Present and Future PET MPI Agents

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Coronary artery disease

- Coronary artery disease (CAD) is a blockage of the arteries that feed the heart muscle.
- CAD is the most common form of heart disease, and is the leading cause of death in the Western world.
- Despite recent advances in therapeutic and diagnostic approaches, CAD remains a primary health problem worldwide.
- Nuclear medicine technology plays a pivotal role in the diagnosis and treatment design for CAD.
- The field of nuclear cardiology was initiated with the development of myocardial perfusion imaging (MPI).
Monitoring Coronary artery disease - History

- In the mid-1970’s the discovery was made that thallium 201 (\(^{201}\text{Tl}\)) (an analog and replacement to \(^{43}\text{K}\)) was extracted by the myocardium and that comparison of its distribution when injected during exercise vs. resting state allowed noninvasive detection of significant coronary stenosis with a gamma camera.

- In the early 1990’s, several novel \(^{99m}\text{Tc}\)-labeled perfusion tracers (\(^{99m}\text{Tc}\)-sestamibi, \(^{99m}\text{Tc}\)-teboroxime, \(^{99m}\text{Tc}\)-tetrofosmin) were developed.

- The emission energy (140-kev) for Tc is better suited for gamma camera, and the shorter half life allows for higher dose injection.

- 8.3 M procedures per year only in the USA, 65% of all noninvasive cardiac imaging for CAD detection and evaluation. 98% of MPI performed by SPECT.

- Poor image quality, continuous redistribution, low maximal dose, low first pass extraction, artifacts because of soft tissue attenuation. Inability to diagnose multi vessel disease.

Filling defect – an area where there is normal uptake in rest but decreased uptake in stress.
Requirements for MPI tracer

- High Intrinsic resolution
- Moderate half life
- In vivo stability
- High accumulation and retention of tracer in the heart with minimal redistribution.
- A linear correlation between blood flow and cardiac extraction (high first pass extraction)
- Rapid washout out from blood & surrounding organs
- Renal clearance
- An understanding of physiological and pathological effects on accumulation
- A simple, reliable and fully automated synthesis
Generators for cardiac imaging

<table>
<thead>
<tr>
<th>Generator System</th>
<th>Parent</th>
<th>Half life</th>
<th>Daughter</th>
<th>Half-life</th>
<th>Main Energy</th>
<th>Application</th>
<th>Application mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mo-Tc</td>
<td>Mo-99</td>
<td>66h</td>
<td>Tc-99m</td>
<td>6h</td>
<td>140Kev Gamma</td>
<td>SPECT imaging</td>
<td>Direct &amp; Labelling</td>
</tr>
<tr>
<td>Sr-Rb</td>
<td>Sr-82</td>
<td>25.5d</td>
<td>Rb-82</td>
<td>75 sec</td>
<td>511keV Gamma</td>
<td>PET imaging</td>
<td>Direct</td>
</tr>
</tbody>
</table>
## Various $^{99m}$Tc agents used in humans

<table>
<thead>
<tr>
<th>complex</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge</td>
<td>Cationic</td>
<td>Neutral</td>
<td>Cationic</td>
<td>Cationic</td>
<td>Neutral</td>
<td>Cationic</td>
</tr>
<tr>
<td>$^{99m}$Tc core</td>
<td>$^{99m}$Tc$^+$</td>
<td>$^{99m}$Tc$^{3+}$</td>
<td>$[^{99m}$TCO$_2]^+$</td>
<td>$^{99m}$Tc$^{3+}$</td>
<td>$[^{99m}$TCN$]^2+$</td>
<td>$[^{99m}$TCN$]^2+$</td>
</tr>
<tr>
<td>Heart Uptake (%ID)</td>
<td>1-4%</td>
<td>2.2%</td>
<td>1.2%</td>
<td>2.2%</td>
<td>3.0%</td>
<td>1.7-2.1%</td>
</tr>
<tr>
<td>Redistribution</td>
<td>minimal</td>
<td>significant</td>
<td>none</td>
<td>none</td>
<td>significant</td>
<td>none</td>
</tr>
<tr>
<td>First pass extraction</td>
<td>55-68%</td>
<td>&gt;90%</td>
<td>54%</td>
<td>29%</td>
<td>75-85%</td>
<td>61%</td>
</tr>
<tr>
<td>Heart clearance</td>
<td>slow</td>
<td>Fast</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
</tr>
<tr>
<td>Liver clearance</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>rapid</td>
</tr>
<tr>
<td>Commercial available</td>
<td>Cardiolite</td>
<td>Cardiotec</td>
<td>Myo-view</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

(1) $^{99m}$Tc-MIBI; (2) $^{99m}$Tc-teboroxime; (3) $^{99m}$Tc-tetrofosmin; (4) $^{99m}$Tc-Q12; (5) $^{99m}$TcN-NOET; (6) $^{99m}$TcN-DBODC5

Monitoring Coronary artery disease

- PET offers higher count sensitivity, better spatial resolution, 3D dynamic acquisition, more accurate attenuation correction.

- The ability to quantify myocardial perfusion in absolute values (mL/min/g tissue) particularly in multivessel CAD. *(SPECT interpretation model is relative and relies, sometimes erroneously, on having at least one myocardial region with normal perfusion.)*

- Limited availability of suitable PET tracers.

- Existing PET MPI probes have short physical half lives, which require in-house production, and more importantly, have sub-optimal pharmacokinetic profiles.
MPI PET Agents

$^{82}\text{Rb}$ – K analog, 76 sec half-life, generator produced (4 weeks), 65% first pass extraction, low intrinsic resolution, moderate linearity with blood flow. FDA approved

$^{13}\text{NH}_3$ – 10 min half-life, cyclotron produced, 80% first pass extraction, high intrinsic resolution, fair linearity with blood flow, diffusion/metabolic trapping ($\text{glutamine synthetase, it may be influenced by other parameters such as cell membrane integrity, intracellular-extracellular pH gradient, and an anion exchange process for bicarbonate}$), high uptake in lung and liver. FDA approved

$^2\text{H}^{15}\text{O}$ – Freely diffusible tracer, 2.1 min half-life, cyclotron produced, metabolically inert, accurate flow estimation, because of its diffusible nature it is impossible to distinguish the LV wall from the cavity. Lack FDA approval

Glover & Gropler, J of Nuclear Cardiology; 2007, 765-768
Xiao Lin, Current Pharmaceutical Design; 2012, 18, 1041
Oxygen-15 Cyclotron production

Gas target

\[ ^{14}\text{N}_2 + 0.5\%_{(v)}\text{O}_2 \xrightarrow{d,n} ^{15}\text{O}_2 (g) \]

Possible impurities: \(^{13}\text{N}, ^{11}\text{C}\)

Energy of productions 8-10 MeV
Oxygen-15 Water

Processing and purification

$[^{15}\text{O}]\text{Water}$

- Chemical and Radiochemical impurities; ozone, nitrogen oxides and $^{15}\text{O}_2$.

\[ ^{14}\text{N}_2 + 0.25\% \text{ O}_2 \rightarrow d,n \]

\[ ^{15}\text{O}_2(^{16}\text{O}_2) \rightarrow \text{sodalime} \]

Continues flow

\[ \text{H}_2/Pd, 175^\circ\text{C} \rightarrow \text{H}_2^{15}\text{O} \]

\[ ^{15}\text{O} \rightarrow ^{15}\text{N} + e^+ + \nu_e + 1.72 \text{ MeV} \]
Nitrogen-13

Production

\[ \text{H}_2^{16}\text{O} \xrightarrow{\text{p,}\alpha} 13\text{NO}_3^- + 13\text{NO}_2^- \rightarrow 13\text{NH}_3 + 13\text{NH}_2\text{OH} \]

Production of \( [^{13}\text{N}] \)-ammonia

Online reduction in-situ

\[ \begin{align*}
\text{He} & \quad 1\% \text{ NaCl} \\
17 \text{ Mev p} & \quad \text{in H}_2\text{O} \\
\text{H}_2^{16}\text{O Target} & \quad 1\text{mM EtOH} \\
\text{cation exchange} & \quad \text{waste} \\
\text{cartridge} & \quad \text{Sterile filter} \\
\text{Rest} & \quad \text{In PBS} \\
\text{Stress} & \quad \theta^+ \text{decay} \quad 13\text{C} + \text{e}^+ + V_e + 1.19 \text{ MeV} \\
\end{align*} \]
Fluorine-18 labeled Triphenyl Phosphonium salts

- So far, 18F-Fluorobenzyl triphenyl phosphonium and 18F- fluorophenyl -triphenyl phosphonium show promising characteristics as MPI agents.
- Originally developed for measurement of the mitochondrial membrane potential, passive diffusion and accumulation in cells in a membrane potential-dependent manner.
- Low radiochemical yield ~ 6%
- High metabolic rate for both.
- TOX ???

Fluorine-18 labeled mitochondria complex I (MC-I) inhibitors

- Cardiac mouse and rat uptake of 9.5 and 3.5 % ID/g at 60 and 15 min post injection, respectively.
- Heart/lung, heart/liver ratios in mice and rats are 14 and 8 and 12 and 3.5 (60 min), respectively.
- Heart/Blood at 15 min of 20.
- In isolated heart, the first pass extraction obtained was higher than 90%.

Clinical studies.

\( ^{18}\text{F}}\)-BMS747158-02 (\(^{18}\text{F}}\)-flurpiridaz)

### Theoretical and measured values of $e^-$ density, logP, $SUV_{\text{max}}$ and clearance

$e^-$ charge density order by $^{15}\text{N}-\text{NMR}$ measurements

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^{15}\text{N}-\text{NMR}$ [ppm]</th>
<th>$SUV_{\text{max}}$</th>
<th>$q$ (N)</th>
<th>LogP</th>
<th>Slope of clearance</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMDPA</td>
<td>70.0</td>
<td>6.83</td>
<td>1.008669</td>
<td>-1.03 ± 0.03</td>
<td>0.01671 ± 0.00263</td>
<td>0.8899</td>
</tr>
<tr>
<td>4_{Ald}-TMA</td>
<td>54.1</td>
<td>5.30</td>
<td>0.120589</td>
<td>-2.03 ± 0.20</td>
<td>-0.00743 ± 0.00085</td>
<td>0.9389</td>
</tr>
<tr>
<td>3_{MeO}-TMA</td>
<td>53.7</td>
<td>4.97</td>
<td>0.103057</td>
<td>-1.99 ± 0.03</td>
<td>-0.07543 ± 0.00191</td>
<td>0.9968</td>
</tr>
<tr>
<td>TMA</td>
<td>53.6</td>
<td>4.32</td>
<td>0.103051</td>
<td>-2.21 ± 0.03</td>
<td>-0.05707 ± 0.00135</td>
<td>0.9972</td>
</tr>
<tr>
<td>3_{Me}-TMA</td>
<td>53.4</td>
<td>4.19</td>
<td>0.077534</td>
<td>-1.78 ± 0.01</td>
<td>-0.04521 ± 0.00162</td>
<td>0.9972</td>
</tr>
<tr>
<td>4_{F}-TMA</td>
<td>53.0</td>
<td>3.73</td>
<td>0.106370</td>
<td>-2.00 ± 0.05</td>
<td>-0.04586 ± 0.00161</td>
<td>0.9938</td>
</tr>
</tbody>
</table>

[C-11]DMDPA and MIBI Biodistribution in Mice

Axial (upper) and coronal (lower) micro PET/CT images of $^{11}$C-ammonium salt derivatives at 10 min after injection

<table>
<thead>
<tr>
<th></th>
<th>DMDPA</th>
<th>4-Ald-TMA</th>
<th>3- MeO-TMA</th>
<th>TMA</th>
<th>3-Me-TMA</th>
<th>4-F-TMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV/ liver</td>
<td>1.2</td>
<td>0.9</td>
<td>1.3</td>
<td>1.2</td>
<td>1.3</td>
<td>0.8</td>
</tr>
<tr>
<td>LV/ lungs</td>
<td>8.3</td>
<td>6.1</td>
<td>8.0</td>
<td>5.6</td>
<td>6.8</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Time activity curves of $^{11}$C-ammonium salts in healthy rats

e⁻ charge density order by $^{15}$N-NMR measurements

FTMA 3-Me-TMA TMA 3-OMe-TMA 3-Ald-TMA DMDPA

Myocardium Uptake

![Graph showing uptake over time for different compounds](image-url)
[**[11C]**]-DMDPA - μPET in SD Rats

μPET: 45’ acquisition  
 Injected dose: 665 µCi  
 Rat weight: 288 g

MIP: 1-20 min

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## Comparison Biodistribution Results in Rats

<table>
<thead>
<tr>
<th></th>
<th>$^{[11]C}$DMDPA (15 min)</th>
<th>FTPP (60 min)</th>
<th>Flurpiridaz (15 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac uptake</td>
<td>5.5 %ID/g</td>
<td>1.7 %ID/g</td>
<td>3.5 %ID/g</td>
</tr>
<tr>
<td>Heart/Blood</td>
<td>80</td>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td>Heart/Lung</td>
<td>7</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Heart/Liver</td>
<td>4</td>
<td>8</td>
<td>3.7</td>
</tr>
</tbody>
</table>
Rat micro-PET/CT

11C- DMDPA

13N- ammonia

Coronal, Axial, Sagital

Abourbeh G et al. WMIC; 2012, Dublin, Ireland.
Time Activity curves Rat Micro-PET

PET/CT scan of [C-11]-DMDPA in pigs. Short axis slices taken 20 minutes post injection clearly show the left ventricle.

Pig with partial coronary occlusion

- Two days prior to the experiment, the pig was given 300 mg of Aspirin and 300 mg Plavix each day.
- Insertion of a semi-open stent for partial occlusion formation through the femoral artery into the coronal artery LCX (left circumflex).
- Angiography to make sure no infarct damage before first PET and at the end of the imaging procedure.
- Through the experiment, coagulation was regularly measured and Heparin was administered according to the results.
Angiography – to determine occlusion and not infarct.

**Rest [C-11]-DMDPA:**
- [C-11]-DMDPA was injected, 5.06mCi/17ml.
- 30 minutes dynamic scan (10X30 sec, 5X60 sec, 4X300 sec).

**Rest [N-13]-NH₃:**
- [13-N]-NH₃ was injected, 16mCi/1.2ml.
- 30 minutes dynamic scan (12X10 sec, 6X30 sec, 3X300 sec).

**Stress [N-13]-NH₃:**
- Stress induction.
- [13-N]-NH₃ was injected 1.5 minutes after beginning of adenosine infusion, 13.98mCi/1ml.
- 30 minutes dynamic scan

**Stress [C-11]-DMDPA:**
- [11-C]-DMDPA was injected 3 minutes after beginning of adenosine infusion, 4.68mCi/8ml.
- 30 minutes dynamic scan
- Angiography
Polar Map Swine

C-11 DMDPA

Rest

Stress

N-13 NH3 Stress

Short axis view: Swine C-11 DMDPA

**Partial coronary occlusion by** Insertion of a semi-open stent through the femoral artery into the coronal artery LCX
Take Home Message

- Major portion of all noninvasive imaging for CAD detection is performed by NM

- Despite the advantages of PET over SPECT (*higher count sensitivity, better spatial resolution, 3D dynamic acquisition, more accurate attenuation correction, ability to quantify myocardial perfusion in absolute values*), a major portion of cardiac imaging is performed with SPECT.

- The recent abundance of PET-CT scanners and the development of novel carbon-11 and fluorine-18 labeled PET MPI agents will have a significant impact on cardiac imaging in the near future.

- This new technology will enable absolute measurements of myocardial blood flow and will significantly improve patient care.
Thanks

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