In The Name of God

Application of nuclear imaging using PET/SPECT techniques for assessment of CVD

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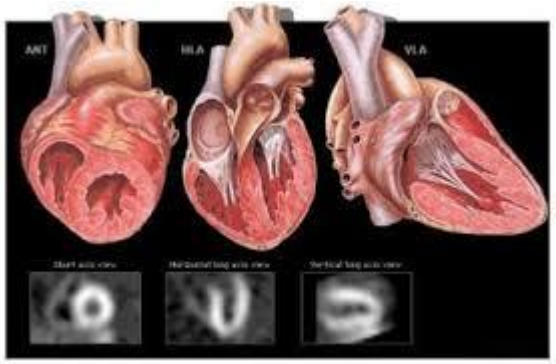
Presentation Outline

- Cardiac imaging in CAD
- Nuclear cardiac imaging
- SPECT & PET imaging in CAD
- Ideal Characteristic of cardiac radiopharmaceutical
- Radiopharmaceutical in cardiac imaging



Cardiac Imaging in CAD

- Cardiovascular diseases are the first cause of death globally.
- Early detection of coronary artery disease (CAD) is a challenge for clinicians.
- Over the past 2 decades there have been several improvements in the methods for the assessment of diagnosis and prognosis in patients with suspected CAD.
- Critical to management of symptomatic patients is the appropriate use of noninvasive diagnostic tests.

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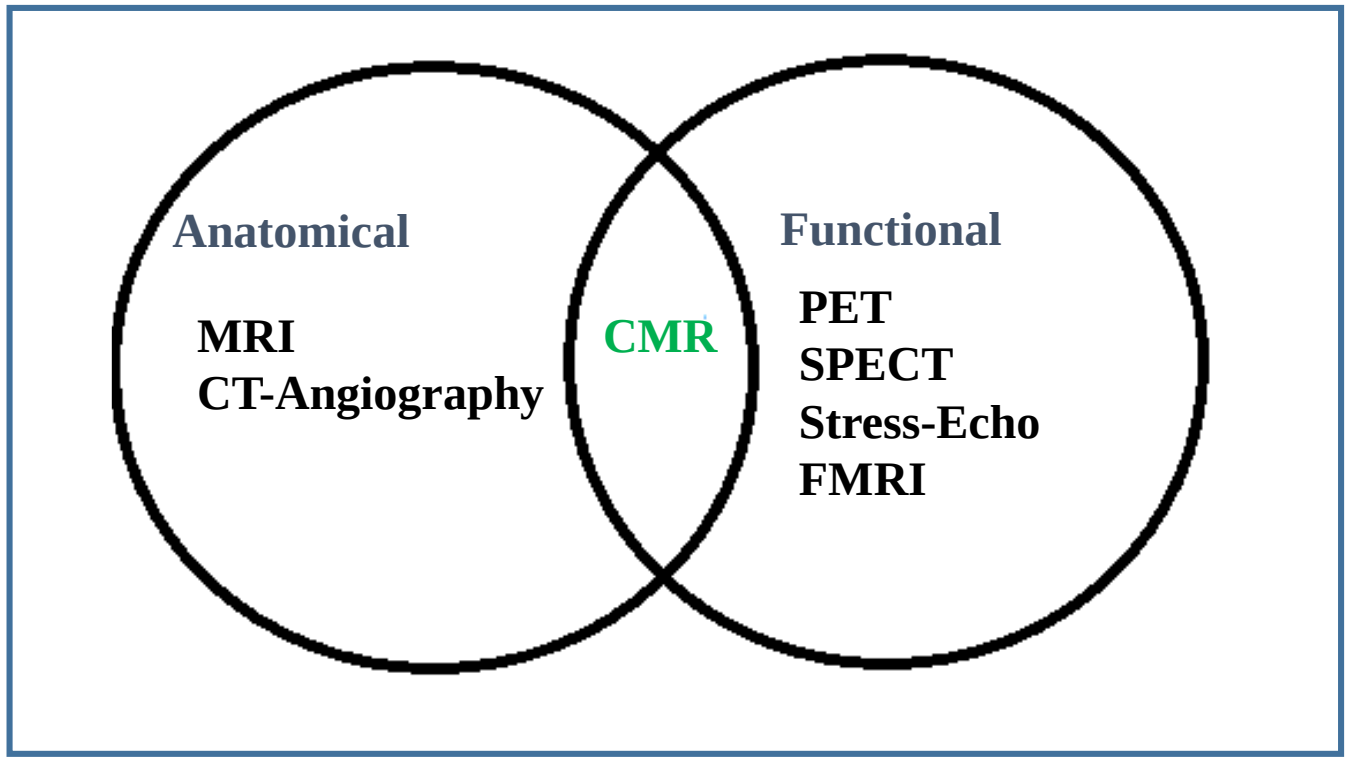
Cardiac imaging modalities in the diagnosis of CAD

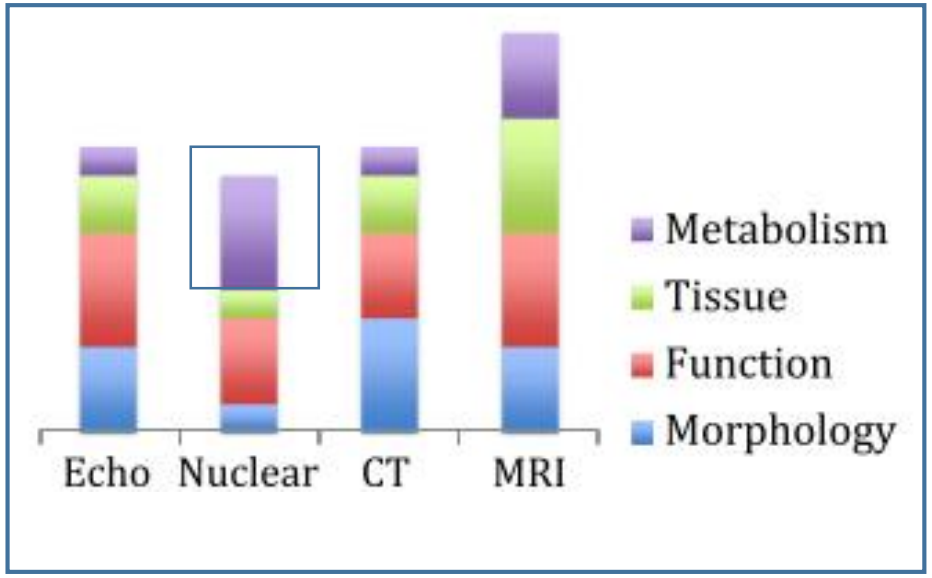
- Coronary CT angiography
- Stress echocardiography (ECHO)
- Myocardial perfusion imaging (MPI)(SPECT)
- MPI (PET)
- Cardiac magnetic resonance imaging (CMR)

Strengths and limitations

Imaging modalities	CCTA	Echo	CMR	SPECT	PET
Advantage	Non-invasive evaluation of coronary anatomy, High negative predictive value, Excellent resolution (approximately 0.6 mm) of coronary artery anatomy	Availability at the beside for analysis without IR	Adaptable for functional and anatomical assessment, excellent image quality, Flow quantification	Wide availability ,functional & quantification, possible in patient with high BMI	High resolution, high spatial resolution
Disadvantage	Absence of functional information, radiation dose (8–24 mSv), contrast dye exposure, and necessity to achieve a slow, regular heart rate,	No-coronary artery stenosis analysis & quantification challenges	Limited availability, presence of contraindications such as arrhythmias, claustrophobia	Low image quality, radiation exp.	Low availability, radiation exp.
Specificity	93%	90%	58%	67%	90%
Sensitivity	90%	45%	97%	72%	81%

Functional versus anatomical imaging for CAD





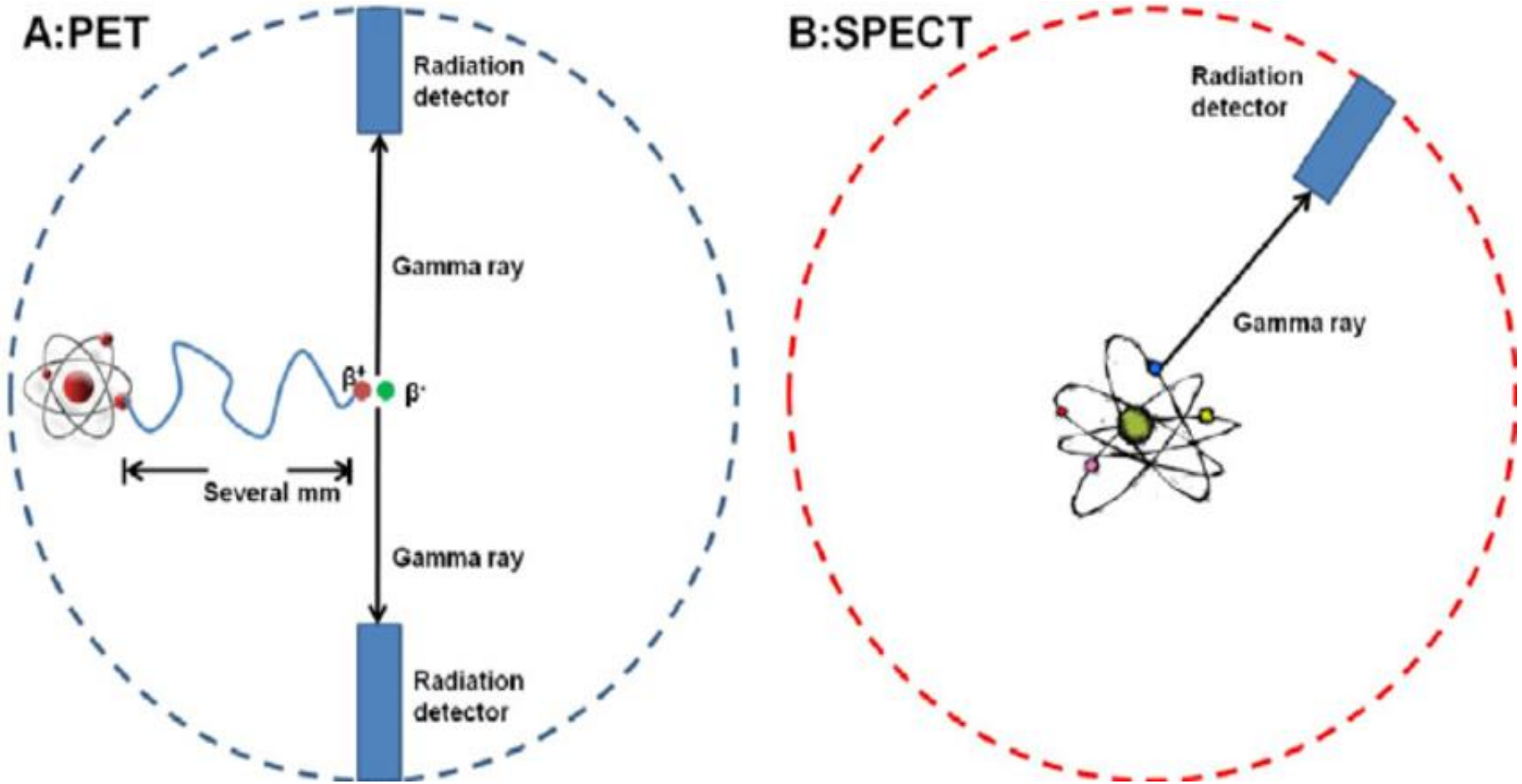
Nuclear cardiac imaging indications

- Diagnosing & assessing CAD
- Cardiomyopathy & identify possible damage to the heart from **chemotherapy/radiotherapy**
- To visualize blood flow patterns to the heart walls, called MPI
- To evaluate the presence and extent of suspected or known CAD
- To determine the extent of injury to the heart following a heart attack, or **myocardial infraction**
- To evaluate the results of bypass surgery or other revascularization procedures designed to restore blood supply to the heart
- In conjunction with an electrocardiogram(ECG), to evaluate **heart-wall movement and overall heart function with a technique called cardiac gating**.

SPECT & PET Strategies

- Cardiac molecular imaging involves the injection of a radioactive label, or "radiotracer", which circulates into the heart. Using either a PET (positron emission tomography) or SPECT (single photon emission computed tomography) scanner, the patient then undergoes a scan of the heart that detects the radioactive signal from the heart and produces a detailed three-dimensional image.

Illustration of PET & SPECT



SPECT *vs* PET in nuclear cardiology

Method	Advantages	Disadvantages
SPECT	SPECT is much more **widely available** than PET. It's also much more affordable. The longer **half-life of the SPECT** radiotracer makes it more widely available and is ideal for cardiac stress testing	SPECT does not provide a **quantifiable estimate** of the blood flow. SPECT resolution is at **12mm to 15mm** and images can be prone to attenuation on older cameras.
PET	Biggest pluses for PET scanning is the superiority of its **image quality.** PET provides high **spatial resolution** and the capability to **provide quantitative estimates** of blood flow.	PET is **less widely available** and much more costly to implement. technicians **need to work very quickly** to get the images required.

Procedure of nuclear imaging

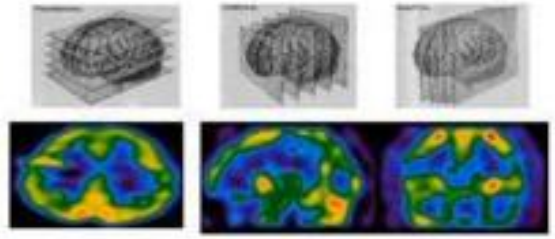
$^{99m}_{43}Tc_{56}$
Technetium
T½ 6.01 h
E 142.6833 keV

Pharmaceutical kit

^{99m}Tc-marked pharmaceutical

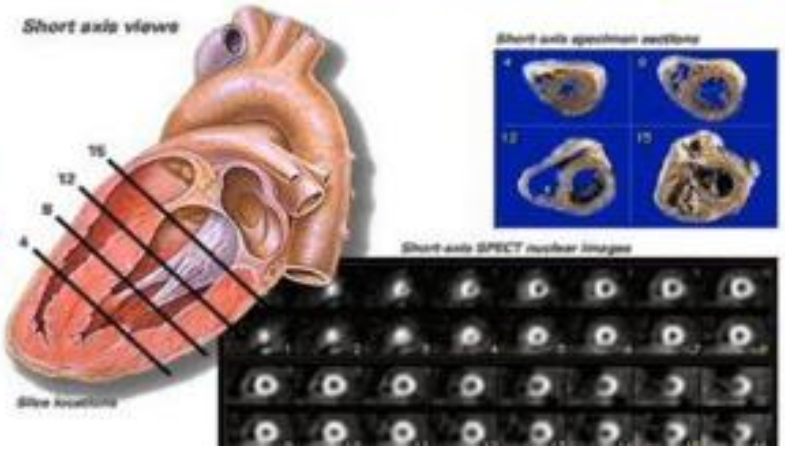
The radiotracer, injected into a vein, emits gamma radiation as it decays. A gamma camera scans the radiation area and creates an image.

Other organs imaging

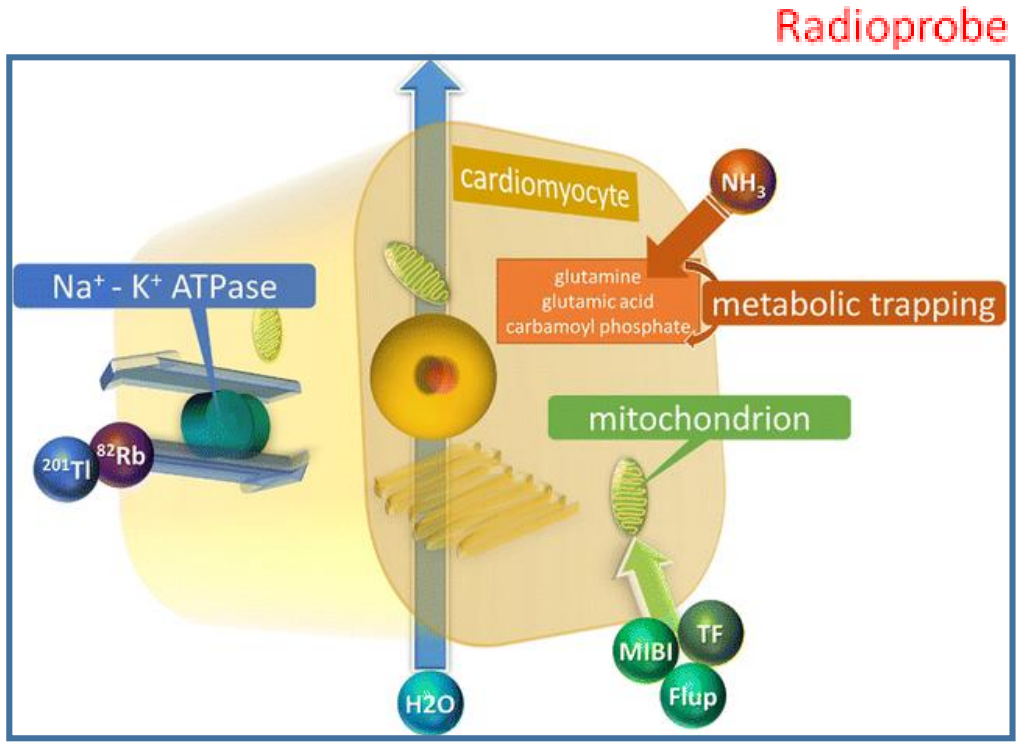


Brain Imaging

Myocardial Imaging



Radiopharmaceutical In Heart Diagnostic Imaging



Important challenges of radiotracer in cardiac imaging

- The kinetics of radiotracers
- Mode of uptake
- Retention and release from the myocardium

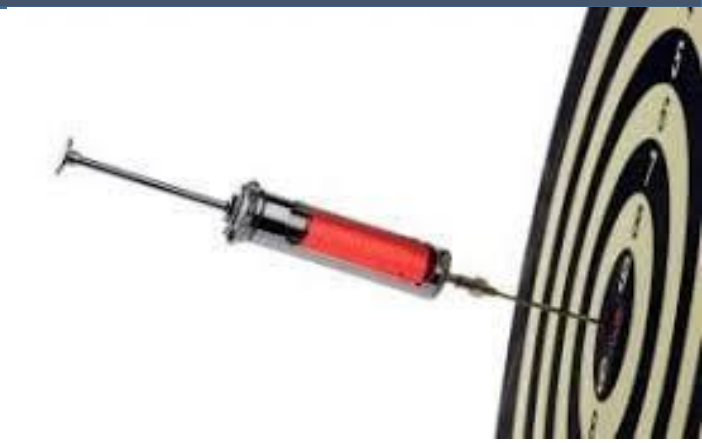
are relevant for designing and implementing optimized nuclear cardiac imaging protocol.

Ideal characteristic of cardiac radiopharmaceutical

- The myocardial uptake of the radiotracer must be proportional to the regional myocardial blood flow over a relatively wide range of blood flows.
- The myocardial uptake should be high enough to allow for detection of regional inhomogeneity by external gamma scintigraphy.
- The initial myocardial distribution of the radiotracer at the time of injection must remain stable during the acquisition time of the images.
- The effect of blood flow on myocardial transport of the radiotracer must be predominant to the effect of metabolic cellular alterations.
- Finally, the agent should be labeled to a radionuclide having adequate physical characteristics to provide high photon flux and optimal counting statistics.

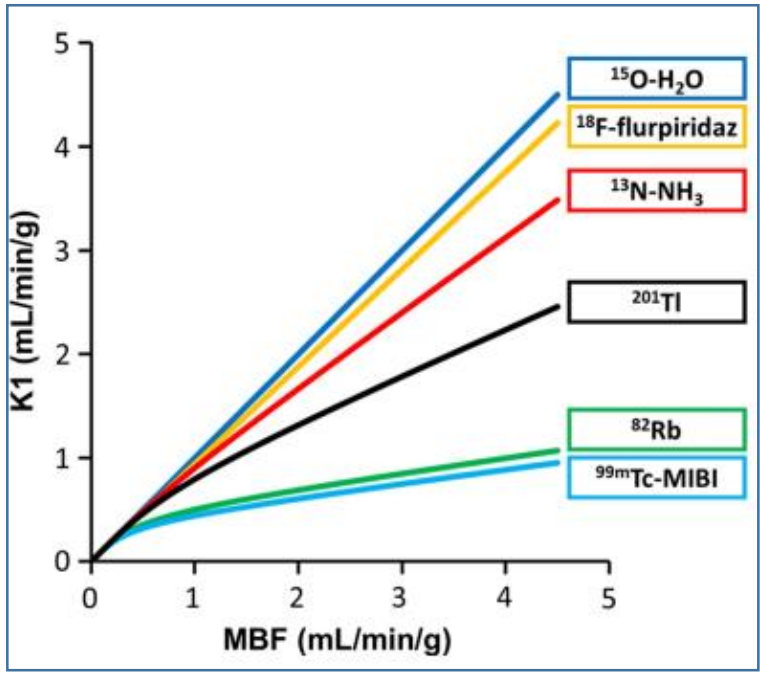
Target of radiopharmaceutical in nuclear cardiology

- Perfusion
- Metabolism
- Sympathetic
- Inflammatory



Perfusion Imaging

- Myocardial blood flow (MBF) is supplied by coronary arteries to preserve adequate myocardial oxygen supply.
- At rest, coronary artery stenosis must exceed 85% to 90% of luminal diameter before there is a significant decrease of MBF.
- Maximal coronary flow has been shown to be reduced with stenosis of 45% to 50% under stress condition.



SPECT tracers for perfusion imaging

^{43}K

- **Initially, the monovalent cation of potassium-43 (^{43}K), γ- emitter, was used for imaging of myocardial perfusion**.

- Main gamma energy of this radionuclide (0.37 and 0.67 MeV)

- ^{43}K has a relatively long half-life (22 hours) and emits relatively high-energy β-particles [300 Kev].

^{201}Tl (Thallous chloride)

- Monovalent cation with biologic properties similar to potassium
- Use for myocardial perfusion imaging & viability
- Low energy photons (69-80keV) degrade the spatial images due to scattering
- Long half life ~ 73h; increases radiation dose to the patient
- Cyclotron produced & expensive

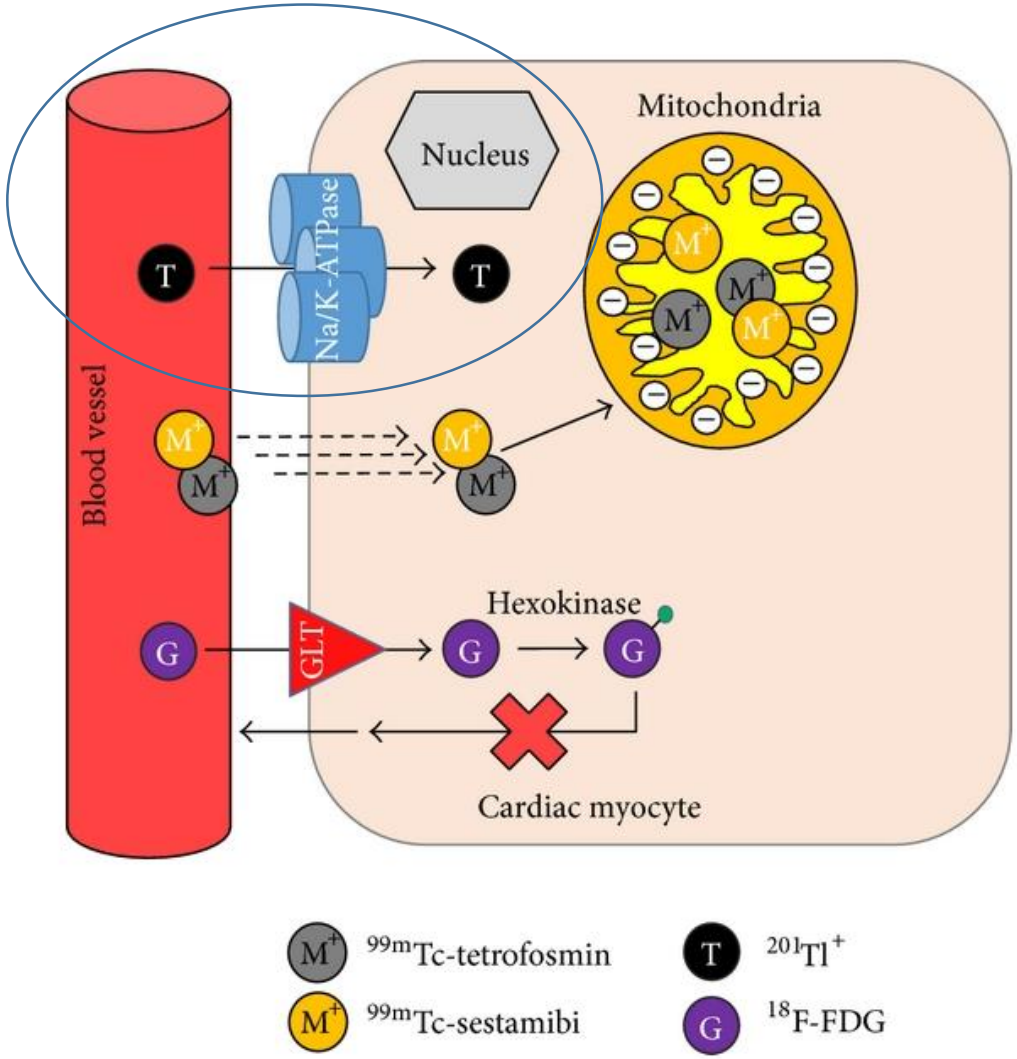
^{201}Tl (Thallous chloride)

- Protocols (Stress & Rest)

- Inject at stress (2-3mCi/74-11MBq)

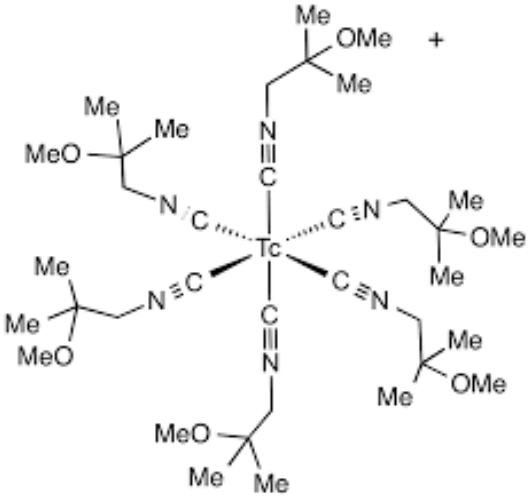
- First imaging 5-10 minutes post-injection

- Redistribution imaging 3-4h post-injection



^{99m}Tc-sestamibi (Cardiolite)

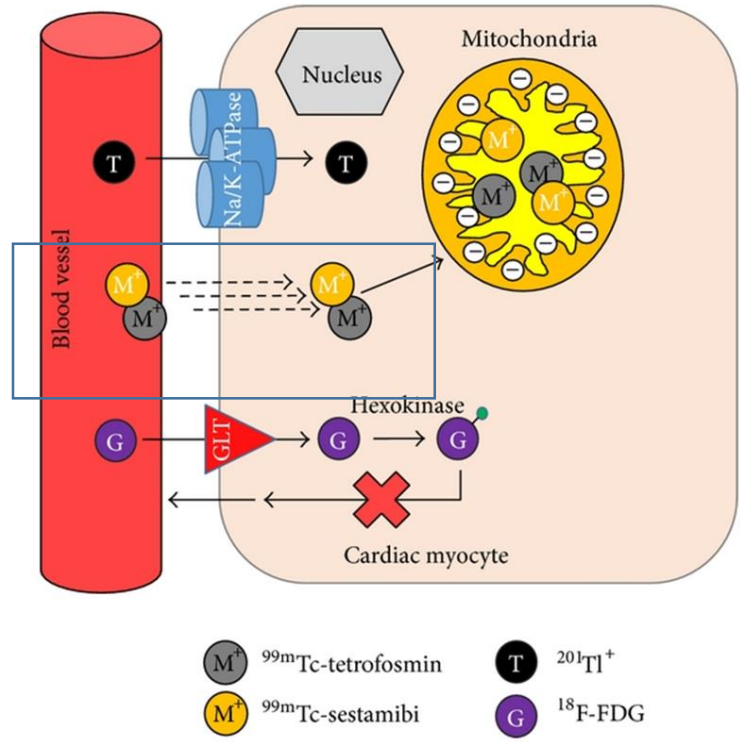
- ^{99m}Tc is a generator-produced agent eluted from molybdenum-99 (99Mo).
- **Half-life is 6 hours.**
- The peak energy level of γ-rays from ^{99m}Tc is about 140keV.



- ^{99m}Tc-sestamibi is rapidly cleared from blood after intravenous administration.

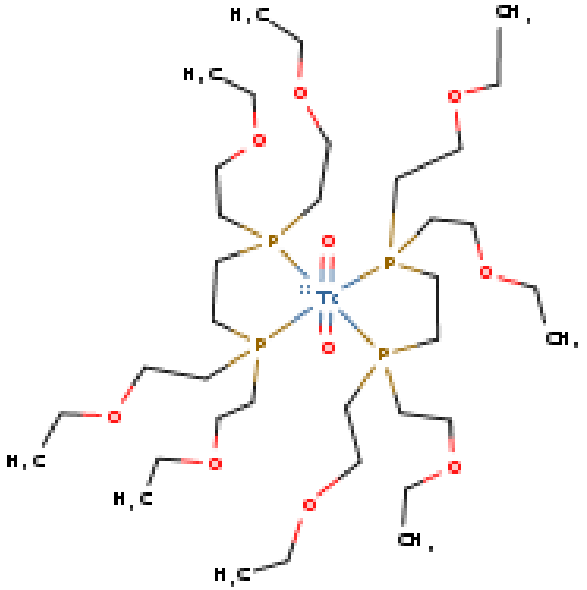
^{99m}Tc-sestamibi (Cardiolite)

- Predominant liver uptake; It is suggested to take fatty meals or milk to hasten the clearance of the hepatic activity.
- Require heating in preparation.
- Redistribution in minimal/not at all.



99mTc-Tetrofosmin (Myoview)

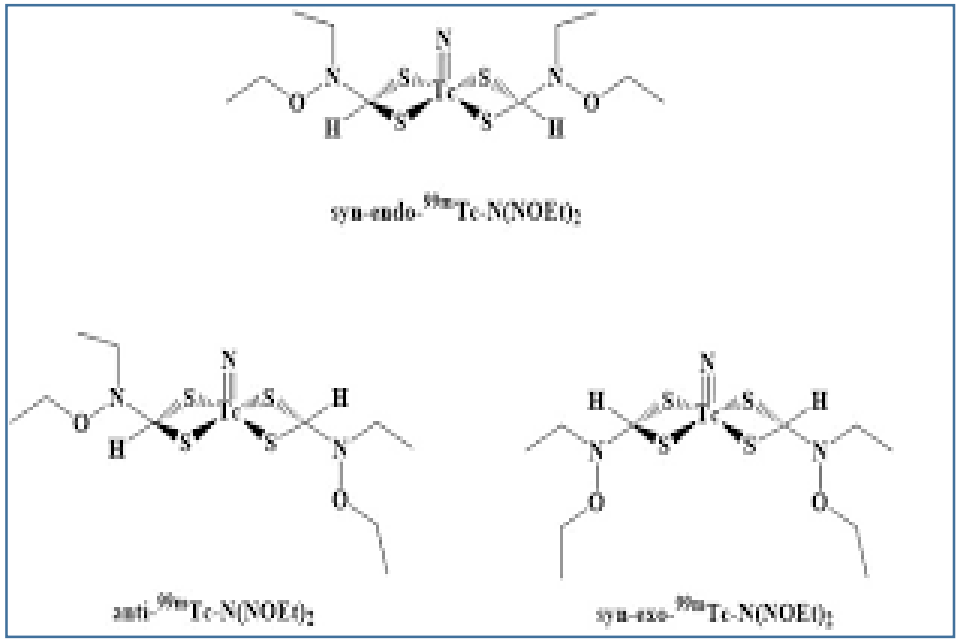
- Indicted for myocardial perfusion abnormalities.
- Rapidly cleared by the blood.
- By 48h, urinary excretion is approximately 40%.
- Fast clearance of the hepatic, lung & gallbladder activity.
- Redistribution is minimal/not at all.



Novel SPECT Tracers

➢Technetium-99m-N-NOET

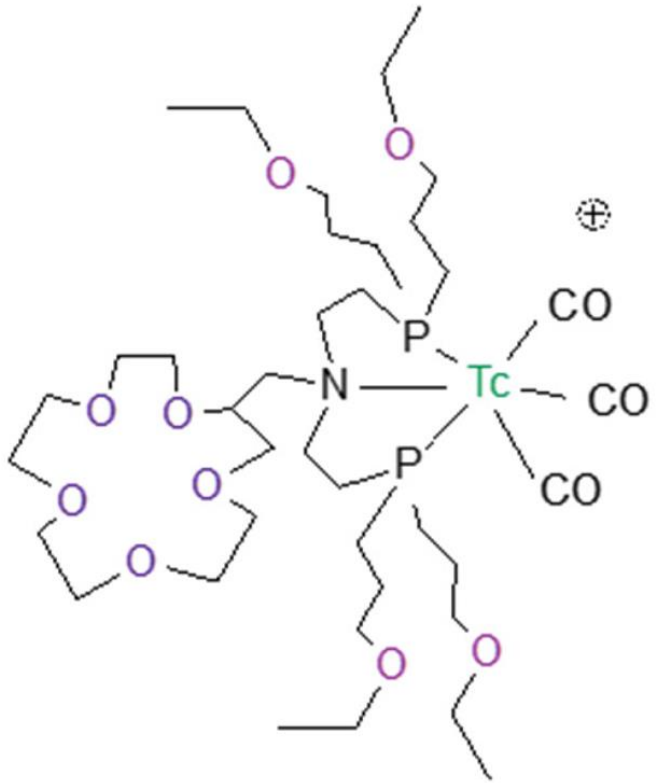
- Lipophilic MPI agent
- High first-pass extraction fraction
- Delayed redistribution kinetics
- Mechanism of uptake has not been clearly elucidated



Novel SPECT Tracers

➢Technetium-99m-15C5-PNP

- High initial cardiac uptake
- Shorter washout half-life in the liver
- Lower residual liver activity
- Higher heart-to-liver

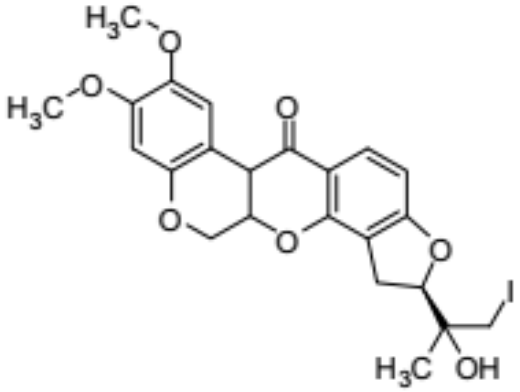


^{99m}Tc-15C5-PNP

Novel SPECT Tracers

➢Iodine-123-CMICE-013

- Physical half-life (13.2 hours)
- Gamma energy (159 keV)
- Good myocardial/liver and myocardium/lung uptake ratios
- High cost of 123I



$^{123/127}$I-CMICE-013 (D)

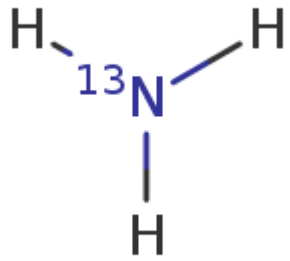
PET tracers for myocardial perfusion imaging

^{82}*Rb-choloride*

- Most widely used tracer
- **Strontium-82 (82Sr)/82Rb** generator-produced tracer
- Physical half-life of ^{82}Rb **(76 seconds)**
- Transported into myocytes through the **Na^+/K^+ adenosine triphosphate (ATP) transport system**

$^{13}NH3$

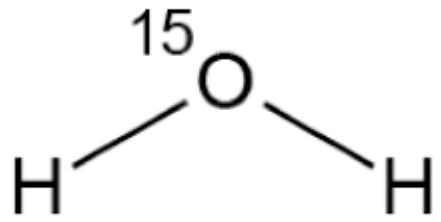
- Cyclotron produced



- Half-life: 9.965 min
- Rapid clearance from the blood pool
- Approved for detecting CAD in cases of CAD unable to be diagnosed with using SPECT MPI.

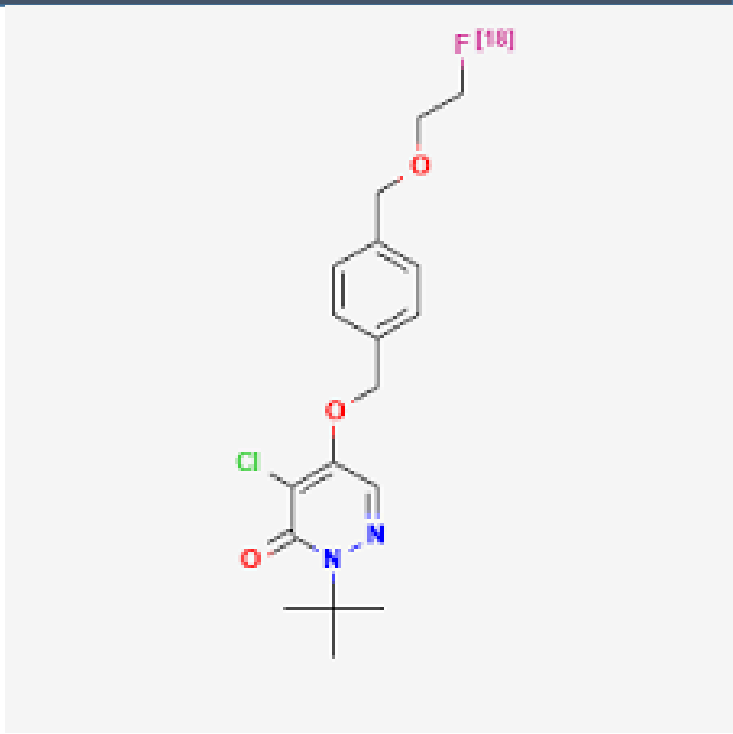
15O-H2O

- Cyclotron produced and limited in availability.
- Half-life: 2 minutes
- Study is performed by administering on-line from the cyclotron with an intermediate conversion of $^{15}O2$ to $^{15}H2O$ in a reaction vessel.



(18F)-flurpiridaz

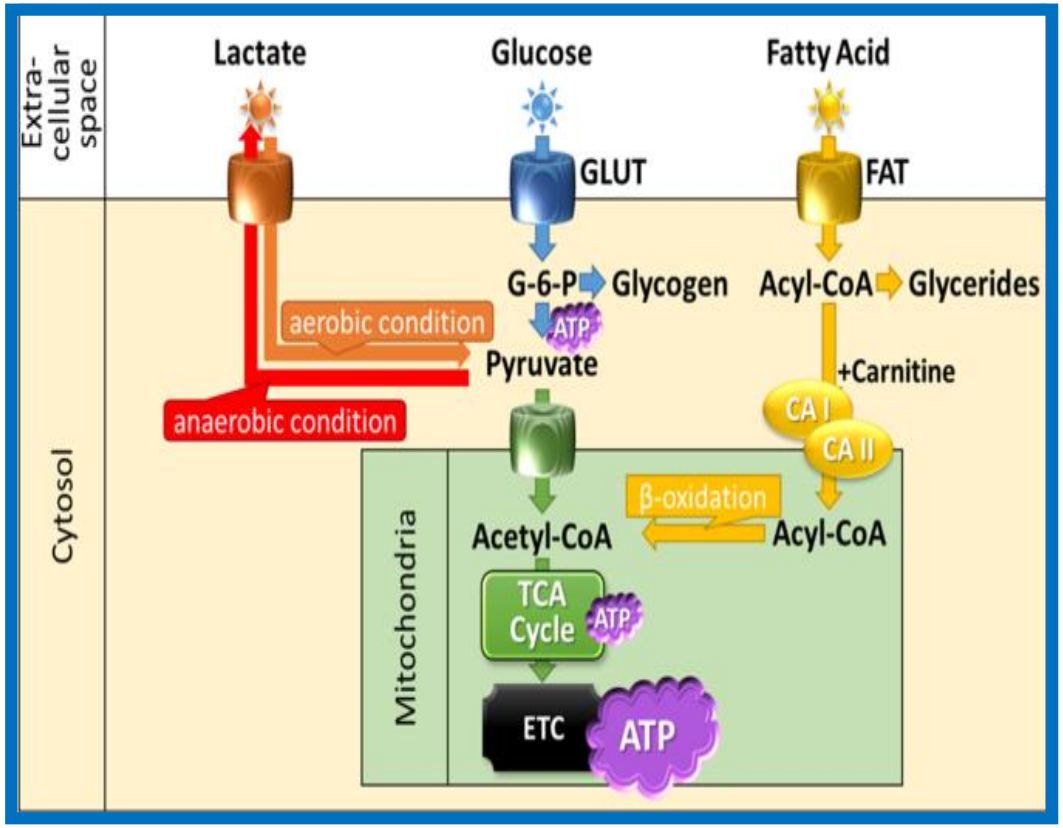
- High first-pass extraction and high affinity in myocardial
- slow washout from cardiomyocytes
- Half-life: 109.8 min



Metabolic Imaging

Pathogenesis of a variety of cardiac disease processes such as:

- Left ventricular hypertrophy
- Myocardial ischemia
- Diabetic cardiomyopathy.

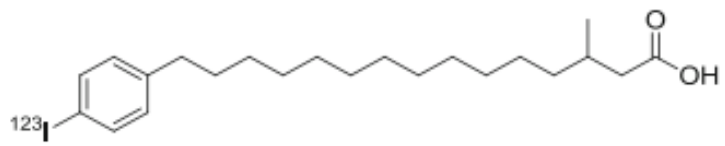


SPECT tracers for metabolic imaging

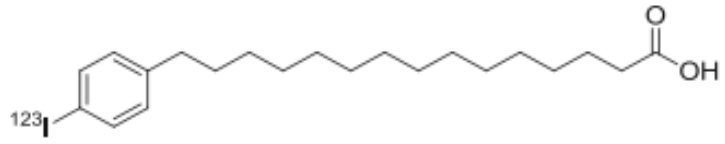
^{123}I-BMIPP & 123I-IPPA

- Iodinated fatty-acid analog used to assess myocardial fatty acid metabolism.
- Rapidly distributed to various organs, such as liver and heart, and cleared rapidly from the blood.
- ^{123}IBMIPP has been approved in Japan only for clinical use.

^{123}I-BMIPP



^{123}I *p*-IPPA

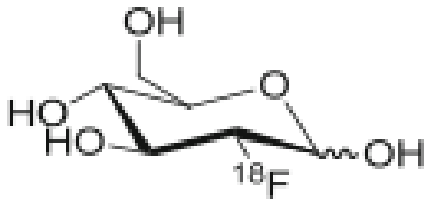


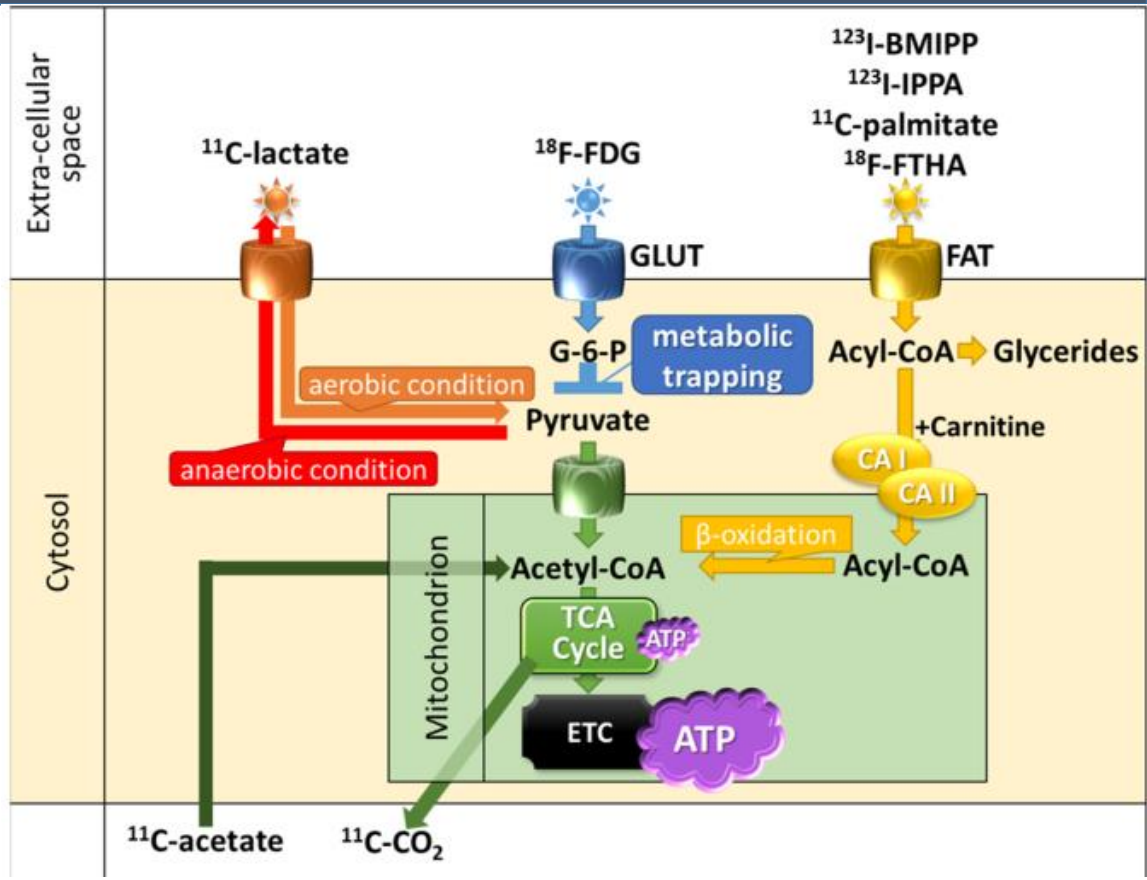
PET tracers for metabolic imaging

18F-FDG

- Mainly employed for the assessment of malignant tumors.

- Accumulates intracellularly without being metabolized during glycolysis, a condition referred to as ‘‘metabolic trapping.

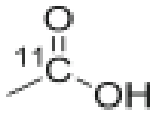


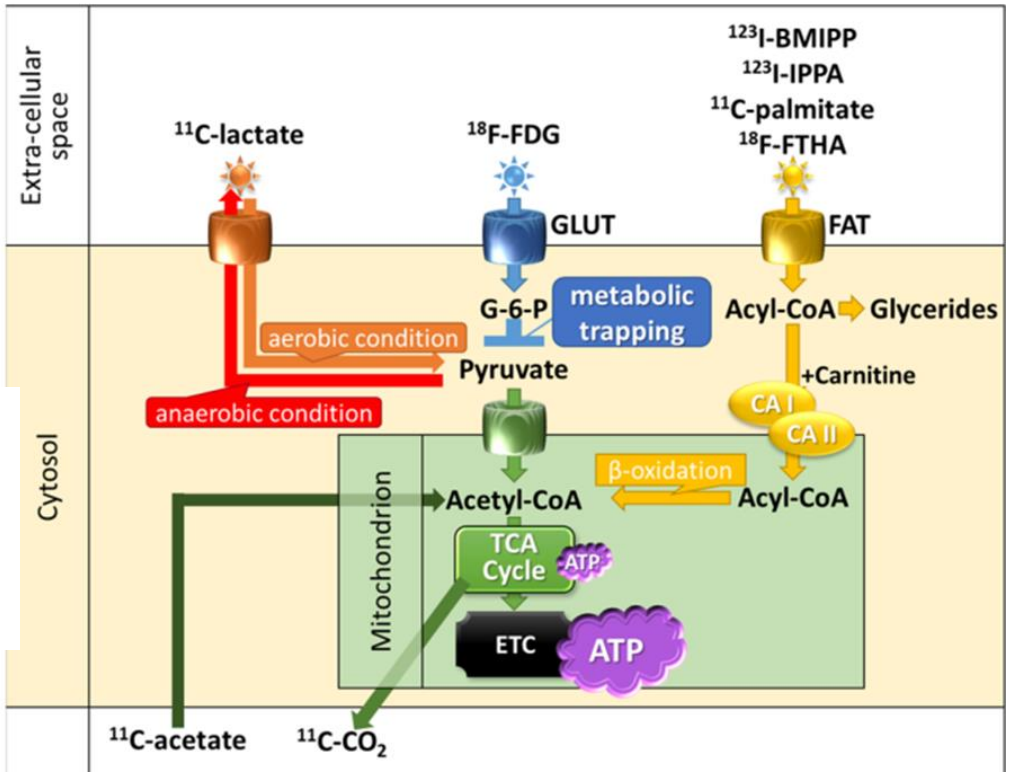


11C-acetate

- For Myocardial oxygen metabolism & blood flow
- For observation of regional myocardial oxygen metabolism in the presence of ischemia, cardiomyopathy and heart HF in a state of deprived energy.

^{11}C-acetic acid

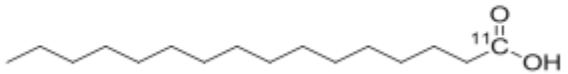


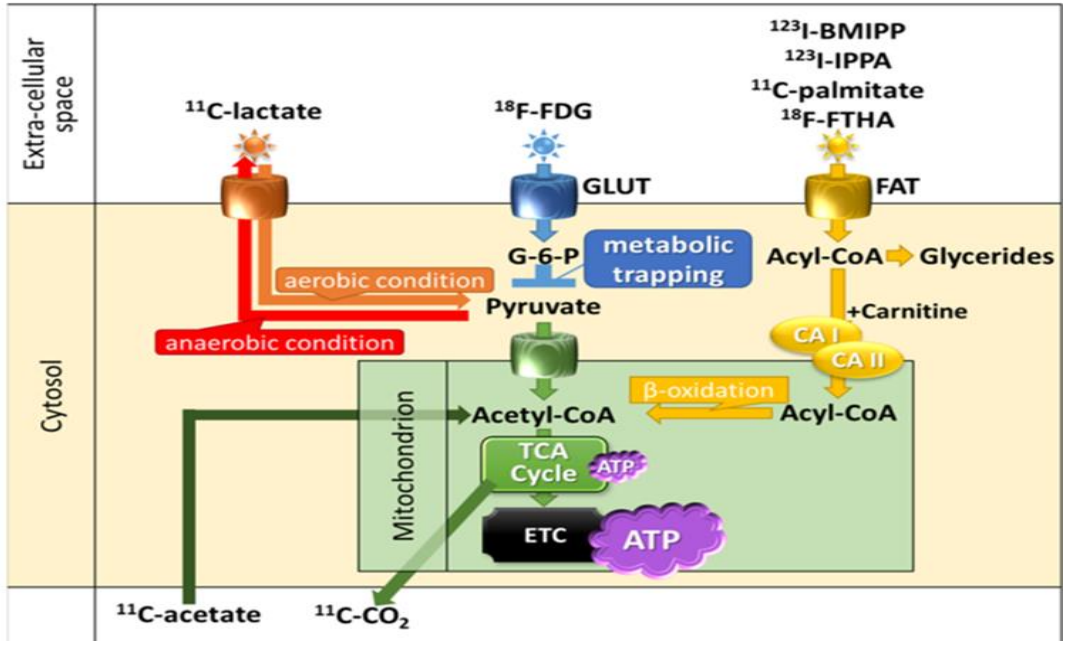


11C-palmitate & 18F-FTHA

- Used to evaluate fatty acid metabolism
- Shift in myocardial metabolism from fatty acid to glucose can be estimated using these fatty acid analogs.

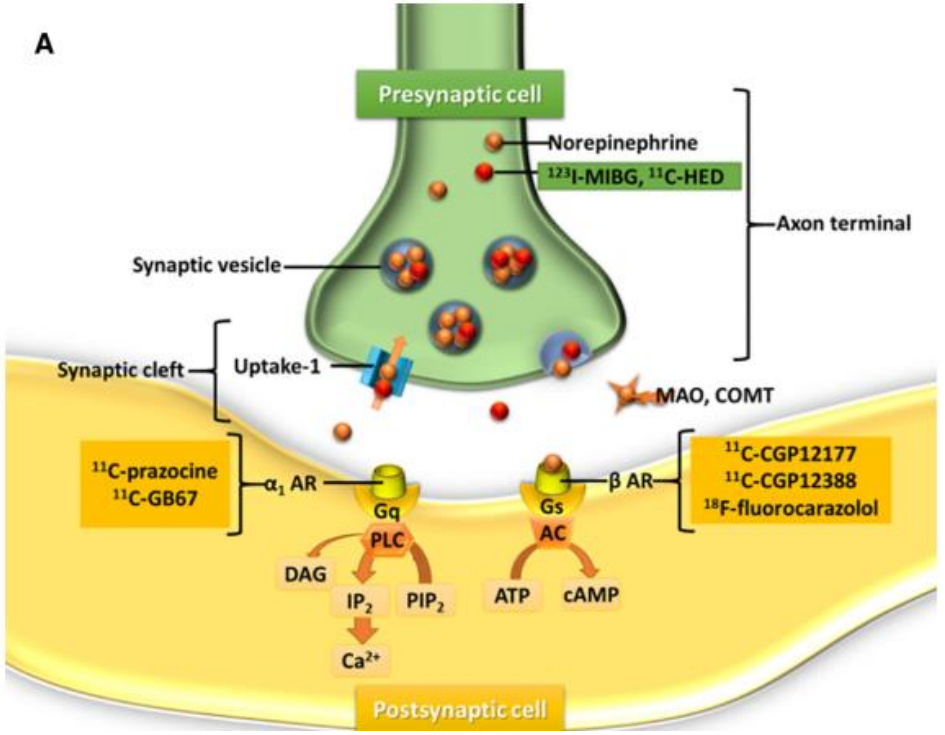
^{11}C-palmitatic acid





Sympathetic Imaging

- In ischemic heart disease, a mismatch region of myocardial blood flow and sympathetic dysfunction is reported as a decision criterion for prediction of fatal arrhythmia and indication for cardioverter-defibrillator implantation.

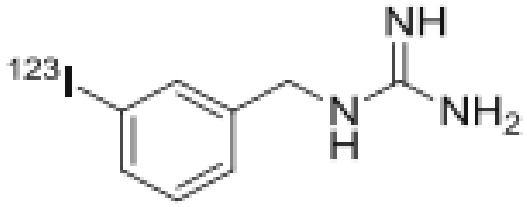


SPECT tracers for sympathetic imaging

(123I-MIBG)

- Widely used as a SPECT tracer to evaluate the presynaptic sympathetic innervation of the heart.
- It is an analog of catecholamine, which is taken up via the uptake-1 mechanism and stored in synaptic vesicles as is NE.

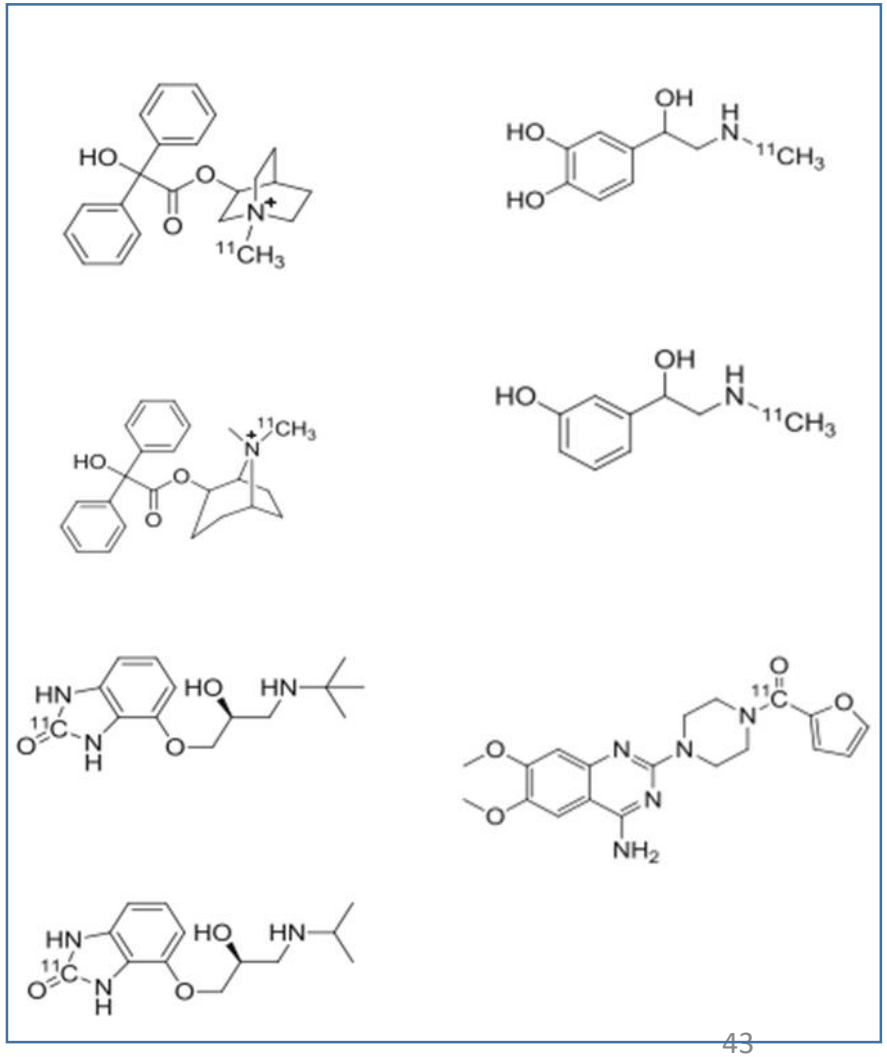
- Information reflecting the process of 123I-MIBG uptake into the synapse terminal, storage in the vesicles, secretion, reabsorption, and release into the blood is obtained from sympathetic imaging



PET tracers for sympathetic imaging

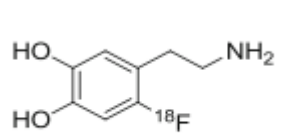
^{11}C-labaled Compounds

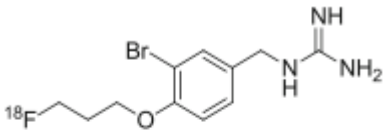
- Assessing postsynaptic sympathetic neuronal functions through measurement of myocardial b-adrenergic receptor (b-AR)
- Directlyregulates LV systolic function
- Clinical role of these has not yet been established

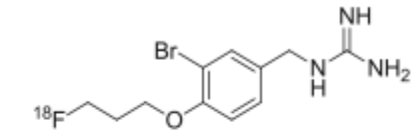


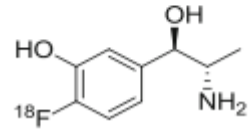
18F-labeled compounds

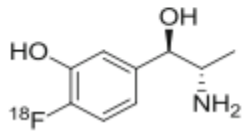
- For evaluating presynaptic neuronal function.

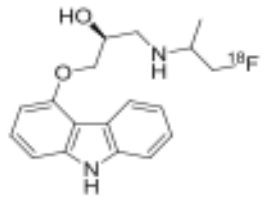


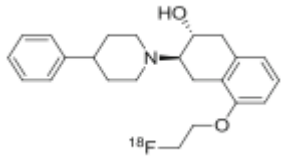












Imaging of Inflammation and Atherosclerosis

- Early inflammation after myocardial infarction is a critical mediator of adverse left ventricle (LV) remodeling leading to functional impairment.

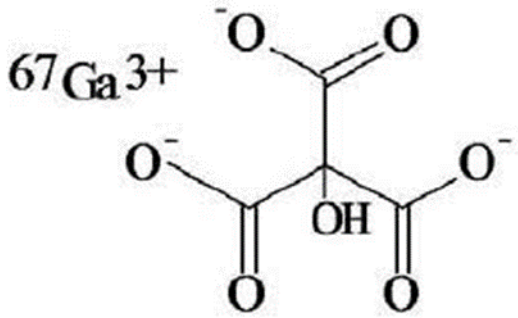
- Increasing evidence suggests that inflammatory cell infiltration and proinflammatory cytokines contribute to myofibroblast trans differentiation and replacement fibrosis.

SPECT radiotracers for Inflammation and Atherosclerosis

67Ga & 111In-WBC

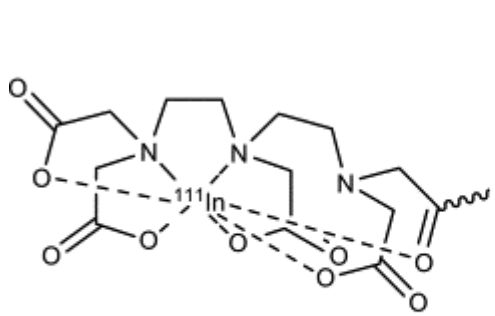
➢ 67Ga

- Detect inflammatory lesions including infection and sarcoidosis.
- half-life of 78.3 hrs.
- electron capture, emitting gamma radiation.
- produced by a variety of reactions in a cyclotron.

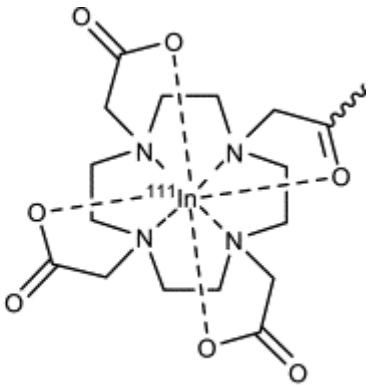


➢ 111In-(WBC)

- valuable in the detection of endocarditis
- highly specific for infectious lesions
- half-life of 67.2 hours
- electron capture



^{111}In-DTPA

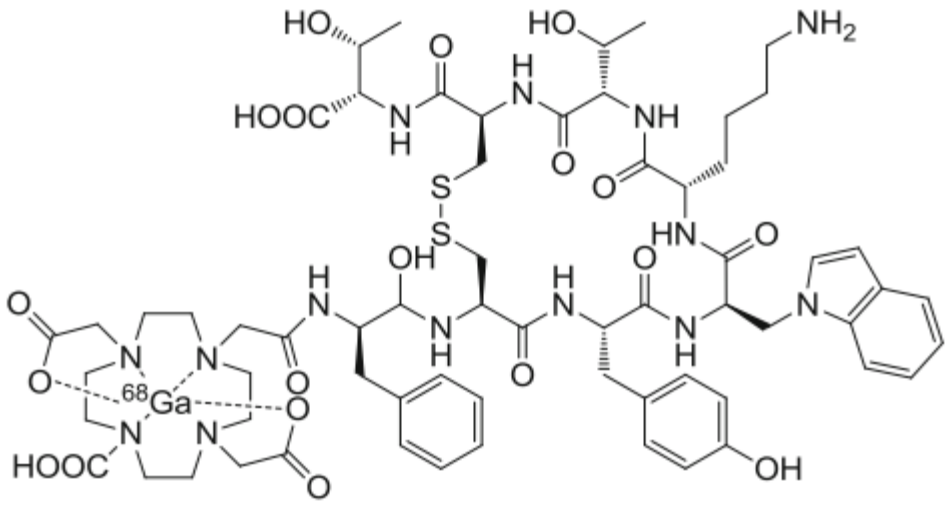


^{111}In-DOTA

PET radiotracers for imaging of Inflammation and Atherosclerosis

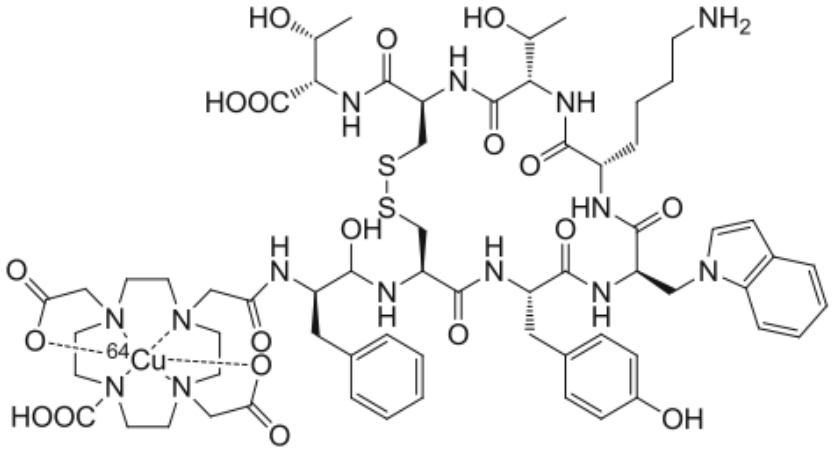
68Ga DOTATATE

- Can be prepared using a generator system and have been applied for clinical oncology imaging.
- uptakes in carotid and coronary arteries in patients with unstable CVD
- uptakes in carotid and coronary arteries in patients with unstable CVD



64 Cu DOTATATE

- has a shorter positron range and longer half-life.
- have improved spatial resolution over that of 68Ga-DOTATATE
- showed positive uptake in carotid atherosclerotic lesions
- Its uptake was positively linked to the expression of membrane receptor CD163.
- uptake was associated with hemorrhagic macrophage migration.

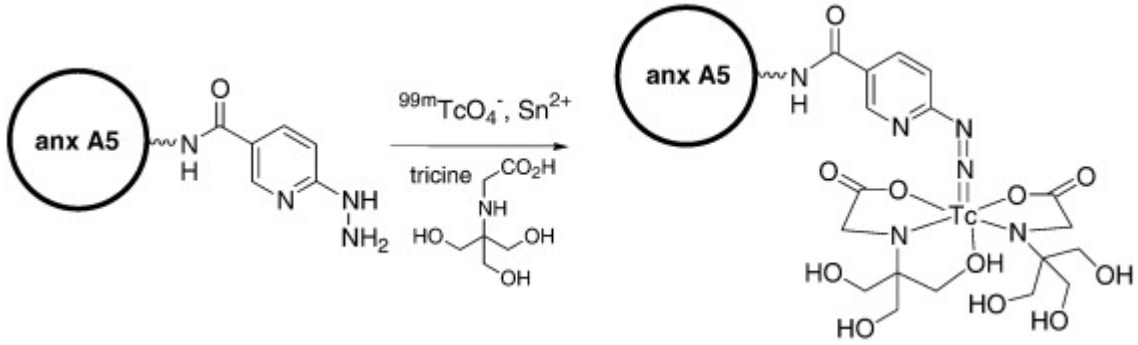


Apoptosis imaging

- Tissue apoptosis is considered to be one of the earlier stages of vascular plaque rupture, and therefore detecting apoptotic lesions may precipitate effective treatments to prevent cardiovascular events.

- **^{99m}Tc-tagged annexin A5**

- Have higher uptake in the carotid arteries of vulnerable stroke patients.
- Accumulates in vascular atherosclerotic lesions.




Thanks for your attention