

CARDIAC NUCLEAR IMAGING AND RADIOTRACERS



Thematic Report By

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The global nuclear medicine diagnostic (PET and SPECT) market is slated to cross \$ 16 billion by 2019, a CAGR that's 12% higher than its current size of around \$ 12 billion.

The market is primarily driven by its diagnostic utility to identify the functional and perfusion status of targeted tissues.

These scans are routinely used to visualize a patient's cardiac physiology, leveraging the advantages of novel radiopharmaceuticals in order to assess metabolism, neural dysfunction, post-transplant cellular response, atherosclerotic pathophysiological progress, as well as tissue viability.

Since their inception, technetium-99m or thallium-201 have been extensively used to perform these scans. Recent novel radiopharmaceuticals agents have also been developed however. Targeted toward specific subcellular process, they're capable of improving diagnostic accuracy and prognostic evaluation.

This report focuses on developments in cardiac nuclear imaging.

We'll cover its advantages, limitations, a few recently discovered clinical indications, as well as some specific radiotracers that are being explored for viability.

We'll also cover what the future holds for this life-saving technology.



Cardiac Molecular Imaging and Nuclear Scans – A Snapshot

Cardiac molecular imaging techniques include cell molecular biology, radiotracers and imaging principles to visualize cardiac functioning. Molecular imaging provides non-invasive, cheaper and in-vivo quantitative modality to study cardiac physiology, over historical in-vitro culture and in-vivo animal studies.

Current molecular imaging techniques mainly include:

- Single Photon Emission Tomography (SPECT Computed)
- Positron Emission Tomography (PET)
- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- High Frequency Ultrasound
- Techniques based on Optical Fluorescence and Bioluminescence

A hybrid combination of these techniques is also being explored to increase the accuracy of method and detect disease specific changes in tissue.

Molecular imaging has been used in variety of cardiac applications; few of them are listed below:

- Image atherosclerotic plaques in ischemic cardiac diseases, fluorodeoxyglucose and NaF are used for characterizing the plaque architecture in early clinical studies.
- It has been experimented to identify the patients with small abdominal aortic aneurysms who are predisposed to the sudden rupture.
- Glucose or fatty acid based analogs have been used for the ischemic cardiac assessment.
- Radiotracers targeted towards the metalloproteinase and renin angiotensin system are used for the post infarct assessment.
- Molecular imaging is used for the sympathetic innervation studies performed on cardiomyopathy patients who are at risk of developing arrhythmia.
- Reporter based gene imaging has been used for the tracking the stem cell transplant assessment in clinical scenario.

Molecular imaging has evolved from many aspects of nuclear imaging. Scintigraphy, SPECT, and PET scans using a radiotracer element and gamma camera to capture an image have been used in clinical diagnostics since last three decades.



Advantages and Limitations of Nuclear Imaging

SPECT and PET are advantageous in their high sensitivity, widespread availability, and low cost, as compared with prevalent techniques. PET also provides better quantitative information and allows the dynamic analysis of cardiac physiology.

This technology does have its limitations however, with spatial resolution, onsite cyclotron requirement for PET scanning, attenuation artifacts, and the partial volume effect to name a few.

Current research has focused on the development of hybrid technologies such as PET/CT and PET/MRI to increase image quantification.



Cardiac Disease Indications for Nuclear Imaging

Current Cardiac Uses of Nuclear Scans			
Disease	Pathophysiological Function to be Assessed	Cellular Component	Nuclear Imaging Sub-type
Cardiac Infarction	Necrosis and reduced perfusion	Pyrophosphate, glucarate and antimyosin antibodies	SPECT
	Cellular apoptosis	<ul style="list-style-type: none"> Annexin V Phospholipid externalization 	SPECT
Cardiac Failure	Angiogenesis after cardiac remodeling	<ul style="list-style-type: none"> Integrin proteins Vascular endothelial growth factor receptors 	<ul style="list-style-type: none"> SPECT PET
	Matrix remodeling and protease activation	<ul style="list-style-type: none"> Integrin Cathepsin RAS Collagen Factor XIII 	<ul style="list-style-type: none"> SPECT PET for RAS
Cardiac Protein Deposition and Infiltration Disease	Amyloidosis	<ul style="list-style-type: none"> Pyrophosphate Amyloid protein 	<ul style="list-style-type: none"> SPECT SPECT and PET
	Sarcoidosis	Metabolic tissue activity	PET
Ventricular Arrhythmia	Cardiac nerve supply	Metaiodobenzylguanidine, Hydroxyephedrine	<ul style="list-style-type: none"> SPECT PET
Cardiac Transplant	Transplant rejection assessment	Annexin V	SPECT
	Stem cell transplantation	Stem cells	<ul style="list-style-type: none"> SPECT PET
	Gene transfer	Matrix metalloproteinases activity	PET
Calcific Aortic Diseases	Leukocyte trafficking and activation	Metabolic activity	PET
	Calcification	Hydroxyapatite	PET
Endocarditis	Leucocyte infiltration and trafficking	<ul style="list-style-type: none"> Labelled monocytes Metabolism of cells 	<ul style="list-style-type: none"> SPECT PET
	Infection	S. Aureus	Fluoro-alpha-methyltyrosine (FMT)
Thrombosis	Platelet activation	Platelet integrin	SPECT



Radiotracers Used for Cardiac Imaging

Radiotracers are primarily used for the assessment of neural dysfunction, post-transplant cellular response, atherosclerotic pathophysiological progress, metabolism, and viability assessment of tissue. Since the inception of the Single photon emission computed tomography (SPECT) myocardial imaging, technetium-99m or thallium-201 has been extensively used. Recent novel radiopharmaceuticals agents are targeted towards the specific subcellular process and capable of improving diagnostic accuracy and prognostic evaluation.

Radiotracers are mainly used for the following assessment parameters in cardiac disease.

■ Myocardial Perfusion Imaging

^{201}Tl and $^{99\text{m}}\text{Tc}$ are most commonly used radiotracers for cardiac perfusion monitoring. $^{99\text{m}}\text{Tc}$ -Sestamibi, $^{99\text{m}}\text{Tc}$ -Tetrofosmin and $^{99\text{m}}\text{Tc}$ -Teboroxime are FDA approved salts used for clinical use. They provide benefits such as nonspecific passive diffusion across myocardial membrane and non-specific localization in cytosolic or mitochondrial subcellular components. Major limitations includes rapid washout at high flow $^{99\text{m}}\text{Tc}$ -Teboroxime which requires the images to be taken in less than 2 minutes, whereas ^{201}Tl creates attenuation artifacts specifically in the inferior wall. Apart from that, $^{99\text{m}}\text{Tc}$ -nitrido complexes provide high cardiac uptake and retention for more than 2 hours, showing promise as novel agents for the future.

Currently ^{123}I -Rotenone, ^{18}F -Flurpiridaz, ^{18}F -Labeled p-fluorobenzyl triphenyl phosphonium cation and $^3\text{NH}_3$ and $^{82}\text{Rb}+\text{salts}$ are being explored for the perfusion imaging of the cardiac tissue.

■ Myocardial Metabolism and Viability

Disruption in the blood flow to the myocardium disturbs metabolic functions of cells, which might lead to reversible damage, necrosis, or remodeling. Uptake of the radiotracers depends on the vitality of tissue and metabolic function is proportional to the nutrient consumption. Radiotracers used for metabolic assessment are usually done using molecules that are sugar intermediates. ^{18}F - FDG has replaced ^{201}Tl , which was used in initial days to assess vitality. ^{18}F -FDG is recently used to assess cardiac myocyte metabolism after Cardiac Resynchronization Therapy (CRT). ^{123}I -BMIPP is another complex which includes fatty acids, and is predominantly used as metabolic fuel for myocytes under rest conditions.

■ Imaging Atherosclerotic Plaques

Atherosclerosis is a chronic progressive condition involving the inflammation of the vascular intimal layer. Recent radiotracers used in PET scans such as ^{18}F -FDG images inflammation in the plaque, showing more promising outcome than prior apoptosis imaging agents targeted towards annexin-V cellular subcomponent. ^{18}F -FDG is primarily concentrated in leukocytes, especially in macrophages, and can hence be effective in early stages. Advanced plaque formation on the other hand involves calcium deposition in atherosclerotic layers. Sodium ^{18}F -Fluorid molecules could be useful to assess the osteoblastic activity.





■ Autonomic Dysfunction, Apoptosis, and Myocardial Infarct Repair

Nuclear imaging of the autonomic dysfunction is primarily targeted towards the norepinephrine analogues; ^{123}I -meta-iodobenzyl guanidine (^{123}I -MIBG) is widely used molecule for this purpose to detect the hyper-adrenergic state. ^{11}C -meta-Hydroxyephedrine is a novel alternative to ^{123}I -MIBG, which is under clinical consideration to assess the sympathetic functions.

Myocyte apoptosis plays pathophysiological role in development of atherosclerotic plaques, ischemia, chronic heart failure, myocarditis, and graft rejection. The radiotracers used for apoptosis purposes overall quantifies the extent of disease process. Molecules such as ^{18}F -labeled 2-(5-fluoropentyl)-2-methyl malonic acid, ^{18}F -(S)-1-((1-(2-fluoroethyl)-1H-(1,2,3)-triazol-4-yl)methyl)-5-(2(2,4-difluorophenoxy)methyl)-pyrrolidine-1-sulfonyl)isatin, and ^{18}F -fluorobenzyl triphenyl phosphonium are currently used radiotracers.

In hybrid techniques the combination of (DTPA-Gd) with the above molecules provides prognostic details.

FDA Approved Tracers

Indication	SPECT	PET
Myocardial Blood Flow	^{201}Tl - chloride $^{99\text{m}}\text{Tc}$ - Sestamibi $^{99\text{m}}\text{Tc}$ - Teboroxime $^{99\text{m}}\text{Tc}$ - Tetrofosmin	^{13}N $[\text{NH}_4]^+$ ^{82}Rb chloride
Blood Pool	$^{99\text{m}}\text{Tc}$ -labeled red blood cells (RBC) or human serum albumin	
Infarction	$^{99\text{m}}\text{Tc}$ -pyrophosphate	

Source - Molecular Imaging: Radiopharmaceuticals for PET and SPECT



What Does The Future Hold?

With the progress in molecular interaction imaging and ongoing cardiac disease pathophysiology research, researchers will be able to reveal the cellular mechanisms, occurring during the disease process.

This understanding of cytological alternations will help to design novel radiotracers by targeting the subcellular components showing the disease-specific activity. However, Technetium-99m radiopharmaceuticals will continue as cornerstones in the development of unique radioelements. Future tracers with improved characteristics and reduced dosimetric value are sure to be game-changers.

Along with the current cardiac states involving the perfusion, apoptosis and inflammation, research may expand into autoimmune, reperfusion/angiogenesis and cardiac gene transfer areas. Imaging modalities such as PET and SPECT have been proven to increase the sensitivity when used in combination with other cardiac imaging modalities such as MRI and CT.

With the development of hybrid systems, future research will be focused on overcoming limitations such as attenuation, dynamic noise cancellation and quantification of disease progress using these novel radiotracers.

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