RADIOISOTOPES AND RADIOPHARMACEUTICALS IN NUCLEAR CARDIOLOGY [#]

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ABSTRACT

RADIOISOTOPES AND RADIOPHARMACEUTICALS IN NUCLEAR CARDIOLOGY. Nuclear medicine studies of the heart represent one of the fastest growing areas of research and clinical interest. Some years ago, nuclear medicine cardiac studies were limited to evaluations of myocardial infarction. Developments in radiopharmaceutical chemistry and instrumentation have made possible advances in cardiovascular nuclear medicine. Techniques and radiopharmaceuticals now exist for the imaging of viable myocardium and the determination of myocardial tissue metabolism, as well as radionuclide angiography to obtain quantitative information of cardiac output, mean transit times, cardiac volumes, and ejection fractions. This paper will firstly describe the anatomy and physiology of the heart as to relate to the radiopharmaceuticals which will be discussed, and will secondly explore various radiopharmaceuticals which have been used for various purposes in cardiac imaging, then will explore radioisotopes which have been proposed for myocardial treatment.

ABSTRAK

RADIOISOTOP DAN RADIOFARMAKA DI BIDANG KARDIOLOGI NUKLIR. Studi jantung secara kedokteran nuklir merupakan salah satu bidang penyidikan dan minat klinis yang paling cepat berkembang. Beberapa tahun lalu, studi jantung secara kedokteran nuklir terbatas pada evaluasi infark jantung. Perkembangan di bidang kimia-radiofarmaka dan instrumentasi telah mendorong kemajuan di bidang kedokteran nuklir kardiovaskular. Teknik-teknik dan radiofarmaka sekarang telah tersedia untuk penyidikan jaringan jantung yang masih hidup dan penentuan metabolisme jaringan jantung, dan juga angiografi radionuklida untuk memperoleh informasi kuantitatif mengenai luaran jantung, waktu transit rata-rata, volume jantung, dan fraksi ejeksi. Makalah ini pertama akan menerangkan anatomi dan fisiologi jantung dalam kaitannya dengan radiofarmaka yang akan dibahas, dan kemudian akan meninjau berbagai radiofarmaka yang telah digunakan untuk berbagai keperluan penyidikan jantung, dan kemudian meninjau radioisotop yang telah diusulkan untuk penanganan masalah jantung.

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INTRODUCTION

Nuclear medicine studies of the heart represent one of the fastest growing areas of research and clinical interest. Some years ago, nuclear medicine cardiac studies were limited to evaluations of myocardial infarction by means of "hot spot" ^{99m}Tc-pyrophosphate imaging or radionuclide angiographic studies. Recent developments in radiopharmaceutical chemistry and advances in nuclear medicine instrumentation have made possible advances in cardiovascular nuclear medicine.

Techniques and radiopharmaceuticals now exist for the imaging of viable myocardium and the determination of myocardial tissue metabolism. Radionuclide angiography is now possible to obtain quantitative information regarding radiopharmaceutical distribution along time-activity curves that can be used to calculate cardiac output, mean transit times, cardiac volumes, and ejection fractions. In general, nuclear medicine studies of the heart can be divided into two categories that are based upon the clinical information which could be obtained : direct imaging of the myocardium (either perfused, healthy, or infarcted tissues), and determination of quantitative cardiac function. These two categories can be divided further into groups based on specific differences in the diagnostic properties of the radiopharmaceuticals that are currently available and employed for these purposes [1].

This paper firstly will describes the anatomy and physiology of the heart as to relate to the radiopharmaceuticals which will be discussed, then secondly will describes radiopharmaceuticals in myocardial imaging and radioisotopes in myocardial treatment.

ANATOMY AND PHYSIOLOGY OF THE HEART

The heart is a muscular organ located in the chest (*thoracic)* cavity and covered by a fibrous sac, named the *pericardium.* Its walls are composed primarily of muscle (*myocardium, cardiac muscle)*, the structure of which is different from either skeletal or smooth muscle. The inner surface of the myocardium, i.e., the surface in contact with the blood within the heart chambers, is lined by a thin layer of cells (*endothelium*) [2].

The cells constituting the heart walls do not exchange nutrients and metabolic end products with the blood within the heart chambers. Cardiac muscle, however, has properties similar to those of both skeletal and single-unit smooth muscle. The individual cardiac muscle cell is stritiated, containing both the thick *myosin* and thin *actin* filaments (myofilaments) described for skeletal muscle [2]. Cardiac myosin is an intracellular contractile protein that exists in large concentrations.
It is readily isolated and purified, is immunogenic, and is not exposed to the extracellular environment in normal viable myocytes [1].

Action potentials in the cardiac muscle membrane lead to the release of calcium from the sarcoplasmic reticulum and thereby to the activation of the actomyosin contractile system [2]. The metabolism of cardiac muscle is designed for endurance, therefore, a continuous supply of oxygen must be maintained to the heart muscle if it is to continue to supply ATP to the contractile machinery [2].

The heart, like all other organs, receives its blood supply via arterial branches (*coronary arteries*) which arise from the aorta [2]. The myocardium receives its blood supply from the left and right coronary arteries, arising from the ascending aorta. The left coronary artery subdivides into the left anterior descending (LAD) and the left circumflex (LCX) arteries. Perfusion to the right atrium and right ventricle is furnished by the right coronary artery [3].

Congestive Heart Failure, "Heart attacks" and arteriosclerosis

The heart may become weakened for many reasons which induces a similar procession of symptoms grouped under the category of *congestive heart failure.* Patients with early mild heart disease may show at rest no significant abnormalities because of the great safety factor in cardiac function [2]. However, the ability to perform exercise is impaired, as evidenced by shortness of breath and early fatigue. Ultimately, the cardiac reserve becomes inadequate to supply normal amounts of blood even at rest, and the patient becomes bedridden [2].

Insufficient coronary blood flow leads to myocardial damage and, if severe enough, to death of the myocardium (*infarction*), a so-called *heart attack* [2]. This may occur as a result of decreased arterial pressure but is more commonly due to increased vessel resistance following coronary arteriosclerosis [2].

Arteriosclerosis is a disease characterized by a thickening of the arterial wall with connective tissue and deposits of *cholesterol.* The mechanism by which thickening occurs is not clear. However, cholesterol is an important physiological substance because it is the precursor of certain hormones and the bile acids [2].

The liver (and other body cells) is capable of producing large quantities of cholesterol, particularly from *saturated fatty acids*. Indeed, it may well be the high content of saturated fatty acids, rather than cholesterol, which causes the ingestion of animal fat to predispose one to *arteriosclerosis* [2]. The mechanism of arteriosclerosis is usually progressive, leading often ultimately to *complete occlusion* [2]. *Acute coronary occlusion* may occur because of sudden formation of a clot on the roughned vessel surface or breaking off of a deposit, which then lodges downstream, completely blocking a smaller vessel [2].

It should be stressed that before complete occlusion many patients experience *recurrent transient episodes* of inadequate coronary blood flow, usually during exertion or emotional tension. The pain associated with this is termed *angina pectoris* [2]. Most arteries of the body subject to the same occluding process, such as, cerebral occlusions (*strokes*) are common in the aged and an important cause of death [2].

RADIOPHARMACEUTICALS IN MYOCARDIAL IMAGING AND MECHANISM OF LOCALIZATION

Nuclear medicine imaging and data processing techniques provide accurate, repeatable assessment of cardiac structure, cardiac function, as well as myocardial perfusion. These approaches have application in patients with coronary artery disease, congenital and valvular heart disease, and cardiomyopathy [3,4]. Myocardial imaging can be used to demonstrate myocardial ischemia or necrosis resulting from myocardial infarction. Infarct avid or "hot spot" myocardial imaging is used to visualize areas of acute myocardial infarction [3].

For most purposes, nuclear medicine studies of the heart can be divided into two categories that are based largely upon the clinical information sought : direct imaging of the myocardium, and determination of quantitative cardiac function.

These two categories can be divided into groups based on specific differences in the diagnostic properties of the radiopharmaceuticals. Table 1 shows various radiopharma ceuticals employed in cardiovascular nuclear medicine studies according to type of diagnostic information obtained.

Table 1. Various Cardiovascular Nuclear Medicine Studies and Radiopharmaceuticals Employed [1].

Imaging Category	Diagnostic Classification	Example of Radiopharmaceuticals
Imaging of Myocardium	I. Avid Infarct	^{99m}Tc-pyrophosphate ^{111}In antimyosin antibody
	II. Myocardial perfusion	^{201}Tl thallous chloride ^{99m}Tc-sestamibi ^{99m}Tc-tetrofosmin
	III.Metabolic activity	Labeled fatty acids Labeled glucose analogues
Quantitative measurement of ventricular function (the radionuclide ventriculogram)	I. First-pass imaging	^{99m}Tc-Na-pertechnetate Short-lived radioisotopes
	II. Equilibrium gated blood pool imaging	^{99m}Tc-Red Blood Cells ^{99m}Tc-HSA

Radiopharmaceutical for Myocardial Infarct Imaging

Although a variety of radiopharmaceutical have been shown to localize in zones of recent myocardial necrosis (infarct-avid agent), the most widely used agent is ^{99m}Tc-pyrophosphate (^{99m}Tc-Pyp) (Table 2). The mechanism of uptake of this agent in regions of necrosis is presumed that they bind to intracellular deposits of inorganic calcium salts, which form in dying myocardial cells. Uptake of Pyp indicates active myocytolysis and other causes of phosphate deposition [4].

However, the mechanism of localization of most of the infarct avid agents can be correlated with a biochemical or physiologic process that occurs during the development of the myocardial infarct. The transformation from normal to irreversibly damaged or necrotic myocardium proceeds gradually following the initial injury [5].

Other investigators have offered alternative explanations for the mechanism of ^{99m}Tc-Pyp localization in infarcted tissue. It was postulated that the localization of the ^{99m}Tc-Pyp is not directly related to mitochondrial calcium phosphate deposits [5]. It has been observed that ^{99m}Tc-Pyp bound to serum proteins retains the ability to adsorb to calcium hydroxyapatite [5], and on the other hand, it is well established that phosphorous compounds have affinity for hydroxyapatite crystals [6].

The application of ^{99m}Tc-Pyp as a means for localizing infarction supported previous observations that calcium influx during irreversible myocardial injury resulted in the formation of a crystalline hydroxyapatite like substance that closely resembled the crystalline material of bone [1,3].

^{99m}Tc-Pyp clears rapidly from blood with less than 9% remaining in blood 3 hr post injection and the blood clearance appear to be triphasic [1,6]. 10-30% of the remaining blood activity is contained in the red cell fraction between 1-3 hours. Between 40-50% of plasma activity is protein bound within the first hour and 55-60% by 3 hours and beyond. Of the total activity administered, 40-50% is deposited in bone. 24-hr cumulative urinary excretion accounts for approximately 60% of the administered activity [1,6].

Development of various new ^{99m}Tc bone seeking radiopharmaceuticals have suggested that these radiopharmaceuticals, medronate and oxidronate, are comparable to ^{99m}Tc-Pyp for myocardial infarct imaging. Comparative clinical analyses, however, support the superiority of ^{99m}Tc-Pyp over all other ^{99m}Tc-bone-seeking radiopharmaceuticals for the detection of acute myocardial infarction [1,6].

Following infarction, the highest concentration ratios of ^{99m}Tc-Pyp between damaged (infarcted) and normal myocardium occur when residual blood flow is 20-40% [1] or 20-60% [5] of normal. With further reductions in blood flow, localization diminishes, and in regions of minimal blood flow (approximately 5%), uptake may appear normal. Where there is no blood flow (for instance, in the central infarct zone), localization fails to occurs [1,5]. Increased liver uptake of ^{99m}Tc-Pyp has also been reported, which is often due to pathophysiological changes [1].

It has been realized that the normal uptake of ^{99m}Tc-Pyp by bone may limit its utility for estimation of infarct size. In an effort to develop infarct imaging agents without some of the clinical problems associated with Pyp, new approaches have been examined. Among these are the use of ^{131}I-antimyosin antibodies (see Table 2), ^{99m}Tc-heparin, and ^{111}In-leukocytes [5]. The cardiac myosin/anticardiacmyosin antibody system was chosen for *in vivo* visualization of myocardial infarction. The rationale for use of a radiolabeled antimyosin antibody is that following myocyte necrosis from myocardial infarct, the intracellular myosin is exposed to the extracellular components[1].

A radiolabeled antibody could therefore penetrate disrupted cell membranes and bind to cardiac myosin, thereby permitting its visualization by scintillation imaging [1]. The faster blood clearance rate of antibody fragment, Fab fragment, and the use of multivalent cations for labeling, such as ^{111}In, ^{68}Ga, and ^{99m}Tc, through a bifunctional chelating agent (such as DTPA) that is covalently bonded to the antibody is the most suitable for imaging studies [1].

Table 2. Radiopharmaceuticals for Myocardial Infarct Imaging

Radiopharmaceuticals	Hypothesis of mechanism	Type of Studies	Ref
^{99m}Tc-Pyrophosphate 15-20 mCi i.v. imaging 90 min. after injection.	Binding to the calcium hydroxyapatite formation or denatured protein or other macromolecules. Calcium is deposited in irreversibly damaged myocardial cells.	Acute myocardial infarction. Myocardial necrosis.	1,3,4, 5,6
^{111}In; ^{68}Ga or ^{99m}Tc-antimyosin Fab fragments	MoAb raised against myosin in cells. Damaged myocytes will expose myosin to the extracellular components.	Acute myocardial infarction.	1,4,5

Radiopharmaceutical for Myocardial Perfusion Imaging

Thallium-201 (^{201}Tl) as thallous chloride is a very sensitif myocardial perfusion imaging agent for detecting the location and extent of myocardial ischemia. Very often this imaging technique is performed as a screening test to determine if a patient should be referred for coronary arteriography, a more invasive procedure. Comparison of stress and rest images is useful in identifying transient myocardial ischemia and in differentiating ischemic from infarcted areas in the myocardium [3,4].

^{201}Tl ion is treated similarly to potassium by myocardial cells. Both thallium and potassium need the Na^+/K^+-ATPase pump for active transport into cells [3,4]. Regional myocardial uptake of ^{201}Tl reflects myocardial blood supply, myocardial cell viability, and integrity of membrane sodium-potassium transport systems. Myocardial uptake and blood clearance of this radiopharmaceutical are rapid, and imaging can be started 5-10 minutes after (2.5-3.0 mCi) intravenous injection, or immediately for stress thallium studies. The normal myocardium perfusion image shows uniform distribution of activity in the left ventricular myocardium, with the ventricular cavity appearing as a central region of decreased counts in the image [3,4].

Myocardial cells in infarcted areas are no longer functional; hence, no thallium will be concentrated in them. If the blood supply is compromised, as in the case of ischemia, less thallium will be presented to the myocardial cells in the ischemic area, and less thallium will be concentrated in that area of the myocardium [3,4].

Thus, on the basis of a single ^{201}Tl chloride imaging study alone, it is not possible to distinguish transient myocardial ischemia, acute myocardial infarction, or myocardial scar from prior infarction [4].

Due to the unfavourable ^{201}Tl physical characteristic (long half life, low energy photon) and high cost, a ^{99m}Tc-labeled imaging agent has become the most sought radiopharmaceutical. For this hypothesis, In 1981 Deutsch has suggested that the ^{99m}Tc should be in nonreduced form within a chelate, preferably in a monovalent cationic molecule with slightly lipophilic nature in order to localize in myocardium with minimal washout [7].

Favorable radiation dosimetry of ^{99m}Tc allows higher activities to be administered, resulting in shorter imaging times with more information in the clinical images [3]. To produce better images for differentiation of ischemia from infarction, ^{99m}Tc myocardial agents seem an attractive substitute for ^{201}Tl because of the higher photon fluxes made possible by the higher millicurie doses.
Moreover, the problem of attenuation in obese patients is less with the higher-energy 140 Kev gamma of ^{99m}Tc compared with the 69-80 Kev mercury x-rays from ^{201}Tl [8].

The introduction of ^{99m}Tc isonitrile compounds provide a radiopharmaceutical that will enhance the quality of myocardial perfusion imaging. Unlike thallium, these compounds do not redistribute into ischemic areas with time [4]. An increase count rate permit a shorter imaging time and increased image quality, as well as decreased radiation dose as compared with thallium, favour the use of the ^{99m}Tc isonitrile compound [4].

One of the agent to date is ^{99m}Tc-MIBI, with 20-25 mCi standard dose used for perfusion imaging, and first-pass radionuclide ventriculography to evaluate both left and right ventricles that can be performed at rest and/or during exercise [8,9]. Attachment 1 summarises comparison of various parameters between ^{99m}Tc-MIBI and ^{201}Tl-chloride.

^{99m}Tc-MIBI accumulates in the heart in proportion to regional myocardial blood flow. Once the tracer has entered a myocardial cell, it is bound in a relatively stable fashion to mitochondria and remains within the cell. No significant redistribution occurs over time, and ^{99m}Tc-MIBI uptake is relatively unaffected by physiologic metabolic changes [9].

It has been demonstrated that the myocardial uptake of the ^{99m}Tc compounds are independent of the Na^+/K^+ ATPase pump [7]. The major metabolic pathways of clearance of ^{99m}Tc-MIBI are the hepatobiliary system (48-hour fecal excretion: 37% of injected dose at rest and 29% at stress) and kidneys (24-hour urinary excretion of 30% of injeced dose at rest and 24% of injected dose after exercise) [9].

^{99m}Tc-Teboroxime and ^{99m}Tc-MIBI can be used to demonstrate myocardial ischemia utilizing a stress/rest technique in a similar manner to ^{201}Tl imaging. However, each behaves very differently in the body and requires its own imaging protocol [3]. Attachment 2 summarises comparison of various parameters between ^{99m}Tc-MIBI, ^{99m}Tc-Teboroxime, and ^{99m}Tc-Tetrofosmin. Different from the ^{99m}Tc-MIBI and ^{99m}Tc-

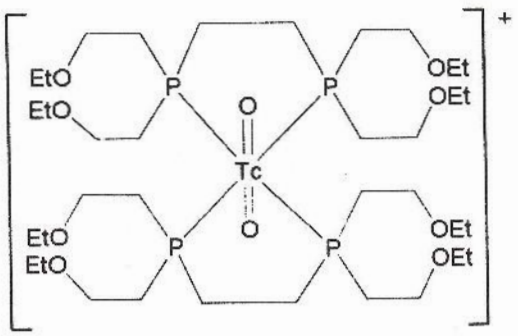
Tetrofosmin, the ^{99m}Tc-Q12 is to be used within 24 h of reconstitution with up to 250 mCi of pertechnetate in 2-3 mL of solution [11]. Figure 1 shows the postulated structures of four myocardial imaging agents.

Radiopharmaceuticals for Gated Blood-Pool Imaging

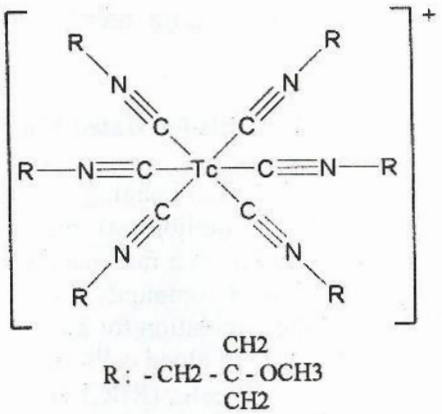
Cardiac functional imaging can be accomplished using one of two techniques, the gated blood-pool (equilibrium) method or the first-pass method. The technique is sometimes referred to as a radionuclide ventriculogram because it examines the function of the ventricle, most commonly the left. The technique requires the use of a tracer that will remain in the circulation for an extended period of time, at least 30 min. Technetium labeled albumin or red blood cells are the tracers most often employed for the study [3].

Labelled red cells (RBC) are preferred because albumin (HSA) leaks from the vascular compartment over time and contributes to high background in the area of the liver. While RBC remain in the circulation, it does take 30-40 min to label RBC with ^{99m}Tc pertechnetate using either *in-vivo*, *in-vitro*, or *in-vivtro* techniques (Table 3). Technetium reduced by the stannous ion is bound to the haemoglobin of the red blood cells. Labelling yield was > 85% [3].

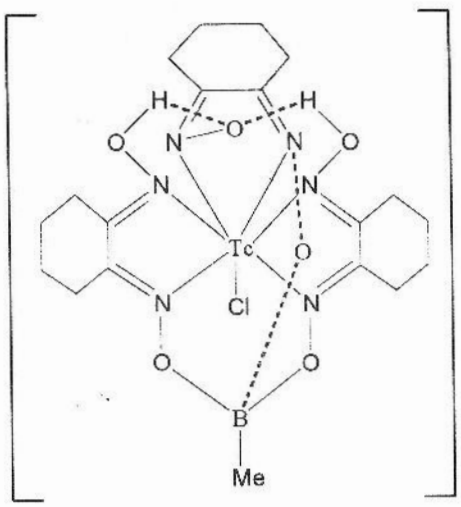
To date ^{99m}Tc-MIBI is also used for both first-pass radionuclide ventriculography and later myocardial images with standard dose of 20-25 mCi, to evaluate both left and right ventricles at rest and/or during exercise [8,9].



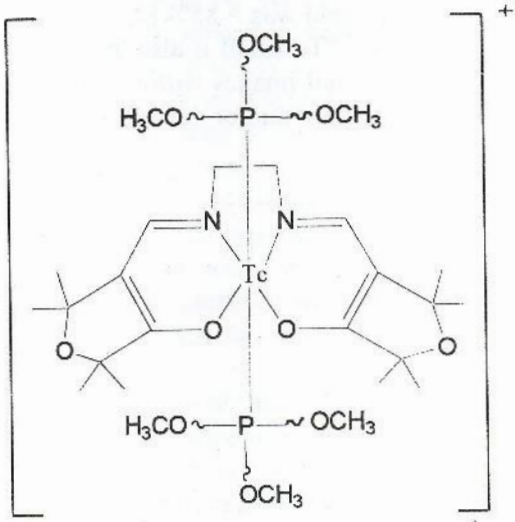
^{99m}*Tc-TETROFOSMIN*



^{99m}*Tc-MIBI*



^{99m}*Tc-TEBOROXIME*



^{99m}*Tc-Q12*

Figure 1. Postulated structures of ^{99m}Tc myocardial perfusion imaging agents [7,11].

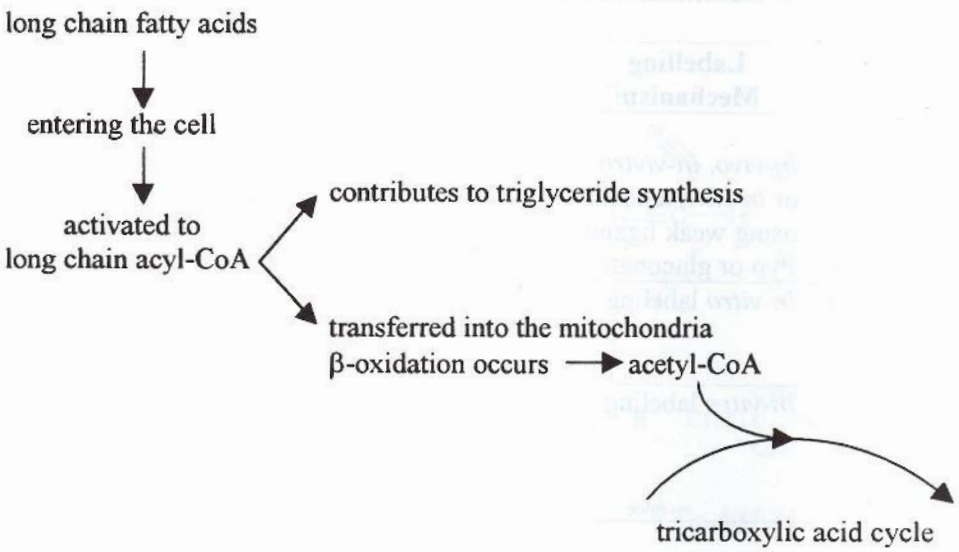
Table 3. Radiopharmaceuticals for Cardiac Blood-Pool Imaging & Ventricular Function

Radiopharmaceuticals	Labelling Mechanism	Hypothesis of mechanism	Type of Evaluation
^{99m}Tc-RBC intravenous inj.[3,4]	*In-vivo, in-vivtro,* or *in vitro* labeling using weak ligand Pyp or gluconate.	Undamaged RBC remains in the intravascular space	-Left ventricular function and regional ventricular wall motion; -images of the heart in systole and diastole; -left ventricular ejection fraction indicating of left ventricular dysfunction.
^{99m}Tc-HSA [3]	*In-vitro* labeling.	HSA remains in the intravascular space	
^{99m}Tc-MIBI [8,9]	*In-vitro* labeling.	Remains in the intravascular space for a few minutes.	

PET Imaging, Myocardial Viability and Metabolic Activity

The human heart has high energy demands and uses a wide range of small molecular metabolic substrate to generate the energy. The heart can metabolize free fatty acids, glucose, lactate, pyruvate, ketone bodies and amino acids [15]. In a normal heart in the fasting state, β-oxidation of free fatty acids is the predominant source of energy production providing approximately 70% of cardiac energy requirements. Carbohydrates are the majority of the remaining 30% of energy production [15]. Scheme 1 simplifies the long chain fatty acids metabolism in the heart.

Metabolic imaging using positron-emitters provides unique information regarding the heart. In particular, the use of ^{18}F-fluoro-deoxyglucose (FDG) for measuring regional glucose metabolism has been widely used. The use of PET has included determination of myocardial viability [14], particularly it is important in patients with persistent angina pectoris [12].



Scheme 1. Free Fatty Acid Metabolism in the Heart [15]

PET imaging can depict regional myocardial blood flow using ^{13}N-ammonia or ^{82}Rb chloride, and regional myocardial metabolism using ^{18}F-FDG and ^{123}I-fatty acids metabolism [4]. Ischemic but viable myocardium increases glucose utilization, which has a lower oxygen requirement than fat metabolism. PET imaging shows that ischemic myocardium has a relative decrease in fatty acid uptake, a relative increase in deoxyglucose uptake, and a relative reduction in perfusion [4,13].

During exercise, lactate plasma levels increase and also provide an important energy source for cardiac metabolism [15]. ^{11}C-palmitate as a tracer of free fatty acid metabolism, ^{18}F-FDG as a tracer of glucose metabolism and ^{11}C-acetate for assessment of myocardial oxidative metabolism have been the basic tools in cardiac PET metabolic imaging and continue to provide insights into a wide range of cardiac diseases [15].

Other report suggested that since myocardial perfusion imaging requires the extraction and retention of ^{99m}Tc-MIBI by the heart, changes in the retention of the tracer between ischemic and infarcted myocardium can aid in the assessment of myocardial viability [9]. Myocardial viability studies with ^{18}F-FDG/^{13}N-ammonia PET and rest/stress ^{99m}Tc-MIBI SPECT has shown that in some cases PET detects viability when MIBI does not, and the use of [^{13}N]-ammonia PET in myocardial studies has been validated world wide [12].

Several fatty acids labeled with ^{123}I have been formulated for studies of myocardial metabolism. Experimentally, a substituted fatty acid with a high myocardial uptake is 15-(p-iodophenyl)-4,4'dimethyl pentadecanoic acid. Such modified fatty acid probably do not reflect myocardial metabolism of endogenous fatty acids but may be of value in defining cardiomyopathies [8].

A sterile solution for intravenous injection containing iodophenyl-pentadecanoic acid p-(^{123}I)-IPPA, a saturated fatty acid, ethanol and human serum albumin, has been used in dosage of 150-185 MBq for the evaluation of myocardial viability and the detection of metabolic dysfunction in diabetics [16]. Summary of these PET myocardial studies is listed in Table 4.

Table 4. PET Imaging, Myocardial Viability and Metabolic Activity

Type of Imaging	Specific Study	Radiopharma-ceutical	Method
Regional myocardial blood flow	Oxygen requirement, Amino acid metabolisme	^{13}N-ammonia	PET imaging
	Na^-/K^+ ATPase Pump	^{82}Rb chloride	PET imaging
Regional myocardial metabolisme	Glucose metabolisme	^{18}F-FDG	PET imaging
	Fatty acids metabolisme	^{123}I-saturated fatty acids : iodophenyl-pentadecanoic acid = p-(^{123}I)-IPPA	PET imaging
Myocardial oxidative metabolism; Myocardial viability	Detection of metabolic dysfunction in diabetics	^{11}C-acetate ^{11}C-palmitate	PET imaging
Myocardial viability	Ratio of amino acid and glucose metabolisme	$^{13}NH_3$/ ^{18}FDG	PET imaging
	Diffusable compounds	^{99m}Tc-MIBI	SPECT

RADIOISOTOPES IN INTRAVASCULAR AND ENDOVASCULAR BRACHYTHERAPY

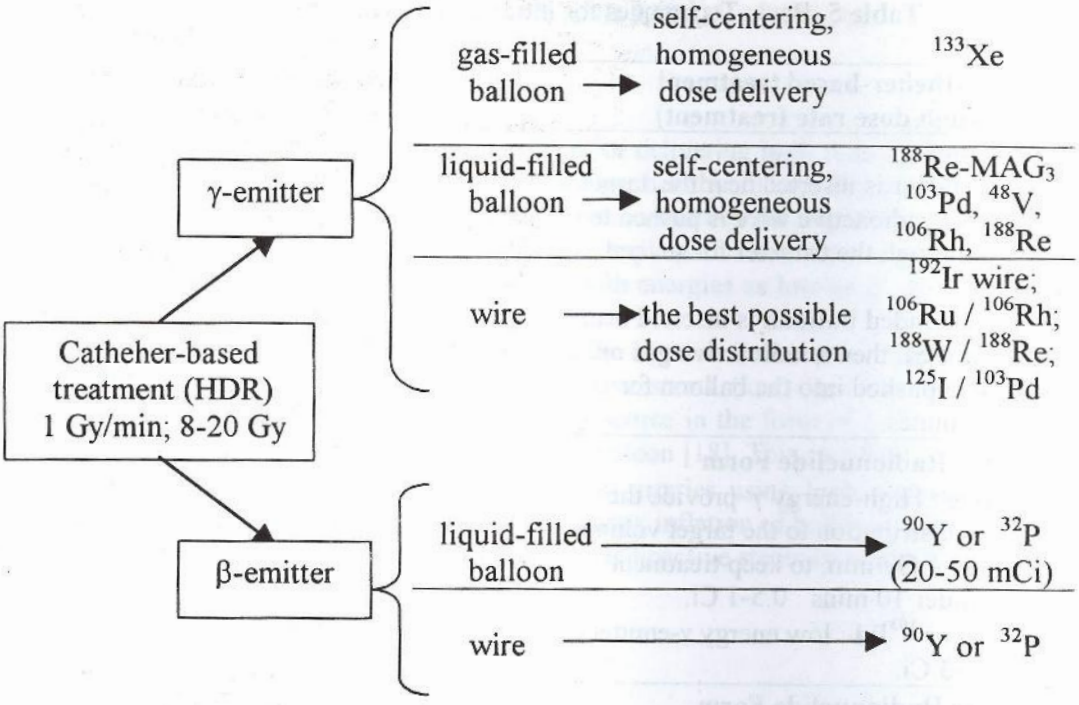
Brachytherapy offers a simple procedure for delivering high radiation doses to a target tissue but minimal doses to the surrounding healthy tissue. Brachytherapy can provide an optimal dose distribution because radiation sources are implanted either in or very close to the target tissue. Brachytherapy implants *in-situ* can be successfully performed with radionuclides that emit photons with energies as low as 20 Kev, enough energy to inhibit cellular reproduction [17].

Delivery of the radionuclides is basically by two techniques, catheter-based systems (high dose rate irradiation) and radioactive stents (low dose rate irradiation) (Table 5). Catheter-based system can use gamma source in the form of a line source or seeds, or a beta source in a form of a liquid filled balloon [18]. This section discussed the intraluminal irradiation of coronary and peripheral arteries using high activity γ or β seeds or wires in conjunction with balloon angioplasty; inflation of balloon catheters with radioactive liquid; and implantation of low activity radioactive stents (see Scheme 2).

Table 5. Basic Techniques for Intravascular Therapy [18,19]

Catheher-based treatment (High dose rate treatment)	**Radioactive stents (Low dose rate treatment)**
Description A lead-catheter is inserted near the target area, then a radioactive **wire** is pushed to the area through the catheter for several minutes. A catheter leaded **balloon** is inserted near the target area, then a radioactive **gas or solution** is pushed into the balloon for several minutes.	**Description** Irradiated Palmaz-Schatz stents with deutrons or protons in cyclotron (mixture of ^{55}Co, ^{56}Co, ^{57}Co, ^{57}Ni, ^{57}Fe); **or** Implantation of single radioisotope into stents (ex.^{32}P); **or** Coating the stents with radioisotope (ex. ^{186}Re and ^{188}Re).
γ-emitter Radionuclide Form **^{192}Ir Wire** : High-energy γ provide the best dose distribution to the target volume Dose rate: 1 Gy/min, to keep treatment ideally under 10 mins : 0.5-1 Ci. **^{125}I Wire** or **^{103}Pd** : low energy γ-emitters require 1-3 Ci.	**γ-emitter Radionuclide Form** **^{192}Ir** stents require activities >100 μCi
β-emitter Radionuclide Form **^{90}Y or ^{32}P**, pure β, limited range of rad. The amount of (β) activity required for adequate dose rate: 20-50 mCi	**β-emitter Radionuclide Form** Requires much lower amounts of activity – typically 1-10 μCi of ^{32}P.
Risks Rupture of the balloon or radiation injury, or occlusion; radiation safety problems.	**Risks** The line source has a centering problem

In balloon angioplasty, an inflated catheter is used to open arteries that are occluded because of plaque formation, a life-threatening condition known as arteriosclerosis. The balloon procedure is designed to crush the plaque, but it often tears the arterial wall as well. Some of the cells in the blood vessel respond to this injury by initiating repair, which often leads to restenosis (reclosing) of the artery. But if the lesion is treated with radiation (on the order of 8-30 Gy), this restenotic effect is inhibited [17]. Irradiation of restenosis by β- or γ- emitting wires have shown to inhibit migration and arterial neointimal proliferation, and therefore is considered to be used for the prevention of restenosis after angioplasty [18].



Scheme 2. Summary of Catheter-Based Treatment

Radionuclide selection for this purposes requires knowledge of the location and radiosensitivity of the target tissues, and the radio-tolerance of normal tissues. Radiation dosimetry, safety, dose homogeneity, and practicality of source manufacture must all be considered. Unlike conventional brachytherapy, intravascular treatment of restenosis requires accurate knowledge of dose at distances of 0.5-5 mm from the source, which presents special calibration and treatment planning problems [19].

Beside the above selection criteria for radionuclide, it should be determined also the level of dose to prevent restenosis without inducing fibrosis or occlusion, determined whether γ-emitter or β-emitter to be used, determined whether the most radiosensitive component is endothelial, smooth muscle cell, or adventitial fibroblast [18,19].

An approach in delivering the radiation is to incorporate radioactive materials into the angioplasty equipment. The stent, a component in most angioplasty procedures, is an expandable metallic mesh that provides mechanical support for the weakened arterial wall. In many cases, however, restenosis occurs despite the stent, which becomes incorporated into the proliferative tissue that forms around the lesion [17].

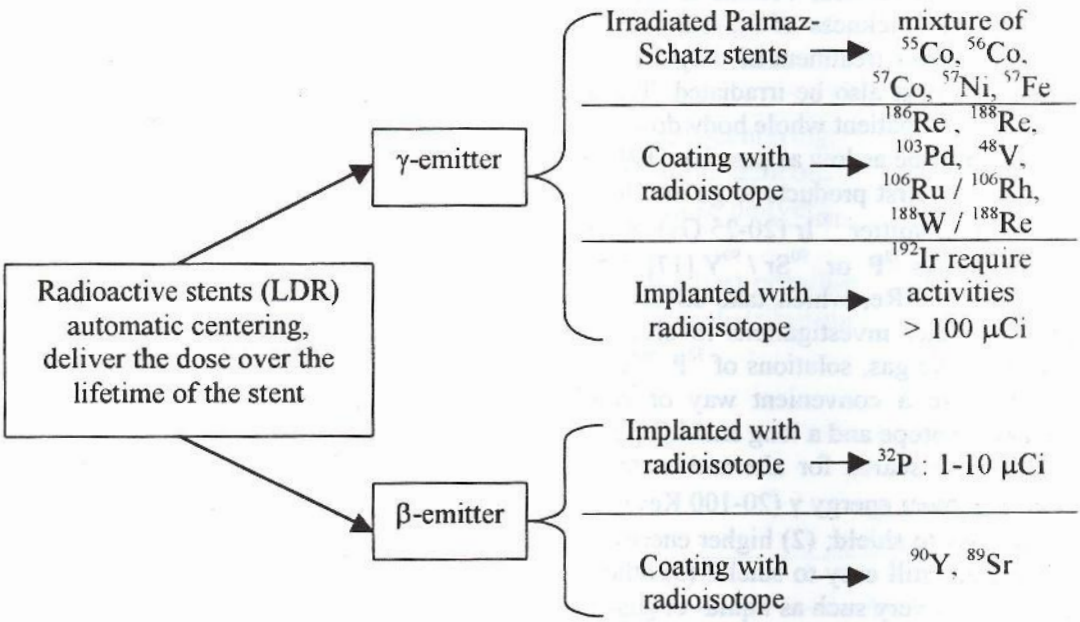
The treatment volume is typically a 2-5 cm length, 3-5 mm in diameter, and arterial wall thickness of 0.5-1.5 mm, but can be larger for diseased vessels. It is not known whether treatment of only the lumen wall is sufficient, or whether the media and adventitia must also be irradiated. Treatment doses of 8-20 Gy have been shown to be effective, but patient whole body dose, dose to normal vessels and myocardium, and dose to staff must be as low as possible [19].

The first products to go into human trials were based on trains of metallic seeds of the γ-ray emitter ^{192}Ir (20-25 Gy). Some later design are based on wire-sources that use the β-emitters ^{32}P or ^{90}Sr / ^{90}Y [17]. Stents can also incorporate ^{103}Pd, ^{48}V, ^{106}Ru / ^{106}Rh, and ^{188}W / ^{188}Re, which take advantage of the longer halflives of the ^{106}Ru and ^{188}W parents. Other investigations involving balloons filled with a radioactive gas or fluid, such as ^{133}Xe gas, solutions of ^{32}P, ^{90}Y, ^{186}Re, ^{188}Re, and ^{166}Ho [17]. The parent-daughter isotopes are a convenient way of combining the advantages of a high-energy beta daughter isotope and a long half-life parent isotope [19].

The search for alternatives to other radionuclide is motivated by three factors [19]: (1) lower energy γ (20-100 Kev) produce dose distributions comparable to ^{192}Ir, but are as easy to shield; (2) higher energy β yield dose distributions superior to ^{90}Sr/ ^{90}Y or ^{32}P and are still easy to shield; (3) other radioisotopes may permit alternate mechanisms for dose delivery such as liquid- or gas-filled radioactive balloons, liquid infusion, etc.

There are various forms of devices which have been offered, for example, the ^{192}Ir radioactive seed ribbon, a nylon ribbon containing an array of small, cylindrically shaped ^{192}Ir radioactive sources, for coronary brachytherapy application [10]. A guidewire embedded in the rest of the 300cm long ribbon helps to push the active ribbon to its target. The source strength is enough to limit the treatment time to <20 min [19].

Scheme 3 summarises many types of radioactive stents that may be produced for brachytherapy. In Table 6 are listed various radioisotopes that can be selected for different types of restenoses. Attachment 3 is an artist illustration of the balloon, wire and the stent insertion into the place.



Scheme 3. Summary of Treatment Using Radioactive Stents

Table 6. Summary of Radionuclides for Brachytherapy [18.19]

Radio-nuclide	Emis-sion	Max energy (Kev)	Average energy (Kev)	Half-life	Dose	Comments
^{192}Ir	γ	670	375	74 d	18.5 GBq	Best dose distri-bution, hard to shield.
^{125}I	x-ray	35	28	60 d	?	Good dose, easy to shiled.
^{103}Pd	x-ray	21	21	17 d	?	- dito above -
^{32}P	β	1710	690	14 d	3.7 GBq	Easy to shield, limited dose penetration.
^{90}Sr/ ^{90}Y	β	2270	970	28 y / 64 h	3.7 GBq	Better than ^{32}P, worse than γ
^{90}Y	β	2270	970	64 h	3.7 GBq	Shorter half life than above
^{186}Re	β γ	1080 130		90 h	11.1 GBq	?
^{188}W/ ^{188}Re	β γ	2130 155(15%)	780 -	69 d / 17 h	3.7 GBq	Similar dose to ^{90}Y.
^{188}Re	β γ	2130 155(15%)	780	17 h	3.7 GBq	Similar dose to ^{90}Y, for balloons
^{48}V	β	690	230	?	?	Possible for radioactive stent
^{133}Xe	β, γ	340	113	6 d	11.1 GBq	Prototype gas-filled balloon.
^{99m}Tc	γ	140	140	5.3 d	?	Prototype liquid infusion catheter
^{106}Ru/ ^{106}Rh	β	3540	1180	6 hour	?	Higher energy β, hard to produce.

? - no available information.

SUMMARY

Nuclear medicine studies of the heart represent one of the fastest growing areas of research and clinical interest. Some years ago, cardiac studies were limited to evaluations of myocardial infarction by means of "hot spot" ^{99m}Tc-pyrophosphate imaging, however, recent developments in radiopharmaceutical chemistry and advances in nuclear medicine instrumentation have made possible advances in cardiovascular nuclear medicine.

Techniques and radiopharmaceuticals now exist for the imaging of viable myocardium and the determination of myocardial tissue metabolism. Radionuclide angiography is now possible to obtain quantitative information regarding radiopharma ceutical distribution along time-activity curves that can be used to calculate various parameters of the heart function. Nuclear medicine imaging and data processing techniques assist in providing accurate, repeatable assessment of cardiac structure, cardiac function, as well as myocardial perfusion.

The human heart high energy demands using a wide range of small molecular metabolic substrate to generate the energy, such as of free fatty acids, glucose, lactate, pyruvate, ketone bodies and amino acids. PET imaging can provide information regarding myocardial viability and metabolic activity of the heart.

Brachytherapy has offered a simple procedure for delivering high radiation doses to a target tissue but minimal doses to the surrounding healthy tissue for the prevention of restenosis after angioplasty. can provide an optimal dose distribution because radiation sources are implanted either in or very close to the target tissue. Delivery of the radionuclides is basically by two techniques. i.e. catheter-based systems (high dose rate irradiation) and radioactive stents (low dose rate irradiation) using either γ- or β-sources.

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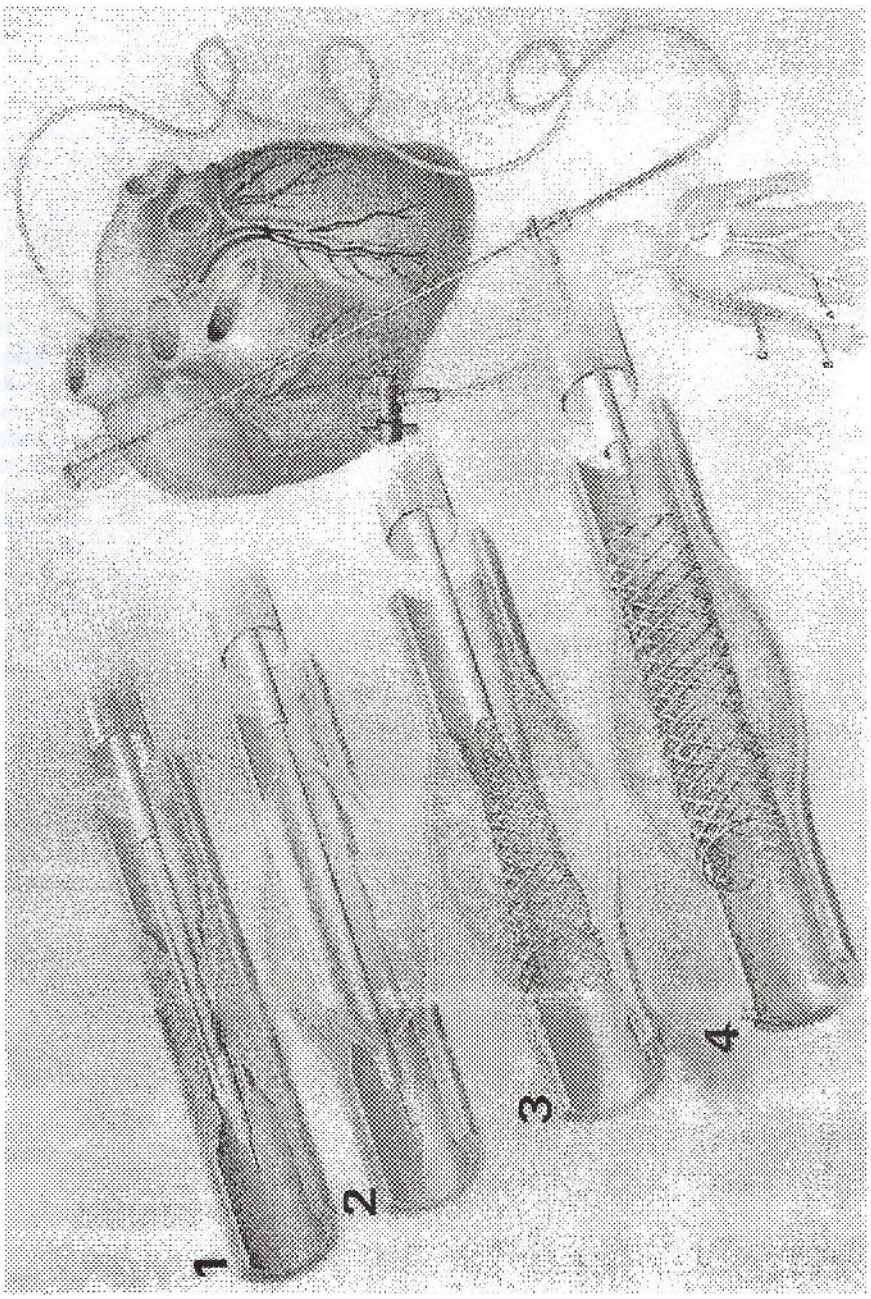
Attachment 1. Comparison of ^{99m}Tc-MIBI and ^{201}Thallium Utilization [4,10]

	^{99m}Tc-MIBI	^{201}Tl-Thallous Chloride
Function / Perfusion	Perfusion and function information with one injection	Perfusion information without function information
Gated Wall Motion	Allows for gating images	Not suited for gated imaging
Imaging Flexibility	Patient imaging may be delayed up to 4 hours after injection due to slow washout and lack of significant redistribution	Rapid redistribution requires almost immediate imaging following injection; total time for stress/rest study 3-4 hrs.
Throughput	Greater flexibility in patient scheduling and throughput	Rigid scheduling requirements
Optimal Photon Energy	Optimal photon energy (140 Kev) for clear imaging	Relatively low photon energy (68-80 Kev), results in reduced image clarity
Higher Dosing	Dosimetry allows administration of doses up to 30 mCi (1110 MBq)/70 kg for better image statistics	Dosimetry limits dosage, yielding suboptimal images
Heart uptake	At rest is 2.84% (1.63%-3.69%) of ID after stress is 3.2% of ID	
24-hour Capability	Readily available in kit form 24 hrs/day	Cyclotron-product, requires advance ordering, T½ of 72 hr
Redistribution	No redistribution.	3-5 hr redistribution to zones of the left ventricle that transiently ischemic, not to infarction zone.

Attachment 2. Comparison of Three Known Myocardial Perfusion Imaging Agents

	^{99M}Tc-MIBI	^{99m}Tc-Teboroxime	^{99m}Tc-Tetrofosmin
Chemical name	Technetium-99m hehakis-2-methoxy-2-isobutyl isonitrile	Technetium-99m chloro-(methyl-boron(1-)-tris (2,2-cyclohexane-dionedioxime	Technetium-99m 1,2-bis [bis(2-ethoxy-ethyl) phosphino]ethane
Other name	^{99m}Tc-RP-30a; SESTAMIBI; HEXAMIBI	^{99m}Tc-SQ 30; 217; CDO-MEB; BATO	^{99m}Tc-P53
Chemical form	Cationic +1, lipophilic complex with Tc(I)	Neutral, lipophilic complex with Tc(III)	Cationic +1, lipophilic complex with Tc(V)
Preparation	1-3 ml, 25-150 mCi with w.b. heating 10' exchange labeling	1 ml 100 mCi with boiling w.b. 15'; "in-situ" template synthesis	4-8 ml, 120-240mCi, gently mix and stand at room temp. for 15 min.
Shelf life	>6 hr at room temp.	6 hr at room temp.	8 hr at room temp.
Patient preparation	Fast for 4hr; no beta blockers 3days; no Ca blockers 2days	Similar with MIBI	?
Myocard imaging dose and time	10-30 mCi; 1-2 hr p.i.	?	6.75 mCi at peak exercise; 13-20 mCi at rest 4 hours later; 30 min p.i.
T½ Blood clearance	4.3 mins; protein binding 1%	Rapid, 39% at 90 sec to 9.5% at 15 mins.	Fast with < 5% of the ID remain in blood at 10 mins.
Myocardial extraction eff.	65% (Tl+ = 85%)	>90% (Tl+ = 85%)	?

	^{99M}Tc-MIBI	^{99m}Tc-Teboroxime	^{99m}Tc-Tetrofosmin
Myocardial uptake	Proportional to the RBF in the heart. Max at exercise 1.5%; Min.at rest 1%	Max 2.3%; only 30% of max remain in myocardium after 1hr.	Mean uptake at 1 hr p.i. 1.2% up to 4hr.
Uptake mechanism	Passive diffusion. 80% of activity in myocyte is bound to –ly charged cytosol, and intracellular binding.	Passive diffusion, unaffected by metabolic inhibitors.	Passive diffusion,retention is due to the ionic reaction between the RP with -ly charged cytosol.
Washout/ Redistribution	Slow, T½ 7hr; no redistribution for several hours after injection. Requires two inj to complete stress/rest images.	Rapid T½ 5.2 min (66%) and T½ 3.8hr (33%). No redistribution. 2 injection for stress/rest images.	Slow, no redistribution for several hours after inject. Requires 2 inj to complete stress/rest images.
Elimination	Both hepatobiliary and renal systems; fecal 37 in 48hr; urinary 27% in 24hr.	Mainly hepatobiliary system	Both renal and hepatobiliary systems, 39% and 34% at 48 hr respectively.
Total time required	Rest/stress study finalized 30-60 min	Rest/stress study for 1-1.5hr.	?
Notes	Also accumulates in thyroid and parathyroid 5 min p.i. Shorter imaging time, better image quality than ^{201}Tl. Also hepatocytes localization, slow clearance from liver.	?	Significant uptake in other organs, uptake in the thyroid is not inhibited by perchlorate administration .
References	3, 4, 6, 7, 11	3, 6, 7	6, 7, 11



Attachment 3. An artist drawing of wire, balloon, and stent insertion into its place.