DEFINITION OF CARDIAC RADIOPHARMACEUTICAL:
A radioactive drug which, when administered for purpose of diagnosis of heart disease, typically elicits no physiological response from the patient. Even though non-radioactive thallium is extremely cardiotoxic, it is not dangerous to administer a 3 mCi IV dose of Tl-201 thallous chloride to a patient since the dose only contains ~40 ng of Tl$^{1+}$. This mass of Tl is much too small to cause any type of physiological response in the patient and the risk:benefit ratio is very much in the patient’s favor.

CATEGORIES OF RADIOPHARMACEUTICALS FOR MYOCARDIAL IMAGING
- Myocardial perfusion agents (Tl-201, Rb-82, Tc-99m agents)
- Blood Pool agents (Tc-RBC)
- Myocardial Viability Agents (F-18 FDG)
- Myocardial metabolism agents (I-123 BMIPP or other long-chain fatty acids)
- Myocardial necrosis agents, for example, labeled monoclonal antibodies (currently unavailable)
- Myocardial Infarction agents (Tc-99m PYP)

OTHER NON-CARDIAC USES OF Tc-99m CARDIAC AGENTS
Tc-99m Sestamibi for parathyroid imaging, breast tumor imaging, and imaging of other malignant tumors.
PROPERTIES OF IDEAL MYOCARDIAL PERFUSION IMAGING AGENT

- Uptake proportional to blood flow
- High heart/background ratio
- Rapid blood clearance, no redistribution, no clearance
- Isotope energy optimal for imaging and dosimetry
- Readily available low cost Tc-99m agent
- Suitable for myocardial perfusion with SPECT
- Xenon-like compound (inert)
- Lipid soluble, crosses cell membranes
- High myocardial extraction efficiency at all flows
- No pharmacologic effects
- Short effective half-life allows repeated studies over short time span
- Minimal radiation dose

PROPERTIES OF THE IDEAL MYOCARDIAL INFARCTION IMAGING AGENT

- High uptake in infarcted area; no uptake in normally functioning myocardium or ischemic areas
- No pharmacologic effects
- Minimizes radiation dose
- Rapid blood clearance
- Instant kit Tc-99m agent with ideal photon energy, low cost and wide availability.

PROPERTIES OF IDEAL MYOCARDIAL IMAGING AGENT FOR DETECTION OF "HIBERNATING MYOCARDIUM"

- Uptake in tissue that is still living, but functioning poorly. Can help to determine if patient is a candidate for revascularization procedure.
- No pharmacologic effects
- Minimizes radiation dose
- Rapid blood clearance
- Radiolabeled sugar analog (e.g., F-18 FDG)
- Low cost and wide availability.
MYOCARDIAL PERFUSION AGENTS: POTASSIUM ANALOGS

- Cs-127 and Cs-129 salts
- Rb-81 and Rb-82 salts
- Tl-199 and Tl-201 salts
- N-13 ammonium ion
- Why do Tl$^{1+}$, Cs$^{1+}$, and Rb$^{1+}$ behave like K$^{1+}$? These monovalent cations have an ionic radius, charge, and charge distribution very similar to that of K$^+$. The heart is fooled by the similarity and there is uptake of these ions equivalent to that of K$^+$.

POTASSIUM 43 AS A REFERENCE STANDARD

- K-43 was the first reference standard for cardiac imaging; it is the physiological tracer
- Its uptake is flow-dependent; 5-8% of injected dose localizes in the heart, which represents fraction of cardiac output passing through the coronary circulation
- Physical half-life is 22 hours
- Count rate peaks 10 minutes post-injection
- Difficult to collimate due to high energy- K$^{43}$ decays to Ca$^{43}$, emitting gamma rays having energies 0.369, 0.627, 0.219, 0.393, and 1.00 Mev
- Radiation dosimetry is a consideration since there are beta- particles emitted with energies of 1.839, 1.218, 0.927, 0.460, and 0.243 MeV with relative abundance of 1.6, 5.4, 83.1, 5.4, and 4.5 percent, respectively.

Rb-82 CHLORIDE FOR RAPID REPEAT STUDIES OF MYOCARDIAL PERFUSION

- Rb-82 has a short physical half-life of 75 seconds and is useful for PET studies
- Tc-99m teboroxime (currently not available) has a short biological half-life for both SPECT and planar imaging and repeated studies can be done during one day.

N-13 LABELED AMMONIUM ION

- Positron emitter; $t_{1/2} = 10$ minute
- Extraction efficiency > than 90%
- Rapid blood clearance
- May be involved in enzymatic processes
- May involve Na+/K+ ATPase mechanism
- Marked lung uptake in all smokers
- Limited availability (requires on-site cyclotron)- it is NOT commercially available
- Image quality similar to that of Tl-201
I-123 FATTY ACIDS

- Highly extractable compounds
- Metabolizable, especially in non-fasting state
- Ultimately produces carbon dioxide
- Images similar to Tl-201
- $t_{1/2}$ equals 13.3 hours; energy equals 159 keV
- Characteristic pattern in patients with ischemic cardiomyopathy
- Currently unavailable but easy to radiolabel

COST PER PATIENT STUDY (COMMERCIAL RADIOPHARMACY) JANUARY 2014

- Tl-201 chloride: $15/mCi, $75 for stress/rest study
- Tc-heart agent: $50-75/dose x 2 doses = $100-150 for stress/rest study

PHYSICAL PROPERTIES: Tl-201

- Low energy (71-80 keV X-rays from Hg-201 daughter)
- Potassium analog; hemical form: Thallous Chloride (Tl-201)
- Perfusion marker under most conditions; redistributes
- Tl-201 is a cyclotron produced nuclide with $t_{1/2} = 73$ hours.
- Limitation: photons easily attenuated by body tissues (71 keV Hg x-rays)
- Long physical and biological half-lives increase radiation dose, limiting patient injectable doses to 5 mCi. Critical organ in males: testes. 3,000 mRem/mCi
- Imaging procedure involves a stress exam followed by a second exam after redistribution which can take anywhere from 4-24 hours

PHYSICAL PROPERTIES: Tc-99m

- Low energy
- Tc-99m is a generator-produced nuclide with $t_{1/2} = 6$ hours;
- Photons easily penetrate body tissues (140 keV $\gamma$-rays)
- Moderate radiation dose per mCi- can inject a max of 40-50 mCi for a stress/rest study

PHARMACOLOGIC PROPERTIES OF THALLIUM-201

- Tl$^{1+}$ ion is a Potassium analog and is a perfusion marker under most conditions.
- Undergoes redistribution so stress-induced ischemia will fill in at rest.
- Imaging procedure typically involves a stress exam followed by a second exam after redistribution which can take anywhere from 4-72 hours
Tc-99m MYOCARDIAL PERFUSION IMAGING AGENTS

- Tc-Sestamibi has a long $c$. Can image up to 6 hr post injection
- Tc-Tetrofosmin has a long $t_{\text{biol}}$. Can image up to 6 hr post injection
- Tc-Teboroxime has a short $t_{\text{biol}}$. Must image within 25 min time window post injection. (Drug is currently off the market)

UTILITY OF Tc-99m SESTAMIBI: A MULTIPURPOSE RADIOPHARMACEUTICAL

- Myocardial perfusion imaging
- Parathyroid adenoma and breast tumor imaging
- Other tumor imaging

Tc-99m SESTAMIBI: PROPERTIES

- Labeled with Tc-99m
- Not a true potassium analog
- Uncouples from flow at high flow rates
- High extraction efficiency
- Long biological half-life
- Ease of preparation; stable for 6 hours

Tc-99m TETROFOSMIN: PROPERTIES

- Labeled with Tc-99m; not a true potassium analog
- Uncouples from flow at high flow rates
- High extraction efficiency
- Long biological half-life
- Ease of preparation; stable for 6 hours

Tc-99m TEBOROXIME: PROPERTIES

- Labeled with Tc-99m
- Not a true potassium analog
- High extraction efficiency
- Short biological half-life
- Neutral and lipophilic (like xenon)
- Rapid myocardial clearance
- Ease of preparation; stable for 6 hours
INDICATIONS FOR USING Tc-99m MYOCARDIAL PERFUSION AGENTS

- Identification of ischemic heart disease
- Detection and localization of myocardial infarction
- Assessment of global ventricular function and wall motion
- Perfusion, wall motion, and first pass studies
- Screening
- Emergency admissions
- Assessment of conventional therapies, thrombolytic therapy, and angioplasty
- Prognostic information
- Pharmacological stress testing

KEY ADVANTAGES OF Tc-99m LABELED CARDIAC AGENTS

- Tc-99m Labeled Kit
- Available 24 hours a day
- Allows more scheduling flexibility
- Higher count rate = better images
- Ideal for SPECT imaging
- Measures perfusion and wall motion
- More diagnostic information from a single study
- Broader clinical applications

COMPARISON OF IMAGE QUALITY OF Tl 201 AND Tc-99m CARDIAC AGENTS

- Tc-99m has more optimal energy
- Higher injected dose means more photons and better counting statistics
- Higher target to background ratio
- More rapid acquisition
- Improved resolution
- Fixed Distribution provides flexibility and permits gating

FUNCTIONAL IMAGING USING Tc-99m CARDIAC AGENTS

- First Pass Ventriculography
- Ejection fraction
- Regional wall motion
- Gated Equilibrium Imaging
- Myocardial wall thickening
- Combined First Pass/Perfusion Study
BROADER CLINICAL APPLICATIONS OF Tc-99M CARDIAC AGENTS

- Acute Interventional Therapy, e.g., thrombolysis, angioplasty
- Cardiac Transplant
- Unstable Angina

Flexibility of Studies Using Tc-99m Cardiac Agents

- Multiple protocols on the same patient
- Planar and SPECT
- More than three views
- Gated and static acquisition
- First pass/Perfusion
- Patient Scheduling
- Imaging time
- Stress testing schedule
- Same day/Two day protocols

OVERVIEW

- Chronic CAD: Tc-perfusion agents surpass Thallium 201 for detection and vessel identification
- Acute MI: accurate for detection and localization
- Ventricular function: accurate for LVEF determination by first pass technique
- Tc-99m is equivalent to TL-201 for detecting coronary artery disease
- The superior physical properties of Tc-99m make it a major advance in nuclear cardiology imaging
INFARCT IMAGING

THE PURPOSE OF USING INFARCT AVID AGENTS:
To evaluate patients presenting with

- chest pain of uncertain etiology; clinical indications could include any of the following
- atypical chest pain
- conduction disturbances
- non-q-wave infarction
- late clinical presentation
- post-CABG

CLINICAL INDICATIONS

- Post-thrombolysis
- Post-cardioversion
- Chest trauma
- Extensive localization of q-wave infarction

IMAGING OF ACUTE MYOCARDIAL INFARCTION: A HISTORICAL PERSPECTIVE

- Hg-197 compounds
- Tc-99m tetracycline
- Tc-99m glucoheptonate
- Tc-99m pyrophosphate
- Tc-99m antimony antibody
- In-111 antimony antibody

Tc-99m PYROPHOSPHATE FOR IMAGING OF ACUTE MIs

- Ideal imaging isotope
- Minimal radiation dose to patient
- Images acute infarcts only, not ischemic areas
- Readily available, inexpensive, simple to prepare
- Reliably detects AMIs within 1-6 days post infarct, ideally 24-72 hours post infarct
- Mechanism involves binding of Tc-PYP to hydroxyapatite crystals formed when circulating phosphate combines with Ca$^{2+}$ ions entering cells at time of cell death
**In-111 ANTIMYOSIN ANTIBODY FOR IMAGING ACUTE MIs**

- F\textsubscript{AB} antibody fragment
- Specific for myocardial necrosis
- Not a flow marker
- Image at 16-24 hours
- Positive up to 14 days post-MI

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**MISCELLANEOUS USES: Sestamibi**

**Prognostic indicator: Breast Tumor Imaging with Tc-99m Sestamibi**

- ~1% of injected dose localizes in the tumor
- Delayed views demonstrate presence of tumor
- May locate lesions missed on mammograms
- Utilized mostly for high-risk patients; not suitable for annual screening
- Image quality is very dependent on position of camera relative to breast
- Possibility of a dedicated conical shaped camera to optimize imaging

**Parathyroid imaging with Tc-99m Sestamibi**

- Localizes preferentially in thyroid, parathyroids, and in parathyroid adenomas
- Early imaging identifies thyroid, parathyroid and adenoma
- Delayed views demonstrate the presence of adenoma only. If subtraction technique is desired, thyroid image may be produced using I-123 sodium iodide