective was to determine the accuracy of ^{13}N-ammonia PET-CT myocardial perfusion imaging (MPI) for detecting CAD.

Methods: We retrospectively evaluated 383 patients with suspected CAD who underwent rest-stress ^{13}N-ammonia PET-CT MPI. Invasive coronary angiography (ICA) was performed within 60 days for all patients with abnormal PET-MPI findings and for selected patients with normal PET-MPI findings.

Results: The mean age of the patients was 64±11 years, and the mean body mass index was 32±7 kg/m^2. Stress perfusion defects were identified in 147 (34%) out of a total of 383 patients. ICA was performed in 213 patients (145 patients with abnormal PET and 68 patients with normal PET). The sensitivity of PET-MPI for detection of obstructive CAD based on ≥50% stenosis was 90%; specificity, 90%; positive predictive value, 96%; negative predictive value, 76%; and diagnostic accuracy, 80%.

Conclusions: PET-MPI with ^{13}N-ammonia affords high sensitivity and overall accuracy for detecting CAD. The addition of coronary artery calcium score (CACS) can improve CAD risk stratification.

Keywords: Positron emission tomography-computed tomography myocardial perfusion imaging (PETCT MPI); ^{13}N-ammonia positron emission tomography-computed tomography myocardial perfusion (^{13}N-ammonia PET-CT myocardial perfusion); coronary artery calcium score (CACS)

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Introduction

Positron emission tomography (PET) myocardial perfusion (MPI) has several advantages over single-photon emission computed tomography (SPECT) MPI. For one, PET-MPI offers higher spatial resolution as PET radiotracers have higher energy than SPECT radiotracers. In addition, PET cameras do not require physical collimation and therefore offer better count sensitivity, better temporal resolution, lower radiation dose and more advanced technology for measurement of myocardial flow reserve (MFR). Accordingly, PET-MPI has higher sensitivity and specificity (1,2), as well as improved image resolution and intrinsic attenuation correction (3). The clinical superiority of PET-MPI was recognized in a joint statement of the American Society of Nuclear Cardiology and Society of Nuclear Medicine and Molecular Imaging (4).

Currently, rubidium-82 (Rb-82) and ^{13}N-ammonia are the only two FDA-approved radiopharmaceuticals used for myocardial perfusion PET. PET-MPI is being increasingly used due to availability of generator-produced Rb-82 at imaging centers that lack a cyclotron. However, Rb-82 has relatively poor resolution. ^{13}N-ammonia has a high extraction rate, as a result of which it is simpler to quantify it; in addition, it provides better image quality than Rb-82 (5), There are several published reviews and meta-analyses that have reported the high sensitivity and specificity of PET-MPI (6,7). However, most of these studies used Rb-82 (8-13), and there is very little information on the diagnostic accuracy of ^{13}N-ammonia as a PET myocardial perfusion radiotracer (14-16). The most exciting literature on the diagnostic accuracy of ^{13}N-ammonia PET-CT myocardial perfusion was published before 1990 and included only a small number of patients. Therefore, there is a need for more data on the diagnostic accuracy of ^{13}N-ammonia PET-MPI. The main aim of this study was to fill in this information gap by investigating the diagnostic accuracy of ^{13}N-ammonia PET-MPI and comparing it with the gold standard, invasive coronary angiography (ICA).

Methods

Study patients

The study participants included 383 patients who underwent PET-MPI based on their clinical indications between July 2014 and January 2018. Eligible patients were identified retrospectively from the nuclear medicine and PET center data base. Patients were excluded if they had undergone treatment for coronary artery disease (CAD), such as previous percutaneous coronary intervention (PCI), CA (for which the findings were abnormal), previous coronary artery bypass grafting (CABG), or previous MPI (for which the findings were abnormal). In addition, 4 patients were excluded because their PET scan could not be used for diagnosis, because of, for example, excessive uncorrected misregistration between the emission and transmission scan and extensive lung uptake. All patients with abnormal PET findings and selected patients with normal PET findings were referred for ICA within 60 days from the PET scan. The study was approved by our hospital's institutional review board.

^{13}N-ammonia PET-MPI

PET was performed with the GE discovery (CVT or 710) PET-CT scanner (GE Medical System, Milwaukee, Wisconsin). Rest data were acquired immediately after injection of 700–900 MBQ of ^{13}N-ammonia into a peripheral vein. Stress data were acquired approximately 4 halftimes (40 min) after the acquisition of the rest data. Stress was induced through adenosine infusion; another 700–900 MBQ of ^{13}N-ammonia was injected 2 min after the adenosine injection, after which a transmission scan was obtained for attenuation correction as previously reported (17). The PET findings were interpreted by two experienced nuclear medicine physicians, and disagreements were resolved by consensus. The 17-segment model and semiquantification scoring system (0 = normal, 1 = mildly abnormal, 2 = moderately abnormal, and 4 = completely abnormal) recommended by the American Society of Nuclear Cardiology (18) were employed. Images were considered to be normal when the summed stress score (SSS) was less than 4, mildly abnormal when the SSS was 4 were employed. Images were considered to be normal when the summed stress score (SSS) was les (19) (*Figures 1*,*2*).

ICA

Conventional ICA was performed within 60 days after PET-MPI. The coronary arteries were divided into segments, according to the method of the American Heart Association, for Coronary Tomography Coronary Angiography (CTCA) analysis (20). The angiograms were analyzed by two interventional cardiologists who were blinded to the CTCA results. Stenosis was considered to be significant if lumen reduction was more than 50%.

Coronary calcification scoring

Prospective ECG gating and dose modulation were utilized to minimize the radiation dose for 64-slice PET-CT scanners. CT was acquired under the following conditions: voltage, 120 kvp; current, 100 mA; collimation, 0.6 mm; total acquisition time, 10 s; radiation dose, approximately 1 mSv. All CT images were reconstructed with 3-mm thickness and a medium smooth filter. Coronary calcium scoring was then performed using Agatston methods (21).

Statistical analysis

Descriptive statistics were presented as means and standard deviations for data measured on the continuous scale, and as proportions for data measured on the categorical scale. The

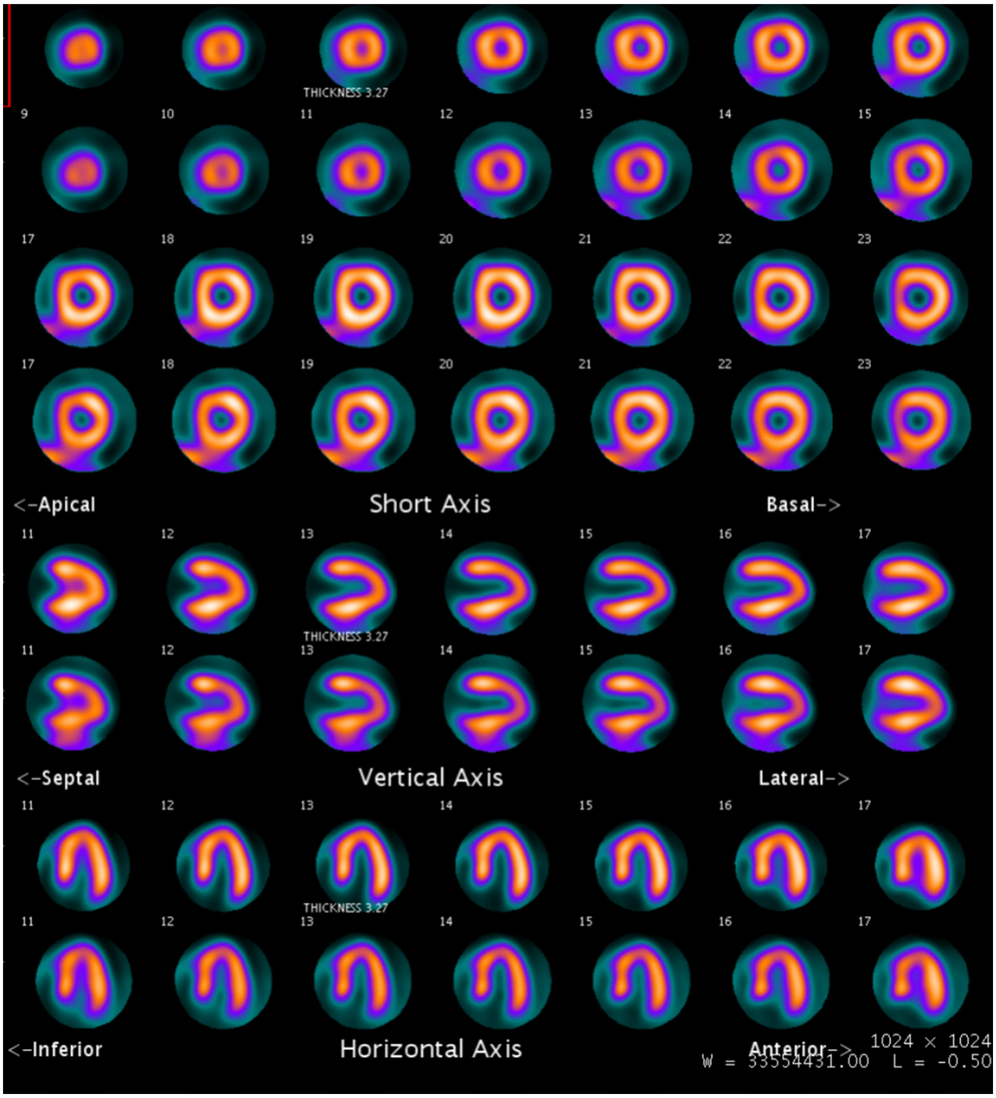

Figure 1 Normal adenosine-stress ^{13}N-ammonia positron-emission computed tomography myocardial perfusion (PET-CT MPI) images. The images demonstrate normal and homogenous radiotracer distribution in both the rest and stress images throughout the left ventricle.

significance of the association between pairs of categorical variables was tested using Pearson's chi-square test. The significance of the difference between group means was tested using one-way ANOVA. Multiple linear regressions for continuous outcomes and multiple logistic regression for dichotomous outcomes were used to evaluate the joint effect of potential risk factors. The type I error rate was set at 5%. The commercial program SPSS (version 20) was used for data analysis.

Results

The total study population was 383, of which 215 (56%) were male and 168 (44%) were female. The mean age was 64±11 years, and the mean coronary artery calcium score (CACS) was 330±589. The majority of patients were obese or overweight, and the mean body mass index (BMI) was 32±7 kg/m^2. Risk factors for CAD were prevalent in all the patients, especially hypertension and diabetes mellitus. The patient characteristics are presented in *Table 1*.

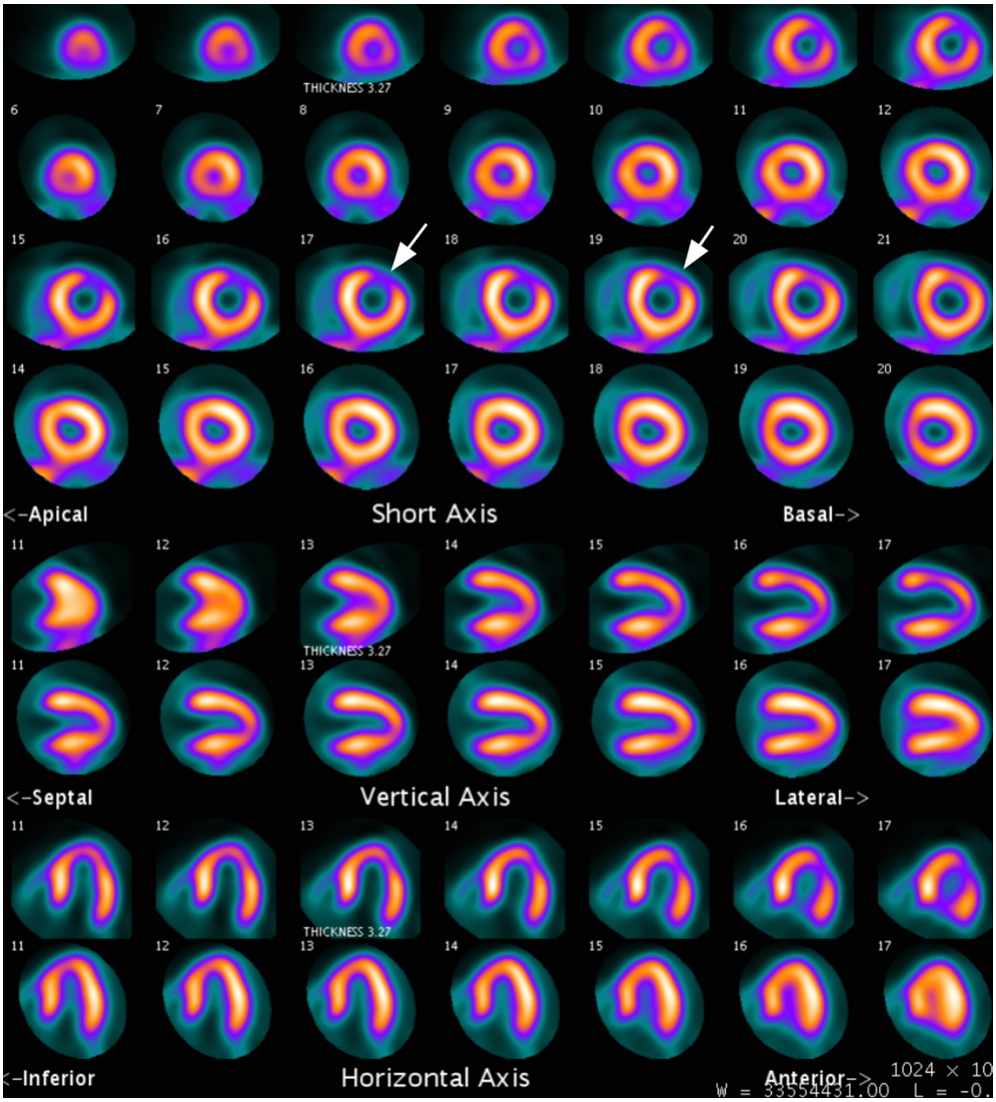

Figure 2 Abnormal ^{13}N-ammonia PET CT MPI images. The images show small moderately severe anterolateral wall ischemia (arrows).

Table 1 Baseline patient characteristics

Factors	Value
Gender (male)	215 (56%)
Age, years	64±11
Body mass index (kg/m^2)	32±7
LVEF % (rest)	59±11
LVEF % (stress)	56±10
Hypertension	349 (91%)
Diabetes mellitus	273 (71%)
Smoking	110 (29%)
CACS	330±589
Abnormal PET MPI	147 (34%)

LVEF, left ventricular ejection fraction.

Diagnostic accuracy of PET-MPI

Out of the total 383 patients, 236 had normal PET-MPI findings, and ICA was performed in only 68 of these patients. Out of these, 52 patients had normal ICA findings (true negative) and 16 patients had abnormal ICA findings (false negative). Of the 147 patients who had abnormal PET-MPI findings, ICA was not performed in only 2 patients. In the remaining 145 patients who underwent ICA, 6 had normal ICA findings (false positive) and 139 had abnormal ICA findings (true positive). The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of PET-MPI was 90%, 90%, 96%, 76%, and 80% respectively.

Table 2 Relationship between CAD risk factors and PET

Parameter	P value (PET)	P value (Cath)	P value (CACS)
Age	0.022	0.021	0.000
Gender	0.061	0.013	0.016
Hypertension	0.898	0.482	0.297
Diabetes	0.214	0.786	0.049
Hyperlipidaemia	0.465	0.933	0.096
Tobacco smoking	0.010	0.810	0.702
Body mass index	0.158	0.598	0.396

PET, positron emission tomography; CACS, coronary artery calcium score.

Table 3 Relationship between CAC score and PET and invasive coronary angiography (ICA)

CAC	PET (n=383)			ICA (n=213)		
	Normal	Abnormal	P	Normal	Abnormal	P
0	129	8	0.000	28	18	0.000
1–300	71	56		17	54	
>300	36	83		13	83	

PET, positron emission tomography; CAC, coronary artery calcium.

Association between CAD risk factors and PET-MPI, ICA, and CACS

Multiple linear regression analysis showed that only age, diabetes, and gender were predictors of CAC (P=0.000, 0.049, and 0.016 respectively). Further, multiple linear regression analysis showed that age and smoking were the only predictors of PET-MPI (P=0.022 and 0.010 respectively). Multiple logistic regression analysis also showed that only age and gender were predictors of ICA (P=0.021 and 0.013 respectively) (*Table 2*).

Relationship between CACS and PET-MPI

The number of patients who had a CACS of 0 was 137 (36%) (Group 1); CACS of 1–300, 127 (33%) (Group 2); and CACS >300, 119 (31%) (Group 3). A strong correlation was found between CACS subgroup and PET-MPI and ICA values (P=0.000 for both correlations) (*Table 3*).

Discussion

The main finding of our study was that ^{13}N-ammonia PET-MPI has high diagnostic accuracy for the detection of coronary artery stenosis of more than 50%; in addition, it had a sensitivity of 90%, specificity of 90%, positive predictive value of 96%, negative predictive value of 76%, and overall diagnostic accuracy of 80%. Notably, the diagnostic accuracy was high in both male and female patients as well as overweight and obese patients (mean BMI, 32±7 kg/m^2).

Although the first report on the superior diagnostic accuracy of ^{13}N-ammonia PET-MPI by Tamaki was published approximately three decades ago (14), very few studies have followed it. Further, the few studies have reported inconsistent results and used a small patient group. The most exciting finding on the diagnostic accuracy of PET-MPI was obtained with Rb-82. The commercial availability of Rb-82 generators is considered to be a key element for the widespread application of Rb-82 myocardial perfusion PET. In contrast, ^{13}N-ammonia requires an in-house or closely located cyclotron. A review article by Di Calri *et al.* in 2007 summarized 9 published studies on the diagnostic accuracy of PET-MPI for detecting more than 50% coronary artery stenosis (22). The overall sensitivity was 90%; specificity, 89%; positive predictive value, 94%; and negative predictive value, 73% (22). Interestingly, 6 out of these 9 studies were performed with Rb-82, 2 were performed with ammonia and Rb-82, and only 1 was performed with ^{13}N-ammonia. A study by Husmann *et al.* reported that the sensitivity of ^{13}N-ammonia PET-MPI was 97% and its specificity was 91% (23). Such a high diagnostic accuracy was probably obtained because most of the study population had CAD: 49 patients had been diagnosed with CAD and only 21 patients were suspected of having CAD (23).

Currently, there are no studies that compare the diagnostic accuracy of ammonia PET with SPECT, the most commonly used technique to assess myocardial perfusion. However, several studies have compared the diagnostic accuracy of PET-MPI with SPECT-MPI in the same or matched patients. For example, Bateman *et al.* compared Rb-82 PET and TC-99m sestamibi in two matched patients and found that the overall diagnostic accuracy with a 50% (87% *vs.* 71%) or 70% (89% *vs.* 79%) angiographic threshold was higher for PET than for

SPECT (9). In another study by Stewart *et al.* in which PET was compared with SPECT in 81 patients, PET was found to have higher specificity (96%) than SPECT (53%) (11). Sampson *et al.* reported that Rb-82 PET-CT MPI had a sensitivity of 93% and specificity of 83% (8). In their study, obstructive CAD was considered if ICA showed more than 70% stenosis. In the present study, 50% or more stenosis was considered to be indicative of obstructive CAD. This may explain the slight difference in the sensitivity and specificity between our study and their study.

The role of ^{13}N-ammonia in predicting functional outcome after coronary revascularization has been studied by Duvernoy *et al.*: preoperative relative uptake greater than 80% and less than 40% was found to have excellent predictive value for functional outcome (24). Further, Sand *et al.* found that MPI with ^{13}N-ammonia and Tc-99m sestamibi had similar results in patients with severe left ventricular function (25). Only one study has reported the long-term outcome of ^{13}N-ammonia: this study by Fiechter *et al.* reported that perfusion findings for ^{13}N-ammonia are strong predictors of long-term outcome in 612 patients for 5.7±2.5 years (26).

Modern PET-CT cameras allow CACS to be acquired as part of the myocardial perfusion imaging protocol. CACS is the most common parameter used for assessing subclinical CAD (27). In our study, using CACS, we found that subclinical CAD was present in 45% of patients with suspected CAD with normal PET-MPI findings. This finding is important as a previous report had shown that adding the CACS to the Framingham risk score (FRS), especially in the case of patients with intermediate FRS values, can improve prognosis (28,29). Our results also reaffirm the findings of Bybee *et al.*, who calculated CACS in 760 patients with no history of CAD and normal Rb-82 PET-MPI stress perfusion findings: in their study, 64% of patients with normal PET-MPI had subclinical CAD, as indicated by the CACS, based on which the authors concluded that subclinical CAD is common in patients without known CAD and normal PET-MPI findings (30). The association of CACS and normal SPECT-MPI has been previously studied by our group in 207 patients with normal SPECT MPI, in which the CACS was zero in 45% and abnormal in 55% (31). Of those with abnormal CACS, 43% had a CACS of 1–300, and 12% had a CACS of more than 300. Furthermore, there was a strong association between CACS and age, male gender, and diabetes (31). In addition, there was a strong correlation between CACS and ICA (P=0.000). Almost 50% of patients with normal ICA findings had a CACS of 0, but obstructive CAD was diagnosed in symptomatic patients based on the CACS alone. In our current study, 12% of patients with a CACS value of 0 had abnormal ICA findings. This high percentage compared to previous reports can be explained as follows: first, this group of patients was at high risk and symptomatic, and second, there is a sampling bias because most patients with normal CACS were not referred for ICA. Kim *et al.* also reported that a CACS value of 0 cannot be used to exclude obstructive CAD in symptomatic patients who were referred for CTCA; the prevalence of obstructive CAD in symptomatic patients with a CACS of 0 was 7.4% in men and 2% in women. Moreover, in their study, it was noted that adverse cardiac events are not negligible in symptomatic patients with a CACS of 0 (32).

Study limitations

Quantitative myocardial blood flow (CFR) was not determined in the majority of patients. Subsequently, it was not included in the data analysis. CFR can improve the diagnostic accuracy of myocardial perfusion, as it can be used to detect balanced ischemia and left main disease that could be missed with static perfusion images only. The severity of obstructive CAD was determined visually rather than quantitatively; however, this is the common clinical practice. Finally, this is a retrospective study that was conducted at a single, tertiary care center and the possibility of a referral bias cannot be excluded.

Conclusions

^{13}N-ammonia PET-CT myocardial perfusion offers very high sensitivity, specificity, and overall diagnostic accuracy for the detection of obstructive CAD. This high diagnostic accuracy is observed in male and female, as well as overweight and obese patients. Adding CACS as a diagnostic factor in patients with unknown CAD and PET-MPI may help in the detection of subclinical CAD, guiding CAD management and prevention, and providing prognostic information.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was waived by the institutional review board for this retrospective study.

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