High diagnostic performance of Rb-PET as compared to ^{99m}Tc-MIBI with CZT gamma cameras for detection of CAD in women and overweight people

Fabien Hyafil; Renata Chequer; Emmanuel Sorbets; Candice Estellat; François Rouzet; Toni Alfaiate; Hamza Regaieg ; Milan Milliner ; Sébastien Leygnac ; Pierre-Yves Marie; Dominique Le Guludec

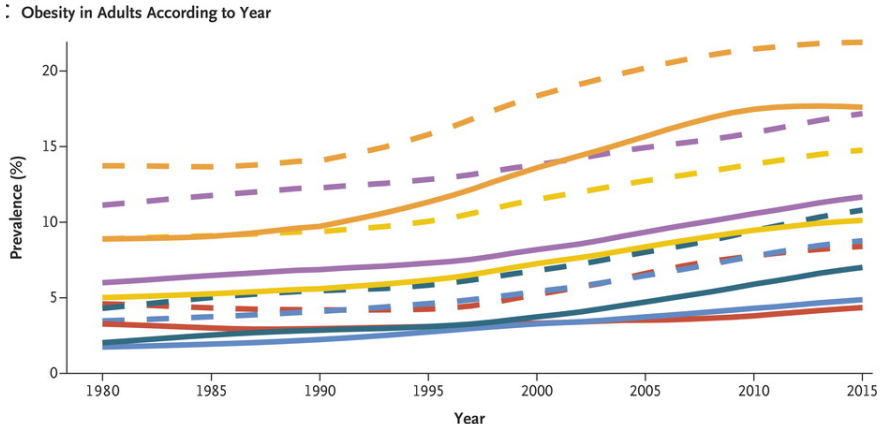
1. AP-HP, Bichat University Hospital, Department of Nuclear Medicine, University Diderot, Paris, France.
2. INSERM, U-1148, DHU FIRE, University Diderot, Paris, France.
3. AP-HP, Avicenne University Hospital, Department of Cardiology, University Paris 13, Bobigny, France.
4. AP-HP, Bichat University Hospital, Department of Cardiology, Paris, France
5. AP-HP, Hôpital Bichat, URC Paris Nord, Paris, France
6. Brambois University Hospital, Department of Nuclear Medicine, Lorraine University, Vandœuvre-lès-Nancy, France

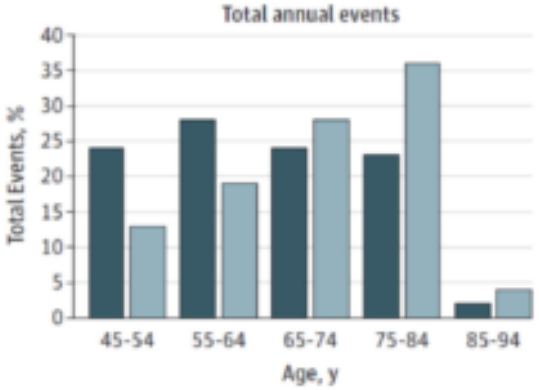
Disclosure slide

- ✓ No conflict of interest, nor financial disclosure in relation to this presentation.
- ✓ This study was fully supported by a grant from the French Ministry of Health (PHRC 2011 AOM11066).
- ✓ FH is advisor for Naogen.

Detection of CAD in women and obese patients

- ✓ Women and obese patients constitute a growing proportion of patients referred for the detection of CAD.
- ✓ Image quality is often lower in women and obese patients than in the general population.
- ✓ Clinical studies focusing on the diagnostic performance of imaging test for the detection of CAD in these groups of patients are, however, scarce.



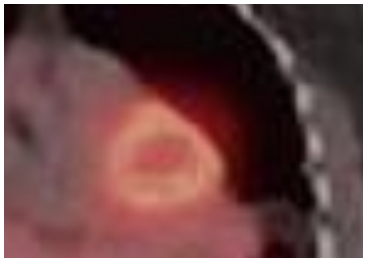


The GBD 2015 Obesity Collaborators. NEJM 2017.

The 2005-2010 National Health and Examination Survey.

Background: CZT SPECT cameras and 3D PET systems

- ✓ In the past 10 years, new generations of SPECT and PET systems have become available for cardiac scintigraphy.
- ✓ CZT gamma cameras offer a dramatic increase in myocardial count rate vs. Na/I cameras and could improve image quality in women and obese patients subjected to important signal attenuation.
- ✓ ^{82}Rb-PET acquisitions in a 3D mode provide MPS images with high signal and accurate attenuation correction and offer to quantify myocardial blood flow.



Objectives of the RUBIS trial

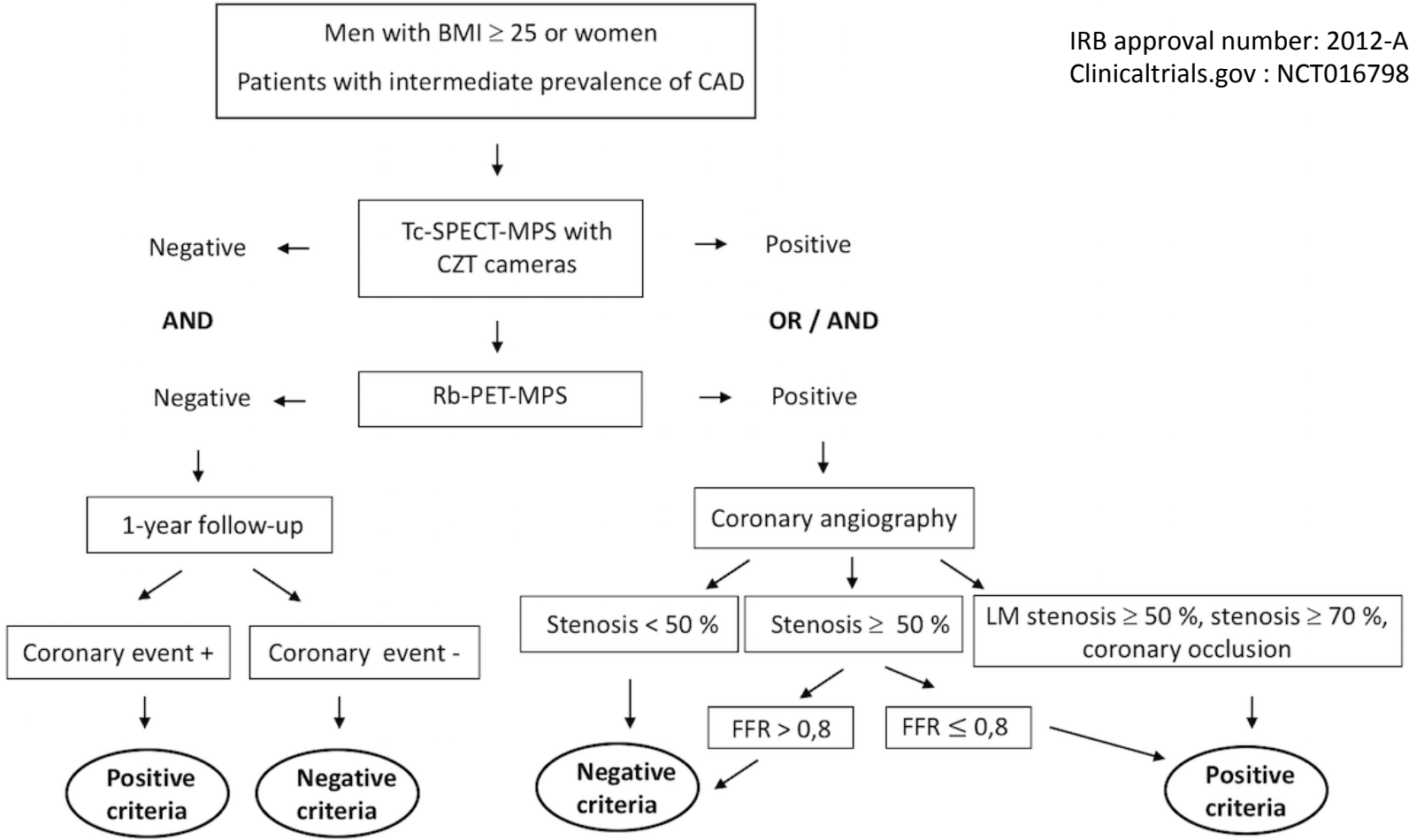
Primary objective: to compare in a population of women and overweight individuals the diagnostic performance for the detection of myocardial ischemia of Tc-MPS-SPECT in association with the best stress feasible (exercise was prioritized) and Rb-PET-MPS in association with pharmacological stress.

Secondary objectives:

- the quality and certainty of image interpretation
- to compare the performance of Tc-MPS-SPECT and Rb-PET-MPS for the detection of balanced myocardial ischemia in patients with three-vessel CAD
- the radiation exposure associated with each imaging technique.

Design of the study

IRB approval number: 2012-A00552-41
Clinicaltrials.gov : NCT01679886



Tc-SPECT-MPS acquisition protocol

Stress protocol

Exercise and combined tests (association with dipyridamole) were prioritized. Pharmacological stress consisted of a standard infusion of dipyridamole during 4 minutes (0.7 mg/kg).

Radionuclide protocol.

The choice of acquisition protocol (one day or two-day) was left at the physician's discretion.
One day protocol: 3 MBq / kg of Tc-sestamibi at stress and 9 MBq /kg of Tc-sestamibi;
Two days protocol: 7 MBq /kg of Tc-sestamibi
If stress-first images demonstrated normal stress ECG, perfusion and LVEF, rest imaging was not performed.

Image acquisition.

All acquisitions were performed on a CZT cardiac-centered camera (D-SPECT; Spectrum Dynamics). Duration of acquisition was in the range between 3 and 15 minutes.

Image reconstruction.

Static and gated image reconstructions were reconstructed with a specific method of iterative reconstruction to compensate for collimator-related loss in spatial resolution.

Rb-PET-MPS acquisition protocol

Stress protocol

Pharmacological stress consisted of a standard infusion of dipyridamole during 4 minutes (0.7 mg/kg).

Radionuclide protocol

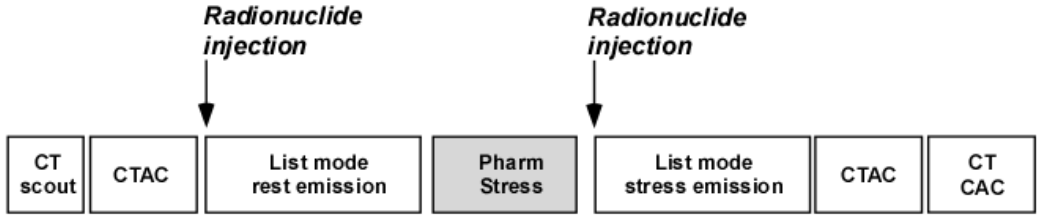
For each PET acquisition, patients were injected intravenously with 10 MBq / kg (minimal dose = 740 MBq; maximal dose = 1480 MBq) of Rb.

Image acquisition

All patients were studied using a whole-body PET-CT scanner. PET acquisitions were acquired in 3D mode and list mode; duration of acquisitions : 8 minutes. Attenuation correction of PET acquisitions was performed using a low-dose CT before the rest and after the stress acquisitions.

Image reconstruction

Dynamic PET acquisitions were reconstructed using FBP into 15 time frames (9 × 10 s, 3 × 30 s, 1 × 60 s, and 2 × 120 s; total, 8 min). Static and gated PET images were reconstructed with acquisitions between 2 and 8 min post injection using an OSEM algorithm (4 iterations, 24 subsets).



Results: population of the study

- ✓ 311 patients (143 women) were included.
- ✓ Mean BMI of patients was 31.8± 6.5 with 41 % of patients with BMI > 30.
- ✓ 31 % patients were symptomatic; average number of CV risk factors: 3 ; 77 % of diabetic patients.

Patients included in the study (n = 311)

3 patients with non interpretable PET were excluded from the analysis.
12 patients with abnormal SPECT or PET could not be evaluated with coronary angiography

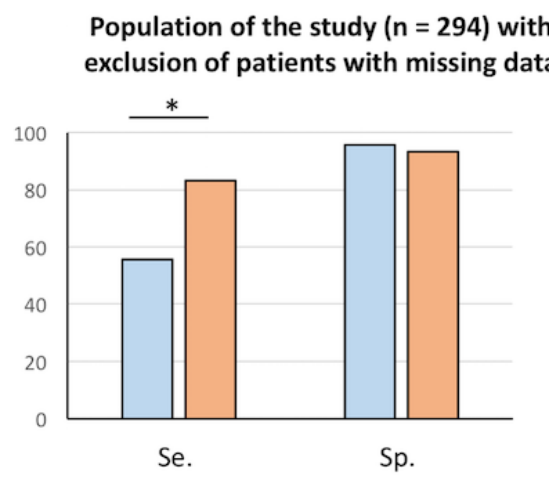
		^{82}Rb-PET-CT	
		Abnormal	Normal
^{99m}Tc-MIBI-SPECT	Abnormal	37	16
	Normal	19	236

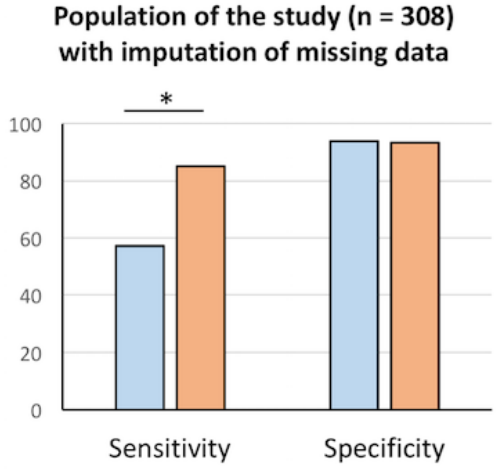
Coronary angiography (n = 63)

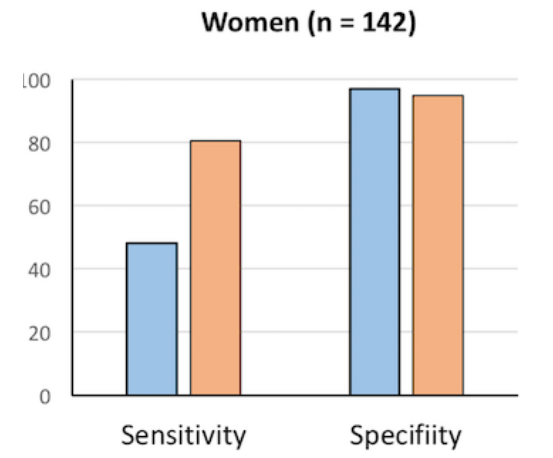
Abnormal (n = 35)
Normal (n = 28)

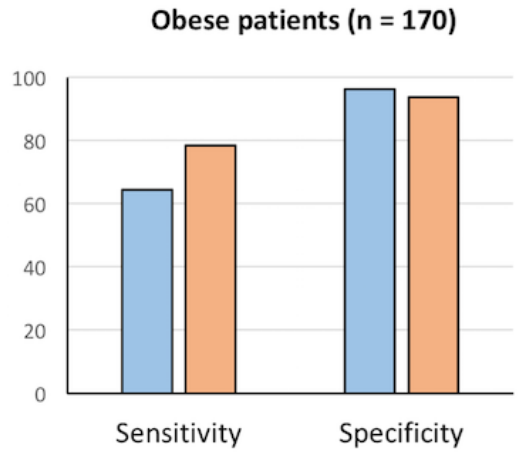
No coronary angiography
Follow-up at 1 year (n = 231)
including two patients with CV events
Lost at follow-up (n = 2)

Diagnostic performance of Tc-SPECT-MPS vs. Rb-PET-MPS









Tc-SPECT-MPS

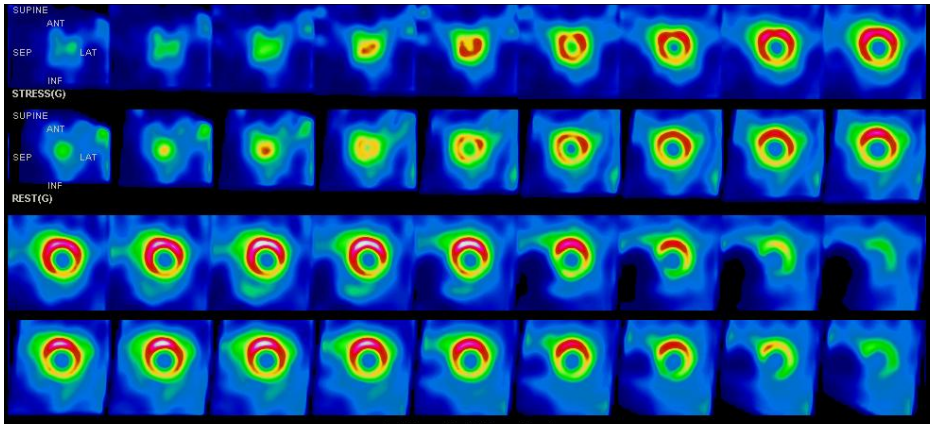
Rb-PET-MPS

	^{99m}Tc-MIBI CZT	^{82}Rb-PET-CT	
	1st analysis (n =296 patients)		
Sensitivity	55.6 %	83.3 %	p = 0.02
Specificity	95.7 %	93.4 %	p = 0.22
Acccuracy	90.8 %	92.2 %	
	2nd analysis (n =308 patients)		
Sensitivity	59.5 %	80.9 %	p = 0.04
Specificity	94.4 %	92.8 %	p = 0.46
Acccuracy	89.6 %	91.2 %	
	Women (n =142 patients)		
Sensitivity	51.8 %	77.1 %	p = 0.18-0.41
Specificity	97.3 %	94.7 %	p = 0.21-0.37
Acccuracy	93.9 %	93.4 %	
	BMI > 35 (n = 76 patients)		
Sensitivity	68.0 %	89.3 %	p = 0.32
Specificity	97.6 %	90.1 %	p = 0.06
Acccuracy	93.9 %	90.0 %	

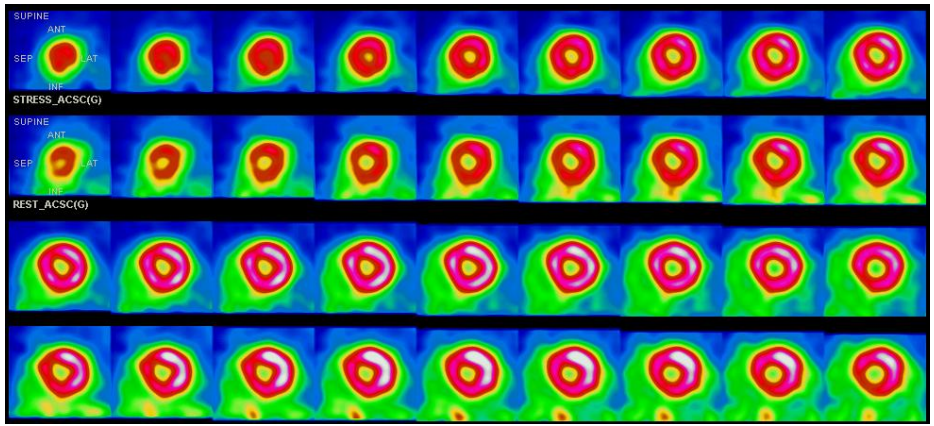
Comparison of image quality and diagnostic certainty

		^{99m}Tc-MIBI CZT	^{82}Rb-PET-CT	
Image quality	Excellent or good	80.4 %	89.6 %	p < 0.05
Diagnostic certainty	Excellent or good	80.4 %	89.6 %	p < 0.05

^{99m}Tc-MIBI CZT

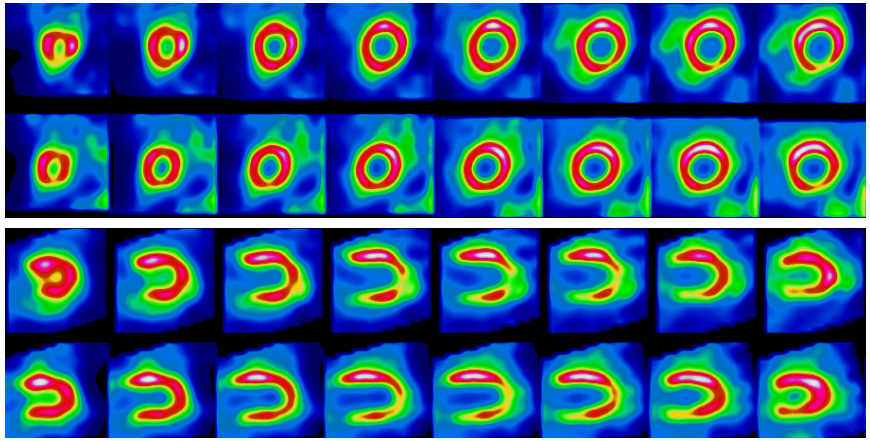


^{82}Rb-PET-CT



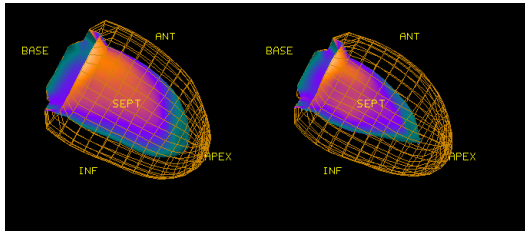
Results: detection of 3-vessel disease or equivalent

^{99m}Tc-MIBI-SPECT-MPS

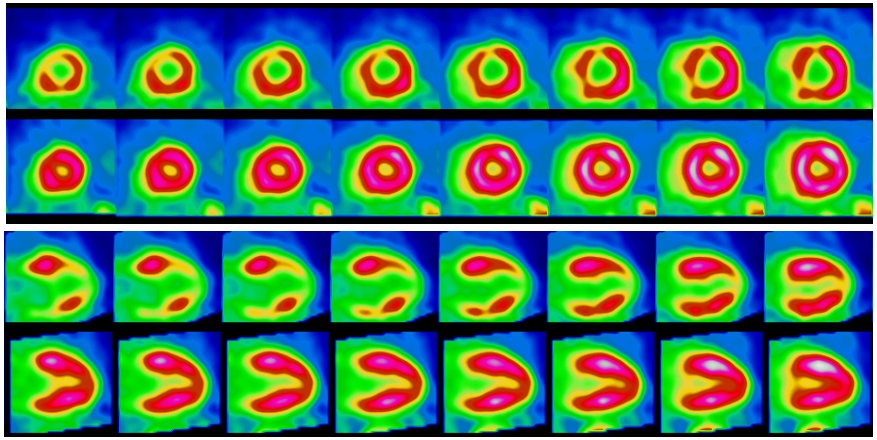


Stress EDV: 86 ml
ESV: 39 ml
LVEF: 55 %

Rest EDV: 90 ml
ESV: 37 ml
LVEF: 59 %

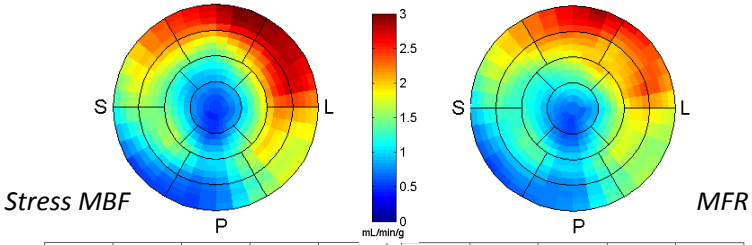


^{82}Rb-PET-MPS



Stress EDV: 136ml
ESV: 76 ml
LVEF: 44 %

Rest EDV: 102 ml
ESV: 41 ml
LVEF: 59 %



Stress MBF *MFR*

	LV	LAD	LCX	RCA
Mean	1.44	1.38	1.96	1.01
%max	53.5	51.4	73.1	37.6

	LV	LAD	LCX	RCA
Mean	1.40	1.44	1.78	0.97
%max	55.9	57.3	70.8	38.5

Results: detection of 3-vessel disease or equivalent

Diff. LVED vol. stress / rest - Tc-SPECT vs. Rb-PET

Threshold ≥ 15 ml vs. 18 ml

AUC = 0.68 vs. 0.75 Se = 44 % vs. 63 % Sp = 88 % vs. 81 %

Diff. LVEF stress / rest - Tc-SPECT vs. Rb-PET

Threshold ≤ - 2 vs. 0 %

AUC = 0.68 vs. 0.82 Se = 75 vs. 75 % Sp = 59 % vs. 83 %

Quantification of myocardial blood flow with Rb-PET

Rb-PET – global stress MBF

Threshold ≤ 1.57 ml/mn/g

AUC = 0.87 Se = 94 % Sp = 70 %

Rb-PET – global MFR

Threshold ≤ 2.0

AUC = 0.85 Se = 88 % Sp = 73 %

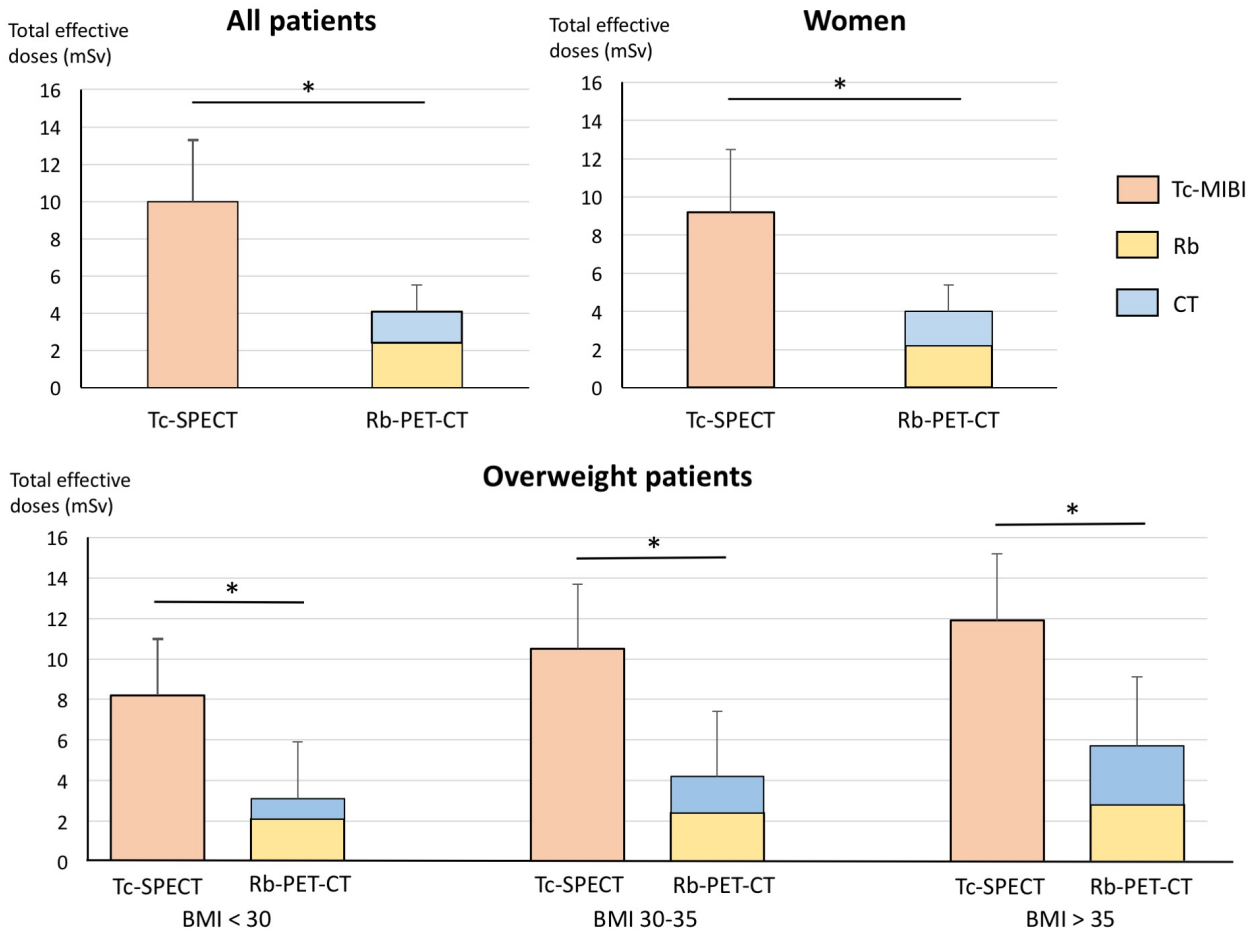
Global stress MBF ≤ 1.57 ml/mn/g + Diff.LVEF ≤ 0 %

Se = 75 % Sp = 95 % Acc. = 93 %

Global MFR ≤ 2.0 + Diff. LVEF ≤ 0 %

Se = 69 % Sp = 94 % Acc.= 93 %

Results: radiation exposure of patients with Tc-SPECT vs. Rb-PET-CT



Conclusions

✓ Rb-PET-MPS provided higher sensitivity for the detection of myocardial ischemia in comparison to Tc-SPECT-MPS thanks to :

- attenuation correction of PET acquisitions in this population of patients with important signal attenuation of SPECT.
- a more accurate detection of patients with three-vessel CAD.

✓ Radiation exposure of patients was ca. 50 % lower with Rb-PET-MPS than with Tc-SPECT-MPS.

✓ The difference in diagnostic performance between both imaging techniques were smaller than anticipated because of the lower prevalence of CAD in the population of the study and the interpretation of SPECT acquisitions by experts.

=> Rb-PET-MPS shows promise for the identification of patients with 3V-CAD.

Acknowledgements

Bichat University Hospital, Paris
Department of Nuclear Medicine
Dominique Le Guludec
Renata Chequer
Sébastien Leygnac
Milan Milliner
François Rouzet
Aziza Touati
Rana Ben Azzouna
Souad Bani

Department of Cardiology
Emmanuel Sorbets
Grégory Ducrocq
Jérémy Abtan

Department of Diabetology
Michel Marre
Ronan Roussel

Department of Clinical Research
Candice Estellat
Caroline Quintin
Toni Alafaiate

Beaujon University Hospital
Department of Nuclear Medicine
Arnaud Dieudonné
Nidaa Mikail

Pitié-Salpêtrière University Hospital
Department of Cardiology
Gilles Montalescot
Johanne Silvain

Department of Diabetology
Agnès Hartemann

Nancy University Hospital
Department of Nuclear Medicine
Pierre-Yves Marie
Wassilla Djaballah
Laetitia Imbert
Véronique Roch

This study was fully supported by the Programme de Recherche Clinique Hospitalier (PHRC) 2010 funded by the French Ministry for Research and promoted by the Département de la Recherche Clinique et de Développement (DRCD) of Assistance Publique – Hôpitaux de Paris.

Patients who accepted to participate in this study.

Diagnostic performance of Tc-SPECT-MPS and Rb-PET-MPS for the detection of balanced myocardial ischemia in patients with 3V-CAD

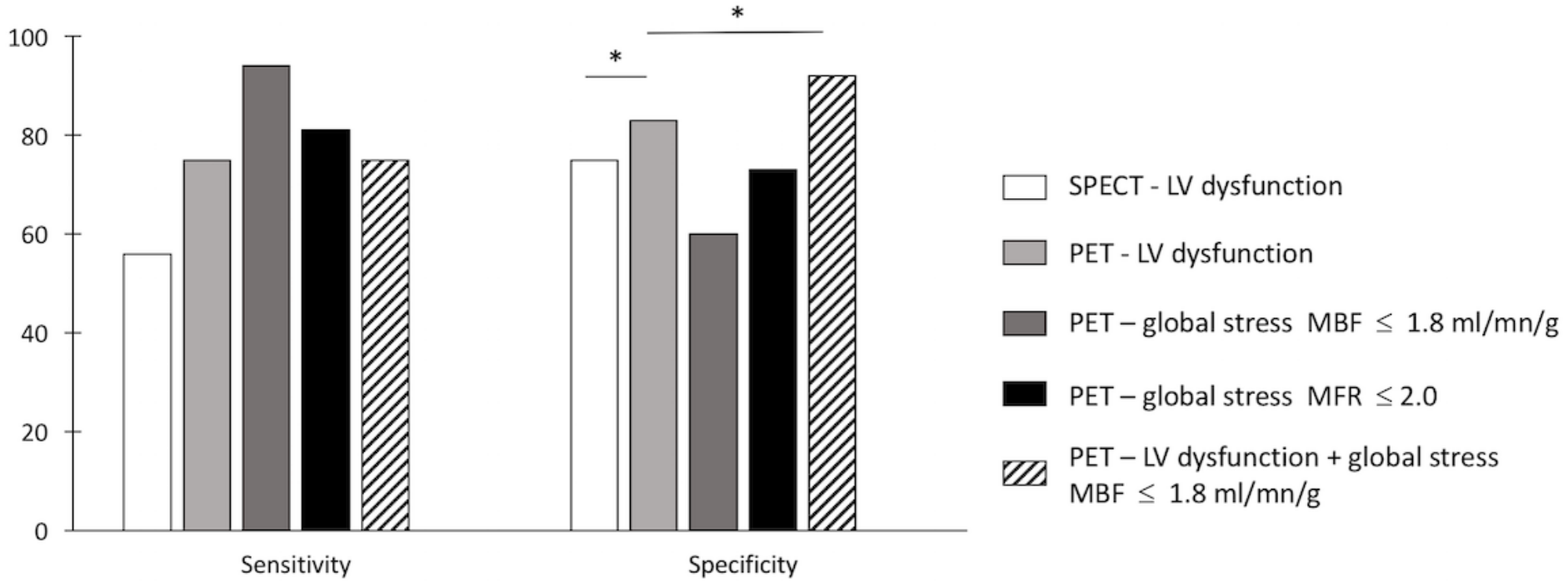


Image analysis

Analysis of MPS.

Experienced nuclear cardiologists analyzed Tc-MPS-SPECT and Rb-MPS-PET studies separately and blinded to the results of each another. Each Tc-MPS-SPECT and Rb-PET-PET was classified as positive or negative after integrating all clinical and imaging information available, including myocardial wall motion and global LV function for SPECT and PET, and flow quantification only for PET.

Stress and rest myocardial blood flow (MBF) were quantified on dynamic PET acquisitions using a one-compartment model for Rb uptake in the myocardium integrated in the FlowQuant software.

Image quality and degree of diagnostic certainty of interpretation were classified as excellent, good, fair or poor.

Study endpoint criteria

Coronary angiography. Coronary angiography was performed using standard technique within 45 days after patient inclusion. The degree of coronary stenosis was evaluated visually. FFR was measured for each coronary stenosis > 50 % with a pressure guidewire during maximal hyperemia induced by an intravenous infusion of adenosine. FFR value was measured for each stenosis along coronary arteries at the exception of critical stenosis (> 70 %) that did not allow for measurement of FFR or occlusion. At the end of the study, all coronary angiograms including FFR results were reviewed by two experienced cardiologists blinded to the results of Tc-SPECT-MPS and Rb-PET-MPS. In case of discrepancy, the angiogram was reviewed with a third cardiologist to reach consensus. Patients were classified as positive for myocardial ischemia in presence of coronary stenosis > 50% and FFR ≤ 0.8, coronary stenosis > 50 % for the left main artery, stenosis > 70 % or vessel occlusion for other vessels.

Follow-up. Patient outcome was determined one year after inclusion by a pre-scripted telephone interview and, in case of clinical events, medical records were collected to identify cardiovascular events. Medical records were reviewed by a committee formed of two cardiologists blinded to the results of imaging. Patients were classified as positive for myocardial ischemia if they had presented during the following year unexplained cardiovascular death, acute coronary syndrome or a coronary angiogram showing a significant coronary stenosis as defined per protocol.

Methods : patient selection

Patients were recruited from October 2012 to December 2014 in two centres in France (Bichat University Hospital, Paris and Nancy University Hospital, Vandoeuvres-lès-Nancy).

Patients were eligible for inclusion in the study if they met the three following conditions:
1. **patient referred for clinically indicated SPECT-MPS**.
2. adult woman, or man with body mass index (BMI) ≥ 25.
3. **pre-test intermediate prevalence of CAD** (in patients with chest pain, estimated prevalence of CAD > 30 % with the Diamond and Forrester clinical score [14] or, in absence of chest pain, presence of ≥ 3 cardiovascular risk factors).

Patients were not eligible in the study if they had known CAD or cardiomyopathy, undergone invasive coronary angiography (CA) or coronary computed tomography angiography in the past two years before inclusion, contra-indication to the injection of dipyridamole, severe renal insufficiency (plasmatic creatinine > 200 µmole.l^{-1}), life expectancy < 2 years, anticipated poor follow-up, potential pregnancy.

The French Institutional Review Board approved the study protocol (IRB number: 2012-A00552-41); all patients provided signed informed consent; the full description of the study design has been registered on clinicaltrials.gov (NCT01679886).

	3-vessel disease or equivalent (n = 13)	1- and 2-vessel disease (n = 21)	Stenosis < 50 % or absence of stenosis (n = 29)	Normal SPECT and PET, no CV event (n = 295)
Tc-SPECT-MPS				
Diff. EDV stress / rest	11 ± 14 ml	2 ± 12 ml	3 ± 15 ml	0 ± 11 ml
Diff. ESV stress / rest	10 ± 13 ml	2 ± 9 ml	4 ± 8 ml	0 ± 8 ml
LVEF stress	52 ± 11 %	58 ± 10 %	56 ± 12 %	63 ± 8 %
LVEF rest	56 ± 11 %	59 ± 8 %	58 ± 12 %	62 ± 8 %
Diff. LVEF stress / rest	- 3 ± 5%	- 1 ± 8 %	- 2 ± 6 %	1 ± 7 %
Rb-PET-MPS				
Diff. EDV stress / rest	**26 ± 19 ml**	13 ± 11 ml	10 ± 10 ml	9 ± 10 ml
Diff. ESV stress / rest	**22 ± 22 ml**	2 ±7 ml	1 ± 7 ml	- 2 ± 7 ml
LVEF stress	46 ± 13 %	59 ± 8 %	58 ± 12 %	64 ± 8%
LVEF rest	53 ± 9 %	54 ± 9 %	55 ± 12 %	57 ± 9 %
Diff. LVEF stress / rest	**- 7 ± 10 %**	4 ± 5 %	3 ± 6 %	7 ± 6 %
Global rest MBF (ml/ mn/g) corrected for workload	0.8 ± 0.2	0.8 ± 0.3	0.8 ± 0.2	0.8 ± 0.3
Global stress MBF (ml/ mn/g)	**1.1 ± 0.3**	1.5 ± 0.7	1.9 ± 0.6	2.1 ± 0.7
Global MFR value	**1.6 ± 0.4**	2.0 ± 0.6	2.6 ± 0.9	2.7 ± 0.9

Study endpoints

Coronary angiography. Coronary angiography was performed using standard technique within 45 days after patient inclusion. The degree of coronary stenosis was evaluated visually. FFR was measured for each coronary stenosis > 50 % with a pressure guidewire during maximal hyperemia induced by an intravenous infusion of adenosine.

All coronary angiograms including FFR results were reviewed by two experienced cardiologists blinded to the results of Tc-SPECT-MPS and Rb-PET-MPS. In case of discrepancy, the angiogram was reviewed with a third cardiologist to reach consensus. Patients were classified as positive for myocardial ischemia in presence of coronary stenosis > 50% and FFR ≤ 0.8, coronary stenosis > 50 % for the left main artery, stenosis > 70 % or vessel occlusion for other vessels.

Follow-up. Patient outcome was determined 1 year after inclusion by a pre-scripted telephone interview and, in case of clinical events, medical records were collected to identify CV events. Medical records were reviewed by a committee formed of two cardiologists blinded to the results of imaging. Patients were classified as positive for myocardial ischemia if they had presented during the following year unexplained CV death, ACS or a coronary angiogram showing a significant coronary stenosis as defined per protocol.

Conclusions

- ✓ In a population of women and overweight patients with high prevalence of attenuation artifacts, Tc-SPECT with CZT cameras was associated to an important heterogeneity of perfusion images that required a non-automated analysis of MPS.

- ✓ Rb-PET-MPS in association to a pharmacological stress provided higher diagnostic performance for the detection of myocardial ischemia than Tc-SPECT-MPS with CZT camera in association to optimized stress protocols.

- ✓ The precise role and the medico-economic impact of Rb-PET-MPS for the detection of myocardial ischemia in this specific population will need to be assessed in future studies including a larger number of patients.

Limitations of the study

- ✓ Patients with both normal Tc-SPECT-MPS and Rb-PET-MPS did not undergo invasive coronary angiography.

⇒ Possible under-estimation of the number of false negatives and thus over-estimation of sensitivity values for both Tc-SPECT-MPS and Rb-PET-MPS. Sensitivities were found to be lower than the ones published in former similar studies.

- ✓ The lower prevalence of myocardial ischemia observed in this study than expected did not provide adequate statistical power for the comparison of the diagnostic performance of Rb-PET-MPS and Tc-SPECT-MPS in the pre-specified sub-groups of women and overweight individuals.

- ✓ No attenuation correction of SPECT images was performed with CZT cameras.