MYOCARDIAL PERFUSION and VIABILITY
SCINTIGRAPHIC STUDIES
NEW DEVELOPMENTS

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IMPROVE DIAGNOSIS - ADDRESS PREVENTION of CORONARY ARTERY DISEASE

1) Discuss PET (\(^{82}\text{Rb}\)) Myocardial Perfusion Scintigraphy
   • How PET (\(^{82}\text{Rb}\)) Improves and shortens the MPS study?
   • How PET (\(^{82}\text{Rb}\)) allows measurements of Coronary Flow Reserve?

2) Discuss the Coronary Microvascular Dysfunction (CMD)
   • Does it precede the development of the plaque?

3) Consider working with the Coronary Flow Reserve (CFR)
   • Can we measure CFR and decide about CMD?
   • Can we add this measurement to our current work up of patients?
The Clinical Need for Nuclear Imaging

- CLINICAL EXAMINATION and rest EKG and ECHO
- TREADMILL ECG TEST
- STRESS ECHO
- CARDIAC ANGIOGRAPHY (Catheterization or CTI)
- MRA

- Myocardial Perfusion Scintigraphy (SPECT and PET) :
  Provide Mostly Functional Information on Diagnosis/Degree/Extend and Prevention of Ischemia

- Fluoro-Deoxy-Glucose (FDG) PET
  Provides information on myocardial viability
SPECT/PET studies Approved for Clinical Use

• FUNCTIONAL IMAGING of CORONARY ARTERY DISEASE

• MYOCARDIAL ISCHEMIA: POST-STENOSIS PERFUSION
  [(SPECT)\(^{201}\text{Thallium/}^{99}\text{Tc-Agents} / (PET) \(^{82}\text{Rubidium}]

• ACUTE MYOCARDIAL INFARCTION
  [(SPECT) \(^{99}\text{Tc-Agents/}^{123}\text{I-FFA}]

• CORONARY FLOW RESERVE: PRE-STENOSIS PERFUSION
  [(PET) \(^{82}\text{Rubidium}]

• MYOCARDIAL VIABILITY
  [(SPECT)\(^{201}\text{Thallium/ (PET) }^{18}\text{F-Deoxy-Glucose}]

We don’t use \(^{82}\text{Rb at UM / JMHC}
Clinical utilization of SPECT myocardial perfusion

- Diagnosis of clinically significant CAD (ischemia) in (a)symptomatic patients
- Preoperative screening for CAD
- Acute chest pain
- Prognosis before or after MI
- Follow up disease or therapy

We offer only SPECT with $^{201}$TI and $^{99m}$Tc-MP agents at UM / JMHC
Three decades of experience in SPECT myocardial perfusion scintigraphy

Based on our experience and thousands of publications

The Tests is Considered

Safe
Accurate
Cost Effective
ONE DAY REST-STRESS Tc-SESTAMIBI
(8mCi-24mCi)
COMPARISON WITH ANGIOGRAPHY

NUMBER OF PATIENTS 108
SENSITIVITY 94%
SPECIFICITY 96%

TN = 72, TP = 31, FN = 2, FP = 3

POSITIVE PREDICTIVE VALUE 91%
NEGATIVE PREDICTIVE VALUE 97%
ACCURACY 95%

First evaluation of our studies
REST THALLIUM AND STRESS Tc-SESTAMIBI
(3mCi and 30mCi)
COMPARISON WITH ANGIOGRAPHY

NUMBER OF PATIENTS 72
SENSITIVITY 90%
SPECIFICITY 97%

TN = 32, TP = 32, FN = 04, FP = 01

POSITIVE PREDICTIVE VALUE 97%
NEGATIVE PREDICTIVE VALUE 88%
ACCURACY 93%

Second evaluation of our studies
DESPITE THE RELATIVE SUCCESS OF SPECT-MPS
THERE IS A NEED TO IMPROVE THE DIAGNOSTIC ACCURACY OF THE MPS STUDIES

As the standards of practice have improved
the quality of SPECT studies is not any more
sufficient or satisfactory

Most of our patients are now borderline cases
and both the PPV and the NPV
need upgrading
Problems with SPECT Myocardial Perfusion Scintigraphy

• No information about STRESS EF and STRESS wall motion

• Attenuation artifacts by breast (women) and diaphragm (men)

• Interference by liver, gall bladder and bowel activity

• Relatively limited resolution

• Time: Very long studies for the patient (3-4 hours+)
A 54 yo well fed lady complains of chest pain during exercise
An Adenosine Tl/MIBI study is presented to you:
RECENT CLINICAL EXAMPLE of Attenuation Artifacts with supine SPECT MPS

In about 50% of our population (ladies overweighed) breast attenuation exists

Is it real or attenuation induced?

What are we supposed to do?

A PRONE STUDY!!
Recent clinical example of attenuation artifacts with prone SPECT MPS

Studies repeated in **prone position**, but even that cannot resolve the issue.

Is it real or attenuation induced?
HOW WE CAN IMPROVE
THE DIAGNOSTIC ACCURACY OF MPS?

There is a proven answer:

BY INTRODUCING RUBIDIUM-82 PET-MPS
PREVENTION

SPECT studies do not address Prevention
“Regular Life”

1. CLINICAL SUSPICION OF CAD
   (Patient Symptoms / Age / Predisposing Factors)

2. NON-INVASIVE TESTING (SPECT)
   a) POSITIVE               b) NEGATIVE
      (Ischemia?)

3. ANGIOGRAPHY
   a) POSITIVE               b) NEGATIVE
      (Stenosis/Obstruction)

4. ANGIOPLASTY
   STENT/Surgery

Prevention of Deterioration of the Disease

- CHANGE LIFE STYLE
- DIET/EXERCISE
- MEDICAL THERAPY
CURRENT CLINICAL PRACTICE
Is focused on
CORONARY ARTERY OBSTRUCTION
CHRONIC OR ACUTE

Plaque

Thrombus
CURRENT CLINICAL PRACTICE
Is focused on
MANIFESTATIONS OF CAD: STENOSIS

RELATION OF CORONARY FLOW TO DEGREE OF STENOSIS

OUR CURRENT PRACTICE

is focused on the

TREATMENT OF THE DISEASE

BUT WHAT ABOUT PREVENTION (?)

Remember Hippocrates:

“(a disease) has a natural cause….It is also curable….”

“…Protecting and Developing Health must rank even above that of Restoring it”.
PREVENTION MEANS CHANGES IN LIFE STYLE

However, there are Objections to change “Regular Life”

“I like breakfast best, ’cause there’s nothing green on my plate.”

Unless there is a “real threat”, nobody wants to change the “Regular Life”
MEDICAL PROGRESS

Coronary Microvascular Dysfunction

Paolo G. Camici, M.D., and Filippo Crea, M.D.
Etiology: The Genes determine CMD but other factors play also role

Pathology: Role for Sympathetic System
### CORONARY MICROVASCULAR DYSFUNCTION

<table>
<thead>
<tr>
<th>Conduit Arteries (diameter &gt; 500 μm)</th>
<th>Prearterioles (diameter 500–100 μm)</th>
<th>Arterioles (diameter &lt;100 μm)</th>
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</thead>
<tbody>
<tr>
<td>Drop in pressure from aorta to capillaries</td>
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<td>Response to flow-dependent dilatation</td>
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<td>Response to changes in intravascular pressure</td>
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<td>Response to metabolites</td>
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**Coronary Microvascular Dysfunction**
WE CAN STUDY THE

CORONARY MICROVASCULAR DYSFUNCTION

BY MEASURING THE

CORONARY FLOW RESERVE (CFR)

“CFR is the magnitude of the increase in coronary flow going from basal coronary perfusion to maximal vasodilatation”
Coronary Flow Reserve and Severity of Stenosis

Fig. 4.9 Relation between myocardial blood flow and coronary vasodilator reserve, and coronary stenoses severity on quantitative coronary angiography. (Figure reproduced with permission from: Reference 18, Campisi R.)

Coronary Flow Reserve in Dyslipidemias and Diabetics

Fig. 4.7 Bar graph illustrating average coronary flow reserve as determined by PET in patients with dyslipidemia (left) and diabetes (right) without clinically overt CAD. (Figure reproduced with permission from: Reference 18, Campisi R, Di Carli MF. Assessment of coronary flow reserve and microcirculation: A clinical perspective. J Nucl Cardiol 2004; 11: 3–11.)
A NEW THEORY IS EMERGING

“Microvascular Disease leads to Obstruction”

Microvascular Disease  Plaque  Thrombus
A NEW THEORY IS EMERGING

Microvascular Dysfunction → Obstruction (partial/total)

REduced Coronary Flow Reserve

No Stenosis

FUTURE CLINICAL PRACTICE

"Regular Life" → Preventing Factors or Clinical suspicion of CAD

82Rb PET-MPS: (Microvascular Dysfunction or Ischemia)

Positive: Prevention of Stenosis
- Change Life Style
- Diet/Exercise
- Medical Therapy

Negative: Prevention of Deterioration
- Angiography
  a) Stenosis
  b) M/V Dysfunction (No Stenosis)

Return to Regular Life
CAN WE MEASURE CORONARY BLOOD FLOW RESERVE?

YES! with PET/MPS!

Myocardial Perfusion with Positron Emission Tomography

using either $^{13}$NH$_3$ (if we have a cyclotron on site) or

$^{82}$Rubidium (we can buy a generator)

We can perform PET MPS

Quantitate the Coronary Blood Flow at Rest
and after Adenosine induced Vasodilatation

Then calculate the Cor. Flow Reserve and
make the diagnosis of Cor. Microvascular Dysfunction
HOW CAN WE IMPROVE
DIAGNOSTIC ACCURACY OF MPS?

BY INTRODUCING RUBIDIUM-82 PET-MPS

HOW WE CAN MEASURE
CORONARY BLOOD FLOW RESERVE?

BY USING RUBIDIUM-82 PET-MPS
Rb-82 PET-Myocardial Perfusion Scintigraphy provides a nearly ideal evaluation of the CORONARY ISCHEMIA DUE TO OBSTRUCTION and, in addition, allows the study of the CORONARY BLOOD FLOW RESERVE.
PET MPS with 82-Rubidium
Clinical Experience

• Has higher accuracy than the SPECT studies

• Provides perfusion and EF both at rest and stress

• With PET/CT corrects for body attenuation artifacts

• The total rest/stress study is completed in 30min

• $^{82}$Rb has a very short half life 75sec (very low radiation)

• It can measure Coronary Flow Reserve!

• It is approved and reimbursed for evaluation of CAD
PET MPS with 82-Rubidium
Technical Issues

- Requires PET/CT facilities
- $^{82}$Rubidium is produced by a generator (commercially available)
- It is performed only as a pharmacologic rest/stress study
- Patient is injected with Adenosine inside the PET/CT camera

therefore the cardiologist or a nurse practitioner needs to be there
Is PET MPS with Rb-82 a new method?

What prompted our interest now?
Rb-82 Users

- Memorial Hospital-Jacksonville
- Crawford Long-Atlanta
- Emory Clinic-Atlanta
- Cleveland Clinic-Cleveland (We visited)
- Montefiore, NY (We visited)
- Mt. Sinai, NY
- Mayo Clinic, Rochester
- Cedars-Sinai, Los Angelos
- Hartford Hospital, Hartford Ct
- Baptist, Nashville
- U of Tennessee
- Yale university
- U of California, SF
Recent Rb-82 Users

- U of Texas
- Johns Hopkins
- University of Maryland
- Mid-America Cardiology
- Buffalo Cardiology
- CardioVascular Assoc-Birmingham
- The Heart Center-Huntsville, AL

Coming on Board

- MUSC
- Shands-Jacksonville
- Oklahoma Heart Center
- University of Miami
We have now our PET/CT Systems (the most efficient) at UMHC and at DFB (promised also at JMH)

so we can offer PET MPS with Rb-82
CardioGen-82® (Rubidium Rb 82 Generator)

**STRONTIUM-82**
- 25 days
- $\varepsilon$ (electron capture)

**RUBIDIUM-82**
- 75 sec
- $e^+$ (positrons)

**KRYPTON-82**
- (monthly replacement)
- Recharge time 10 min
CardioGen-82 (the commercial $^{82}$Rb Generator)

- THE GENERATOR (monthly replacement)
  Recharge time 10 min

- THE INFUSION SYSTEM

- We can buy two generators for our facilities or one and transfer it back and forth if needed
Rubidium $^{82}$Rb PET-Myocardial Perfusion Scintigraphy

The Infusion System

Inject NS

RUBIDIUM-82

PATIENT INFUSION

Inject NS

IMAGING

Rest
LVEF 61%

Adenosine

Peak Stress
LVEF 50%

75 sec $e^+$ (positrons)

Decay
CARDIOVASCULAR SCINTIGRAPHY

What we are offering now and what we can offer *with Rb-82*
CELLULAR RETENTION
Rubidium: Potassium Analogue

SPECT-PET
MOLECULAR LEVEL

Rubidium Tetrofosmin

Thallium
Sestamibi
Teboroxine

Rubidium

Pump

Mitochondria

Na\(^+\)-K\(^+\) ATPase

Nucleus
Blood supply by a stenotic artery at Rest may suffice. We must apply Stress to increase the need and elicit Ischemia. Or dilate the normal vessels (adenosine) which generates the DEFECT.
METHODS OF STRESS TESTING

SPECT-PET

- Physical Exercise *(only SPECT)*
  - Treadmill/Bicycle

- Pharmacologic Stress *(SPECT or PET)*
  - Vasodilators: Adenosine, Dipyridamole
  - Catecholamines: Dobutamine
THE SPECT EXPERIENCE

TYPICAL STUDIES OF SPECT MPS
SPECT PROTOCOL FOR SPECT MPS
(MIXED PROTOCOL)

INJECTION AND ACQUISITION PROTOCOL

**TI-201**
3.0 mCi

**Tc-MYOVIEW or Tc-SESTAMIBI**
25 mCi

30min    20-30min          ? 20min            ?(>1 hour)       20-30 min

Duration of protocol: 3-4 hours+

REST STUDY
201Tl (3-4 mCi) injection at rest; imaging at 30 min (4hr,24hr)

STRESS STUDY
99mTc-Agents (20-30 mCi) injection at peak stress; imaging at 30min-1hr
A patient has a SPECT MPS because of angina pectoris
SPECT STUDIES

ISCHEMIA IN THE DISTRIBUTION OF THE LAD

a severe reversible defect

Rest EF = 50%
• A patient has a SPECT MPS because of angina pectoris
SPECT STUDIES

ISCHEMIA IN THE DISTRIBUTION OF THE RCA

a mild reversible defect

Rest EF=55%

REST Volumes and WM WNL
Studies need repeat in **prone position**, but even that cannot resolve the issue.

**Is it real or attenuation induced?**
QUANTIFICATION OF MPS

a) **Function:** at Rest: WM, Volumes, EF (global and regional)
b) **Severity** of ischemia: mild, moderate, severe
c) **Extend** of ischemia: percent of total wall found ischemic
d) **Vessel(s)** involved: Single, Two, Multiple, LAD/LCx/RCA
SPECT

EDGE DETECTION, LVEF, EDV, ESV

ONLY AT REST

LVEF = 58%

Germano et al 1995
QUANTIFICATION OF EXTENT OF CAD

SPECT

SHORT AXIS

Apical
Mid-Ventricular
Basal

VERTICAL LONG AXIS

1 2 3 4 5 6
7 8 9 10 11
12 13 14 15 16
17 18 19 20
EXTEND OF ISCHEMIA AFFECTS PROGNOSIS
THE SEVERITY OF HYPOPERFUSION ON REST / STRESS MYOCARDIAL SCINTIGRAPHY IS A PREDICTOR OF CARDIAC EVENTS

5000 pts with SPECT studies followed 642 +/- 226 days

Event rate (% per year)

- Normal scan (N = 2946)
  - Cardiac Death: 0.3
  - Myocardial Infarction: 0.5

- Mildly abnormal scan (N = 884)
  - Cardiac Death: 0.8
  - Myocardial Infarction: 2.7**

- Moderately abnormal scan (N = 455)
  - Cardiac Death: 2.3
  - Myocardial Infarction: 2.8

- Severely abnormal scan (N = 898)
  - Cardiac Death: 2.8*
  - Myocardial Infarction: 4.2*

# Interpretation of Myocardial Perfusion Scintigraphy

<table>
<thead>
<tr>
<th>Rest Study</th>
<th>Stress Study</th>
<th>Conclusion</th>
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THE PET EXPERIENCE
AT OTHER CENTERS

TYPICAL STUDIES OF PET $^{82}\text{Rb}$ MPS
**82Rb PET/CT Protocol**

- **Rb-82** 50-60 mCi
- **Adenosine**
- **Duration of protocol 20-30 minutes**

**Time of Recharging the Generator** 10 min
Case # 1  Normal Rb-82 MPS

PET

TID Ratio 0.96
PET

Case # 1  Normal Rb-82 MPS

PEAK STRESS
LVEF 76%

REST
LVEF 67%
• A patient with angina pectoris is evaluated
Case # 2  Abnormal Rb-82 MPS

Reversible defect in AS wall
Case # 2  Abnormal Rb-82 MPS

PEAK STRESS
LVEF 58%

REST
LVEF 68%
• A patient with angina pectoris is evaluated
Case # 3

- The apical portion of the left ventricle is relatively underperfused in the peak stress images.

- Much larger left ventricular cavity at peak stress.

- The TID ratio was 1.63.
**PET**

*Case # 3*

**PEAK STRESS**
LVEF 50%

**REST**
LVEF 61%

Courtesy of Mid-America Heart Institute
QUANTIFICATION OF MPS

a) **Function:** Rest and Stress: WM, Volumes, EF (Glob/Reg)
b) **Severity** of ischemia: mild, moderate, severe
c) **Extend** of ischemia: percent of total wall found ischemic
d) **Vessel(s)** involved: Single, Two, Multiple, LAD/LCx/RCA
QUANTIFICATION OF EXTENT OF CAD

PET
## PET

**INTERPRETATION OF MYOCARDIAL PERFUSION SCINTIGRAPHY**

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**PET**

**Coronary Flow Reserve and Severity of Stenosis**

![Graph showing myocardial blood flow at rest and stress](image)

**Fig. 4.9** Relation between myocardial blood flow and coronary vasodilator reserve, and coronary stenoses severity on quantitative coronary angiography. (Figure reproduced with permission from: Reference 18, Campisi R.

PET vs. SPECT: An MPI Case Review

Attenuation Correction
• A patient with angina pectoris is evaluated
Case # 4  SPECT MPI Images (questionable)
<table>
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<tr>
<th></th>
<th>PET</th>
<th>SPECT with AC</th>
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<tbody>
<tr>
<td><strong>Overall Accuracy</strong></td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Individual Vessels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>90%</td>
<td>76%</td>
</tr>
<tr>
<td>LCx</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>RCA</td>
<td>90%</td>
<td>77%</td>
</tr>
<tr>
<td><strong>All Coronaries</strong></td>
<td>88%</td>
<td>77%</td>
</tr>
<tr>
<td><strong>Image Quality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>80%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>No Artifacts</strong></td>
<td>90%</td>
<td>50%</td>
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</table>

- TM Bateman, GV Heller, AI McGhie, JD Friedman, SJ Cullom, JA Case. Mid-America Heart Institute. 2005
Advantages of PET MPS

• Improved efficiency and throughput time\textsuperscript{2,7}
• Lower radiation exposure (Rubidium very short T1/2)\textsuperscript{1,2}
• Fewer attenuation artifacts (CT attenuation correction)\textsuperscript{1,2}
• Improved resolution and quality of study\textsuperscript{2,7}
• Provides EF and WM at rest and stress

Technical Issues with PET MPS

• Only pharmacologic stress test can be done and not exercise test
• Patients must be placed within the PET camera first and then injected with stress agents (dipyridamole and adenosine) and with Rubidium (or Ammonia)
PET MPI provides better Image Quality than SPECT MPI\textsuperscript{1,12,16}

\begin{figure}
\centering
\includegraphics{image.png}
\caption{Image quality scores for PET and SPECT perfusion and ECG-gated scans.}
\end{figure}

Pharmacologic Stress MPI Patients\textsuperscript{1,15}

A recent study by Tim Bateman, MD, Gary Heller, MD, PhD and colleagues concluded,

“Our investigation provides evidence that for patients who require pharmacologic stress, \textit{PET imaging may be preferable to SPECT}.”

Potential Application of PET: Coronary Flow Reserve

- Patient history:
  Multiple risk factors for CAD
  Mild chest pain
- Scan interpretation:
  Minimal apical and infero-lateral ischemia
  Patient’s CFR 1.3 indicating severe diffuse disease
  (Normal CFR >2.0)
PET MPS with 82-Rubidium

The Challenge

45 yo Male
Asymptomatic
Evaluated For Prevention

Coronary Flow Reserve

no Stenosis <50% 50-70% 70-90% >90%

Stenosis Severity

0 0.5 1 1.5 2 2.5
A NEW THEORY IS EMERGING

“Microvascular Disease leads to Obstruction”

He is here
What do you recommend?

Microvascular Disease  Plaque  Thrombus
PET MPS with 82-Rubidium
Clinical Experience

• Has higher accuracy than the SPECT studies

• Provides perfusion and EF both at rest and stress

• With PET/CT corrects for body attenuation artifacts

• The total rest/stress study is completed in 30min

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• It can measure Coronary Flow Reserve!

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PET MPS with 82-Rubidium
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• Requires PET/CT facilities

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<td>13. CardioGen-82 package insert.</td>
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The MYOCARDIAL VIABILITY issue

Scar vs. Hibernation

Clinical significance of viability studies

The Benefit of the Positron Emission Tomography with $^{18}$ Fluoro-Deoxy-Glucose
### PET-FDG

#### THE VIABILITY ISSUE

**SCAR v/s HIBERNATING MYOCARDIUM**

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A 45 yo lady with atypical chest pain has an exercise and rest MPS
PERFUSION: ANTERIOR WALL FIXED DEFECT

= Scar or Hibernation

Anterior Wall  Severe Unchanged (Fixed) Defect
A 55 yo man with typical chest pain has an exercise and rest MPS
MPS: NO ISCHEMIA; FIXED SEVERE DEFECT: SCAR v/s HIBERNATING MYOCARDIUM

STRESS MIBI

REST THALLIUM

Anterior Wall Severe Unchanged (Fixed) Defect
**PET-FDG**

**MYOCARDIAL VIABILITY POST (OR PRE) MI:**

If Perfusion shows a fixed (rest + stress) defect then do

18F-DEOXY-GLUCOSE (FDG)-PET Study results:

a) No Defect on FDG = MISMATCH
   = HIBERNATING myocardium: Angioplasty

b) Same Defect on FDG = MATCH
   = Myocardial INFARCTION: Medical Therapy
A 63 yo patient with a history of heart attack and an inconclusive EKG had MPS and FDG/PET study
FDG PET FOR MYOCARDIAL VIABILITY
PERFUSION/METABOLISM MATCH = SCAR

Inferolateral Wall  Severe Matching Defect on MPS and FDG

MEDICAL THERAPY INDICATED
Compare Perfusion with Viability
FDG-PET FOR MYOCARDIAL VIABILITY

**PERFUSION/METABOLISM MISMATCH =**

**= VIABLE HIBERNATING MYOCARDIUM**

Anteroseptal Wall  Severe Defect on MPS but viable (Mismatching) on FDG

REST THALLIUM

FDG PET

Short axis slices from the apex (left) to the base of the heart

REVASCULARIZATION INDICATED
PERFUSION / $^{18}$FDG MISMATCH ES UNDERLINE THE NEED FOR REVASCULARIZATION

- Among 43 patients with Mismatch in Perfusion/FDG, 26 who were revascularized showed increased survival as compared to those (17/43) with medical therapy.
- Among 70 patients with No-Mismatch in Perfusion/FDG, there was no difference in survival between 17 patients who were revascularized and 53 treated medically.

DiCarli AJC 1994
Please explain to us what we see in the next picture and what lessons we learn from it.
PERFUSION/\(^{18}\)FDG MISMATCHES UNDERLINE THE NEED FOR REVASCULARIZATION

In Mismatch, Revascularization Increases Survival

DiCarli AJC 1994
MYOCARDIAL PERFUSION and VIABILITY
SCINTIGRAPHIC STUDIES
NEW DEVELOPMENTS

George N. Sfakianakis MD
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Director, Division of Nuclear Medicine,
University of Miami, Florida