ORIGINAL ARTICLE

Clinical performance of Rb-82 myocardial perfusion PET and Tc-99m-based SPECT in patients with extreme obesity

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Background. **We evaluated the performance of stress imaging with technetium-99m-labeled tetrofosmin single-photon emission computed tomography (SPECT) and rubidium-82 positron emission tomography (PET) in patients with extreme obesity, defined as body mass index ≥40 kg/m^2.**

Methods. **We identified patients with extreme obesity who underwent angiography in our center and either stress SPECT or PET within the previous six months. Cohorts of patients with extreme obesity and a <5% pretest likelihood of CAD who underwent SPECT (N = 25) or PET (N = 25) were also included.**

Results. **In total, 108 patients who underwent SPECT (N = 57) or PET (N = 51) were identified. Scan interpretation was classified as definitely normal or abnormal in 83.3% of PET and 60.5% of SPECT scans, respectively (*P* < .01). PET demonstrated higher diagnostic accuracy and normalcy rate. PET was found to have higher specificity for the pooled cohort. Similar findings were observed using stenosis cut-offs of ≥50% and ≥70%.**

Conclusions. **In patients with extreme obesity, PET enabled more definitive scan interpretation with less artifact compared to SPECT. PET provided higher diagnostic accuracy and specificity in the detection of obstructive coronary artery disease. (J Nucl Cardiol 2019;26:275–83.)**

Key Words: Myocardial perfusion imaging • PET/CT • SPECT • obesity

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Abbreviations

AC	Attenuation correction
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
Rb-82	Rubidium-82
SPECT	Single-photon emission computed tomography
Tc-99m	Technetium-99m

See related editorial, pp. 284–287

INTRODUCTION

Several studies have compared the accuracy of single-photon emission computed tomography (SPECT) and positron emission tomography (PET) in the evaluation of patients for coronary artery disease (CAD).[1–3] However, there is limited data comparing these techniques in obese patients and to our knowledge none comparing patients with extreme obesity.

Obesity is defined by the World Health Organization as a body mass index (BMI) $\geq$30 kg/m^2 with three subclassifications: (1) class I (BMI 30-34.9 kg/m^2); (2) class II (BMI 35-39.9 kg/m^2); and (3) class III (extreme obesity, BMI $\geq$ 40 kg/m^2). The prevalence of all classes of obesity has been increasing steadily with a disproportionate increase in extreme obesity.[4] Obesity is known to be an independent risk factor for cardiovascular disease.[5]

The diagnosis of CAD in patients with extreme obesity is challenging.[6] Clinically, exertional chest pain, dyspnea, and reduced activity tolerance have a lower specificity for the diagnosis of CAD in extreme obesity as they can result from deconditioning and a sedentary lifestyle.[6] The physical exam and electrocardiogram are less sensitive in the detection of cardiovascular disease and often underestimate its severity.[5]

Coronary angiography, considered as the gold standard for the anatomic diagnosis of obstructive CAD, is technically more challenging in the extreme obesity population and is associated with an increased risk of complications such as major bleeding and in-hospital mortality.[7,8] We have shown that transradial access for coronary angiography may mitigate some of this risk compared to the transfemoral approach in patients with extreme obesity.[9] Nonetheless, procedural risk remains a consideration, and it may be preferable to pursue non-invasive risk stratification whenever feasible in this patient population.[6] However, non-invasive diagnostic imaging modalities have limitations, and there is no consensus on the optimal modality.[10] Hence, the objective of the current study was to evaluate the diagnostic accuracy of Technetium-99m (Tc-99m) tetrofosmin SPECT versus Rubidium-82 (Rb-82) PET myocardial perfusion imaging in patients with extreme obesity.

METHODS

All consenting patients that undergo coronary angiography at our center are included in a prospective registry that includes demographic data including height and weight. Review of the CAPITAL Percutaneous Coronary Intervention (PCI) registry at the University of Ottawa Heart Institute yielded 21,103 consecutive angiography or PCI procedures performed between January 2007 and August 2010, as described previously.[9] A cohort of 564 patients with a BMI $\geq$ 40 kg/m^2 were retrospectively identified, of whom 37 had undergone a SPECT and 46 had undergone a PET in the preceding 6 months (Figure 1).[9] Patients were excluded if they had a history of prior myocardial infarction (MI), PCI, or coronary artery bypass grafting (CABG) leaving the SPECT and PET groups with 32 and 26 patients, respectively.

In addition, a second cohort of patients with extreme obesity was identified that had either a PET or SPECT myocardial perfusion imaging scan during the same time period with a low (<5%) pretest likelihood of CAD. These patients had a normal resting ECG and no history of diabetes or CAD. They were identified as having a <5% pretest likelihood of significant CAD based on Diamond-Forrester analysis.[11] A total of 25 low-likelihood patients were included in each group. These patients did not undergo angiography but

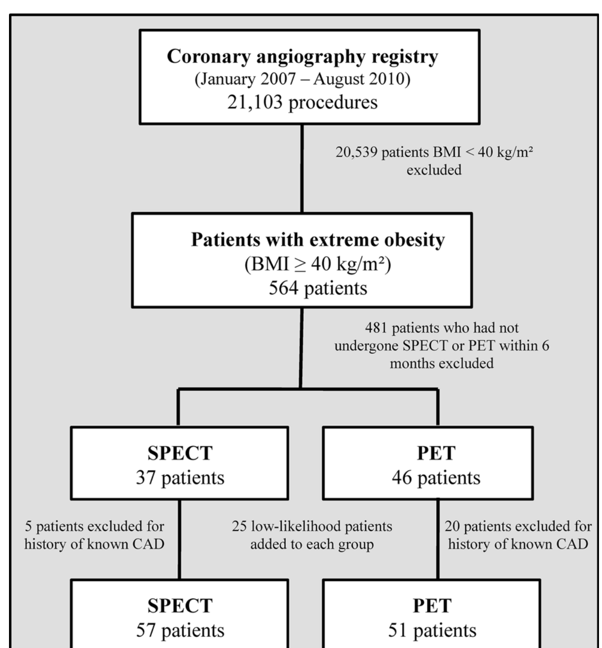

Figure 1. Cohort identification.

were included as negative controls to compensate for post-myocardial perfusion imaging bias in the main cohort, which allows an independent evaluation of normalcy as a surrogate for specificity.

The medical records of eligible patients were systematically reviewed to collect information on baseline patient characteristics and imaging study technical information. This study was reviewed and approved by the University of Ottawa Health Science Network Research Ethics Board.

Coronary Angiography Interpretation

Coronary angiograms were interpreted by two independent cardiologists blinded to the clinical and imaging data. Discrepancies between normal and abnormal arteries were settled by consensus. Significant CAD was primarily defined by the presence of ≥50% stenosis on coronary angiography. In a secondary analysis, CAD was defined by the presence of focal stenosis ≥70%. Left main coronary artery disease was attributed to both the left anterior descending and left circumflex territories.

Myocardial Perfusion Imaging Scan Preparation

The pretest preparation was identical for patients undergoing both PET and SPECT. All patients fasted overnight, refrained from caffeine ≥12 hours and theophyllines for ≥48 hours before scanning, and held their antianginal medications on the morning of the test in accordance with current guidelines.[12] For patients undergoing pharmacological stress, dipyridamole 0.14 mg/kg/min was infused over 5 minutes. For patients undergoing exercise stress, a symptom-limited exercise treadmill test was performed according to the Bruce protocol.[13]

SPECT Protocol

SPECT imaging was performed using either a E-Cam (Siemens, Hoffman Estates, IL) or Infinia-Hawkeye 4 cameras (GE Healthcare, Waukesha, WI). Either a 1- or 2-day rest and stress protocol was performed using Tc-99m-tetrofosmin (550-1110 MBq) injected at rest and at peak of stress.[14] Both static and gated images were acquired using a list-mode acquisition according to the guidelines of the American Society of Nuclear Cardiology.[15] Rest and stress images were acquired at 45 and 30-60 minutes after Tc-99m-tetrofosmin injection, respectively. Static and gated images were reconstructed using Ordered-Subset-Expectation-Maximization (OSEM 10 subsets, 2 iterations) with resolution recovery, fifth-order Butterworth filter, and 0.52 cycles/cm cut-off frequency. Attenuation and scatter correction were not performed.

PET Protocol

Patients were positioned in a PET-CT system (Discovery 690 or Rx PET-VCT, GE Healthcare, Waukesha, WI), and a low-dose CT scan was acquired for attenuation correction (AC). 10 MBq/kg of Rb-82 was administered intravenously using a custom elution system, and a 10-minutes Rb-82 dynamic PET scan was acquired with a parallel list-mode acquisition.[16]

After rest imaging, dipyridamole stress was administered as described above, and a second dose of 10 MBq/kg of Rb-82 was given 3 minutes after completion of the vasodilator infusion. Stress PET acquisition was performed in the same manner as the rest images with a second low-dose CT scan for AC afterward. Review of the PET-CT image alignment for AC was performed prior to reconstruction of each study, with manual adjustment where required, using the vendor ACQC software.[17] Images were reconstructed using Fourier rebinning and filtered back projection with a 12-mm, 3-dimensional Hann window of the ramp filter. The list-mode data from 2 to 10 minutes were replayed to reconstruct standard perfusion and electrocardiographic-gated 8-frame images with 12 and 16 mm Hann filter, respectively.[18]

Image Interpretation

Semi-quantitative visual analysis was performed using Corridor-4DM software (INVIA, Ann Arbor, MI). Perfusion image defects were graded visually using a standard 17-segment model and 5-point scoring system.[19] Coronary artery territory was defined by the location of the abnormal uptake: left anterior descending artery (anterior, septal, anteroseptal, apical); right coronary artery (inferior, inferoseptal); and left circumflex artery (antero- and inferolateral, lateral). Summed stress score, summed rest score, and summed difference score were recorded for each patient. A summed stress score ≥4 was considered abnormal.[20] The left ventricular ejection fraction during rest and stress were determined using automated analysis of the electrocardiographic-gated images. Scans were reviewed by two independent readers blinded to clinical and angiographic data. An additional blinded observer was used to independently review any discrepancies. Imaging artifacts, specifically soft tissue attenuation, breast attenuation, and apical partial volume thinning, were reported using standard guideline definitions.[21]

Statistical Analysis

Continuous variables were described as either mean ± standard deviation and were compared using 2 sample *t* tests. All categorical variables were described as frequency (%) and compared using the χ^2 statistic. The sensitivity, specificity, and diagnostic accuracy values for SPECT and PET were also compared using stenosis ≥50% and ≥70% cut-off values with the χ^2 statistic. Fisher's exact test was used for χ^2 testing when cell count data were less than 5. The normalcy rate, the proportion of normal perfusion scans in patients with <5% pretest probability of CAD, was also determined.[22] Statistical significance was defined as a P value <0.05. Statistical analyses were conducted using SPSS version 19.0 (IBM Corporation, Armonk, NY).

RESULTS

The SPECT and PET groups were comparable in terms of baseline characteristics both amongst the patients who underwent coronary angiography (Table 1) and the low-likelihood patients (Table 2). There was no difference in the prevalence of obstructive CAD between the SPECT and PET groups.

The majority (73.7%) of SPECT scans were performed using a two-day protocol and with pharmacologic stress (91.2%) (Table 3). PET scans were less likely to have any type of artifact (PET 7.8% vs. SPECT 30.4%, $P = .01$), which was driven by less soft tissue (PET 0% vs. SPECT 10.7%, $P = .03$) and breast attenuation (PET 2.0% vs. SPECT 19.6%, $P = .01$) artifact. PET scans were also more likely to be interpreted as definitely normal or abnormal (PET 83.3% vs. SPECT 60.5%, $P < .01$).

The results of the comparisons between PET and SPECT were similar using both ≥50% and ≥70% stenosis cut-off values for obstructive CAD (Tables 4 and 5). PET demonstrated a higher diagnostic accuracy in the detection of obstructive CAD relative to SPECT. The normalcy rate in the low-likelihood patients was also higher in the PET group (PET 96% vs. SPECT 76%, $P = .04$). No difference was observed in the specificity of the tests in patients who underwent angiography. However, when the data for these patients and the low-likelihood patients were pooled, PET was found to have a higher specificity relative to SPECT. No significant difference was observed in the sensitivity of the two imaging modalities. These differences in test performance were preserved in two separate stratified analyses to include only patients who underwent: (1) pharmacologic stress testing with dipyridamole and (2) two-day SPECT protocol.

DISCUSSION

Diagnosis and risk stratification of CAD in patients with extreme obesity is challenging and represents a growing area of importance with increasing rates of obesity in North America. While there are data

Table 1. Baseline patient characteristics in SPECT and PET groups

	SPECT (N = 32)	PET (N = 26)
Age (years)	57.0 ± 9.5	54.6 ± 12.5
Female sex	21 (65.6)	15 (57.7)
BMI (kg/m^2)	46.0 ± 5.8	45.4 ± 4.3
Cardiac risk factors		
Hypertension	29 (90.6)	19 (73.1)
Diabetes	20 (62.5)	13 (50.0)
Hypercholesterolemia	26 (81.3)	18 (69.2)
Smoking history	15 (46.9)	18 (69.2)
Family history of premature CAD	10 (31.3)	8 (30.8)
Medical history		
TIA/CVA	3 (9.4)	4 (15.4)
Chronic kidney disease	5 (15.6)	8 (30.8)
Medications		
ACE inhibitor	22 (68.8)	12 (46.2)
Aspirin	26 (81.3)	17 (65.4)
Beta-blocker	19 (59.4)	15 (57.7)
Clopidogrel	13 (40.6)	8 (30.8)
Statin	22 (68.8)	14 (53.8)
Pretest probability of CAD (%)	49.1 ± 5.5	53.9 ± 6.0
Angiographic prevalence of CAD		
Single vessel disease	6 (18.8)	4 (15.4)
Double vessel disease	6 (18.8)	7 (26.9)
Triple vessel disease	3 (9.4)	3 (11.5)

Categorical variables frequency (%), *continuous variables* mean ± standard deviation, *N* number of patients, *BMI* body mass index, *CAD* coronary artery disease, *CVA* cerebrovascular accident, *TIA* transient ischemic attack
There were no significant differences ($P < .05$) between the study groups

Table 2. Baseline patient characteristics in low-likelihood patients

	SPECT (N = 25)	PET (N = 25)
Age (years)	46.9 ± 10.0	45.1 ± 7.6
Female sex	20 (80.0)	21 (84.0)
BMI (kg/m^2)	46.8 ± 7.4	45.9 ± 5.7
Cardiac risk factors		
Hypertension	9 (36.0)	15 (60.0)
Diabetes	0	0
Hypercholesterolemia	4 (16.0)	9 (36.0)
Smoking history	6 (24.0)	8 (32.0)
Family history of premature CAD	7 (28.0)*	16 (64.0)*
Medical history		
TIA/CVA	0	0
Chronic kidney disease	0	0
Medications		
ACE inhibitor	3 (12.0)	7 (28.0)
ASA	5 (20.0)	2 (8.0)
Beta-blocker	5 (20.0)	2 (8.0)
Clopidogrel	0	0
Statin	3 (12.0)	6 (24.0)

Categorical variables frequency (%), *continuous variables* mean ± standard deviation, *N* number of patients, *BMI* body mass index, *CAD* coronary artery disease, *CVA* cerebrovascular accident, *TIA* transient ischemic attack
* $P<.05$

Table 3. Imaging characteristics

	SPECT (N = 57)	PET (N = 51)	*P* value
Indication for study			
Angina	48 (84.2)	34 (66.7)	**.03**
Pre-operative	5 (8.8)	10 19.6)	.10
Other	4 (7.0)	7 (13.7)	.34
Two-day protocol	42 (73.7)	0	–
Stress protocol			
Dipyridamole	52 (91.2)	50 (98.0)	.12
Dobutamine	0	1 (2.0)	.47
Exercise	5 (8.8)	0	.059
Imaging artifact			
Any	17 (30.4)	4 (7.8)	**.01**
Soft tissue attenuation	6 (10.7)	0	**.03**
Breast attenuation or shifting	11 (19.6)	1 (2.0)	**.01**
Apical partial volume	0	3 (5.9)	.10
Study interpretation*			
Definitely normal or abnormal	69 (60.5)	85 (83.3)	**<.01**
Probably normal or abnormal	45 (39.5)	17 (16.7)	**<.01**
Transient ischemic dilatation	4 (7.0)	11 (21.6)	**.05**

Bold values indicate statistical significance (P value $\leq$ 0.05)
Categorical variables frequency (%), *continuous variables* mean ± standard deviation
* Interpretation data represents combined totals of two independent readers

Table 4. Accuracy data using ≥50% stenosis cut-off value

	SPECT	PET	*P* value
Sensitivity	11/15 73.3% (44.9-92.2)	12/14 85.7% (57.2-98.2)	.41
Specificity*	7/17 41.2% (18.4-67.1)	8/12 66.7% (34.9-90.1)	.18
Specificity[a]	26/42 61.9% (45.6-76.4)	32/37 86.5% (71.2-95.5)	**.01**
Normalcy rate	19/25 76.0%	24/25 96.0%	**.04**
Diagnostic accuracy	37/57 64.9% (51.1-77.1)	44/51 86.3% (73.7-94.3)	**.01**

Bold values indicate statistical significance (*P* value ≤ 0.05)
*Specificity calculation including only patients who underwent angiogram
[a]Specificity calculation including all patients (those who underwent angiogram as well as the low-likelihood group)

Table 5. Accuracy data using ≥70% stenosis cut-off value

	SPECT	PET	*P* value
Sensitivity	9/12 75.0%	12/14 85.7%	.49
Specificity*	8/20 40.0%	8/12 66.7%	.14
Specificity[a]	27/45 60.0%	32/37 86.5%	**.01**
Normalcy rate	19/25 76.0%	24/25 96.0%	**.04**
Diagnostic accuracy	36/57 63.2%	44/51 86.3%	**.01**

Bold values indicate statistical significance (*P* value ≤ 0.05)
*Specificity calculation including only patients who underwent angiogram
[a]Specificity calculation including all patients (those who underwent angiogram as well as the low-likelihood group)

comparing SPECT and PET in the diagnosis of CAD in the general population, there are essentially no data comparing their accuracy in patients with extreme obesity who may be at higher risk of disease and adverse outcomes.[1–3] These patients are also at a high risk of false-positive testing due to imaging artifacts which could lead to potential harm from subsequent invasive procedures. We demonstrate higher diagnostic certainty, lower prevalence of image artifacts, greater accuracy, and higher specificity in the detection of obstructive CAD with Rb-82 PET relative to Tc-99m SPECT in patients with extreme obesity.

There are few studies directly comparing the diagnostic accuracy of PET and SPECT. Mc Ardle et al performed a systematic review and meta-analysis comparing these modalities which reported a higher overall accuracy for Rb-82 PET based on a receiver operator curve analysis (area under curve: SPECT 0.90 vs. PET 0.95, $P < .0001$).[3] However, only studies that used AC for SPECT were included, which was not performed in this study, and the analysis was not stratified for obesity. Superior accuracy of PET was also demonstrated in a meta-analysis that reported higher sensitivity (PET 92.6% vs. SPECT 88.3%, $P = .035$) with PET, but no difference in specificity between the two modalities (PET 81.3% vs. SPECT 75.8%, $P = .39$).[23]

Bateman et al compared matched cohorts of patients that underwent either Tc-99m SPECT or Rb-82 PET and performed a sub-group analysis of patients with a BMI ≥ 30 kg/m^2. They found greater diagnostic accuracy for PET compared with SPECT (PET 85% vs. SPECT 67%, $P < .02$) in patients with a BMI ≥ 30 kg/m^2.[2] Our results support the greater accuracy of PET versus SPECT in the extreme obesity population (diagnostic accuracy: PET 86.3% vs. SPECT 64.9%, $P = .02$). Several studies support the notion that both SPECT and PET have a role in diagnosis and prognostication in patients with extreme obesity and suspected CAD.[20,24–26] However, our study is one of the first to compare the diagnostic accuracy of these modalities specifically in patients with extreme obesity.

PET has several technological advantages over SPECT imaging that improve image quality, particularly in obese patients. Such benefits include coincidence detection resulting in better count statistics, routine and reliable CT AC, and the ability to quantify myocardial blood flow in absolute terms (although this was not reported in this study). Furthermore, the short half-life of Rb-82 (76s) enables a low radiation dose to the patient (<2 mSv) compared to Tc-99m SPECT (approx 10 mSv).[27] The short half-life also results in faster imaging times for PET: 30-45 minutes vs. 4 hours for 1-day Tc-99m SPECT.

In contrast, advantages of SPECT over PET include its increased availability, greater number of expert interpreters, and lower cost.[10] Furthermore, recent advances in camera technology including solid-state detectors with greatly increased count sensitivity and hybrid SPECT-CT systems to provide CT AC may decrease the incidence of attenuation artifact in extreme obesity patients.[28,29] These technologies were not employed in this study and therefore their potential impact in this extreme obesity population remains unclear.

We did not compare the prognostic value of PET or SPECT in patients with extreme obesity in this study. However, this has been previously demonstrated in the obese population. In a study of 265 obese (BMI $\geq$ 30 kg/m^2) patients, normal and abnormal SPECT studies were associated with 0.6% and 3.3% annual cardiac death rates, respectively.[30] In a sub-group analysis, Yoshinaga et al reported cardiac event rates of 0% in patients with a normal SSS and 6% in those with an abnormal SSS with PET imaging.[20] A recent study reported a 0.1% annual incidence of cardiac death among the severely obese patients (BMI $\geq$ 35 kg/m^2, N = 1344) with a normal PET study with mild, moderate, and severe perfusion deficits associated with annual cardiac death rates of 0.80%, 1.29%, and 4.83% respectively.[26]

There are limitations to this study. First, it is a single-center, retrospective, observational study and the small sample size may have limited our ability to detect small but clinically significant differences. We endeavored to offset this bias by including a low-risk population as negative controls to evaluate normalcy, according to previously established methods.[22,31] Second, there may be a referral bias, as the decision to refer patients for either PET or SPECT with or without subsequent invasive angiography was made by the treating physician based on the clinical context. As such, it is possible that there are differences in the baseline characteristics between the groups. Non-significant *P* values comparing these baseline characteristics do not rule out clinically meaningful differences due to the small sample size. Third, the SPECT technology used did not include AC, prone imaging, and other newer advances such as solid-state detectors. AC methods may have particular benefit in extreme obesity patients where the incidence of attenuation artifact is higher. As such, our conclusions apply to supine non-AC Anger-camera SPECT. The results may not be generalizable to centers that have adopted AC-SPECT, prone imaging, or newer solid-state SPECT technologies. The PET cohort did not include myocardial flow reserve quantification, which has been shown to improve detection of multivessel disease and to have incremental prognostic value.[32,33] Finally, coronary angiography did not include the use of fractional flow reserve, which would have added functional data to the anatomical standard and potentially improved the validity of the comparison with myocardial perfusion imaging.

NEW KNOWLEDGE GAINED

PET appears to offer advantages over SPECT in the diagnosis of obstructive CAD in patients with a body mass index $\geq$40 kg/m^2. In our study, PET had fewer artifacts in addition to higher diagnostic accuracy and specificity. This may allow more appropriate selection of patients for invasive angiography, which has a higher rate of complications in this patient population.

CONCLUSIONS

In patients with extreme obesity, Rb-82 PET allowed more definitive scan interpretation with fewer artifacts relative to standard Tc-99m SPECT. PET provided higher diagnostic accuracy and specificity in the detection of obstructive CAD. Further large studies are required to definitively evaluate these modalities in the patient population with extreme obesity.

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