IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
April 2021 Vol.:21, Issue:1

Recent Advances of Myocardial Infarction

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Harsha Hosur*, Mukhund Handral

PES University, Bangalore, Karnataka, India

Submitted: 20 March 2021
Accepted: 27 March 2021
Published: 30 April 2021

www.ijppr.humanjournals.com

Keywords: myocardial infarction, CT, MRI, Heart Failure

ABSTRACT

Purpose of Review: The major cause of mortality in India is cardiovascular diseases (CVDs), with 52% of the population suffering from CVDs before the age of 70. The largest proportion of CVDs is due to myocardial infarction (MI). Some patients still experience heart failure after myocardial infarction, despite advancements in medical and surgical therapy. Primary percutaneous coronary intervention is now the recommended reperfusion technique for patients with acute ST-segment-elevation myocardial infarction, aimed at restoring artery patency linked to epicardial infarction. Considerable improvements in the understanding and treatment of coronary artery disease have been seen in recent years. This paper will aim to concentrate on some of these areas of greatest interest. **Recent Findings:** In both pre-clinical and clinical trials, positron emission tomography (PET) has emerged as a widely used modality for imaging myocardial inflammation. Recent advancements in PET instrumentation, such as total body imaging, will allow high sensitivity to study multi-organ dysfunction simultaneously (e.g., heart and brain inflammation after a heart attack). Hybrid PET/MR imaging is an emerging modality of imaging. The purpose of inflammation imaging is to monitor the mechanism non-invasively and quantitatively to identify and monitor the best therapeutic strategies for intervention. This study provides an overview of the application of hybrid PET/MRI to myocardial infarction inflammation imaging. Several clinical and preclinical studies have indicated that another significant independent indicator of adverse left ventricular remodeling is the existence and magnitude of MVO, and recent research supports the suggestion that MVO might be more predictive of major adverse cardiovascular events than the size of the infarction itself. **Summary:** This review aims to summarize and present scientific evidence on developments in MI research and pharmacological/non-pharmacological MI care. With the assistance of PubMed, Google Scholar, Springer, and other online tools, data was gathered.

LIST OF ABBREVIATIONS

MI	myocardial infarction
NSTEMI	non-ST segment elevation myocardial infarction
STEMI	ST-segment elevation myocardial infarction
CT	Computerized Tomography
MRI	magnetic resonance imaging
CMRI	Cardiac magnetic resonance imaging
PET	Positron emission tomography
BOLD	Blood Oxygen Level-Dependent
CEST	Chemical Exchange Saturation Transfer
FDG	Fluorodeoxyglucose
MVO	Microvascular obstruction
PCI	percutaneous coronary intervention
HF	Heart failure

A myocardial infarction (MI) that is often referred to as "heart attack" happens when blood flow to the heart is abruptly interrupted and the heart muscle is killed. This disorder also results from the occlusion of one or more coronary arteries that supply the heart with an atherosclerotic plaque, causing an insufficient supply of oxygen and nutrients and causing infarction or death of the heart muscle tissue called myocardium.[1] While the usual symptoms of MI include crushing or pressure-like chest pain associated with nausea, diaphoresis (sweating), palpitation, dyspnea (shortness of breath), and anxiety. Symptoms may be atypical or even absent i.e about 64% of people with MI have no obvious symptom, which is called silent MI.[2] It usually occurs in patients with known ‘‘risk factors,’’ that is, hypertension, cigarette smoking, hyperlipidemia, diabetes, obesity, sedentary lifestyle, history of heart disease or other vascular diseases such as stroke, family history of heart disease, and abuse of certain drugs such as cocaine, amphetamines, etc. A patch of pallor in the cardiac muscle is the earliest emergence of the infarct. Later on, it is yellowish and dry, and the edges are hemorrhagic. There is a certain potential for the infarcted region to spread, leading to a new emergence of symptoms.[3]

MI is distinguished between non-ST segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction, depending on the electrocardiogram trace (STEMI).[4] The consequence of transmural myocardial ischemia involving the complete

thickness of the myocardium is STEMI, while NSTEMI does not spread across the entire myocardial wall. Under the definition of the acute coronary syndrome, STEMI, NSTEMI, and dysfunctional angina pectoris are established. Concept of the acute coronary syndrome.[5]

Recent advances in MI

Conventional CT (Computerized Tomography) angiography has an advantage in evaluating coronary stenosis with 95-99% sensitivity and 97-99% accuracy, compared with intrusive coronary angiography.[6] Myocardial research, however, is constrained by artifacts of motion and beam-hardening.[7] Dual-energy CT is opening up a new age for cardiac imaging with the development of the CT technique in which attenuation data from various energies are used to classify material properties. For the study of myocardial activity, CT perfusion imaging, late iodine enhancement CT imaging, and CT strain imaging are now used. In addition to correcting beam-hardening artifacts to improve image quality, the dual-energy CT technique also generates iodine maps to increase precision in MI evaluation. The iodine map represents the distribution of iodine that is associated with myocardial perfusion and blood flow in the myocardium.[8] CT perfusion imaging is used for myocardial injury evaluation of fixed and reversible perfusion defects. From myocardial perfusion imaging, qualitative and quantitative analyses can be obtained. As the reference standard for testing myocardial fibrosis or scarring, CMRI (Cardiac magnetic resonance imaging) is used. In the meantime, CMRI acquired myocardial extracellular volume fraction is now considered a valid parameter for the evaluation of diffuse myocardial fibrosis.[9] To test regional cardiac function using cardiac CT, myocardial strain imaging has emerged as a quantitative method.[10] Conventional myocardial strain imaging enables the degree of two-dimensional (2D) strain reduction to be defined by MI, which primarily tests strain in three orthogonal directions of myocardial motion: longitudinal strain, circumferential strain, and radial strain.[11] Recently, for the identification of regional cardiac dysfunction with MI, the three-dimensional maximum principal strain acquired from cardiac CT can also be used.[12] Technological developments in CT imaging have expanded the scope for MI evaluation more than traditional CT imaging, which is useful for the detection of diseases and clinical management.[13]

1) PET Imaging

Positron emission tomography (PET) can quantify and track the molecular expression of immune cells quantitatively, making it one of the most promising imaging modalities to examine the immune system's function in myocardial recovery or post-myocardial infarction

remodeling. A typical technique for PET is to use a radiotracer, which is a small "tagged" molecule with a positron emitter that is either connected to, absorbed, or enzymatically influenced by the body's molecular targets.[14] Alternatively, biomolecules, generally referred to as immuno-PET imaging, such as radiolabeled monoclonal antibodies, engineered antibody fragments, or synthetic peptides designed to bind to molecular targets, can be used.[15]

2) Nanoparticles

Due to their unique advantages, including amplification of the target signal, [16] a large surface area that enables target binding, and the ability to deliver therapeutic agents, radiolabeled nanoparticles have recently emerged as an effective strategy for molecular imaging.[17] Macroflor demonstrated a clear association with macrophages found by histology in atherosclerotic plaques of mice and rabbits[18] as well as in infarcted myocardium of mice.[19]

a) Conventional PET scanner b) total-body PET scanner.

With the recent construction of the world's first PET/CT total-body scanner, called EXPLORER, we can now encompass the entire human body within the PET scanner's field of view (FOV) and simultaneously enable imagery of all body tissues and organs.[20] This is in contrast to whole-body PET scanners, which, as a collection of image sets acquired at distinct bed locations, cover much of the body. Total-body PET imaging may have important implications for the study of systemic diseases (e.g., cancer, inflammation, vascular disease, and infectious disease), the monitoring of cellular and nanoparticle-based therapies, the assessment of pharmacokinetics and toxicology of medications, the analysis of normal tissue physiology and metabolism, and the study of multi-organ diseases or disorders requiring the involvement of one (e.g., the heart-brain axis after myocardial infarction or stroke).[21] Findings from preclinical and clinical cohort studies indicate that after myocardial infarction, the immune system plays a vital role in left ventricular recovery. Molecular imaging is important for the non-invasive visualization of immune cells recruited to the damaged cardiomyocytes due to restricted access to myocardial tissue after myocardial infarction in patients so that we can better understand the specific role of immune subsets in post-injury myocardial recovery and improve immune modulation agents.[22]

3) MRI in myocardial inflammation post-myocardial infarction

Due to its high spatial resolution, excellent soft-tissue contrast, and ability to minimize and/or quantify cardiac and respiratory motion, the MRI is an attractive modality to use for Post-MI.[23]

a) Functional Imaging

Owing to the thinness of the atrial wall, approaching the resolution of MRI, the imaging of smaller cardiac structures such as those associated with the atria has become more difficult. Developments such as phase-contrast flow imaging, in which the velocity of moving magnetic moments (flow) is proportional to the phase shift[24] and its successor, 4D Flow, have helped to estimate the effects of valve defects on the ventricular regurgitant fraction. Attempts are under development to apply 4D Flow to explore the symptoms of atrial fibrillation.[25]

b) ‘‘Scar’’ Imaging

The distribution volume of gadolinium chelates such as Gd-DTPA has been extensively shown to conform to the extracellular space in the myocardium. This is measured as the ratio of the myocardial Gd-chelate concentration divided by the blood concentration, which is also referred to as the coefficient of partition and designated as k. If the hematocrit is known, i.e. Vd = k 9, the volume of distribution can be determined from k (1 - Hct). K in post-MI myocardial tissue has been shown to increase from approximately 0.45 to 0.9 mLg-140-42 in both humans and dogs.[26]

c) Myocardial Blood Flow

Myocardial blood pressure can be assessed after a transmural resolution bolus injection of gadolinium chelate.[27,28] Full heart coverage may not always be necessary, however, and two bolus injections are frequently used to account for signal saturation,[29] raising the amount of Gd-chelate required by developing methods to solve these problems.[30,31,32] The increased difficulty of the use of Gdchelates, which have a much lower extraction fraction compared to PET methods such as those using 13NAmmonia or 15O-water56-58, has been seen in contrast to determinations using PET.[33] It is important to remember here that while Gd-chelates are extracellular, 13N-Ammonia enters and is trapped in living cells.[34]

d) BOLD MRI Contrast

For the noninvasive analysis of the brain, Blood Oxygen Level-Dependent (BOLD) contrast in MRI has been widely used. Venous blood contains higher amounts of oxyhemoglobin with a related reduction of deoxyhemoglobin content due to the reduced extraction fraction of oxygen as blood volume increases.[35] In comparison, dobutamine administration resulted in an improvement in coronary blood flow but no substantial change in T2* compatible with a lack of change in myocardial venous deoxyhemoglobin. New MRI approaches for cardiac BOLD calculation have recently shown significant promise to suggest a capacity for myocardial ischemia assessment comparable to SPECT and PET methodologies.[36]

e) Chemical Exchange Saturation Transfer (CEST)

The transition of chemical exchange saturation (CEST) depends on the preferential saturation and exchange of protons of interest to free protons imaged with MRI[37,38,39] from metabolites. Changes in protein concentration[40], glutamate[41], creatine[42], glycosaminoglycan, and most importantly pH (acidoCEST)[43,44] and D-glucose (glucoCEST) [45,46,47] have been identified utilizing CEST. The latest promising findings indicate its efficacy in post-MI measuring myocardial creatine kinase [48,49] and hyaluronan synthesis.[50]

f) PET imaging post-myocardial infarction

While a large number of PET probes for cardiac analysis have been created, to date only a few have been used in clinical practice for use in post-MI patients[51]. Post-MI PET imaging is more widely conducted with 18F-FDG, even if it is important to inhibit stable myocyte glucose uptake concurrently with flow tracers to test ischemia. It has been shown *in vitro* that the absorption of 18F-FDG is higher in M1 macrophages than in M2 macrophages. When isolated from the human THP-1 monocyte cell line[52], the absorption of M1 macrophage is double that of M2. In comparison, the absorption of 18F-FDG in M1 macrophages is 10 times greater than M2[53] when primary monocytes from human blood are used. As the absorption of 18F-FDG by neutrophils and monocytes can be close to that of M1 macrophages, this is further blurred.

g) Hybrid PET/MR in Cardiology

Data collection has been the main disadvantage of standalone PET (i.e. concurrent PET/CT) as the heart travels through the combined cardiac and respiratory processes. Which is in

contrast to cardiac MRI, where breath-hold or respiratory gating[54] can be paired with ECG synchronization of the cardiac cycle. However, PET respiratory gating results in a loss of 50 percent of the data, and splitting the cardiac period into eight phases results in a cumulative loss for each portion step of 15/16th of the data obtained. Methods for capturing cardiac MR images taken at various points in the respiratory cycle have been developed[55,56] but to date, they have not been used successfully to reduce/eliminate the impact of motion on the PET data without losing such MRI capabilities[57-60]. The respiratory and cardiac motion of the heart may be monitored by MRI (e.g., 3D navigator echoes and motion-sensitive MRI acquisitions) and PET reaction lines may be transferred to a fixed cardiac position (e.g., practical residual power end-diastole).[61-63]

h) Hybrid PET/MRI as a Convergent Technology

There is a need for near-perfect registration between PET and MRI as well as other considerations to attain convergence. For all PET radioisotopes, a significant weakness of PET is the one typical signal (511 keV extinction radiation). During some data processing, this restricts PET to a single radiopharmaceutical, while there is the potential to capture a spectrum of image comparisons in MRI dependent on various pulse sequences and proton encounters with static and changing magnetic fields. For instance, in a single imaging session, a post-MI analysis that involves both blood flow (e.g., 13N ammonia) and inflammation (e.g., 18F-FDG) by PET is difficult to achieve. One option is to use contrast-enhanced MRI1[64] or BOLD MRI[65] to conduct myocardial blood flow measurements, which during cardiac exams may improve acquisition time and dosage. In diseases such as heart sarcoidosis, this would be particularly useful where it would be helpful to study blood flow and inflammation.[66,67]

i) Future Opportunities with Hybrid Cardiac PET/MRI

The use of PET radiopharmaceuticals was focused on poor (but not zero) unspecific binding for anatomical signal localization before hybrid imaging in PET (i.e., PET/CT). The trend of setting up PET probes without non-specific binding can now be further engaged with the automatic registration of the MRI image to the PET distribution without the need for an extra radiation dose from CT. This allows, for example, to track PET-labelled cells. If hybrid PET/MRI correctly documented the PET and MRI images, as seen in the section 'Injecting Labeled Inflammatory Cells,' the tracking of 89Zr-labeled cells could be feasible, while this could not be done consistently with PET/CT or sequential PET/MR. 89Zr appeals to

longitudinal imaging for its 3.3-day half-life, since it can be tracked within the body for as long as 30 days.[68]

4) Microvascular obstruction (MVO)

-CMR-defined MVO is now a well-established adverse prognostic marker that appears in half of active primary percutaneous coronary intervention (PCI) patients with STEMI.[69,70] Attempts to further increase outcomes in these patients to date have been targeted at minimizing infarct size with modest results. There is an unmet need for future trials to determine whether it will potentially be successful to treat both infarct size and MVO using a mixture of therapies to further enhance performance in this community of patients.

Pharmacological Strategies to Reduce MVO and Limit Infarct Size

a) β - blockers - tests have shown METOCARD-CNIC: IV metoprolol up to 15 mg before reperfusion and IV metoprolol up to 15 mg before reperfusion. EARLY BAMI: 5 mg IV metoprolol 2 boluses before reperfusion in STEMI indicates a reduction in infarct size (CMR at 5-7 d). The possible effect of O2 intake on cardiomyocytes has been reduced. The potential effect of neutrophil platelet coaggregation inhibition on microcirculation is shown.[71-73] EARLY BAMI: IV metoprolol 2 5 mg bolus before STEMI reperfusion reveals the size of infarction (CMR at 30 d). [74]

b) Adenosine - Tests found AMISTAD-II: infusion of adenosine 50 or 70 μg/kg·min within 3-4 hours began either after initiation of fibrinolysis or before coronary intervention within 15 minutes. Composite of chronic HF, rehospitalization for HF and death at 6mo; infarct size (technetium-99 m sestamibi) as endpoints are seen in STEMI. No variations in health outcomes; infarct duration. Afterload, ATP degradation, Cellular Ca2+ influx, Oxidative stress indicates the possible effect on cardiomyocytes. The potential effect of coronary microvascular vasodilation on microcirculation, adherence to neutrophils and neutrophil-mediated cellular damage, platelet aggregation, oxidative stress.[75,76]

c) Statins - Tests have shown that SECURE-PCI: atorvastatin is 80 mg before and 24 h after the scheduled PCI, STEMI Scale of infarct (CKMB), and LVEF. Microvascular dilation, endothelial activity, platelet activation, inflammation, immune response. Possible effect on microcirculation.[77]

d) Atrial natriuretic peptide - Tests have shown that J-WIND: intravenous carperitide 72 h infusion began before PPCI. STEMI, as an end-stage, MVO by CMR on days 2 to 7. The outcome was the scale of the infarction, the LVEF. End-diastolic strain, coronary collateral blood flow, mitochondrial potassium ATP channel activation indicates possible influence on cardiomyocytes. Potential effect on microcirculation demonstrated by an intracoronary clot and endothelial cytotoxicity caused by neutrophils.[78]

e) Intracoronary fibrinolytic therapy - Experiments shown T-TIME: Intracoronary alteplase 10 mg or 20 mg during PPCI (after reperfusion of the infarct-related coronary artery and before stent implant). To STEMI, MVO by CMR as an endpoint on days 2 to 7. Intracoronary clot. Possible effect on microcirculation shown.[79]

5) Recent updates on myocardial infarction diagnosis

In addition to aspirin, frequent use of antiplatelet agents such as clopidogrel, prasugrel, or ticagrel or decreases morbidity and mortality in patients. The key care of patients with acute ST-segment elevation MI is PCI promptly. Drug-eluting coronary stents with primary coronary involvement are stable and beneficial. Direct thrombin inhibitor treatment during PCI is non-inferior to unfractionated heparin and glycoprotein IIb/IIIa receptor antagonists and is consistent with substantial bleeding reduction. Intracoronary use of an antagonist of glycoprotein IIb/IIIa can decrease the size of the infarct. Further cardioprotection may be provided by pre-and post-conditioning strategies.[80]

In patients with acute MI, thrombolytic medications have decreased mortality, but new therapies have limited effectiveness in obtaining and sustaining immediate vessel patency in the longer term. Complete perfusion is restored in only 54 percent of patients by the strongest existing thrombolytic therapy, rapid tissue plasminogen activator, although streptokinase does this in only 30 percent. In major clinical trials, thrombolytic drugs such as recombinant plasminogen activator and prourokinase are being developed but must be tested. The prospect of antithrombin drugs newly established to decrease arterial re-occlusion is unclear. New medications blocking platelet receptors appear to have the greatest ability to increase immediate and long-term vessel patency rates. Compared to thrombolytic, the greater advantages of primary angioplasty have not been definitively established.[81] In acute coronary syndrome, thrombus formation happens under conditions of elevated shear stress and is mainly driven by platelet aggregation. During intracoronary thrombus formation, this dominance of platelet aggregation illustrates the drastic impact antiplatelet therapies have on

clinical results. Aspirin was the first antiplatelet therapy that induced a halving in event rates in patients with acute coronary syndrome: such a large impact size has rarely been exceeded in other realms of cardiology.[82] Given the remarkable success of aspirin, it is therefore unsurprising that adjunctive antiplatelet therapies have been explored to improve on these advantages, especially as there are several platelet activation pathways outside the pathway of cyclooxygenase. There is, however, a compromise between minimizing the occurrence of potential coronary problems and causing harm due to an elevated risk of bleeding, as platelets are necessary for primary hemostasis.[83] The P2Y12 (adenosine phosphate) receptor antagonists are a class of drugs that have achieved general popularity because, at the cost of small reductions in bleeding, they tend to offer an additional thrombotic defense. Their use is mainly related to declines in chronic MI and, in a few studies, decreases in coronary attacks and mortality. There are other anti-platelet therapies available,[84] but they have variable net clinical value, and only dual antiplatelet therapy with aspirin and P2Y12 receptor antagonism will be included for this review.[85,86]

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