RADIOTRACERS FOR MYOCARDIAL PERFUSION IMAGING

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OVERVIEW

1- IDEAL RADIOPHARMACEUTICAL FOR MPI
2- PHYSIOLOGICAL CHARACTERISTICS
3- ASSOCIATED DIAGNOSTIC ACCURACY
4- RELATIVE ADVANTAGES AND DISADVANTAGES
5- CONCLUSIONS
INTRODUCTION

• **201 THALLIUM**

  • USED SINCE MORE THAN 25 YEARS
  • MAJOR RADIOPHARMACEUTICAL IN NUCLEAR CARDIOLOGY
  • WELL KNOWN BIOLOGICAL CHARACTERISTICS
  • MAJOR DRAWBACK: PHYSICAL CHARACTERISTICS

• DEVELOPMENT OF 99mTc-MPI AGENTS

  • DESIRABLE
  • ESSENTIAL
IDEAL RADIOPHARMACEUTICAL FOR MYOCARDIAL PERFUSION IMAGING

- HIGH MYOCARDIAL EXTRACTION AND HIGH RETENTION
IDEAL RADIOPHARMACEUTICAL FOR MYOCARDIAL PERFUSION IMAGING

- **HIGH MYOCARDIAL EXTRACTION AND HIGH RETENTION**

- **LINEAR RELATIONSHIP BETWEEN MYOCARDIAL UPTAKE AND CORONARY BLOOD FLOW (AT HIGH FLOW RATES)**
IDEAL RADIOPHARMACEUTICAL FOR MYOCARDIAL PERFUSION IMAGING

- High myocardial extraction and high retention
- Linear relationship between myocardial uptake and coronary blood flow (at high flow rates)
- Low extra-cardiac activity (lung, liver)
IDEAL RADIOPHARMACEUTICAL FOR MYOCARDIAL PERFUSION IMAGING

• HIGH MYOCARDIAL EXTRACTION AND HIGH RETENTION

• LINEAR RELATIONSHIP BETWEEN MYOCARDIAL UPTAKE AND CORONARY BLOOD FLOW (AT HIGH FLOW RATES)

• LOW EXTRA-CARDIAC ACTIVITY (LUNG, LIVER)

• MYOCARDIAL REDISTRIBUTION ($T^{1/2} = 1-2$ HOURS)
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• HIGH MYOCARDIAL EXTRACTION AND HIGH RETENTION

• LINEAR RELATIONSHIP BETWEEN MYOCARDIAL UPTAKE AND CORONARY BLOOD FLOW (AT HIGH FLOW RATES)

• LOW EXTRA-CARDIAC ACTIVITY (LUNG, LIVER)

• MYOCARDIAL REDISTRIBUTION (T½ = 1-2 HOURS)

• LABELED TO ⁹⁹ᵐTÉCHNETIUM
IDEAL RADIOPHARMACEUTICAL FOR MYOCARDIAL PERFUSION IMAGING

• HIGH MYOCARDIAL EXTRACTION AND HIGH RETENTION

• LINEAR RELATIONSHIP BETWEEN MYOCARDIAL UPTAKE AND CORONARY BLOOD FLOW (AT HIGH FLOW RATES)

• LOW EXTRA-CARDIAC ACTIVITY (LUNG, LIVER)

• MYOCARDIAL REDISTRIBUTION ($T^{1/2} = 1-2$ HOURS)

• LABELED TO $^{99m}$TECHNETIUM

• EASY AND STABLE LABELING
COMPARISON BETWEEN 2 RADIOTRACERS FOR MPI

1- PHYSICAL CHARACTERISTICS (RADIOISOTOPES)

2- PREPARATION AND QC PROCEDURES

3- BIOLOGICAL CHARACTERISTICS
   • BIODISTRIBUTION
   • MYOCARDIAL UPTAKE
   • MYOCARDIAL RETENTION
   • UPTAKE VS FLOW

4- IMAGING CHARACTERISTICS
   • TIMING BETWEEN I.V. AND IMAGING
   • MYOCARDIAL REDISTRIBUTION
   • LEVEL OF ADJACENT ORGAN UPTAKE
COMPARISON BETWEEN 2 RADIOTRACERS FOR MPI

5- DIAGNOSTIC ACCURACY
   • SENSITIVITY, SPECIFICITY
   • EXTENT AND SEVERITY OF PERFUSION DEFECT
   • EXERCISE VS PHARMACOLOGIC

6- PROGNOSIS AND VIABILITY

7- APPROVED CLINICAL INDICATIONS

8- DOSIMETRY

9- EXTENT OF CLINICAL EXPERIENCE

10- COST EFFECTIVENESS
RADIOTRACERS FOR MYOCARDIAL PERFUSION IMAGING

• APPROVED BY FDA
  
  - $^{201}$ THALLIUM
  - $^{99m}$Tc-SESTAMIBI (CARDIOLITE, DUPONT)
  - $^{99m}$Tc-TEBOROXIME (CARDIOTEC, BMS)
  - $^{99m}$Tc-TETROFOSMIN (MYOVIEW, AMERSHAM)

• UNDER INVESTIGATION
  
  - $^{99m}$Tc-FURIFOSMIN (TECHNECARD, MALLINCKRODT)
  - $^{99m}$Tc-N-NOET (CIS-BIO)
## EXTRACTION IN ISOLATED RABIT HEART

<table>
<thead>
<tr>
<th></th>
<th>E MAX</th>
<th>PScap</th>
<th>ENET</th>
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<tbody>
<tr>
<td>1 - ²⁰¹THALLIUM</td>
<td>0.73</td>
<td>1.30</td>
<td>0.57</td>
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<tr>
<td>2 - ⁹⁹ᵐTc-SESTAMIBI</td>
<td>0.39</td>
<td>0.44</td>
<td>0.41</td>
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<td>3 - ⁹⁹ᵐTc-TEBOROXIME</td>
<td>0.81</td>
<td>2.31</td>
<td>0.67</td>
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<tr>
<td>4 - ⁹⁹ᵐTc-TETROFOSMIN</td>
<td>0.36</td>
<td>0.40</td>
<td>0.23</td>
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<tr>
<td>5 - ⁹⁹ᵐTc-FURIFOSMIN</td>
<td>0.26</td>
<td>0.48</td>
<td>0.12</td>
</tr>
<tr>
<td>6 - ⁹⁹ᵐTcN-NOET</td>
<td>0.48</td>
<td>1.02</td>
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</table>
Blood Flow and Tracer Uptake

The ideal perfusion tracer would track myocardial blood flow across the entire range of physiological flows.

The available perfusion tracers "roll off" at higher levels of flow.

The different tracers begin to reach a plateau at different levels of myocardial blood flow.
Tracer Uptake

Relationship Between Tracer Uptake and Myocardial Blood Flow

Myocardial Tracer Uptake vs. Myocardial Blood Flow (ml/min/g)

- O-15-H₂O
- Teboroxime
- TI-201
- N-13-NH
- Rb-82
- Tc-99m Sestamibi
- Tc-99m Tetrofosmin

Berman, Leppo, 1997
<table>
<thead>
<tr>
<th></th>
<th>Isotope</th>
<th>Charge</th>
<th>Diffusion Limitation (ml/min/gr)</th>
<th>Eff. Dose Eq (rem/dose)</th>
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<tr>
<td>1</td>
<td>$^{201}$Thallium</td>
<td>CATION</td>
<td>2.5-3.0</td>
<td>1.05</td>
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<tr>
<td>2</td>
<td>$^{99m}$Tc-SESTAMIBI</td>
<td>CATION</td>
<td>2.0-2.5</td>
<td>1.0</td>
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<tr>
<td>3</td>
<td>$^{99m}$Tc-TEBOROXIME</td>
<td>NEUTRAL</td>
<td>&gt; 3.0</td>
<td>1.70</td>
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<td>4</td>
<td>$^{99m}$Tc-TETROFOSMIN</td>
<td>CATION</td>
<td>1.5-2.0</td>
<td>0.85</td>
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<tr>
<td>5</td>
<td>$^{99m}$Tc-FURIFOSMIN</td>
<td>CATION</td>
<td>1.5-2.0</td>
<td>0.90</td>
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<tr>
<td>6</td>
<td>$^{99m}$TcN-NOET</td>
<td>NEUTRAL</td>
<td>2.5-3.0</td>
<td>0.80</td>
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## MYOCARDIAL KINETICS IN HUMAN

<table>
<thead>
<tr>
<th></th>
<th>MYOCARDIAL REDISTRIBUTION</th>
<th>UPTAKE (% I.D.)</th>
<th>CLEARANCE (T½)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- $^{201}$ Thallium</td>
<td>YES</td>
<td>3 - 4%</td>
<td>3-4 HRS</td>
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<tr>
<td>2- $^{99m}$Tc-SeSTAMIBI</td>
<td>NO</td>
<td>1 - 2%</td>
<td>&gt; 7 HRS</td>
</tr>
<tr>
<td>3- $^{99m}$Tc-TEBOROXIME</td>
<td>YES</td>
<td>2 - 3%</td>
<td>7-9 MIN</td>
</tr>
<tr>
<td>4- $^{99m}$Tc-TETROFOSMIN</td>
<td>NO</td>
<td>0.6 -1.5%</td>
<td>&gt; 6 HRS</td>
</tr>
<tr>
<td>5- $^{99m}$Tc-FURIFOSMIN</td>
<td>NO</td>
<td>1.0 -1.5%</td>
<td>&gt; 6 HRS</td>
</tr>
<tr>
<td>6- $^{99m}$TcN-NOET</td>
<td>YES</td>
<td>2.5-4.0%</td>
<td>2 - 3 HRS</td>
</tr>
</tbody>
</table>
EFFECTIVE HALF-LIFE

1- DENOTES THE HALVING OF RADIOACTIVE MATERIAL IN LIVING ORGANS BY MEANS OF:
   1- RADIOACTIVE DECAY
   2- BIOLOGICAL EXCRETION

\[
\frac{1}{T_e} = \frac{1}{T_p} + \frac{1}{T_b}
\]

Te : Effective half-life
Tp : Physical half-life
Tb : Biological half-life
<table>
<thead>
<tr>
<th></th>
<th>TECHNICAL AND IMAGING CHARACTERISTICS (I)</th>
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<tbody>
<tr>
<td></td>
<td>LABELING</td>
</tr>
<tr>
<td>1</td>
<td>$^{201}$THALLIUM</td>
</tr>
<tr>
<td>2</td>
<td>$^{99m}$Tc-SESTAMIBI</td>
</tr>
<tr>
<td>3</td>
<td>$^{99m}$Tc-TEBOROXIME</td>
</tr>
<tr>
<td>4</td>
<td>$^{99m}$Tc-TETROFOSMIN</td>
</tr>
<tr>
<td>5</td>
<td>$^{99m}$Tc-FURIFOSMIN</td>
</tr>
<tr>
<td>6</td>
<td>$^{99m}$TcN-NOET</td>
</tr>
<tr>
<td></td>
<td>MYOCARDIAL FIRST PASS GATED SPECT COUNTS</td>
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<tr>
<td>---</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>1-</td>
<td><strong>201 Thallium</strong></td>
</tr>
<tr>
<td>2-</td>
<td><strong>99mTc-Sestamibi</strong></td>
</tr>
<tr>
<td>3-</td>
<td><strong>99mTc-Teboroxime</strong></td>
</tr>
<tr>
<td>4-</td>
<td><strong>99mTc-Tetrofosmin</strong></td>
</tr>
<tr>
<td>5-</td>
<td><strong>99mTc-Furifosmin</strong></td>
</tr>
<tr>
<td>6-</td>
<td><strong>99mTcN-Noet</strong></td>
</tr>
</tbody>
</table>

|   | **99mTc-Sestamibi**                     | Yes                                    |
|   | **99mTc-Teboroxime**                    | ± (LU)                                 |
|   | **99mTc-Tetrofosmin**                   | Yes                                    |
|   | **99mTc-Furifosmin**                    | Yes                                    |
|   | **99mTcN-Noet**                         | ± (LU)                                 |

**CHUM**
201 THALLIUM: ADVANTAGES

1- USED SINCE 1977

2- EXTENSIVE CLINICAL EXPERIENCE

3- MAJOR RADIOPHARMACEUTICAL IN NUCLEAR CARDIOLOGY

4- WELL KNOWN DIAGNOSTIC, PROGNOSTIC AND PREDICTIVE VALUES

5- WIDELY USED FOR MYOCARDIAL VIABILITY ASSESSMENT

6- NO PREPARATION (READY TO USE)
THALLIUM: ADVANTAGES

7- GOOD BIOLOGICAL CHARACTERISTICS
   • REDISTRIBUTION (ONE INJECTION)
   • HIGH FIRST PASS EXTRACTION
   • GOOD CORRELATION WITH HYPEREMIC ZONES

8- “STANDARD” SCHEDULING

9- “REASONABLE” COST
THALLIUM: LIMITATIONS

1- SUBOPTIMAL IMAGE QUALITY
   • LOW ENERGY
   • SOFT-TISSUE ATTENUATION

2- INCREASED DOSIMETRY
   • TYPE OF RADIATION
   • PROLONGED HALF-LIFE
3- Decreased injected dose
   - Low photon flux
   - Increased imaging time
   - Limited gated SPECT

4- Variable redistribution

5- Limited availability
99mTc-SESTAMIBI

\[
\begin{align*}
\text{RCN} & \quad \text{CNR} \\
\text{CNR} & \quad \text{RCN} \\
\text{CNR} & \quad \text{CNR}
\end{align*}
\]

\[
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\text{O} \\
\text{CH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3 \\
\text{C} \\
\text{CH}_3
\end{array}
\]
$^{99mTc}$-SESTAMIBI: ADVANTAGES

1- OPTIMAL CHARACTERISTICS FOR SPECT
   - BETTER DIAGNOSTIC ACCURACY

2- SIMULTANEOUS PERFUSION AND FUNCTION STUDIES
   - GATED SPECT
   - FIRST PASS STUDIES

3- NEW AND UNIQUE INDICATIONS
   - THROMBOLYSIS
   - UNSTABLE ANGINA
   - ACUTE CORONARY SYNDROMES
99mTc-SESTAMIBI: ADVANTAGES

4- ACQUISITION CAN BE REPEATED IF NECESSARY
   • INSTRUMENTATION MALFUNCTION
   • SIGNIFICANT PATIENT MOTION

5- SCHEDULING FLEXIBILITY

6- SHORT TIME ACQUISITION, IF NEEDED

7- NO IMAGE “DEGRADATION”
   • RAPID REDISTRIBUTION
   • “UPWARD CREEP”
   • RESPIRATORY MOVEMENTS

8- MAJOR RADIOPHARMACEUTICAL MPI AGENT
$^{99m}$Tc-SESTAMIBI: LIMITATIONS

1- LESS LINEAR RELATIONSHIP BETWEEN UPTAKE AND CBF

2- NO SIGNIFICANT MYOCARDIAL REDISTRIBUTION
   - 2 SEPARATE INJECTIONS FOR COMPLETE DIAGNOSIS

3- LABELING AND QC PROCEDURES
99mTc-SESTAMIBI: LIMITATIONS

4- LONGER TIME INTERVAL BETWEEN I.V. AND IMAGING
   • MODIFIED INJECTION PROTOCOLS
   • MODIFIED SCHEDULING

5- SUB-DIAPHRAGMATIC ACTIVITY
   • ARTIFACTS
99mTc-TEBOROXIME
**$^{99mTc}$-TEBOROXIME: ADVANTAGES**

1. $^{99mTc}$-LABELING

2. HIGH MYOCARDIAL EXTRACTION AND UPTAKE

3. VERY GOOD LINEAR RELATIONSHIP BETWEEN UPTAKE AND CBF

4. FAST MYOCARDIAL WASHOUT
   - RAPIDLY COMPLETED STUDIES
   - CAN BE REPEATED

5. IDEAL FOR PHARMACOLOGIC STUDIES
99mTc-TEBOROXIME: LIMITATIONS

1) LABELING AND QC PROCEDURES

2) VERY SHORT MYOCARDIAL T½
   - NO ROOM FOR TECHNICAL MISTAKES
   - LIMITED GATED SPECT

3) PERSISTENT LIVER UPTAKE

4) HIGH INITIAL LUNG UPTAKE
   - NO FIRST PASS STUDIES
99mTc-TETROFOSMIN
99mTc-Tetrofosmin: Advantages

1- Same as those of 99mTc-Septamibi

2- Faster Liver Clearance
   • Decreased time interval between injection and imaging
   • Especially after a rest or after pharmacologic vasodilation injection

3) Easy labeling procedure
$^{99m}$Tc-Tetrofosmin: Limitations

1. Lower myocardial extraction and uptake (15-25% less than $^{99m}$Tc-Sestamibi)

2. Less linear relationship between uptake and CBF

3. Less accurate than $^{201}$Thallium and $^{99m}$Tc-Sestamibi with pharmacologic stress test
DIPYRIDAMOLE
TETROFOSMIN
DIPYRIDAMOLE
SESTAMIBI
99mTcN-NOET
$^{99m}$TcN-NOET: ADVANTAGES

1. $^{99m}$Tc-LABELING
2. HIGH MYOCARDIAL EXTRACTION AND UPTAKE
3. MYOCARDIAL REDISTRIBUTION
   - SIMILAR IMAGING PROTOCOLS THAN $^{201}$THALLIUM?
   - MYOCARDIAL VAIBILITY ASSESSMENT?
99mTcN-NOET: LIMITATIONS

1- VERY LIMITED CLINICAL EXPERIENCE
2- NOT APPROVED BY THE FDA
3- INITIAL INCREASED LUNG UPTAKE
4- PERSISTENT LIVER UPTAKE
99mTcN-NOET STUDY  S-REDIST.
99mTcN-NOET STUDY
99mTcN-NOET STUDY
<table>
<thead>
<tr>
<th>AGENT</th>
<th>1/2-LIFE</th>
<th>DOSE</th>
<th>MEAN POSITRON RANGE</th>
<th>PRODUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-15 Water</td>
<td>2.0 min</td>
<td>60–100 mCi</td>
<td>1.1 mm</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>N-13 Ammonia</td>
<td>9.8 min</td>
<td>7–20 mCi</td>
<td>0.7 mm</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>Rb-82</td>
<td>75 sec</td>
<td>20–60 mCi</td>
<td>2.4 mm</td>
<td>Generator</td>
</tr>
</tbody>
</table>
Myocardial Perfusion PET Tracers

O-15 Water

- Requires on-site cyclotron
- Most closely meets criteria for an ideal flow tracer
- Extraction fraction approaches unity and does not decline with higher flows
- Remains in blood pool - poor quality images with low target to background ratios
- Not suitable for clinical imaging, not FDA approved, not payable by Medicare
- Used mostly for measuring myocardial blood flow in research studies
**Myocardial Perfusion PET Tracers**

**N\textsuperscript{-13} Ammonia**

- Requires nearby (on-site) cyclotron
- Half-life 10 minutes
- Excellent myocardial uptake & retention
- Bolus (10–20 mCi)
- Applicable to exercise or pharmacologic stress
- Established flow quantification ability
- FDA approved and Medicare reimbursed
- \(1/2\)-life long for through-put efficiencies
- In some patients, increased lung retention; frequent excess liver & bowel uptake
- Lower counts in lateral wall in some normal patients
Myocardial Perfusion PET Tracers: Rubidium-82

• Half-life 75 seconds
• Strontium-82 generator q28 days
• Radionuclide always available (facilitates add-ons)
• Can re-image in minutes if technical problems (should almost never have a poor quality study)
• TI-201 - like kinetics: high extraction at high flows (enhances detection of mod-severity CAD)
• FDA approved and Medicare reimbursed
• Short half-life (technically challenging; pharm stress only; less useful for very obese)
• Flow quantitation not as well validated
Advantages of PET Perfusion

- Image quality
- Diagnostic accuracy
- Risk stratification
- Rapid procedure
- Added information: blood flow, calcium, Coronary CT
Why Develop New Tracer?

- Current agents are proven, but have limitations
  - Less than optimal first-pass extraction
  - “Roll-off” at high blood flow
  - Inability to quantify flow reserve in routine clinical setting
  - Inability to diagnose “balanced ischemia”
Ideal PET Agent Characteristics

- Available as unit dose from a regional cyclotron (F-18 labeled)
- High extraction fraction & Rel. Linearity w/ Hyperemia
- Ideal PET resolution (Positron Energy)
- Potential for both rest-exercise and pharm stress imaging
- Potential for absolute quantitation (Perf & Abs Flow)
Mitochondrion

The electron transport chain is a series of protein complexes located at the inner membrane of the mitochondria.
First-pass uptake; isolated rabbit hearts

* Indicates $p<0.05$

- BMS-747158-02 (n=4)
- $^{201}$Tl (n=3)
- $^{99m}$Tc-sestamibi (n=3)

**Coronary perfusion flow (ml/min/g)**

* Indicates $p<0.05$
Occlusion Model in Pigs

(M. Schwaiger, TUM)
First Human Study of BMS-747158

Coronal

Sagittal

Axial
Flurpiridaz F18 vs. Rb-82 for PET Myocardial Perfusion Imaging

Flurpiridaz F18
- Unit dose
  - Total cost to customer $\alpha[#doses]$
  - COGS $\sim\alpha[1/#doses]$
- Cyclotron produced
- F-18 positron range (0.18 mm*)
- Moderate half life (110 min)
  - Pharmacological Stress
  - Exercise Stress
  - Shielded weighting rooms
- 95% low flow extraction fraction
- Radiation Dose: 6.9/6.2 mSv/study (pharm/exercise)

Rb-82
- Generator (~4 weeks use)
  - Total cost to customer $\alpha[1/#doses]$
  - COGS $\alpha[#generators]$
- Reactor-derived (parent)
- Rb-82 positron range (0.56 mm*)
- Very short half life (1.25 min)
  - Pharmacological stress only
  - Very rapid patient study
- 45% low flow extraction fraction**
  - ~20% high flow rate extraction fraction
- Radiation Dose: ~4.7 mSv/study
CONCLUSION

• VARIOUS $^{99m}$Tc-LABELED PERFUSION IMAGING AGENTS
• DIFFERENT IMAGING AND BIOLOGICAL CHARACTERISTICS
• DIFFERENT INJECTION AND IMAGING PROTOCOLS
• NEED MORE “HEAD-TO-HEAD” COMPARATIVE STUDIES
• INCREASING THE ROLE OF NUCLEAR CARDIOLOGY
HAVE I OVERLOADED YOU ??