

 **NUCLEAR PHARMACY CONFERENCE**
 Saturday, October 7 - Sunday, October 8, 2023

**F-18 FLURPIRIDAZ
 ASSESSMENT OF
 MYOCARDIAL PERFUSION-
 SPECIFIC PROCEDURES
 ACCORDING TO
 LITERATURE**

Wendy Galbraith, PharmD, FAPhA, BCNP
 Wendy-galbraith@ouhsc.edu

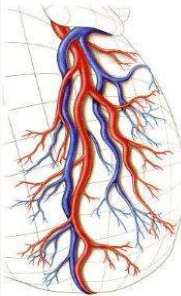
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OBJECTIVES

1. Recall the Properties of PET and SPECT MPI tracers
2. Describe the PET imaging technology used for myocardial imaging
3. Identify clinical applications for F-18 flurpiridaz

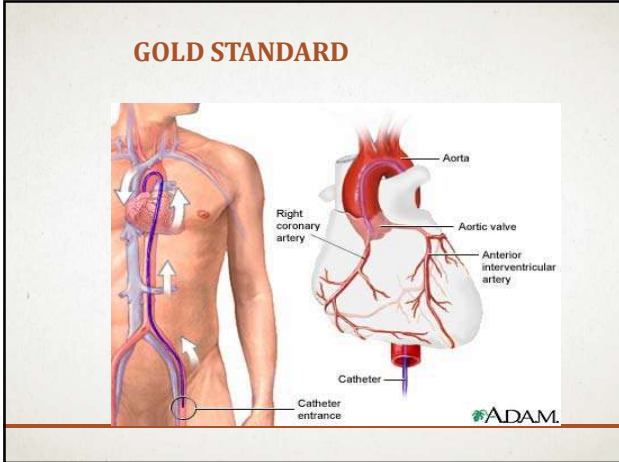
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CARDIAC IMAGING



- #1 Nuclear medicine procedure
- 1975 Tl-201 used for perfusion & viability
- 1990 Tc99m-perfusion agents
- 2005 PET agents

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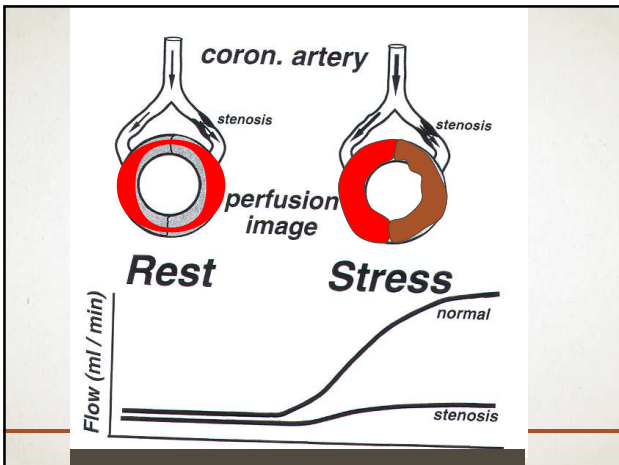


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CARDIAC CATHERITIZATION PITFALLS:

- 1) Inability to image small vessels, underestimating disease
- 2) May not distinguish hypoperfused viable myocardium vs. infarcted tissue
- 3) 6-10x more expensive than MPI study
- 4) Invasive procedure increases risk of morbidity and mortality

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ANATOMY

Base
Almond sprinkle
Vanilla Hazelnut Ice cream
Apex
www.drsvenkatesan.co.in

A
B
C

Anterior
Septum
Inferior
Lateral wall

Anterior
Apex
Inferior

Apex
Septum
Lateral wall

<https://drsvenkatesan.files.wordpress.com/2013/07/base-of-heart-apex-waht-is-the-shape-of-the-heart.jpg>
<https://thoracickey.com/nuclear-cardiology/>

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NORMAL MPI-TRADITIONAL PRESENTATION

Papandrianos, et.al. Appl. Sci. 2022, 12(15), 7592.

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PERFUSION RADIOPHARMACEUTICALS

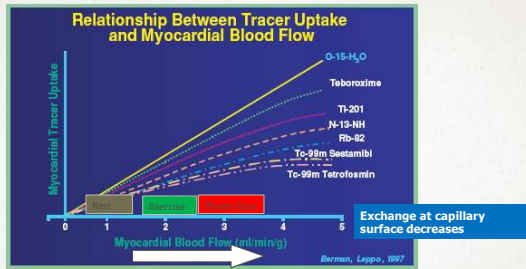
- Ideal tracer:
 - Myocardial extraction of RP is proportional to coronary artery blood flow
 - High extraction fraction
 - Negligible interference w/myocardial visualization from adjacent organs and tissue
 - No significant attenuation of the agent by tissues between the heart and the camera
 - Retained in the myocardium to allow for image acquisition
 - High photon yield detectable w/standard equipment
 - Low cost, patient safety, availability

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MYOCARDIAL IMAGING AGENTS

SPECT AGENTS	Application
Tc99m-PYP	Cardiac Amyloidosis
Tc99m RBC & Tin in kits	Blood Pool agent
Tl-201 chloride	Perfusion agent-not on market
Tc99m sestamibi	Perfusion agent
Tc99m tetrofosmin	Perfusion agent
I-123 Iobenguane	Sympathetic innervation
PET AGENTS	
Rb-82 chloride	Perfusion agent
N-13 Ammonia	Perfusion agent
F-18 FDG	Metabolism agent

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From Bateman, et al. ACC 51st Annual Scientific Session, March 17-20, 2002, Atlanta, Georgia, USA

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Property	²⁰¹ Tl	^{99m} Tc Sestamibi	^{99m} Tc Tetrofosmin
Half-life	73 hr	6 hr	6hr
Photon Energy	68-80 keV (94%)	140 keV (88%)	140 keV (88%)
Availability	Cyclotron	Generator-local	Generator-local
Chemistry	+1 Cation Hydrophilic	+1 Cation Lipophilic	+1 Cation Lipophilic
Mechanism of uptake and retention	Active Na/K ATPase Redistributes- 20 min	Passive Diffusion Fixed mitochondria associated >7 hrs	Passive Diffusion Fixed cytosol associated >6 hrs
% activity in target organ	~4%	~ 1.2%	~ 1.0%
Adm. Activity	2-4mCi (74-148MBq)	10-30mCi (370-1110MBq)	10-30mCi (370-1110MBq)
First-pass Study	No	Yes	Yes

Adapted from Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine, 4th Ed 2020, Kowalsky & Weatherman

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PET Property	⁸² Rubidium	¹³ N Ammonia	¹⁸ F DG
Half-life	75 sec	10 min	109 min
Positron avg. energy and range in tissue	1.5 MeV/ 7.1 mm*	0.4 MeV/ 1.8 mm	0.25 MeV/ 0.6 mm
Availability	Sr-82 Generator	Cyclotron-on site	Cyclotron-w/in 2 hr
Chemistry Uptake Mechanism	Rubidium cation Active Na/K ATPase Pump	Uncharged lipophilic Trapped as N-13 glutamine	Nucleophilic Sub. Facilitated Uptake
Administered Activity	50-60 mCi	10-20 mCi	0.1 mCi/kg
Critical Organ	Kidney= 1.92 rad/ 60 mCi	Bladder= 0.6 rad/ 20 mCi	Bladder=3.2 rem/ 10 mCi

*2016 Maurizio, C

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PET MYOCARDIAL IMAGING

- PET imaging has certain advantages
 - higher spatial resolution (PET 6-10 mm; SPECT 10-15 mm)
 - Improved attenuation correction-CT
 - Quantification of blood flow
 - Higher specificity
 - Higher sensitivity
 - Stress testing must be performed with Pharmacologic agents

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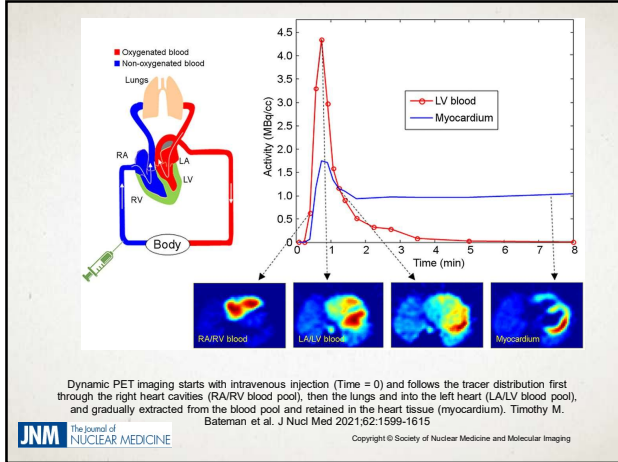



•On June 3rd 2011, an individual was stopped at the US/Canada border due to gamma ray emission sensors detecting radiation in the individual. The individual recalled he had a PET MPI, using Rb 82, in Sarasota FL, on February 17th 2011 and no other nuclear medicine studies since then.

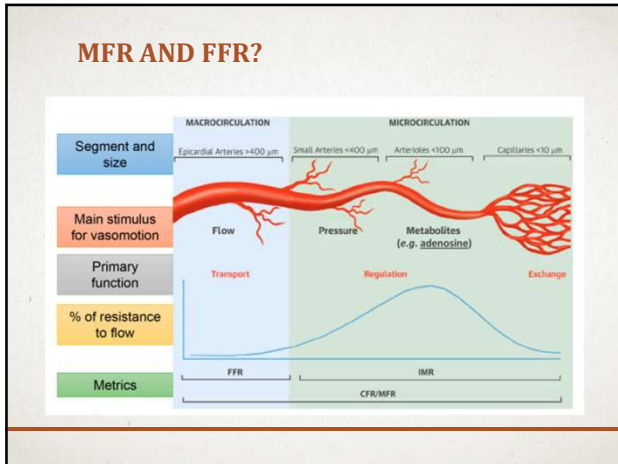
•Another individual around the same time a, was stopped at the Miami airport due to detection of radiation in the body. He too had had a PET MPI with Rb82, in Nevada, in late February 2011.

**Customs and Border Protection:
Homeland Security**

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PET RADIOPHARMACEUTICALS USED FOR MBF QUANTIFICATION

- Can be performed in PET with
 - N13 ammonia
 - Rb 82 chloride
 - O 18 water

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MYOCARDIAL BLOOD FLOW QUANTIFICATION

- Rest MBF
 - Normal coronary arteries, resting MBF is 0.8 - 1.2 mL/g/min
- Stress MBF
 - Normal flow usually increases 3-4 fold during stress
- MFR = Myocardial Flow Reserve
 - Ability of the myocardium to increase blood flow in response to stress
 - Stress MBF/Resting MBF
 - Normal is typically 3-4 (No units)

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CORONARY FLOW RESERVE (CFR) OR MYOCARDIAL FLOW RESERVE (MFR)

- The consensus is that a coronary flow reserve higher than 2 had a better recovery six months after a heart attack.
- A coronary flow reserve lower than 2 means you have a higher suspicion of flow limiting ischemia or diffuse micro-vascular disease

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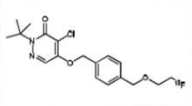
UTILITY OF MFR

- Will it ever provide enough information to routinely predict obstructive stenosis and replace MPI -NO
 - Does rule out diffuse CAD from left main and 3-vessel disease
 - Microvascular disease – present with chest pain, but a normal finding on coronary angiography and MPI
 - Risk factors that decrease CFR include Diabetes, hypertension, age, obesity
 - CAD of intermediate severity (40% to 70% occlusion) will have significant variability in MFR

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NON-FDA APPROVED PET DRUG ¹⁸F-FLURPIRIDAZ

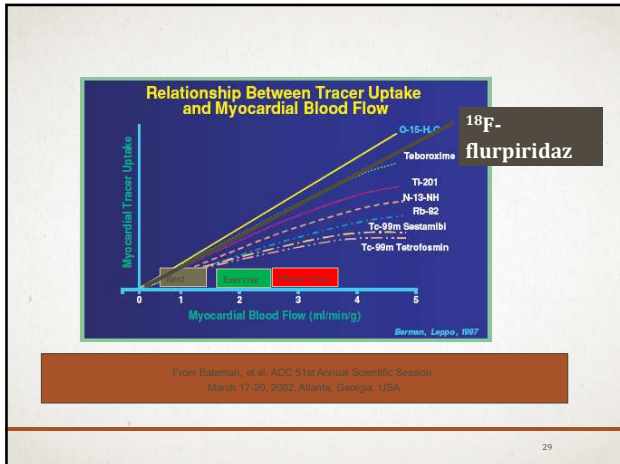
- 109-min half-life (large delivery range)
- Positron range 1.6 mm
- First-pass extraction fraction is 94%
- Structural analog of pyridaben (pesticide)
- Selectively binds to mitochondrial complex-1 (MC-1)



Yu M, et al. *J Nucl Cardiol.* 2007;14:789-98.
Bengel FM, et al. *J Am Coll Cardiol.* 2009;54:1-15.

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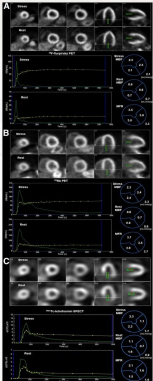
MFR COMPARISON

Y axis kBq/mL

X axis time (s)

MBF sum in mL/min/g

MFR has no units



Flurpiridaz
MFR 3.3

Rb-82 chloride
MFR 3.7

Tetrofosmin
MFR 1.9

Examples of absolute myocardial blood flow quantification. Piotr J. Slomka et al. *J Nucl Med* 2021;62:168-176

JNM The Journal of NUCLEAR MEDICINE Copyright © Society of Nuclear Medicine and Molecular Imaging

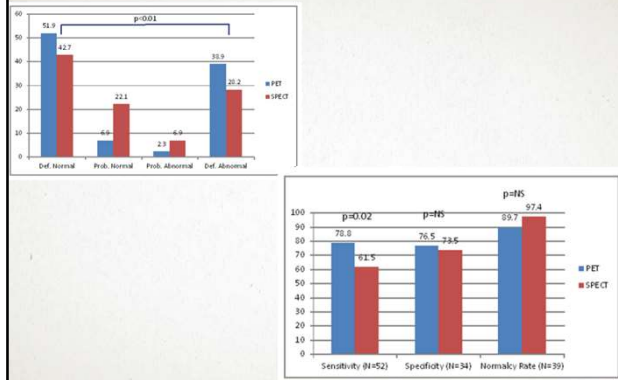
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F-18 FLURPIRIDAZ PHASE II

- Objective: Compare flurpiridaz diagnostic performance to Tc-99m mibi for image quality, interpretative certainty, defect magnitude and detection of coronary artery disease (CAD)(>50% stenosis) on invasive coronary angiography (ICA)
- 143 patients
- 21 centers
- rest-stress PET and Tc-99m SPECT-MPI
- Eighty-six patients underwent ICA
- 39 had low-likelihood of CAD
- Images were scored by three independent, blinded readers

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PHASE II RESULTS

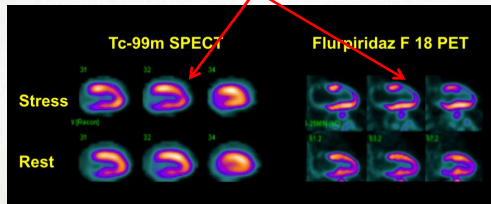


Berman, et al. J Am Coll Cardiol. 2013 January 29; 61(4): 469-477

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VERTICAL SLICE- ANTERIOR TOP / INFERIOR BOTTOM

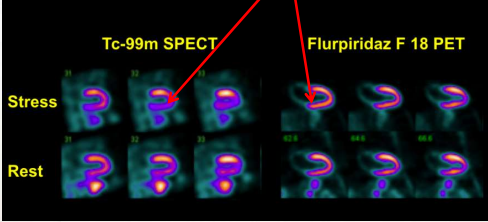
significant disease in the left anterior descending coronary artery



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VERTICAL SLICE- ANTERIOR TOP / INFERIOR BOTTOM

A false positive partially reversible inferior defect is present on the Tc-99m SPECT images due to soft-tissue attenuation. The flurpiridaz F-18 PET study, however, provided superior image quality and was normal.



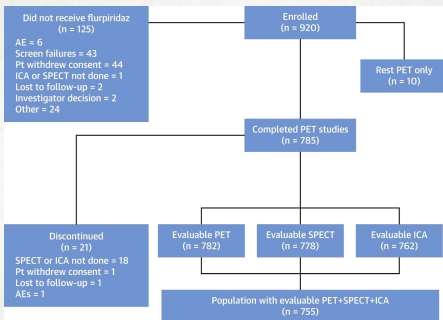
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FLURPIRIDAZ PHASE III COMPLETED 2020

- Fluorine-18 flurpiridaz is a novel positron emission tomography (PET) myocardial perfusion imaging tracer.
- This study sought to assess the diagnostic efficacy of flurpiridaz PET versus technetium-99m-labeled single photon emission computed tomography SPECT for the detection and evaluation of coronary artery disease (CAD), defined as $\geq 50\%$ stenosis by quantitative invasive coronary angiography (ICA).

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FLURPIRIDAZ PHASE III



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A PHASE 3 MULTI-CENTER STUDY OF FLURPIRIDAZ IN PATIENTS WITH CAD

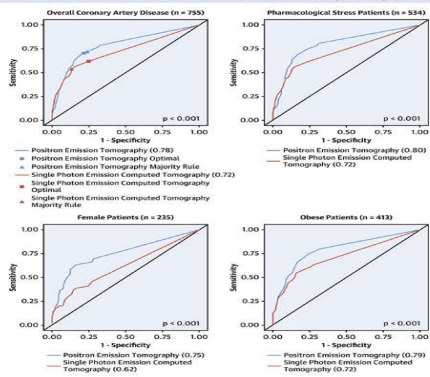
1. Overall summary of sensitivity of flurpiridaz F18 PET MPI (qualitative image quality of excellent or good) vs. SPECT MPI by majority rule vs. truth standard (angio \geq 50% stenosis and confirmed MI).

2. Overall sensitivity of flurpiridaz F18 PET MPI in coronary territories (Qualitative Diagnosis vs. SPECT MPI by majority rule vs. truth standard (angiographic stenosis greater than or equal to 50% stenosis and confirmed MI); left descending coronary artery (LAD), left circumflex artery (LCX), right coronary artery (RCA), and non - LAD).

3. Diagnostic efficacy of flurpiridaz F18 PET MPI sensitivity versus SPECT MPI sensitivity by majority rule in the detection of CAD using invasive coronary angiography as the truth standard, in subgroups: pharmacologic stress, females and BMI \geq 30.

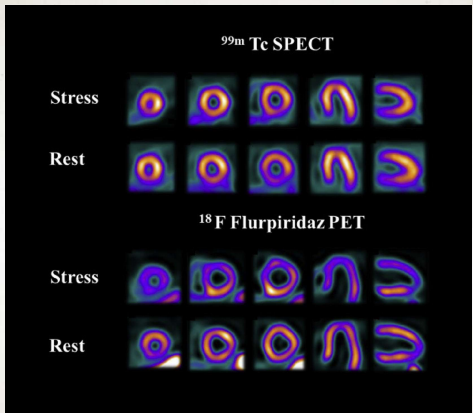
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CENTRAL ILLUSTRATION: ROC Analyses of ¹⁸F Flurpiridaz PET Versus Technetium-99m-Labeled SPECT for Detection of Coronary Artery Disease

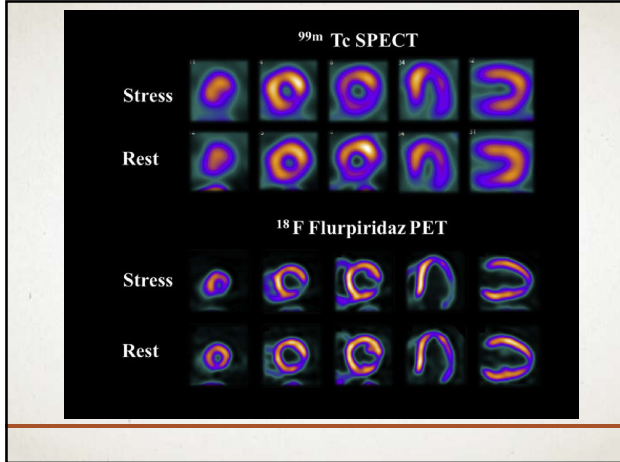


Maddahi, J. et al. J Am Coll Cardiol. 2020;76(4):391-401.

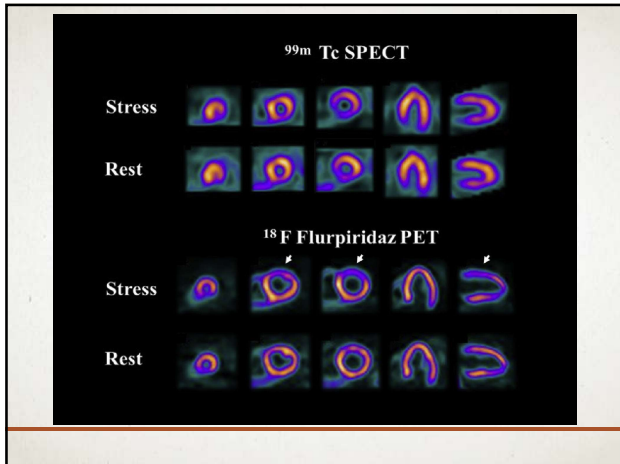
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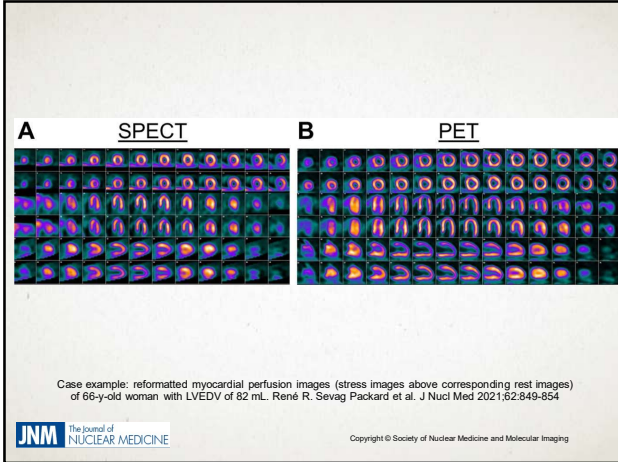


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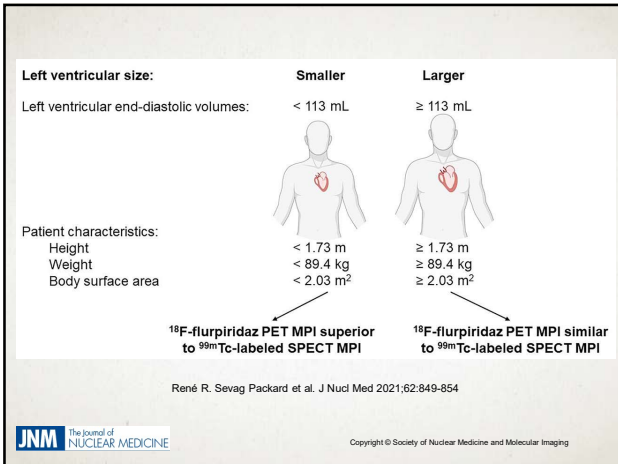
FLURPIRIDAZ PHASE III CONCLUSIONS

- Superior discrimination of CAD by flurpiridaz PET versus SPECT in the overall population, in women, obese patients, and patients undergoing pharmacological stress testing (p < 0.001 for all)
- Flurpiridaz PET was superior to SPECT for:
 - defect size (p < 0.001),
 - image quality (p < 0.001),
 - diagnostic certainty (p < 0.001),
 - radiation exposure (6.1 ± 0.4 mSv vs. 13.4 ± 3.2 mSv; p < 0.001)

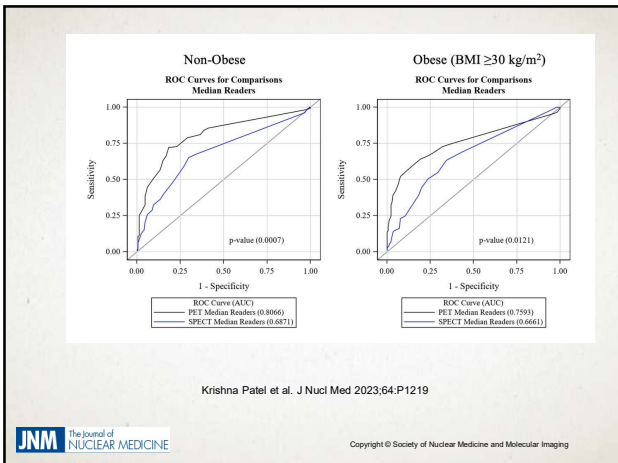
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PET QUANTIFICATION F-18 FLURPIRIDAZ PROTOCOL

- 18F-Flurpiridaz PET Segmental and Territory Myocardial Blood Flow Metrics: Incremental Value Beyond Perfusion for CAD Categorization

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FLURPIRIDAZ PET IMAGING & QUANTIFICATION PROCEDURES

- NPO 3 hours – no caffeine for 12 hours
- Two flurpiridaz PET imaging sessions REST/STRESS with Regadenoson
- Position patient supine in PET/CT scanner
- CT imaging of the chest
- PET imaging acquisition start 10 seconds prior to flurpiridaz
- Flurpiridaz 3 mCi administered intravenously as a bolus over 10 s, followed by a 5- to 10-mL saline flush.
- Dynamic list-mode data collected for 10 min
- Thereafter, the list-mode data framed into a scan sequence of 12 × 10, 4 × 30, 1 × 60, and 1 × 300 s
- Images reconstructed with iterative algorithm with no filtering (e.g. using a 2-dimensional ordered-subset; 8 subsets and 21 iterations)
- Stress study performed approximately at 30 min after the rest injection, Pharm stress agent administered with 5 mL saline flush followed by 6 mCi flurpiridaz 30 seconds after stress agent followed by a 5- to 10-mL saline flush
- Time-activity curve values measured before the stress injection are averaged and subtracted from the stress time-activity curve before the modeling analysis is performed

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OVERVIEW OF PET TRACERS

Property	⁸² Rb-chloride	¹³ N-ammonia	¹⁵ O-water	¹⁸ F-flurpiridaz
Isotope production method	Generator	Cyclotron	Cyclotron	Cyclotron
Isotope half-life (min)	1.27	10	2.0	110
Positron range (mm) RMS	2.6	0.57	1.0	0.23
Image resolution (mm) FWHM	8	5	6	5
Effective dose (mSv/Ci/kg)	1	2	1	20
Peak stress/rest* extraction (%)	35/70	95/100	100	95/100
Peak stress/rest* retention (%)	25/70	50/90	0	55/90
Spillover from adjacent organs	Stomach wall	Liver and lung	Liver	Early liver
Regulatory status	FDA-approved; 2 suppliers	FDA-approved; ANDA required for onsite production	Not FDA-approved	Phase 3 trials partially completed
Typical rest dose for 3D/2D (mCi [†])	30/45	10/15	20/30	2/3
Typical stress dose for 3D/2D (mCi [†])	30/45	10/15	20/30	6/7
Protocol features	Rapid protocol	Permits exercise [‡] ; delay of 4-5 half-lives between rest and stress unless different doses used	Rapid protocol; no tracer retention for routine MPI	Permits exercise [‡] ; different doses for rest and stress required

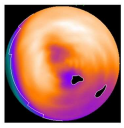
RMS root mean square (standard) deviation, FWHM full width at half maximum achievable using PET scanner with 5-mm spatial resolution. FDA Food and Drug Administration, ANDA abbreviated new drug application.
 *Peak stress = 3-4 mL/minute/g, rest = 0.75-1.0 mL/minute/g.
 † 1 mCi = 37 MBq.
 ‡ Exercise protocols do not allow quantification of MBF.

ASNC/SNMMI position statement JNucCard Jan/Feb 2018

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AI AND SPECT

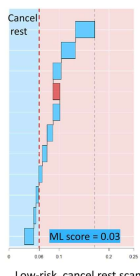
Prediction of Major Adverse Cardiovascular Events (MACE) from stress only procedure



MD-diagnosis: abnormal

Obtain rest scan

Personalized contribution of features for MACE risk



Cancel rest

ML score = 0.03

Low-risk, cancel rest scan

Age 53 y/o
 Body mass index 51
 Female
 Stress TPD 2 (8%)
 Exercise duration 9 min
 No past PCI
 Peak heart rate 144 bpm
 Weight 141 kg
 Stress TPD (4%)
 Exercise stress
 Remaining features

No Major Adverse Cardiovascular Events during 6.8 years of Follow-up

Example of explainable AI and possible implementation showing prediction of major adverse cardiovascular events (MACE) from stress-only data with machine learning (ML). Piotr J. Stomka et al. J Nucl Med 2021;62:168-176

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THANK YOU!



12 Oklahoma Sooners
(6 - 0)

34 - 30



3 Texas Longhorns
(5 - 1)

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