Delayed Hyper-Enhancement in Cardiac MRI Compared to Nuclear Perfusion Scintigraphy in Identification of Viable Myocardium in Patients of Myocardial Infarction – A Study

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ABSTRACT

Background: Myocardial infarction is the leading cause of death and disability worldwide. Nuclear perfusion scintigraphy is the gold-standard technique, which is highly specific in differentiating viable from scarred myocardium in patients of myocardial infarction. Dysfunctional myocardium with areas of residual viable tissue may show functional recovery after revascularization. The aim of this study was to determine the effectiveness of Cardiac MRI in detecting viability of myocardial tissue as compared to ⁹⁹ᵐ-TC Sestamibi perfusion scan in patients with myocardial dysfunction who were awaiting revascularization procedures. Study methods: 42 patients (35 male and 7 females) of myocardial infarction in age group 31-78 yrs were evaluated using cardiac MRI and cardiac nuclear perfusion scans and the results were compared. Pearson Chi-Square test and Fisher’s Exact Test were used for statistical evaluation. P value <0.005 was considered statistically significant. Results: Both the techniques detected trans-mural myocardial infarcts at similar rates. However, cardiac MRI was able to detect sub-endocardial infarcts in 33% cases, which were totally missed on nuclear perfusion imaging. MRI was found to be more sensitive than nuclear perfusion scans for detecting sub-endocardial infarcts. The sensitivity of delayed hyper enhancement cardiac MRI for detection of viable myocardium was 100% with a specificity of 47.83%. The positive predictive value of the modality was 61.29% with a diagnostic accuracy of 71.43%. Conclusion: Contrast enhanced MRI was found to detect sub-endocardial infarcts at a higher rate and has high sensitivity in the detection of viable and irreversibly damaged myocardium in comparison to nuclear perfusion scans.

Key words: Ischemic heart disease, Myocardial viability, Myocardial dysfunction, Contrast enhanced MRI, ⁹⁹ᵐ-TC Sestamibi.

INTRODUCTION

Myocardial infarction is the leading cause of death due to ischemic heart disease (IHD) in India and is also one of the most common causes of morbidity worldwide.¹ Previously only people living in high income group countries were primarily thought to be affected by IHD, but recent studies and data confirm that IHD is the leading cause of death and disability in low and middle income countries which includes India, and the rates are increasing disproportionately when compared to those in high-income countries.² In 2010-2013 itself, IHD accounted for 23 % of total and 32 % of all deaths in adult population in India.³ The “Global burden of disease study”, estimate of age standardized cardiovascular death rate of 272 per 100,000 population in India is higher than the global average of 235 per 100,000 population.⁴ Following myocardial infarction, prolonged ischemia and subsequent reperfusion can lead to myocardial inflammation and severe tissue damage by several immune mediated mechanisms.⁵ These cellular changes prime both the infarcted and non-infarcted cardiomyocytes for progressive ventricular dysfunction that eventually leads to a decline in function and heart failure.⁶ An early intervention at the time of reperfusion after the onset of acute MI has been shown to limit infarct size and restore blood flow in the ischemic tissue.⁷

“Myocardial Viability” is a concept which is based on the premise that in patients who have suffered myocardial infarction, even severely dysfunctional myocardium with areas of residual viable tissue may show functional recovery after revascularization.⁸ Differentiation of reversible and irreversible injury to myocardial tissue is of prime importance, as an appropriate course of action depends on whether the involvement is already trans-mural or whether some or all of the ‘at risk’ region contains focal areas of viable tissues in myocardium, which may be endangered in case of a future ischemic episode.⁹ Reversal of myocardial contractility may be of relevance in patients with reduced ventricular function but viable myocardium, as revascularization procedures may significantly improve long-term survival in them. Recent advances in the field of medicine and cardiology per se have led to the availability of a variety of non invasive methods to assess myocardial viability such as Thallium-201 SPECT / ⁹⁹ᵐ-TC Sestamibi perfusion scan, low-dose Dobutamine stress echocardiography, Cardiac 18-FDG-PET scan, contrast enhanced cardiac MRI (CeMRI) for delayed hyper-enhancement.

MATERIALS AND METHODS

The present study was aimed to determine the effectiveness of contrast enhanced Cardiac MR (CeMRI) in detecting the viability of myocardial tissue as compared to Tc-⁹⁹m Sestamibi perfusion scan in patients who have had myocardial infarction. A prospective observational clinical study was carried out comprising of a non-randomized sample of 42 patients (35 male and 07 females) of myocardial infarction (acute / chronic) in age group of 31 to 76 years with a median age 55.5 yrs, who presented to our tertiary care hospital and were awaiting coronary re-vascularization procedures. Necessary clearance from the institutional ethical committee was obtained and a written informed consent was taken from the patients at the time of their enrolment. The diagnosis of myocardial infarction was based on clinical signs and symptoms, typical ECG changes, cardiac enzyme markers (TROP-T and CK-MB) and ECHO findings. None of
the patients had undergone coronary angioplasty or any other revascularization procedure before the study was performed. All the patients had no contraindication to MRI or to use of intravenous gadolinium contrast agents (i.e. contrast allergy / GFR < 30 ml/min). Patients having bundle branch block ECG patterns / unstable angina were excluded from study. The individuals enrolled for study were subjected to a complete medical history and clinical case record evaluation and the findings were noted down on a printed performa. Evaluation for myocardial viability was done by Tc-99m Sestamibi scan. The patients were then subjected to cardiac CeMRI for demonstration of delayed hyper-enhancement.

### Cardiac MRI protocol

Cardiac MR was performed on a 1.5 T magnet (Symphony, Siemens Medical Solutions, Erlangen, Germany) using a body coil. Cardiac sequences were gated to the patient’s cardiac cycle using ECG leads with image acquisition done at end of expiration. Localizers were acquired in three orthogonal planes followed by scout imaging in short axis, 2 chamber and 4 chamber views. Dark blood axial images were acquired along with TRUFI cine sequences in short axis, 2 chamber and 4 chamber views. For late gadolinium enhancement, multiple sequences with varying inversion time (TI) values were acquired and selected images with most appropriate TI were studied 15 minutes after i/v injection of gadolinium chelate contrast (0.1–0.2 mmol/kg) for delayed hyper enhancement.

Inversion time set to null normal myocardium was in the range of 180 – 230 ms.

### Image evaluation

The images produced were evaluated using vendor provided auto analysis software and PACS workstations and were analysed by a radiologist. The short-axis images were acquired and from these the heart was divided into three equal-sized regions (basal, middle, and apical) and sliced into 17 segments (based on the 17-segment model as proposed by Schiller et al.) Segment 17 was however not included for measurement of wall thickness due to high incidence of false positive results associated with its measurement. Various measurements were done as follows:

i) Hyper-enhanced myocardium was identified 15 min after contrast administration as white regions with image intensities of >2 standard deviations (SD) above non enhanced myocardium which appeared dark after adequate nulling using double inversion recovery sequences.

ii) The wall thickness of this hyper-enhanced myocardium was then studied on the 17-segment model for each patient. The extent of hyper enhancement in each segment was graded as a percentage of the total wall thickness into different grades with Grade 0 - depicting no enhancement, Grade 1 - involving 1% – 25% of wall thickness, Grade 2 - involving 26-50 %, Grade 3 - involving 51%–75% and Grade 4 - involving > 75% of wall thickness.

iii) Endo and epicardium were defined as the inner 50% (Grade 2) and outer 50% (Grade 3), respectively. Trans mural extent was described as Grade 4 of involvement. The myocardial tissue was divided into two groups based on the delayed hyper enhancement on MRI as “Viable myocardium” (involvement of ≤ 50 % wall thickness) and “Non-viable myocardium” (involvement of ≥ 50 % wall thickness).

### Tc-99 Sestamibi perfusion protocol

Patients were subjected to a standard 12-lead ECG and SPECT myocardial perfusion imaging was performed subsequently. Patients were made to exercise on a treadmill (Bruce protocol) for 5 - 10 minutes up to a workload of 10.2 Mets. A total dose of 296 MBq (MCi) 99m TC MIBI was injected IV at peak stress and cardiac SPECT images were acquired thereafter. Rest study was conducted 3 hrs after completion of the stress study.

### Image evaluation

The end point criterion was adequate level of exercise. Exercise tolerance was measured and ECG changes during the stress study were noted. Perfusion images were acquired in short axis, vertical and horizontal long axis for any defects and whether the defects reversed / persisted at rest suggestive of viable myocardial tissue / scar tissue. The images were analysed for presence or absence of perfusion defect and its extent. A nuclear medicine specialist reported the result.

### RESULTS

Data was recorded on a pre-designed Performa and was managed on a Microsoft Excel sheet. Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) was used for Data analysis. The results of delayed hyper-enhancement on cardiac MRI were compared to the results of nuclear perfusion scan. Pearson Chi-Square test and Fisher’s Exact Test were used for statistical evaluation. In this study P value 0.0016 was considered statistically significant (Table 1 and 2).

Out of the 42 patients studied, 14 (33.3 %) patients had acute MI, 27 (64.2%) patients had acute MI and 01 (2.3 %) patient had chronic MI.

### (A) Cardiac CeMRI

i) **Territorial involvement of myocardial infarct on MRI** - Out of 42 patients studied, 22 patients (52.38 %) had anterior wall MI, 13 patients (30.95 %) had inferior wall MI, 05 patients (11.90 %) presented with anterolateral wall MI and posterior wall MI was present in 02 patients (4.76 %).

ii) **Segmental Involvement of infarcts** - A total of 672 (16 segments x 42 patients) myocardial segments were studied for delayed hyper enhancement by cardiac MRI based on 17-segment model proposed by AHA (apical segment was not included). Delayed hyper enhancement was present in 98 segments constituting 14.58 % of the studied segments, with varying extent of the wall involvement.

The mean signal intensity of the hyperenhanced myocardium on delayed MRI was 114.71 ± 21.162 and the mean signal intensity of the non enhanced myocardium was calculated as 26.52 ± 11.662. Probability that the difference in SI of enhanced and unenhanced myocardium was due to chance was 0.0004.

iii) **Myocardial wall involvement by infarct on MRI** - Normal myocardium with no evidence of delayed hyper enhancement was observed in 11 patients (26.19 %), 09 (21.42 %) patients had infarcts involving 0-25 % wall thickness, 11 (26.19%) patients were found to have 25-50 % wall thickness involvement by infarcts and in 04 (9.52 %) patients infarcts involving 51-75 % wall thickness were found. Transmural infarcts involving > 75 % wall thickness were observed in 07 (16.66 %) patients (Figure1).

### (A) Tc-99 Sestamibi Nuclear perfusion:

Nuclear perfusion scintigraphy studies showed viable myocardium in 19 patients (45.24 %) [normal study was observed in 11 patients (37.89 %) and reversible perfusion defects were seen in 08 patients (42.10 %)]. Fixed perfusion defects suggestive of non-viable myocardial myocardial tissue were seen in 23 patients (54.76 %).

05 patients (50 %) out of 10 patients with normal nuclear perfusion studies showed normal MR studies with no delayed enhancement while 05 (50 %) patients had delayed hyper enhancement on MRI which was
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Table 1: Original Table

<table>
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<th>MRI</th>
<th>99Tc Sestamibi/Thallum 201</th>
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<tr>
<td></td>
<td>Viable</td>
<td>Nonviable</td>
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<tr>
<td>Viable count</td>
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</tr>
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<td>Percent</td>
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<tr>
<td>Nonviable Count</td>
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<tr>
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<td>23</td>
</tr>
<tr>
<td>Percent</td>
<td>45.2%</td>
<td>54.8%</td>
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</table>

Chi-Square test Value df P value Association is
Pearson chi-Square 12.311 1 0.0016 Significant
Fisher’s Exact Test 0.0003 Significant

Figure 1: Extent of myocardial enhancement observed on CeMRI.

Figure 2: Distribution of viable vs non-viable myocardium on nuclear perfusion scan.

Figure 3: Scatter diagram showing the correlation between CeMRI & nuclear perfusion scan in detecting myocardial viability detecting myocardial viability on MRI and nuclear perfusion scans was statistically significant (Figure 3).

Statistical performance of MRI

The sensitivity of delayed hyper enhancement MRI for detection of viable myocardium in the study group was 100 % and the specificity was 47.83 %. The positive predictive value of the modality in detecting viability was 61.29 % with a diagnostic accuracy of 71.43 %.

DISCUSSION

The most common implicating event in causation of myocardial infarction is coronary artery occlusion secondary to embolization by an unstable coronary plaque. Hypoxia caused by such an occlusion causes initial cellular changes in the myocardial tissues in the territory supplied by the occluded vessel, which causes a progressive decline in the ventricular function and sometimes heart failure, if a large area is involved. Without critical blood supply, the inflammatory mediators such as cytokines are activated in the infarcted region that leads to the initiation of cellular processes of necrosis, apoptosis and autophagy, which further leads to loss of functional cardiomyocytes.10,11 These processes occur simultaneously in the hypoxic tissue as the affected cells struggle to survive or die. These inflammatory pathways are critically involved both in repair as well as remodeling of the infarcted myocardium. β-adrenergic receptors (AR) serve as critical regulators of cardiac function at the level of the myocardium and in circulation.12 Post myocardial infarction, β-adrenergic signaling in myocardial cells is seen to be associated with cardiac hypertrophy, ventricular remodeling and apoptosis. A study by Shashi Bhushan et. al. (2012)13 demonstrated that selective β2-adrenoreceptor stimulation attenuates myocardial cell death and preserves cardiac function after ischemia–reperfusion injury.13 Altering the initial cell responses to ischemia may enhance cardiomyocyte survival and ultimately preserve myocardial function following MI.11 Early and effective restoration of the vital blood supply to the at risk myocardium is the most effective current clinical therapy aimed at improving blood flow to the non perfused myocardial cells.14 Therapeutic approaches targeting specific components of the inflammatory response hold promise for patients with myocardial infarction Cardio-protective effect of interventions for patients experiencing MI is very essential to restore cardiac function. Dysfunctional myocardium with focal areas of viable tissues has the potential for contractile recovery after reperfusion.15 This distinction...
between viable myocardial tissue and non viable necrotic tissue is a pre-operative predictor of the benefit of any revascularization procedure. Location of viable myocardium, especially in the sub-epicardial location, may have an important influence on long-term ventricular function. The principle of determination of myocardial viability on CeMRI is based on the observation that infarcted area (ncrosed tissue), enhances avidly, 10-15 minutes after intravenous contrast administration. This delayed hyper enhancement has been shown to correlate precisely with the actual extent of infarct as observed in various animal and human studies. Viability imaging thus reliably helps to identify areas of hibernation and viable or non-viable myocardium.

A combination of delayed hyper-enhancement on CeMRI and assessment of segmental wall motion by cine-MRI yields better information about myocardial contractile reserve. In general, presence of mild degrees of hyper-enhancement (involving <25% of the segment) with normal wall motion suggests that contractile function of that segment will recover, whereas the presence of higher degrees of hyper-enhancement (>75% of the segment) strongly suggests that no effective recovery of contractile function will occur even after revascularization. The outcome after revascularization however, is less clear in dysfunctional segments showing intermediate degrees of hyper enhancement (>25% and <75%). In such cases, trans-mural infarcts were found to be associated with no recovery of contractile function.

The present study conducted at our hospital also showed that cardiac MRI using delayed hyper enhancement technique and nuclear perfusion studies detected trans-mural myocardial infarcts at similar rates. However, cardiac MRI was able to detect sub endocardial infarcts (< 50 % wall thickness) in some cases (33%), which were totally missed in nuclear perfusion imaging that had demonstrated a normal study. Thus MRI was found to be more sensitive than nuclear perfusion scans for detecting sub endocardial infarcts. It was also found that the sensitivity of delayed hyper enhancement on MRI for detection of viable myocardium was 100 % with a specificity of 47.83 %. The positive predictive value of the modality was 61.29 % with a diagnostic accuracy of 71.43 %.

The general idea that SPECT misses small infarcts has been previously reported by, which also demonstrated that SPECT was poor at picking up small sub endocardial infarcts as compared to the MR imaging.

In a study by Anja et al. a comparing contrast enhanced cardiac MRI with SPECT also found that SPECT not only misses some infarcts, but also a large proportion of patients in whom infarct is missed, the SPECT scan is completely normal. In a large proportion of such patients, delayed-enhancement cardiac MRI was able to detect sub-endocardial infarcts in 92%, whereas SPECT detected only 28%. Due to low spatial resolution and degradation of image quality associated with SPECT, the study is limited, especially in the detection of small and sub endocardial infarcts.

Thus to conclude, necrotic myocardium and scar resulting from myocardial infarction, may be distinguished from normal myocardium by magnetic resonance imaging (MRI), an operator independent technique, which is quite safe for patients. Contrast enhanced MRI (CeMRI) seems to be clinically useful and reproducible in scar detection. Though nuclear perfusion study is the gold standard for demonstrating myocardial viability, CeMRI is more sensitive in demonstrating sub-endocardial infarcts which is possibly because of higher contrast and spatial resolution of the MRI as compared to nuclear imaging. The excellent tissue characterization function enables MRI to detect viable myocardium accurately. Contrast enhanced MRI provides information on tissue perfusion, cellular integrity and membrane function and has the potential to replace or complement other commonly used techniques in the diagnosis of viable and irreversibly damaged myocardium.

CONFLICT OF INTERESTS

The authors have none to declare.

CONCLUSION

Contrast enhanced MRI has high sensitivity in the detection of viable and irreversibly damaged myocardium and has the potential to replace or complement nuclear perfusion scans in detecting myocardial viability in patients of myocardial infarction.

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ABBREVIATION USED

IHD: Ischemic heart disease, MI: Myocardial infarction, CeMRI: Contrast enhanced magnetic resonance imaging, SPECT: Single photon emission computed tomography.

REFERENCES

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