Tracing ischemic memory by metabolic pathways: BMIPP and beyond

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Review Article

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ABSTRACT

Myocardial ischemia (MI) resulting in infarction is an important cause of mortality and morbidity worldwide. Acute ischaemia rapidly impairs myocardial contractile function. Myocardial dysfunction persisting for several hours after transient non-lethal ischaemia, eventually resulting in full functional recovery is termed as *myocardial stunning. Hibernation* is now thought to be the consequence of repetitive bouts of ischaemia and stunning due to normally occurring increases in myocardial metabolic demand in the setting of significant coronary stenoses. We need robust investigations to identify and treat MI early. Myocardial perfusion imaging has established itself as the earliest investigation that can identify ischemia with or without infarction in an acute setting. However, recent data reveals that metabolic changes precede perfusion abnormalities during an ischemic or infarction episode; thus the renewed interest in the myocardial metabolic imaging. Concept of myocardial metabolic imaging is gaining momentum with the wider availability of positron emitting radio isotopes. Myocardial metabolism has been widely studied using ^{123}I-BMIPP [15-(p-Iodophenyl)-3-methylpentadecanoic acid] and BMIPP was synonymous for ischemic memory imaging, (IMI). It was based on the fact that one can capture the still picture of the ongoing ischemic insult as a "*memory image*" past the acute episode. BMIPP imaging was primarily based on its ability to memorize the area at risk for a couple of weeks, even after reperfusion therapy. We aim to elaborate in this review the various radiotracers that can be used to identify myocardial metabolic disorders at its inception so that it may be possible to provide early management options.

Key words: Ischemic memory; BMIPP; ^{18}F-FDG PET; ^{99m}Tc Labelled-Annexin; SPECT; Hibernation; Molecular probes

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INTRODUCTION

Recent progress in the understanding of the molecular-genetic mechanisms has introduced new biologically based approaches towards the understanding of myocardial ischemia [1, 2]. Ischemic memory imaging (IMI) is an interesting concept that revolves around the functional and metabolic changes that occur during an ischemic episode or an infarction. There occurs a change in the metabolic substrate immediately after a true myocardial ischemia or an infarction, which may persist for hours thereafter, even after resolution of ischemia, thus making it a highly sensitive and specific marker. This change in metabolic substrate is capitalized for imaging. The concept that substrates get altered during an ongoing pathophysiological process; a disease specific "*metabolic foot print"* may emerge in future which can be radiolabelled and serve as a guide to identify cardiovascular diseases much earlier [3].

Most of the substrate based imaging studies in the past were based on myocardial fatty acid (FA) metabolism. Normal myocardium uses FA as a metabolic substrate. During ischemia when myocardial perfusion decreases, FA metabolism cannot be maintained because β-oxidation of FA in mitochondria needs large amounts of oxygen. There is a switch of substrate to glucose which uses anaerobic glycolysis that requires less oxygen consumption. This distinct adaptation of myocytes during an ischemic episode is known as "*Metabolic Stunning*" [3]. Once this phenomenon occurs, there is a decrease in FA substrate analogue like BMIPP which gets more pronounced than the reduction in flow tracers. On the contrary, anaerobic glucose metabolism relatively increases during ischemic event, presenting increased or preserved FDG uptake in the area with decreased perfusion. This typical pattern of myocardial perfusion metabolism mismatch is the hallmark of myocardial hibernation thus signals viable myocardium [4, 5]. When myocardial perfusion decreases further, glucose anaerobic metabolism also declines finally and myocardium becomes non-viable indicated by absent perfusion and metabolism – matched defects.

Manifestations of ischemia & techniques employed for its diagnosis [6]

Ischemic cascade clearly depicts the onset and progression of events following ischemia (Figure 1). It shows that metabolic events are the first to manifest in an evolving MI. Although electrocardiogram and echocardiogram are widely used as screening tools for angina evaluation; the ischemic cascade shows that these changes occur much later during an ischemic event. Perfusion abnormalities herald the onset of ischemia and MPI has till date served as a robust "gatekeeper" investigation for CAD evaluation.

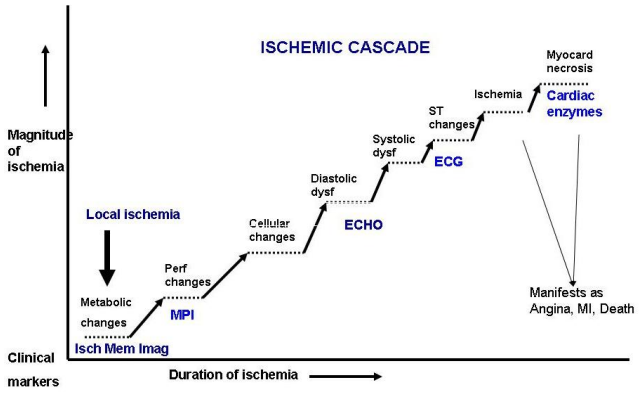

Fig 1. Manifestations of ischemia (ischemic cascade) showing the specific sequence of events starting with decreases in myocardial blood flow leading to detectable perfusion defects due to ischemia. It also highlights the effect and duration of ischemia and indicates when certain investigations are likely to become positive.

New data reveal that metabolic changes although subtle supersede perfusion abnormalities. These metabolic changes can be utilized for ischemic memory imaging as metabolic recovery lags behind perfusion for almost 24-30 hours. Table 1 provides the list of techniques for identifying ischemia as tools for that can be used for 'ischemic memory remembrance'.

Table 1: Techniques for identifying ischemic memory.

Nuclear techniques	Non nuclear techniques
- RNV : Radionuclide ventriculography (stress, rest, nitrate enhanced) - PET : ^{18}F-FDG, ^{15}N-NH$_3$, ^{18}F-Flurpiridaz - Gated SPECT MPI: FDG with hybrid camera, ^{201}Tl, ^{99m}Tc agents - New MOLI agents	- Echocardiography (rest, stress, contrast) - Cardiac MRI (rest, stress, contrast) - Optical bioluminescence - Florescence molecular tomography - XRAY CT - Ultrasonic microbubble imaging

Table 2: List of fatty acids used for imaging [11].

Straight chain FA for SPECT	***Methyl-chain fatty acids:***
	a. 16-Iodohexadencanoic acid (IHXA)
	b. 17-Iodoheptadecanoic acid (IHDA)
	Aromatic fatty acids:
	a. 15-(p-Iodophenyl)-pentadecanoic acid (p-IPPA
	b. 15-(o-Iodophenyl)-pentadecanoic acid (o-IPPA
	Isosteric fatty acids:
	a. 15-(p-Iodophenyl)-6-tellura pentadecanoic acid (TPDA)
	b. 17-Iodo-9-tellura heptadecanoic acid (THDA)
Straight chain FA for PET	^{11}C-Palmitate
Branch chain FA for SPECT	a. 14-(p-Iodophenyl)-b methyltetradecanoic acid (BMTA)
	b. 3-10 [13-(40-Iodophenyl)]-3-(p-phenylene)tridecanoic acid (PHIPA)
	c. 15-(p-Iodophenyl)-3-methylpentadecanoic acid (BMIPP)
	d. 15-(p-Iodophenyl)-3,3-dimethyl pentadecanoic acid (DMIPP)
	e. 9-Methyl pentadecanoic acid (9MPA)
Branch chain FA for PET	a. ^{11}C beta methyl heptadecanoic acid
	b. 14-(R,S)-18F-fluoro-6-thiaheptadecanoic acid (FTHA)
	c. 16-18F-fluoro-4-thia-palmitate (FTP)
	d. trans-9(RS)-18F-fluoro-3,4(RS,RS) methyleneheptadecanoic acid (FCPHA)

Tracing 'ischemic memory' by targeting different metabolic pathways [7]

PET and SPECT are the most translatable noninvasive molecular imaging platforms nowadays. Wider availability of higher end clinical scanners and versatile radiolabelled compounds can be used to understand the clinical utility of metabolic substrate imaging [1].

A. Imaging myocytes through beta oxidation of fatty acids: BMIPP

Myocardial imaging with radiolabeled fatty acids (FA) has been used since 1965 [8]. Various FAs have been investigated for myocardial imaging which are listed in Table 2. ^{131}I labeled oleic acid was the first to be introduced [8]. Initially straight chain FAs were tried. Poe et al reported that the washout rate of straight chain FA's from myocardium reflected the back diffusion of deiodinated free iodine and it was not because of β-oxidation as previously stated [9]. Later branched chains FA were used because of its better imaging characteristics. Table 3 provides the salient features of branched and straight chain FA used for cardiac metabolic imaging. Certain structural modifications of FA were incorporated to enhance the imaging characteristics of these tracers in myocytes [10].

The most popular branched chain FA that has been studied is iodinated BMIPP [15-(p-Iodophenyl)-3-methylpentadecanoic acid] having a methyl group at the β-3 position that inhibits mitochondrial β-oxidation and allows prolonged myocardial retention of BMIPP [11, 12]. It was commercially introduced in Japan in 1993 as '*Cardiodine'*. Other iodinated fatty acid analogues that were used include DMIPP, 15-(p-iodophenyl)-3,3-dimethylpentadecanoic acid and IPPA, 15-(p-iodophenyl)pentadecanoic acid straight-chain analogue [10]. Historically '*metabolic memory or cold spot imaging*' is synonymous to BMIPP imaging and is performed as a rest only study [12]. It is injected under fasting conditions and SPECT imaging is initiated 20 - 30 min later. The mechanism of myocardial BMIPP retention depends on regional perfusion [13]. Figure 2 provides the mechanism of action of BMIPP in myocytes. Classically mismatch of glucose and FA metabolism in areas of myocardial ischemia and reperfusion are described [14]. BMIPP has been extensively studied in the clinical setting of acute myocardial infarction (AMI) and unstable angina pectoris.

Table 3: Characteristics of straight and branched chain fatty acids used for imaging.

Fatty Acid	Properties	Advantages	Disadvantages
Straight chain FA	-Marker of beta oxidation - Uptake reflects FA oxidation - Measures regional washout kinetic or clearance	- Provides a direct measure of metabolism - Similar kinetics to ^{11}C-Palmitate	- Poor quality images (limited sensitivity of SPECT camera) - Rapid dynamic acquisition not possible - Back diffusion of non metabolites
Branched chain FA	- Metabolic trapping concept - Uptake does not reflect FA oxidation - Measures absolute regional uptake & retention	- High quality, excellent images - Best suited for SPECT studies	- Necessary to have perfusion study as uptake depends on flow - Uptake is based on FA uptake & turnover rate of lipid pool

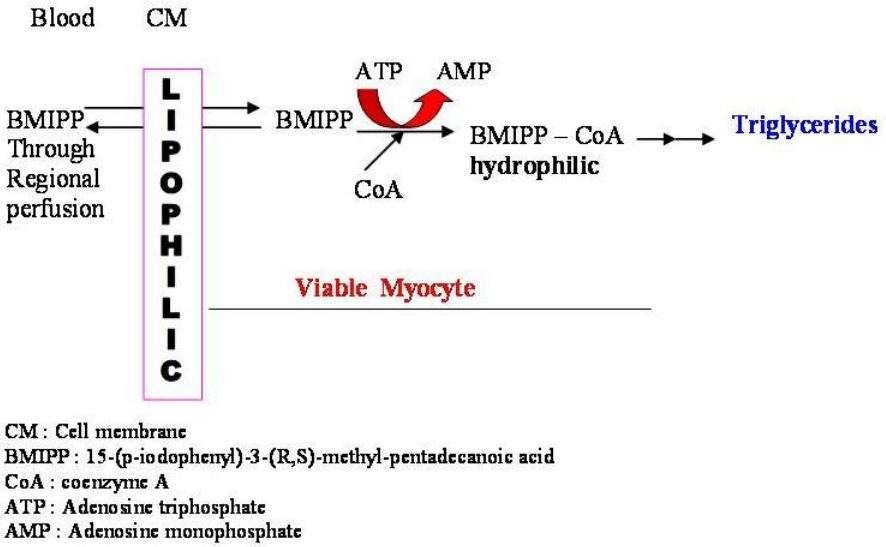

Fig 2. Depicts the mechanism of BMIPP uptake and retention in a viable myocyte.

BMIPP imaging can detect prolonged metabolic abnormality or stunning in patients with acute chest pain up to 2 days after cessation of symptom [14].

Even in patients with chronic stable coronary artery disease without MI, discordant BMIPP uptake less than perfusion tracer is a common finding. Only in such cases a concomitant MPI is a prerequisite for BMIPP imaging [15]. Comparison of BMIPP and stress-reinjection thallium SPECT in 45 patients with chronic coronary artery disease demonstrated that most of the segments (118/124) with discordant BMIPP uptake less than reinjection-thallium were associated with demand ischemia indicated by reversible thallium defects [16]. When reversible thallium defects were analyzed, approximately half of the segments evidenced discordant BMIPP uptake less than reinjection thallium. On the other hand, around 80% of the segments with fixed thallium defects demonstrated concordant reduction of both tracers, suggesting myocardium with reduced or poor viability has metabolic abnormality similar to the degree of resting perfusion abnormality. When reversible thallium defects were analyzed with respect to the evidence of discordant BMIPP uptake less than thallium and regional wall motion abnormality, wall motion was more severely impaired in the segments with discordant BMIPP uptake less than thallium than those without such discordance in both subset of patients with and without old myocardial infarction.

Unlike stress SPECT MPI imaging which is more sensitive; BMIPP imaging is more specific. BMIPP imaging can be performed without exercise or pharmacologic supplementation. Therefore, BMIPP imaging at rest may be an alternative imaging modality for those who cannot perform adequate exercise testing or pharmacologic stress MPI, such as

those presenting with acute chest pain and patients with end stage renal disease with hemodialysis.

In patients with hibernating myocardium, reduced BMIPP uptake implies impaired myocardial flow reserve and may reflect the adaptive substrate shifts or metabolic remodeling. Kontos et al [17] analyzed the performance of BMIPP to detect ACS in emergency room. BMIPP imaging increased sensitivity of identifying ACS from 43% to 81% ($p<0.001$). In stable angina, incongruent reduced BMIPP uptake when compared with ^{201}Tl perfusion abnormalities at rest is the hallmark of patients with unstable angina. This pattern of less BMIPP uptake than Tl-201 are more often encountered in coronaries with severe stenoses and related to regional wall abnormalities. Taki et al. [18] showed that the degree of BMIPP reduction correlated with the degree of stress perfusion, wall motion abnormalities, and coronary stenosis severity.

B. Imaging myocytes through carbohydrate metabolism: ^{18}F FDG

Glucose metabolism is an integral part of human metabolism and glucose labeled radioligands have been used to tracer this pathway. With wider availability of PET systems, favorable tracer kinetics and high quality images ^{18}F-FDG fares better for myocardial ischemia and viability evaluation. Schelbert was the first to use FDG imaging for identification of ischemic myocardium in a canine model in 1982 [19]. Studies have shown that increased FDG uptake may persist for 24 hours or longer after a period of transient ischemia thus making it an ideal radiopharmaceutical for memory imaging [20].

Tillisch et al [21] compared the 18F-FDG uptake in patients with advanced CAD pre and revascularization and showed that imaging of viable myocardium was superior with ^{18}F-FDG-PET compared to SPECT.

Following are the cited mechanisms of FDG uptake in myocardial ischemia [22-24];

a) FDG undergoes facilitated transport into the sarcolemma and competes with endogenous glucose then for hexokinase-mediated phosphorylation. FDG-6-phosphate is trapped in the cytosol and the myocardial uptake of FDG is thought to reflect overall anaerobic and aerobic myocardial glycolytic flux providing a relative or absolute myocardial glucose quantification.

b) Brief ischemic spells may induce glucose transporter 4 sarcolemma translocation and activate glycogen synthase, resulting in increased glycolytic flux enhancing FDG uptake into myocytes.

c) Prolonged ischemia of around 20min can accelerate regional glycolytic flux presumably by enhancing the translocation of the GLUT transporters from cytoplasmic stores to active sites on the sarcolemma. This persists for 24 hours or longer and it is noted that despite post revascularization restoration of regional function there is a 25% reduction in regional ^{13}N NH4 blood flow and a 50% increase in FDG uptake.

d) Stimulation of alpha adrenoreceptors during myocardial ischemia producing an increase in glucose transporter thus leading to increased myocardial FDG uptake.

Disadvantages of using FDG imaging in ischemia maybe related to a preferential increase in FDG uptake in ischemic myocardium due to a metabolic switch, inability to resolve subtle hot spot areas of transmural or non transmural MI. [23, 24]. Furthermore, myocardial distribution of FDG in a fasting status is heterogeneous even in healthy subjects [25]. Gropler et al. [26] have highlighted this point and in their study they report a relatively underestimation of ischemic myocardium on delayed 24 hour FDG images that those with the BMIPP.

C. Imaging of myocytes through oxidative metabolism: ^{11}C-Acetate

Myocardial oxygen consumption (MVO_2) and blood flow estimation serve as important markers for identifying ischemia and infarct. ^{11}C acetate has been introduced as it allows estimation of MVO_2 on a segmental level and is a non invasive procedure. Myocardial extraction of acetate is high and once it is transported intracellularly it gets converted to (C-1) acetyl Co A by acetyl Co A synthetase in the mitochondrial matrix. Because acetate has no other pathways for myocardial metabolism, it can be used to estimate the TCA cycle flux thus MVO_2. In normal subjects, uptake and clearance of ^{11}C is homogeneous and monoexponential [27]. In patients with MI, uptake of ^{11}C acetate in the center of the infarct zone, delineated by perfusion imaging with ^{15}O, is markedly depressed and clearance is prolonged. The diminished clearance directly reflects the reduction of myocardial oxidative metabolism. Studies have shown that patients with transmural, complete MI clearance of ^{11}C acetate was markedly diminished in peri infarct and infarct regions (to 68% of normal in peri infarct, 48% in infarct and 21% in central infarct regions [28]. Substrates of this metabolic pathway may prove to be promising for studying myocardial ischemic memory.

D. Imaging of myocytes through amino acid metabolism

Much of our current investigations are focused on tracers targeting myocardial fatty acids and carbohydrates; in contrast, tracers in protein and

amino acid metabolic pathways are underexplored. In comparison to fatty acids and carbohydrates, amino acids are a more heterogeneous group of small organic compounds. The intermediary metabolism of amino acids in the body was first investigated with radio isotopes by Schoenheimer in 1942 [29]. Branched-chain amino acid (BCAA) catabolism is essential to maintain amino acid metabolism in myocardium [30]. Under aerobic conditions branched chain amino acids like leucine, isoleucine, and valine, are oxidized in the Krebs cycle. The rate-limiting step in their catabolism is the α-ketoacid dehydrogenase reaction, an enzyme regulated by phosphorylation and dephosphorylation. Huang et al. has recently reviewed the role of defects in BCAA metabolism in heart disease [31]. In spite of the physiologic importance of BCAA metabolism and myocardial protein turnover in general, no metabolic imaging strategies have yet been applied in clinical practice.

L-Arginine (L-Arg) is considered a semi-essential amino acid in most adult mammals, but under certain conditions where the synthesis of L-arginine is decreased and/or its catabolism is increased, L-arginine becomes an essential amino acid. It plays a central role in the biosynthesis and myocardium must import L-Arg from the circulation to ensure adequate intracellular levels of this amino acid. There is accumulating evidence that the L-arginine-nitric oxide pathway has an important role in the pathophysiology of cardiac diseases. Very few studies are available that investigate the use of radiolabelled amino acids like ^{11}C / ^{13}N glutamate and methionine.

^{11}C glutamate appears to be a promising agent in studying ischemic myocardium given by the anaerobic metabolism of glutamate to both alanine [32] and succinate [33]. Mudge et al demonstrated that there is an enhanced extraction of glutamate and enhanced myocardial release of alanine in ischemic patients [34]. Another agent that has been tried is ^{13}N-glutamate with mixed results. Its uptake in ischemia may be varied; either increased [35, 36] or unchanged [37], relative to blood flow tracers. Likewise, ^{14}C-methionine has also been investigated in the infarcted area, and its uptake corresponded closely to macrophage infiltration at 3 to 7 days after reperfusion [38]. Morooka et al [39] reported increased uptake of ^{11}C-methionine in infarcted areas during the acute phase of MI, while ^{201}Tl and ^{18}F FDG uptake were reduced. Further studies are needed to validate the use of these tracers in IMI.

E. Imaging of myocardium using its sympathetic innervation

Another novel pathway that can be harnessed in identifying ischemic insult is the sympathetic innervation imaging of myocardium. Neurohumoral changes are known to occur in myocardial dysregulation and alterations in autonomic innervation have also been studied [40]. Various pre synaptic adrenergic tracers like ^{123}I-MIBG, ^{11}C-HED and post synaptic adrenergic tracers like ^{11}C-CGP 12177 have been used experimentally. One of the first studies in patients early after an MI showed that area of reduced ^{11}C-HED retention exceeded perfusion defects in myocardium especially in non Q wave MI patients [41]. This is further supported by data that there is a higher sensitivity of sympathetic neurons to ischemia compared to regional decreases in HED retentions in absence of resting perfusion defects in patients with advanced CAD but with no evidence of MI [41]. However further data is awaited before we can utilize these agents for IMI.

F. Miscellaneous agents

1) Imaging of myocytes through 'Hot spot' infarct avid agents:

Infarct avid agents were used in the past to identify myocardial infarction during acute presentations. ^{99m}Tc pyrophosphates and glucarate were popular. Their mechanism of uptake was varied and involved changes that occur during apoptosis or cell necrosis Highlights of a few of these agents have been described below:

^{99m}Tc- Pyrophosphate: Uptake of ^{99m}Tc-PYP in the infarcted myocardium is based on targeting of calcium phosphate deposited in the mitochondria [42, 43]. Scan is best performed between 6 hours upto 7 to 10 days after onset regardless to reperfusion therapy. Being primarily a bone agent reliable interpretation later on becomes difficult. PYP concentration is maximal in areas with moderate reduction of myocardial blood flow (20–40%), and is low in regions with severely reduced flow. This may result in the so-called doughnut pattern in large MI, where the maximal uptake occurs at the periphery of the infarct, with probable overestimation of the necrotic tissue [44].

^{111}In labeled antimyosin Fab: Antimyosin is a Fab fragment of a monoclonal antibody that binds with human myosin exposed in myocytes irreversibly damaged by an ischemic event. Labeled with ^{111}In, the antibody is taken up into acutely necrotic tissue and can be imaged by planar or single photon emission computed tomography (SPECT) techniques. It is highly specific for identifying myocardial necrosis however poor background clearance of tracer makes it a poor agent of choice. Maximum tracer uptake is seen in areas with severe flow impairment [45]. No allergic reactions to antibody injection have been reported, nor have there been documented significant increases in human antimouse antibody titers postinjection. Due to relatively slow blood clearance, the optimal imaging

time is 24 to 48 hours post-injection. Old infarcts and areas with normal myocardium show no tracer uptake.

^{99m}Tc glucaric acid: Glucaric acid is a six-carbon dicarboxylic acid sugar labeled with ^{99m}Tc [46]. Mechanism of uptake is based on binding to positively charged histones within disintegrated nuclei and reduced subcellular organelle proteins in necrotic myocytes [47]. It has favourable kinetics and its uptake appears to be limited to 9 h after the onset of acute MI; allowing differentiation of acute from recent MI.

^{99m}Tc labeled Tetracyclin: This is another infarct avid agent which has been remotely used in clinical practice. Studies have shown that its uptake in myocytes is dependent on both the degree of necrosis and residual blood flow [48]. Rabbit model was used by Dewanjee et al to study the various chelate concentration. The uptake decreased from the center of the infarcted area toward its periphery, but it was higher near the epicardial surface than toward the endocardium. ^{99m}Tc-PYP is concentrated in the same infarcted areas as ^{45}Ca ion or ^{32}P-pyrophosphate, but to a much greater degree. The uptake is dependent on both the degree of necrosis and residual blood flow. Gel filtration experiments with rabbit serum indicate that ^{99m}Tc-PYP, tetracycline, and diphosphonate are mainly protein-bound, whereas ^{32}P-PYP is not. Subcellular localization studies show that ^{99m}Tc-tetracycline and ^{99m}Tc-PYP are bound primarily to soluble protein and only a small fraction is associated with nuclei, mitochondria, and microsomes. The uptake of technetium chelates in myocardial infarcts was thought to be due to the formation of polynuclear complexes with denatured macromolecules rather than to the deposition of calcium in mitochrondria.

Infarct avid agents were limited primarily because of its availability, cost and inherent drawbacks of the agents being used. With the availability of better SPECT and PET tracers and newer molecular probes, time has come to look beyond BMIPP as a surrogate marker for antecedent ischemia.

2) Newer apoptotic agents:

Limitations encountered with previously used infarct avid agents has been overcome with newer SPECT (^{99m}Tc-labeled annexin) and PET agents i.e annexin labeled with ^{11}C, ^{64}Cu, ^{68}Ga, ^{94m}Tc and ^{18}F . Other radiolabelled probes such as C2A synaptotagmin domain I or beta 2 glycoprotein I, duramycin, hypericin, lactadherin, are undergoing preclinical studies to identify and measure key biological functions like apoptosis, necrosis, myocardial and neuronal phosphoinositide turnover [49]. Apoptosis or programmed cell death was first described by Kerr et al [50]. Chronic myocardial apoptosis is a key feature of post-infarct myocardial remodeling. Unlike necrosis, apoptosis may be amenable to intervention. Cells undergoing apoptosis express phosphatidyl serine, PS on their cell membrane, which can be used as an indirect signal of an ischemic event. Studies have shown that significant ^{99m}Tc-annexin A5 uptake was found in the culprit lesions of only patients with a recent, but not remote, history of ischemia [51]. Similarly in post-infarct setting of reperfusion therapy, the delayed SPECT images clearly show an intense accumulation of Annexin V at the site of infarct [52] Kenis et al [53] evaluated use of ^{99m}Tc-labeled AA5 intravenously at the time of reperfusion to detect recent ischemic events in experimental rabbit model. They reported that ^{99m}Tc-AA5 uptake in the ischemic region was 9 ± 3 fold higher than in the normal myocardium. Future prospective outcome studies in a larger group of patients will help determine its true discriminatory potential. Certain other agents targeting apoptosis that are in preclinical stages are C2A domain of synaptotagmin I, Hypericin, ^{99m}Tc-Lactadherin and PS-binding peptide-6 (PSBP-6*Y).*

^{99m}Tc-C2A-GST: (C2A domain of synaptotagmin I fused with glutathione-s-transferase): GST is exclusively present within the synaptic vesicles binding to PS. Studies in a rat and pig model of acute myocardial infarction show increased ^{99m}Tc-C2A-GST uptake in the area at risk [54-57]

Hypericin (Hyp): Hyp is a non-porphyrin agent which can be used both as SPECT (^{99m}Tc, ^{123}I, ^{131}I) and PET tracer (^{64}Cu) for imaging necrosis. These derivatives are efficient and yield reproducible results. ^{123}I-Hyp microSPECT/CT images in rabbit models showed I-Hyp retention in infarcted but not in normal myocardium. Rabbit models show a hepatobiliary route of excretion for this tracer [58]. It has been used in preclinical models of myocardial infarction.

^{99m}Tc Lactadherin: Lactadherin is an opsonin, which binds with high affinity to PS on exposed apoptotic cells via its C1C2 domains [59]. In contrast to ^{99m}Tc-annexin, ^{99m}Tc-lactadherin has a low renal uptake and may be the preferred tracer for imaging PS externalisation in the kidneys. Recommendations regarding the clinical use of ^{99m}Tc-lactadherin must await tracer kinetic studies in patients.

PSBP-6: This is another new radiolabeled small-molecular-weight peptide, single amino acid chelate used for the evaluation of apoptosis [60].

3) Classic Flow based tracers: SPECT based myocardial perfusion imaging:

The utility of conventional MPI in establishing the diagnosis of an AMI or acute coronary syndrome (ACS) is beyond doubt, but its use is restricted by the need for injecting the patient during or very close to

the time of chest pain onset [61] which is not the case with iodinated tracers. Commonly used MPI agents are ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin which can depict areas of infarct or ischemia when injected intravenously in acute setting before and after reperfusion therapy is instituted. Since washout of ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin is negligible, the image after reperfusion still reflects the perfusion at the time of injection. This phenomenon represents the "frozen image of jeopardized myocardium" similar to the ^{123}I-BMIPP depicted "*Memory Image*" [62]. By combining both perfusion and metabolism, a mismatch phenomenon in areas at risk (less BMIPP uptake than perfusion), can predict functional recovery of this myocardial segment [63]. In other words, since the mismatch area of myocardial perfusion and fatty acid metabolism is viable, even jeopardized, cardiac events may occur in this area in the future. These studies suggest that recovery of FA metabolism will lag behind the recovery of myocardial perfusion [64]. It can also extend the time window for identifying myocardial ischemia long after resolution of chest pain and restoration of resting myocardial blood flow [65, 66].

Investigators have used many different tracer combinations (pyrophosphate PYP, ^{201}Tl, ^{99m}Tc-MIBI, or ^{99m}Tc-tetrofosmin) along with BMIPP to estimate myocardial viability (Figure 3). Myocardial PET is preferred nowadays [67].

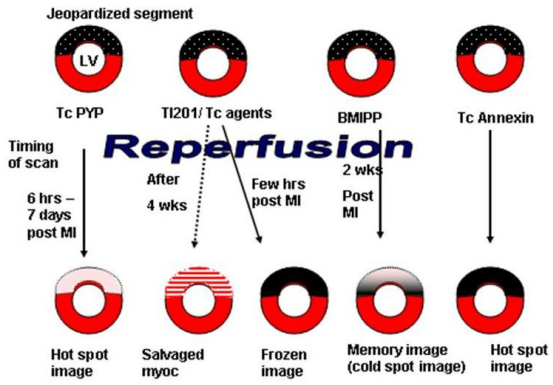

Fig 3. Representation of jeopardized and salvaged myocardium using different viability tracers (^{99m}Tc-pyrophosphate PYP, ^{201}Tl, ^{99m}Tc-MIBI, or ^{99m}Tc-tetrofosmin) and fatty acid metabolism (^{123}I-BMIPP).

4) Newer PET based myocardial perfusion agents:

^{18}F Flurpiridaz: Preliminary data with the ^{18}F Flurpiridaz, suggest that it is useful for both detection of regional myocardial perfusion abnormalities and calculation of myocardial flow reserve [68]. The complex binds to mitochondria. As cells undergo apoptosis, for example, mitochondrial transmembrane potential decreases, reducing retention of tracers that localize in mitochondria. On the other hand, when myocardium becomes ischemic, mitochondria become hyperpolarized leading to tracer retention in ischemic segments.

^{18}F-TPP: Gurm et al. [69] describe the regional myocardial distribution of a new fluorinated analog of tetraphenylphosphonium, [^{18}F]-fluorophenyltriphosphonium (^{18}F-TPP), as an indicator of myocardial perfusion in pigs. F-Phe-TPP rapidly localizes in the myocardium and is retained without significant redistribution over intervals of 30 min. Regional tracer distribution mirrors relative myocardial perfusion. Preliminary data suggest that this agent will be useful for myocardial perfusion imaging. Additional studies are needed to evaluate the low extraction fraction and clarify the lack of correlation of F-Phe-TPP uptake and absolute flow.

An algorithm (Figure 4) is provided that highlights different modalities for identifying myocardial viability in suspected cases of ACS, Hibernation or stunning.

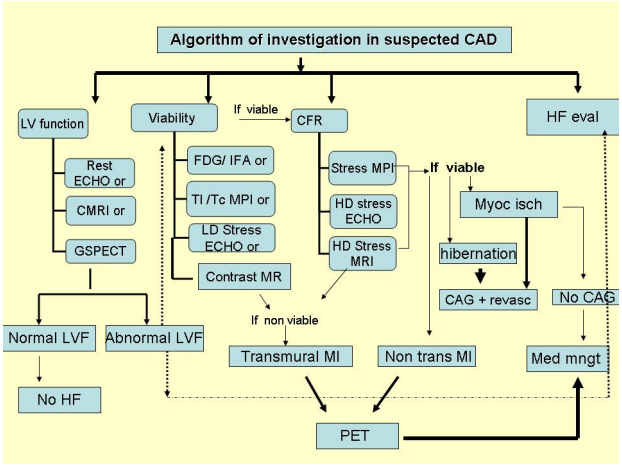

Fig 4. Algorithm highlights different modalities for identifying myocardial viability in suspected cases of ACS, hibernation or stunning.

5) Molecular imaging (MOLI) agents:

^{99m}Tc-labeled collagelin [70], is a biotinylated peptide which mimics the collagen binding site of glycoprotein VI, and specifically binds to collagen in vitro. It has a high-affinity to bind with collagen, thus serves as agent for scintigraphic detection of infarct fibrosis represented as a site of increased uptake to site of myocardial fibrosis post infarction. Collagelin was discovered and synthesized from a bacterial peptide library using an antibody against antiglycoprotein VI. After in vitro characterization, collagelin was labeled with ^{99m}Tc for in vivo SPECT imaging. Rats with prior healed MI (>3 weeks old) received intravenous ^{99m}Tc-collagelin. In vivo

SPECT imaging revealed a hot spot corresponding to the site of fibrotic areas dense in collagen fibers while surrounding non infarcted myocardium showed minimal uptake. The collagelin probe thus expands the armamentarium of imaging agents designed to assay fibrosis.

^{99m}Tc-labeled Cy5.5-RGD imaging peptide (CRIP): is another agent which is used to identify myocardial remodeling. Its uptake is based on sites where fibrinogenesis is taking place with the help of myofibroblasts [71].

^{99m}Tc-labeled losartan: This agent is used for imaging angiotensin receptor II upregulation after MI. Verjans et al [72] evaluated and found it feasible to perform noninvasive imaging of angiotensin II (AT) receptor upregulation in a mouse model of post-myocardial infarction heart failure. They concluded that in vivo molecular imaging of AT receptors in the remodeling myocardium could play a role in identification of subjects likely to develop heart failure.

^{111}In-labeled affinity peptide (^{111}In-DOTA-FXIII): Factor XIII has been found to be crucial in organizing the new matrix of myocardial scar. Labelling Factor XIII with DOTA peptides helps in imaging transglutaminase factor XIII activity which indirectly reveals a healing infarct [73]. Expression of transglutaminase factor XIII (FXIII) is involved in extracellular matrix turnover and regulation of the inflammatory response after ischaemic injury. Research is underway in animal models as of now and needs validation [73].

^{111}In- or ^{99m}Tc-labeled radiotracers for imaging metalloproteinase (MMP): MMPs are a family of zinc containing enzymes which are being evaluated as prospective agents to identify cardiomyocyte injury. Following AMI, several cytokines and proteolytic enzymes are released. Among these MMPs are important proteolytic enzymes that cause extracellular matrix degradation and myocytes changes in both infarcted and non infarcted myocardium. Of the various MMPs, MMP-9 is especially elevated in AMI. Significant tracer retention has been found 1 to 3 weeks post MI in regions of reduced ^{201}Tl uptake. MMP-targeted radiotracers display selective binding kinetics to the active MMP catalytic domain. Su et al performed initial non imaging studies and dual isotope hybrid micro SPECTCT using radiolabelled MMPs and ^{201}Tl [74]. Although this tracer looks promising Chen et al [75] showed that the MMP-9 level in myocardium after AMI was leukocyte derived and may be falsely positive in inflammatory conditions as a result of myocardial intervention and in cases of total atherosclerotic burden. Further research and clinical studies are essential to gain understanding of the role of MMPs in AMI.

CONCLUSION

Molecular imaging studies are yielding unparalleled insight into in vivo cardiovascular biology. There is a strong demand for accurate noninvasive imaging approaches of myocardial substrate metabolism leading to improved patient management paradigms. As metabolic recovery post ischemia or infarction lags behind myocardial perfusion for 24-30 hours, metabolic stunning is a powerful tool that can be used for ischemic memory imaging. Various ^{18}F based FA analogs hold promise as their myocardial kinetics in general parallel FA uptake and beta oxidation. FDG imaging is another prime example where an enzyme –specific radiolabelled probe takes part in an enzyme- metabolic trapping mechanism to amplify target tissue signals. Emphasis remains on developing highly sensitive imaging agents with better safety and pharmacokinetic profiles, and on new detection technology designed to address specific disease entities. Adequate clinical testing of promising molecular imaging agents remains a priority in the field.

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