Present & Future SPECT tracers. 
Thallium in the era of Tc-99m Shortage

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No more alone
What should we measure from contrast ECHO?

(digital and two dimensional)

**ACUTE**

- infarct size --> hypoperfusion accurately measured
- viability --> in progress

**CHRONIC**

- stress ischemia --> + sensitivity (need for?)
- prognosis --> demonstrated in small groups
The MRI standards:
Volume, thickness, wall motion & mass
What should we measure from CMRI?
(digital and tridimensional)

ACUTE
• infarct size --> measurable
• viability --> standard

CHRONIC
• stress ischemia --> early in the development
• prognosis --> indirect (volume, EF..)
"The strengths of Nuclear Cardiology"

- Intrinsically 3D
- Real measure of perfusion
  (pts die for IHD not for CAD)
- Easy quantitation
- Simultaneous evaluation of perfusion and LV function
A potential winner, if:

able to provide the best team and the best technology!
The ischemic Cascade

- Chest pain
- Global dysfunction
- Wall motion abnormality
- Perfusion heterogeneity

Stress time

O2 Demand
A potential winner requires:

- Reliable equipments & technology
- Reliable processing software for SPECT and Gated-SPECT
- Optimal tracers
- Clinical skill
Tc99m-labelled radiopharmaceuticals

Sestamibi

$R = -(CH_2OCH_3)_3$

Tetrofosmin

BATO complex

NOET
Uptake mechanisms:

- **201TI**:
  - passive diffusion through cell membrane (partially)
  - Na/K ATP dipendent pump (partially)

- **99mTc-Sestamibi**
  - passive diffusion through cell membrane
  - Bound to mitochondrial fractions

- **99mTc-Tetrofosmin**
  - passive diffusion through cell membrane
  - Bound to cytosol
Characteristics of tracers which can interfere with the reliability of a perfusion study

1. The uptake curve
2. Uptake mechanism
3. The energy (and, consequently, the resolution)
4. The in vitro and in vivo stability
Implications of non-linear uptake curves

1. **Intercept above zero**
   - Overestimation of reduced flow
   - Reduced defect contrast
   - Overestimation of viability

2. **Reduced slope of linear portion**
   - Reduced extraction and hence low counts

3. **Early plateau**
   - Underestimation of high flow
   - Reduced defect contrast
Cardiolite Tetrofosmin Thallium

Normalised perfusion

Cardiolite $y = 0.71x + 0.31$
Tf $y = 0.71x + 0.28$
Ff $y = 0.69x + 0.31$
NOET $y = 0.76x + 0.25$

31 open chest dogs, coronary occlusion + dipyridamole hyperaemia
16 dogs, adenosine, ex vivo, microsphere

pig
microspheres
dipyridamole
Tracer Characteristics:

<table>
<thead>
<tr>
<th></th>
<th>Thal</th>
<th>Tebor</th>
<th>MIBI</th>
<th>Tetrof</th>
<th>Furif</th>
<th>NOET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraction (max)</td>
<td>0.80</td>
<td>0.89</td>
<td>0.39</td>
<td>0.30</td>
<td>0.26</td>
<td>0.48</td>
</tr>
<tr>
<td>Extraction (5 min)</td>
<td>0.60</td>
<td>0.71</td>
<td>0.41</td>
<td>0.30</td>
<td>0.12</td>
<td>0.24</td>
</tr>
<tr>
<td>Cell injury reduces uptake</td>
<td>++++</td>
<td>+/-</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Myocardial clearance</td>
<td>mod</td>
<td>rapid</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>mod</td>
</tr>
<tr>
<td>Redistribution</td>
<td>yes</td>
<td>yes</td>
<td>minimal</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Measure hyperaemic flow</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

*After Leppo JA*
• No better tracers available
• Optimize the use of what we have........
73 yr old male
weight: 69Kg
heiht: 160cm

(1970) Previous inferior MI
Hypertension
Dislipidemia
Overweight
Rest EKG
Previous inferior MI
Stress EKG (maximal bicycle exercise)
Positive for inducible ischaemia
Stress-rest 99m-Tc Cardiolite
LV Volume Curve

EF = 76%
EDV = 76 ml
ESV = 18 ml
SV = 58 ml
Mass = 100 gm

End Diastole
End Systole

Estimated % Thickening

> 40%
35% to 40%
10% to 25%
0% to 10%
-10% to 0
Abnormally increased lung uptake
... stress.....
Peak exercise ECHO demonstrating a mitral valve insufficiency consistent with papillary muscle ischemia.
Stress-rest 99m-Tc Cardiolite

Papillary muscle
LHR in normal subjects and in infarcted Pts with exercise EF higher or lower than 40%

Tl201 or Tc99m-tracers
Extent and Severity of Perfusion Defects
The effects of resolution
Exposure to Low-Dose Ionizing Radiation from Medical Imaging Procedures


ABSTRACT

Background The growing use of imaging procedures in the United States has raised concerns about exposure to low-dose ionizing radiation in the general population.

Methods We identified 952,420 nonelderly adults (between 18 and 64 years of age) in five health care markets across the United States between January 1, 2005, and December 31, 2007. Utilization data were used to estimate cumulative effective doses of radiation from imaging procedures and to calculate population-based rates of exposure, with annual effective doses defined as low (<3 mSv), moderate (3 to 20 mSv), high (20 to 50 mSv), and very high (>50 mSv).

RESULTS The median age of the study population was 42 years. The annual rates of radiation exposure increased with higher income, education, and health care market density, and decreased with patient age, insurance status, and health status. The most prevalent imaging procedures were chest radiography, mammography, and CT for all indications. The median effective dose in the study population was 0.3 mSv, which is comparable to the background radiation dose.
• 952,420 non elderly adults (between 18 and 64 years of age)
• Annual effective doses defined as low (3 mSv), moderate (>3 to 20 mSv), high (>20 to 50 mSv), or very high (>50 mSv)
• High and very high doses were incurred in 18.6 and 1.9 enrollees per 1000 per year, respectively.
• CT and nuclear imaging accounted for 75.4% of the cumulative effective dose,

Courtesy of M. Rehani - IAEA
Is there a cancer risk from radiation exposure?

A-bomb data show a statistically significant increase at > 50 mSv

Relative risk

1 CT scan sequence

3-phase CT liver scan

4-5% of CT scan patients

Organ dose (mSv)

100 200 300 400

Courtesy of M.Rehani – IAEA (modified)
## Pt Radiation Exposure for Cardiology tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Activity (mCi)</th>
<th>Approximate Radiation (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT 99mTc-.....</td>
<td>12+20</td>
<td>≈ 8.5</td>
</tr>
<tr>
<td>Stress only</td>
<td>15</td>
<td>≈ 4</td>
</tr>
<tr>
<td>Coronary angiogram</td>
<td></td>
<td>≈ 8-15</td>
</tr>
<tr>
<td>MSCT</td>
<td></td>
<td>≈ 15-20</td>
</tr>
<tr>
<td>PET+MSCT</td>
<td></td>
<td>≈ 20-30</td>
</tr>
<tr>
<td>SPECT 201 Tl</td>
<td>3+1</td>
<td>≈ 25-30</td>
</tr>
</tbody>
</table>

10 mSv ≈ 2-3 radiation induced neoplasms/ 10000 exposures
10 mSv ≈ 300 chest x-Rays
<table>
<thead>
<tr>
<th>Radiofarmaco</th>
<th>Dose efficace mSv/MBq</th>
<th>Miocardio mGy/MBq</th>
<th>Midollo mGy/MBq</th>
<th>Vescica mGy/MBq</th>
<th>Ovaio mGy/MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc-MIBI</td>
<td>0.006</td>
<td>0.0025</td>
<td>0.0063</td>
<td>0.024</td>
<td>0.0038</td>
</tr>
<tr>
<td>(dose somministrata: 700-800 MBq)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{201}$TI</td>
<td>0.16</td>
<td>0.28</td>
<td>0.055</td>
<td>0.052</td>
<td>0.10</td>
</tr>
<tr>
<td>(dose somministrata: 80-100 MBq)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Radiation exposure and research

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Social benefit level</th>
<th>Risk Category</th>
<th>Overall risk(*)</th>
<th>Corresponding effective dose(mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not significant</td>
<td>Not significant</td>
<td>I</td>
<td>&lt;1 su 1,000,000</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Mild</td>
<td>Mild</td>
<td>IIa</td>
<td>~ 1 su 100,000</td>
<td>0.1-1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate</td>
<td>IIb</td>
<td>~ 1 su 10,000</td>
<td>1-10</td>
</tr>
<tr>
<td>Moderate</td>
<td>Substantial</td>
<td>III</td>
<td>&gt;1 su 1,000</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

* Overall risk (lethal cancer, non-lethal cancer, and hereditary disorders) increases by 2-3 folds in children and decrease by a factor of 5-10 in over fifty yrs old adults.

European Commission 1999 (guidelines for radiation exposure to radiation for biomedical research)
RISK INDEX
ICRP 60

The diagram shows the attributable lifetime risk in percentage per sievert (\%Sv) as a function of age at the time of exposure (year) for males and females. It compares the risk for average males and average females.
Flexibility of TC-99m MPI tracers:

- Single day
- Dual day
- Stress-rest
- Rest-stress
- Single stress
- ER imaging

Increased Lab Throughput
Lower cost
Feasibility and Diagnostic Accuracy of a Gated SPECT Early-Imaging Protocol: A Multicenter Study of the Myoview Imaging Optimization Group


A cost-effective sestamibi protocol in the managed health care era
Elisa Milan, MD, Raffaele Giubbini, MD, Giuseppe Gioia, MD, Arturo Terzi, MD, and Ami E. Iskandrian, MD

J Nucl Cardiol 1997;4:509-14.)
Limitations of 201-Tl Imaging

• Poor resolution (>2 cm in SPECT imaging)
• Long half-life (low activity, low counts)
• High pt radiation exposure
• Limited flexibility
.... the iterative reconstructions with compensation strategies (AC, AC SC, and AC SC RC) demonstrated better detection accuracy than did FBP reconstructions for the overall detection of CAD as well as for the localization of perfusion defects in the 3 vascular territories. In general, the trend was for an increase in the Az for the progression from FBP to OSEM with AC, to OSEM with AC SC, and to OSEM with AC SC RC.

Evolution for Cardiac  
Dual day acquisition

7 min. acquisition  
Including CT  

15 min. acquisition  
Including CT
Evolution for Cardiac

Dual day acquisition
Evolution for Cardiac  Dual day acquisition
New detectors: Cadmium Zinc Telluride (CZT)

No need of photomultipliers
- higher spatial resolution
- higher energy resolution
- small size

Able:
- to improve image contrast
- to allow a real multi-isotope imaging
- to limit dose (acquisition time)

- intrinsic spaziale resolution = 2.4 mm/pixel
- efficiency 4-5 folds higher than anger camera
- need refrigerating systemesto
- energy limit of 200 keV
- modules of 4 x 4 cm 16 pixel
L’hardware ...
Multi-pinhole Collimator

- Static simultaneous acquisition
- Possibility of input function acquisition (quantitative measures)
- Optimization of detector-body surface distance (improvement in resolution)
Current Status: SPECT MPI Agents

• Advantages
  – Valuable in coronary disease diagnosis and prognosis
  – Established imaging protocols
  – Established LV function capability
  – Exercise and pharmacologic stress
  – Widely available

• Disadvantages
  – False positives due to image artifacts
  – Decreased heart uptake at high flow rates ("roll off")
    • Reduced apparent defect severity
  – Difficulty with balanced flow reduction
  – Reduced ability to identify non-transmural lesions
Why PET MPI?

• Scanner properties
  – Higher spatial resolution
  – Greater sensitivity
  – Validated attenuation correction

• Quantification of myocardial perfusion and flow reserve

• Higher photon energy \rightarrow reduced artifacts

Current Status: PET MPI Agents

• $^{13}\text{NH}_3$ and $\text{H}_2^{15}\text{O}$:
  – Production requires on-site cyclotron

• $^{82}\text{Rb}$:
  – Production is feasible by a generator
    Costly, requiring high patient throughput to be practical
  – Extraction fraction is lower than $^{13}\text{NH}_3$
  – Resolution is worse than $^{13}\text{NH}_3$ (positron range is more)
  – Rest-exercise imaging is not feasible

Ideal PET MPI Imaging Agent

- High cardiac uptake with minimal redistribution
- Near linear myocardial uptake vs. flow up to 5 mL/min/g or more (high first pass extraction fraction)
- High target to non-target ratio (vs. lung, liver, bowel)
- Usable for both exercise and pharmacologic stress
- Usable for quantitation of absolute myocardial flow
- Available as unit dose (\(^{18}\)F-labeled compound)

Adapted from: Glover, D and Gropler, R., J. Nucl. Card 14:6 p765-8
Chemical Structure of BMS747158

Mitochondrial Complex 1 (MC-1) Inhibitor

2-tert-Butyl-4-chloro-5-[4-(2-(18F)fluoro-ethoxymethyl)-benzyloxy]-2H-pyridazin-3-one

First Pass Uptake in Isolated Rabbit Hearts

- **BMS747158 (n=4)**
- **201TI (n=3)**
- **99mTc-sestamibi (n=3)**

* Indicates p<0.05

Pre-Clinical Cardiac PET Imaging with BMS747158


Normal Rat

Coronary ligation in Rat

Normal primate

Phase 1 Studies of BMS747158

**Study 101:** Safety, dosimetry, and biodistribution. Single injection at rest.

- 13 healthy subjects
- Gender: 12 males and one female
- Mean Age: $23.4 \pm 4.9$ years
- Mean Injected dose: $6.27 \text{ mCi} \pm 0.56$

*Maddahi J, et al. JNM 2008; abstract in press*
First Human Study of BMS747158

Maddahi J, et al. JNM 2008; abstract in press
Phase 1 Studies of BMS747158

Study 102: Safety, dosimetry, and biodistribution. Separate day injection at rest and stress

- 12 healthy subjects
- Gender: 10 males and 2 females
- Mean Age: 22 - 37 yrs (mean=28.6 yrs)
- Mean Injected dose: 2.5 mCi (Day 1)
  3.4 mCi (Day 2)

Maddahi J, et al. JACC 2009; abstract in press
Radiation Dose Comparison – Stress and FDG

BMS747158 Preliminary Stress Dosimetry Comparison

Mean of Adenosine Stress, Full (n=5)
Mean of Exercise Stress, Full (n=5)
18F-FDG from ICRP 80

Maddahi J, et al. JACC 2009; abstract in press
Rest and Stress Myocardial SUVs

Maddahi J, et al. JACC 2009; abstract in press
Exercise

Adenosine

BMS747158

Maddahi J, et al. JNM 2008; abstract in press

Ver. 18Aug 09
BMS747158 Phase 2 Clinical Studies

BMS747158-201 (first in patient)

- **Cohort 1**: develop a one-day rest/stress imaging protocol; safety
  - Patients with reversible defects on SPECT

- **Cohort 2**: assess diagnostic efficacy compared to SPECT in detecting CAD; safety
  - Patients classified as low, intermediate or high pre-test likelihood (ACC/AHA Guidelines for exercise testing)
Comparison of image quality between 18F-BMS (images averaged from 15 to 20 minutes after injection) and 13NH3 (images averaged from 5 to 10 minutes after injection) in a normal heart.

Correlation between MBF measured with 18F-BMS PET with a 3-compartment (3C) model and radioactive microspheres

Study 201, Patient 006-003

J. Maddahi, UCLA
Conclusions:

- No new Tc99m-tracers in the pipeline of RF companies
- Good perspectives for F18-labelled PET tracers
- No justification for the use of 201-Tl (unless for viability in >60 yrs old pts)
- Need for optimization of acquisition & processing with new technologies