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Role of Stress Cardiac MRI in Management of Patients with Moderate (50-69%) Coronary Artery Stenosis - A Single-Center, Pilot Study in North Indian Population

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Abstract

Coronary artery disease (CAD) is one of the most common cardiovascular diseases in India. Even after the availability of data on the usefulness of stress CMRI; we are still not using stress CMRI in the management of patients with CAD in India. Our study was a prospective, pilot study from the Himalayan belt of North India; wherein we tried to assess the role of stress CMRI in the management of patients with moderate coronary artery stenosis.

Keywords: Stress cardiac MRI, adenosine, coronary artery disease, inducible ischemia, revascularization.

Introduction

Coronary artery disease (CAD) is one of the most common cardiovascular diseases in India. Myocardial infarction (MI) occurs when the blood supply to heart muscles is significantly reduced, or the energy requirement of heart muscles is raised significantly, due to exercise/stress/other factors. The prevalence of CAD has increased significantly in India over the last 60 years, from 1% to 10% in the urban population, and from <1% to 5% in the rural population. **[1,2]**

Indian guidelines for CAD management and event prevention, are shown in **Figure 1**. According to these guidelines, patient's with insignificant stenosis (<70%), patients with diffuse triple vessel disease (TVD), or patients with left ventricle (LV) dysfunction, are not suitable candidates for coronary revascularization.**[3]** However, patients with < 70% coronary stenosis, may show an inducible ischemic change in coronary territory. In such patients with an inducible ischemic change in coronary territory, coronary revascularization can significantly improve the patient's symptoms.

In the current scenario, multiple non-invasive imaging techniques are available for cardiac assessment, like Myocardial Nuclear Perfusion Imaging, Stress Echocardiography, and Cardiac Magnetic Resonance Imaging (CMRI). Out of all these imaging modalities, CMRI has emerged as a highly sensitive and specific test, for non-invasive cardiac assessment.

CMRI can accurately evaluate cardiac structure and function, detect inducible cardiac ischemia, calculate left ventricle ejection fraction (LVEF), characterize and assess the viability of myocardial tissue, and detect MI. **[4,5]** Stress CMRI uses pharmacological agents like adenosine and dipyridamole, to induce stress. **[6,7]**

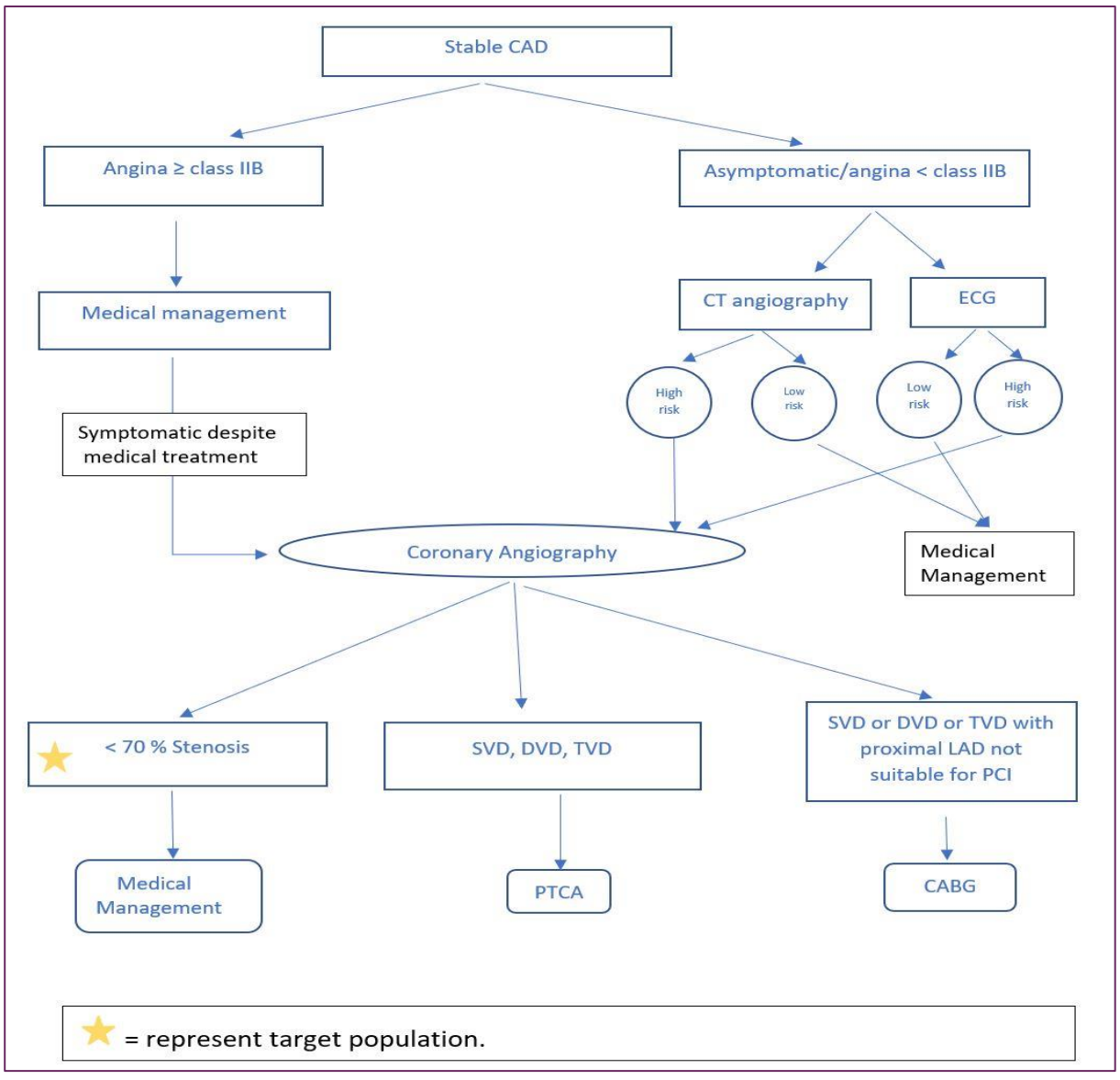
William F Fearon et al, did a study in 2018 in which they did a FAME 2 trial (Fractional flow reserve versus angiography for multivessel evaluation), and compared percutaneous coronary intervention (PCI), guided by fractional flow reserve, with best medical therapy, in patient's with stable CAD, to assess clinical outcome and cost-effectiveness, with 3 years follow up for each patient.**[8]** They found that there was a yearly and sustained improvement of angina (10.2% vs. 28.5% at 1 month, and 5.2% vs. 9.7% at 3 years), in favor of Fractional Flow Reserve (FFR) guided PCI. PCI of lesions with reduced fractional flow reserve was also economically attractive, compared with medical therapy alone, in patients with stable CAD.

Eike Nigel et al, did an MR-INFORM trial in 2019 and concluded that among patients with stable angina and risk factors for CAD, myocardial perfusion CMRI was associated with a lower incidence of PCI, as compared to those based on an FFR-based strategy.**[9]** Moreover, myocardial perfusion CMRI was also non-inferior to FFR based strategy, for major adverse cardiac events.

Even after the availability of data on the usefulness of stress CMRI, we are still not using stress CMRI in the management of patients with CAD in India. Our study was a prospective, pilot study from the Himalayan belt of North India,

wherein we tried to assess the role of stress CMRI in the management of patients with moderate coronary artery stenosis (CAS).

Figure 1: Indian guideline for CAD management and event prevention.



Aims and Objectives

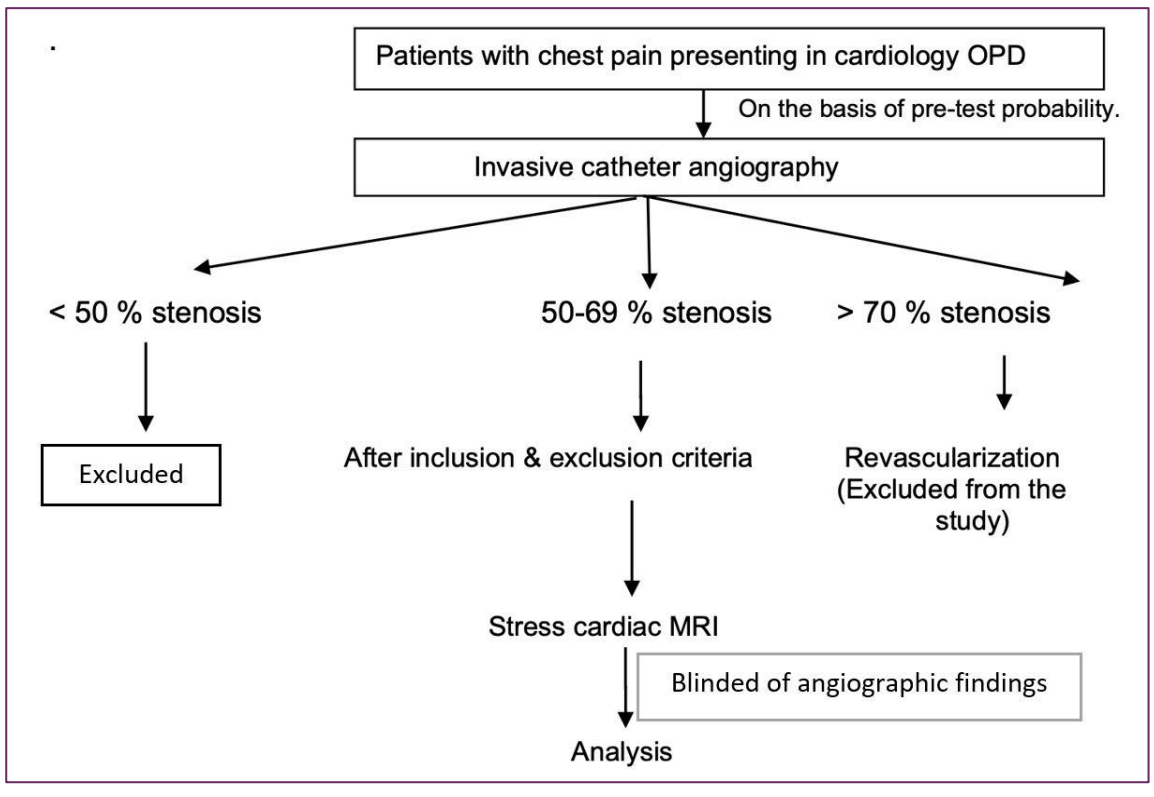
To assess the role of stress CMRI in the management of patients with moderate CAS.

Material and Method

This study was a single tertiary care center, prospective, cross-sectional study, done over a period of 18 months, and included patients with chest pain, coming to the Cardiology department of the institute. Patients underwent catheter angiography, based on pre-test probability. If coronary artery stenosis (CAS) was found to be >70 % in any coronary artery, then coronary artery stenting was done.

Patients having 50-69% CAS, underwent stress CMRI. Reporting radiologists were kept blinded to conventional catheter angiography findings. Vitals and hemodynamic changes (including systolic and diastolic blood pressure, and pulse rate) of all patients were recorded before & during adenosine administration and monitored continually throughout the scan. Real-time electrocardiographic monitoring was performed, to identify heart block or arrhythmia. All patients were explained about the study, and the adverse effects of adenosine, they might feel during the scan. A flow chart explaining the study design is shown in **Figure 2**.

Figure 2: Flow chart of study design.



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Exclusion Criteria

a. Patients with acute coronary syndrome (ACS).
b. Vessels territories with previous coronary artery stenting.
c. Patients who didn't give consent.
d. Patients who didn't undergo MRI, or had a history of claustrophobia, or anxiety.
e. Serum creatinine > 1.4 mg/dl.
f. History of contrast allergy.
g. Known hypersensitivity to adenosine.
h. Known or suspected broncho-constrictive or broncho-spastic disease.

Patient Preparation

a. Informed written consent was taken for stress CMRI.
b. Adenosine was used as a stress agent.
c. Two intravenous lines were used, one for gadolinium-based contrast agent (GBCA) and one for adenosine, one in each arm.
d. Blood pressure cuff was used in a way, that didn't interfere with GBCA or adenosine infusion.
e. Crash cart with appropriate resuscitative medications, supplies, and equipment with drugs such as ß-blocker (esmolol or metoprolol), nitroglycerin, aminophylline, bronchodilators, epinephrine, and antiarrhythmic drugs were available on-site.

MRI Protocol

MRI was performed using a 3T MRI machine (GE, Discovery 750W) with the patient in the supine position.

a. Cine imaging was performed, with the patient at rest, to assess LV function.
b. Adenosine was injected in a dose of 140 microgram/kg/min for 4 minutes, with close monitoring, to assess stress perfusion.
c. Resting perfusion scan was done 10 minutes later, to assess rest perfusion.
d. Delayed enhancement imaging was thereafter done after 5 minutes.

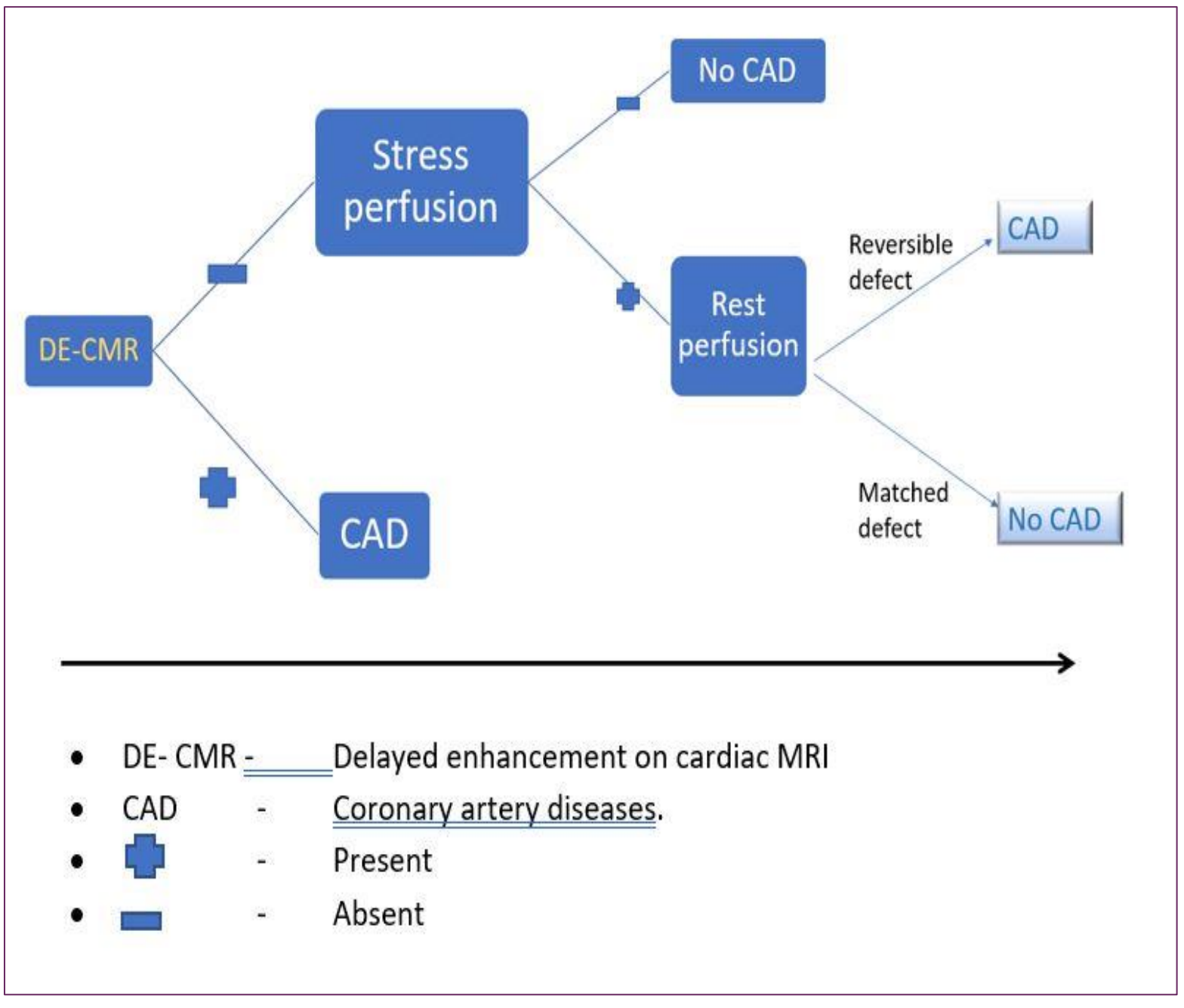
Essential steps during Stress CMRI

a. Breath-hold was performed after expiration, to keep uniformity during CMRI scan.
b. Adenosine was infused with continuous electrocardiographic and blood pressure monitoring. Adequate stress was considered when there was an increase of at least 10 beats per minute, in pulse rate.
c. Rest perfusion imaging was performed by using the same sequence, as used for the stress scan, and by using the same contrast dose, with a time interval of 10 minutes.
d. 5 minutes after the rest scan, delayed enhancement imaging was done using a segmented inversion recovery sequence, in the same imaging plane, as used for cine imaging.

Image Analysis

a) Stress CMRI was analyzed according to the algorithm shown in **Figure 3**.

Figure 3: Algorithm used for Stress Cardiac MRI analysis.



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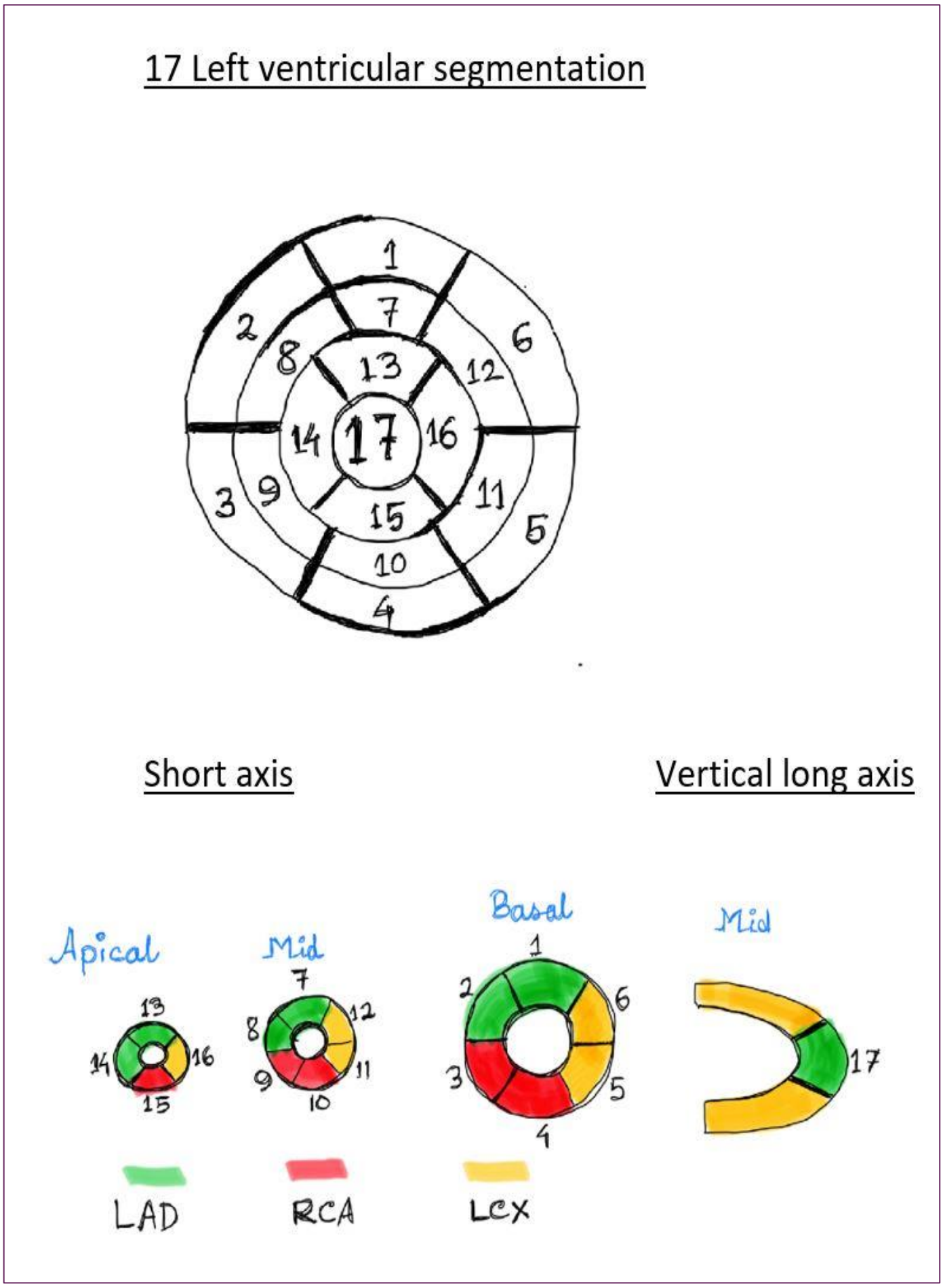
b) A diagrammatic representation of AHA 17 segments of LV, and coronary artery territory, is shown in **Figure 4**

Figure 4: Diagrammatic representation of AHA 17 segments of LV ventricle and coronary artery territory.



LAD: Left Anterior Descending Artery; LCX: Left Circumflex Artery; RCA: Right Coronary Artery.

Observation and Result

A total of 30 patients underwent stress CMRI, with the youngest participant being 32 years old, and the oldest patient being 76 years old. 14 (46.7%) patients were in the age group of 51-60 years; 6 (20.0%) patients were in the age group of 31-40 years; 4 (13.3%) patients were in the age group of 41-50 years; 4 (13.3%) patients were in the age group of 61-70 years; and 2 (6.7%) patients were in the age group of 71-80 years **(Table 1)**.

Table 1: Basic Demographic details

Basic Details	Mean ± SD || Median (IQR) || Min-Max || Frequency (%)
Age	
31-40 Years	6 (20.0%)
41-50 Years	4 (13.3%)

51-60 Years	14 (46.7%)
61-70 Years	4 (13.3%)
71-80 Years	2 (6.7%)
Gender	
Male	24 (80.0%)
Female	6 (20.0%)
Weight (Kg)	72.00 ± 9.83 || 74.00 (67.50-78.00) || 55.00 - 89.00
Height (cm)	168.53 ± 9.96 || 172.00 (162.00-173.50) || 152.00 - 187.00
BMI (Kg/m2)	25.23 ± 1.09 || 25.45 (24.45-26.23) || 23.19 - 26.71
BMI	
23.0-24.9 Kg/m2	12 (40.0%)
25.0-29.9 Kg/m2	18 (60.0%)

24 (80.0%) patients were male, and 6 (20.0%) patients were female. Multiple risk factors were observed in participants. 22 (73.3%) patients had a history of hypertension; 18 (60.0%) patients had diabetes mellitus; 14 (46.7%) patients had a history of smoking; 12 (40.0%) patients had a previous history of CAD. All 30 (100%) patients had a history of chest pain, and 16 (53.3%) patients had a history of dyspnea.

All participants were on multiple drug therapy for existing comorbidities. 30 (100.0%) patient's were taking aspirin, 30 (100.0%) patient's were taking statins, 24 (80.0%) patient's were taking beta-blockers, 12 (40.0%) patient's were taking angiotensin-converting enzyme inhibitors, and 18 (60.0%) patient's were taking oral hypoglycemic medication. Mean Heart Rate (BPM) was 74.07 ± 7.81; mean Systolic BP was 121.87 ± 10.32 mm Hg; and Diastolic BP was 71.33 ± 10.05 mm Hg.

A total of 90 coronary vessels were assessed, out of which 18 were excluded due to a history of previous coronary artery stenting. The final study included 72 coronary vessels **(Table 2)**. CMRI showed normal findings in 44 (61.1%) coronary vessel territories and inducible ischemia in 28 (38.8%) coronary vessel territories. Following was the distribution of 44 coronary vessels with less than 50 % stenosis: 8 left anterior descending (LAD) territory, 18 left circumflex (LCX) territory, and 18 right coronary artery (RCA) territory. Following was the distribution of 28 coronary vessels which showed inducible ischemia: 18 LAD territory, 6 LCX territory, and 4 RCA territory.

Table 2: Table showing different parameters of coronary vessels and their individual frequency. Fisher's exact test was used to explore the association between 'Vessel' and 'Vessel stenosis and MRI findings'.

Details	**Frequency (%)**
Vessel	
LAD	30 (33.3%)
LCX	30 (33.3%)
RCA	30 (33.3%)
Vessel Stenting	
Done (excluded)	18 (20.0%)
Not Done	72 (80.0%)
Vessel Stenosis	
Normal / <50%	38 (52.8%)
50-69%	34 (47.2%)
MRI Findings	
Normal	44 (61.1%)
Inducible Ischemia	28 (38.8%)

We retrospectively correlated stress CMRI with findings of invasive catheter angiography. LVEF was calculated by CMRI using cardiac VX software. The mean (SD) of left ventricular ejection fraction (LVEF) (%) (MRI) was 49.80 (10.46), with LVEF (%) (MRI) ranging from 35 - 70. Mean (SD) of LVEF (%) (Echocardiography) was 50.80 (9.47), with LVEF (%) (Echocardiography) ranging from 40 - 65. There was a very strong correlation between LVEF (%) (Echocardiography) and LVEF (%) (MRI), and this correlation was statistically significant (Interclass Correlation Coefficient = 0.92, p = <0.001).

Adverse effects experienced by patient's during stress CMRI were recorded. 24 (80%) patient's experienced no adverse event, 4 (13.33%) patients experienced palpitation, and 2 (6.66%) patient's experienced chest pain as an adverse event. During the analysis of images, 3 patterns were found:

a) Normal finding on rest, stress, and delayed sequence **(Figure 5-7)**

Figure 5: Normal myocardial findings on rest scan. Short axis section showing normal myocardium on rest scan.

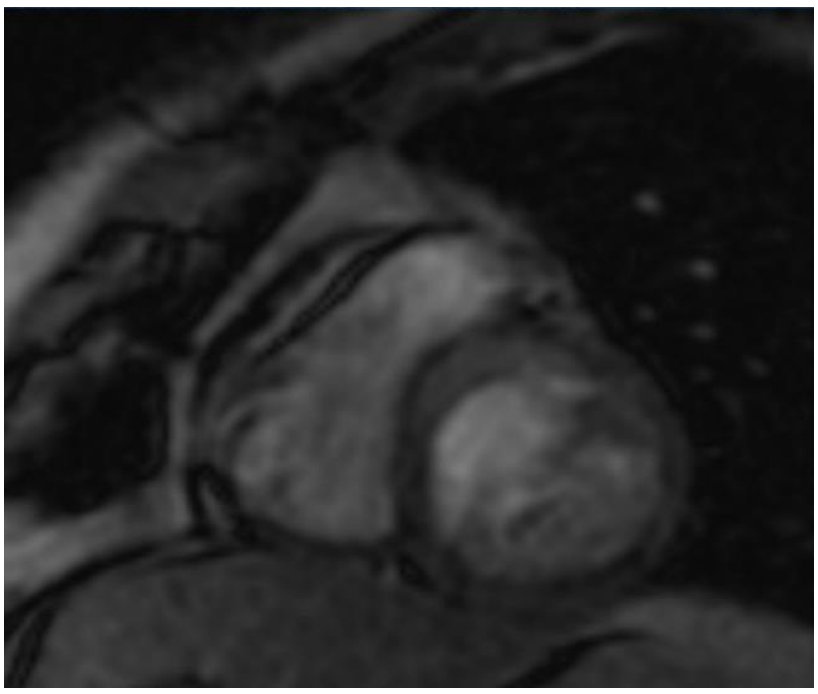


Figure 6: Normal myocardial findings on adenosine stress scan. Short axis section showing no hypointense area.

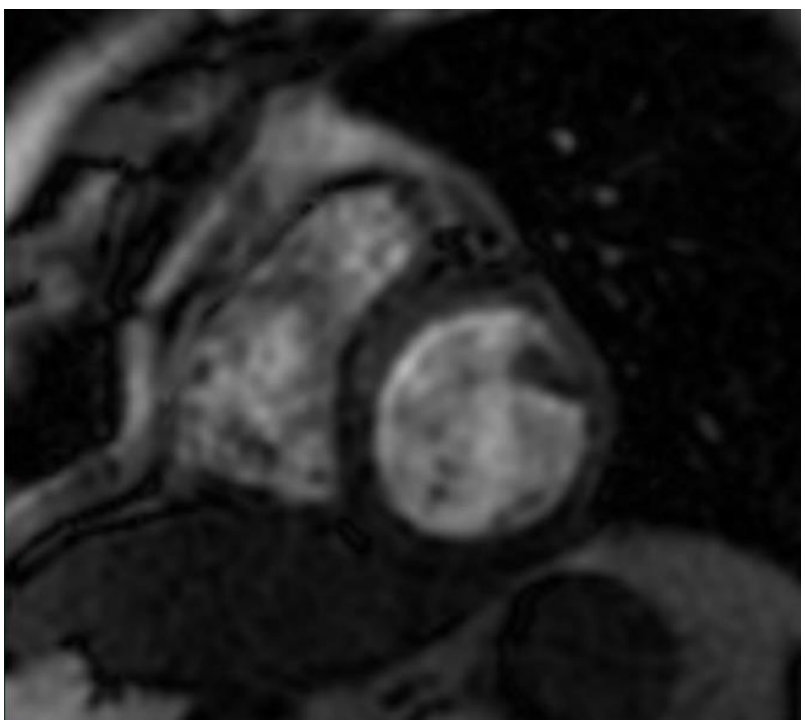
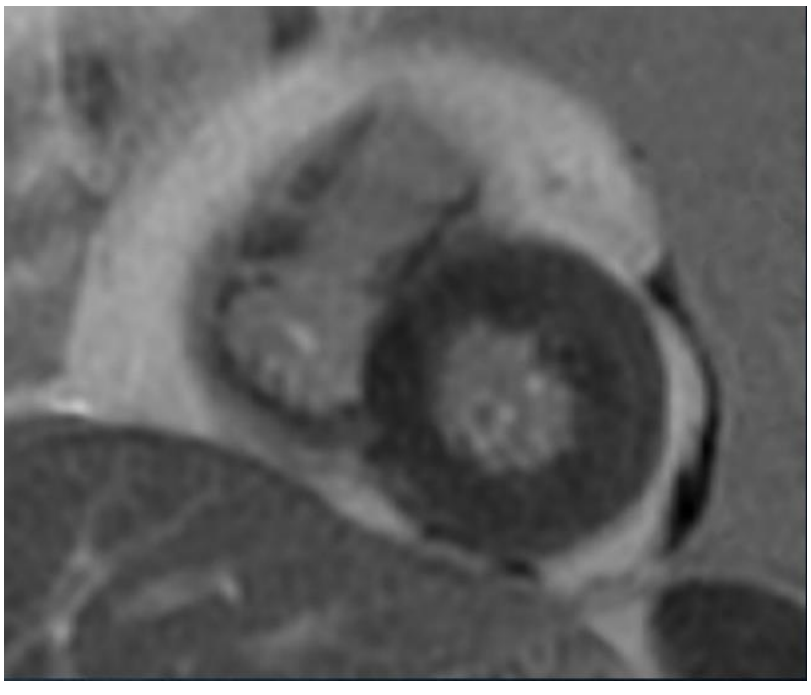


Figure 7: Normal myocardial findings on a delayed scan. Short axis section showing no late gadolinium enhancement.



b) Reversible hypointense area suggestive of stress-induced reversible ischemia **(Figure 8-10)**

Figure 8: Inducible ischemia findings on rest scan. Short axis section showing no hypointense signal in respective LAD & RCA territories on rest scan.

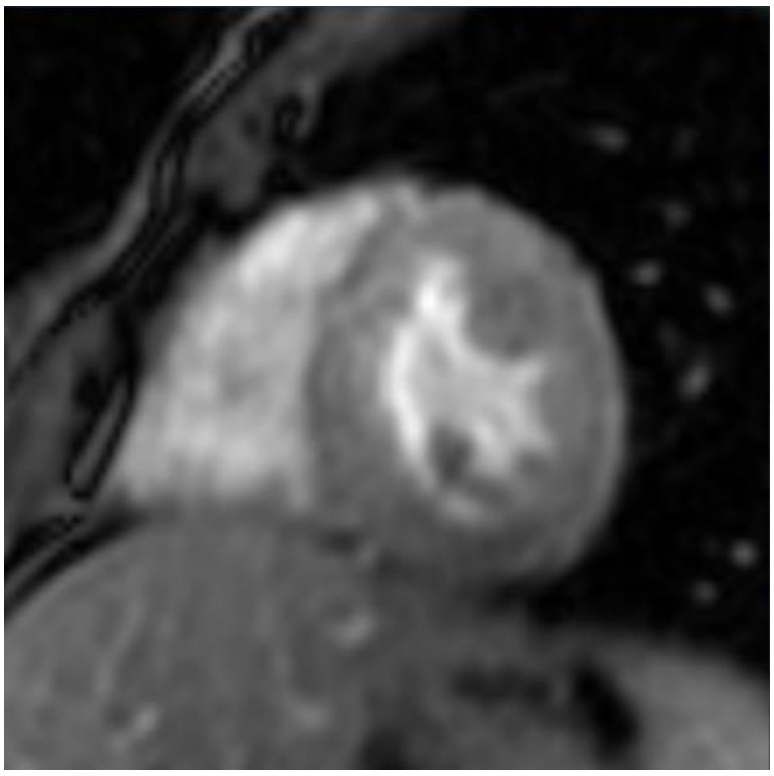


Figure 9: Inducible ischemia findings on adenosine stress scan. Short axis section showing hypointense signal in LAD & RCA territories on adenosine stress scan.

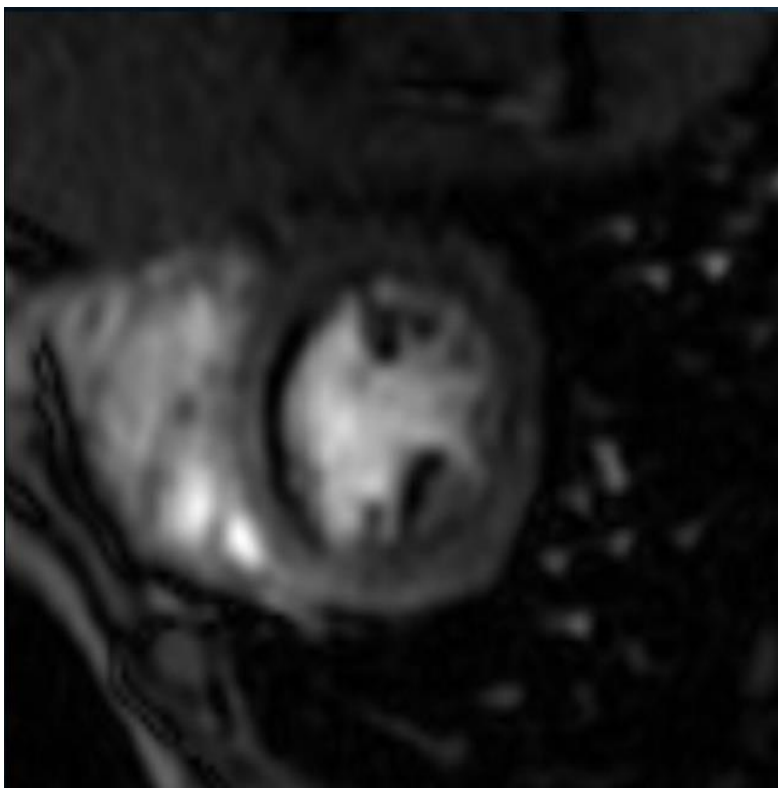
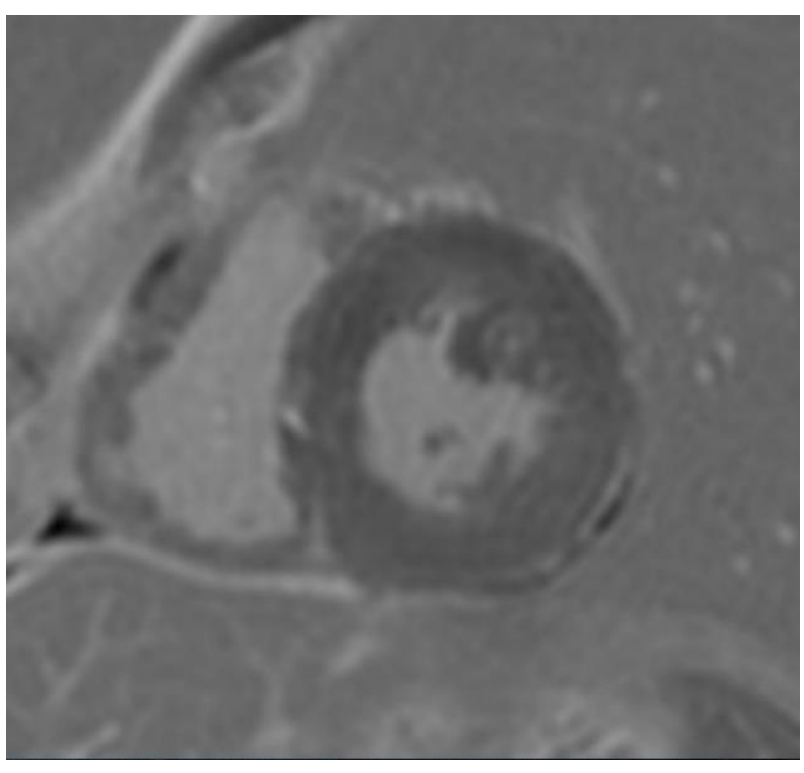


Figure 10: Inducible ischemia findings on the delayed scan. Short axis section showing no late gadolinium enhancement.



c) Late gadolinium enhancement is suggestive of an old infarct **(Figure 11-13)**

Figure 11: Infarcted myocardial findings on rest scan. Short axis section showing thinning of the mid/basal inferior lateral myocardium, however no abnormal signal in myocardium on rest scan.

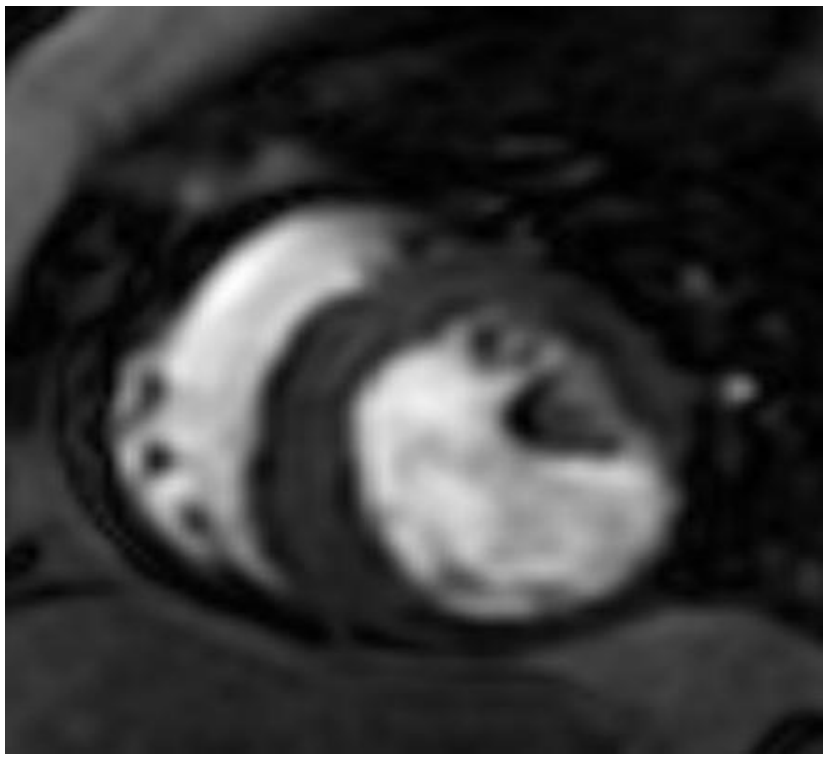


Figure 12: Infarcted myocardial findings on adenosine stress. Short axis section showing thinning of the mid/basal inferior lateral myocardium, however no hypointense area on adenosine stress scan.

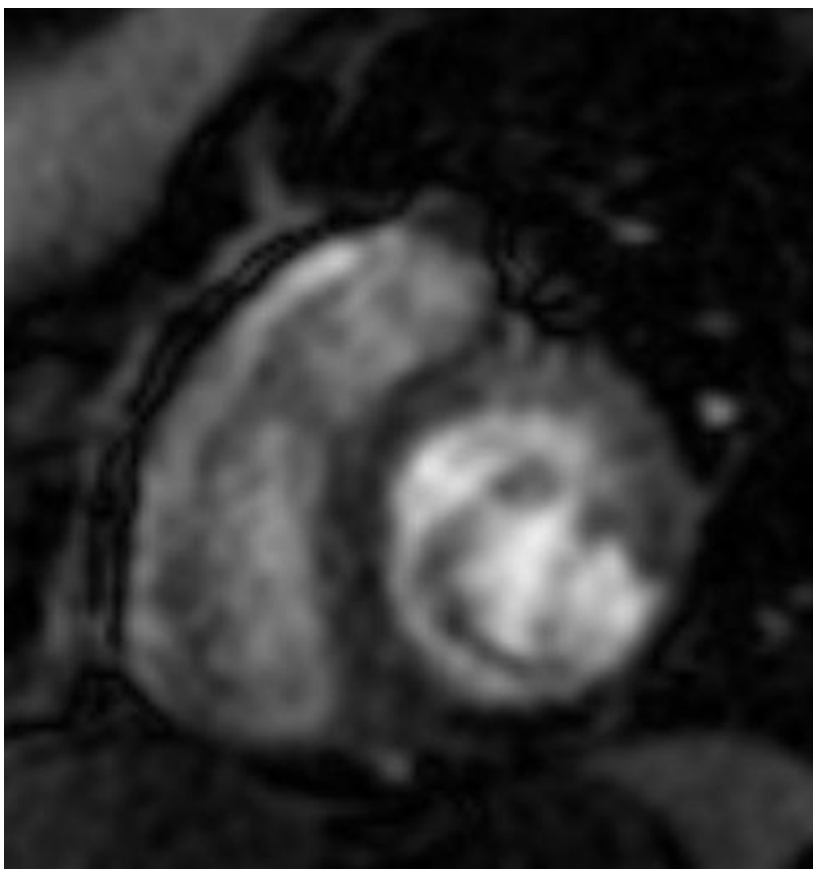
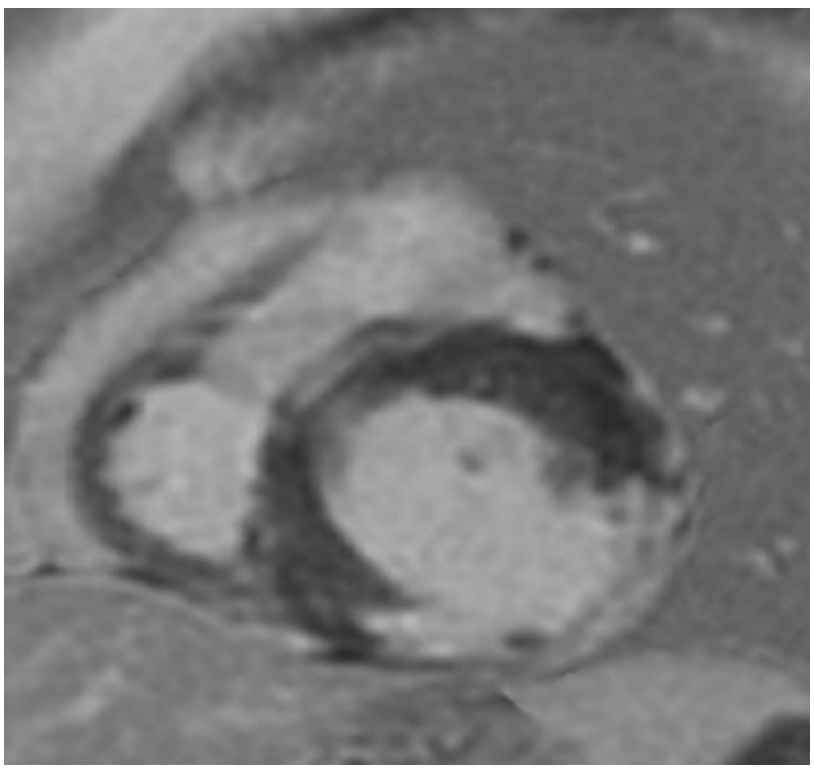


Figure 13: Infarcted myocardial findings on the delayed scan. Short axis section showing thinning of the mid/basal inferior lateral myocardium and late gadolinium enhancement in LCX and RCA territories on delayed scan.



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36 (81.8%) patient's had <50% CAS, and normal findings on CMRI **(Table 3)**. 8 (18.2%) patient's had 50-69% CAS, and normal findings on CMRI. 2 (7.1%) patients had <50% CAS, and inducible ischemia on CMRI. 26 (92.9%) of patient's had 50-69% CAS and inducible ischemia on CMRI. There was a significant difference between various groups in terms of the distribution of vessel stenosis ($\chi 2 = 19.143$, p = <0.001).

Table 3: Association between Vessel Stenosis and MRI Findings in respective vessel's territory (n = 72). Chi-squared test was used to explore the association between 'MRI Findings and 'Vessel Stenosis'. There was a significant difference between the various groups in terms of the distribution of Vessel Stenosis ($\chi 2 = 19.143$, p = <0.001).

Coronary artery stenosis	MRI Findings on Stress Cardiac MRI			Chi-Squared Test	
	Normal	Inducible Ischemia	Total	$\chi 2$	P Value
Normal/<50%	36 (81.8%)	2 (7.1%)	38 (52.8%)	19.143	<0.001
50-69%	8 (18.2%)	26 (92.9%)	34 (47.2%)		
Total	44 (100.0%)	28 (100.0%)	72 (100.0%)		

In the present study, sensitivity was 81.81%, specificity was 92.9%, positive predictive value was 94.73%, negative prediction value was 76.47%, and diagnostic accuracy was 86.11% when we compared imaging findings on conventional coronary angiography (excluding <50% and >70% CAS) with imaging findings on stress CMRI. Based on the above findings, risk stratification was done, and patients were advised PCI if they had 50-69% CAS on conventional coronary angiography, and inducible ischemia on stress CMRI.

Discussion

CAD is one of the most common causes of morbidity in India. In the last three decades, the prevalence of CAD has increased, both in the urban and rural populations of India. According to the existing management algorithm, patients with < 70 % CAS, are managed with medical treatment only, with no role of PCI in these patients. In our study, we did stress CMRI in patient's with 50-69% CAS on conventional coronary angiography. Our study is in agreement with guidelines recently introduced by the European Society of Cardiology (ESC), for the management of patients with chronic coronary syndrome (CCS).**[10]** American and European management guidelines have already included stress CMRI, for the assessment of patients with CAD. In outcome trials, functional imaging tests have been associated with fewer referrals for CMRI, compared with a strategy relying solely on anatomical imaging. **[11.12,13]** Functional assessment (stress CMRI) is also recommended for decision-making (PCI) after invasive coronary angiography has been performed.

In the last 20 years, many studies have been done to assess the role of CMRI. One of the earliest studies was done in 2001 by Schwitter J et al, in Switzerland.**[14]** They compared Cardiac Perfusion with Positron Emission Tomography and Coronary Angiography. In our study, stress CMRI imaging findings were compared with imaging findings on conventional coronary catheter angiography. In both studies, most of the patients were overweight, hypertension was a common risk factor, and most patients were on multidrug therapy. In their study, patients with previous MI were excluded, and the performance of the MRI technique in those patients was not determined. Similarly in the present study, the vascular territories with previous infarction and stenting were excluded.

Schwitter J et al, in another study, found a sensitivity of 87 % and specificity of 85 %, when they compared stress MRI with invasive coronary angiography. In the present study, invasive coronary angiography was followed by stress CMRI, with a sensitivity of 81.81%, specificity of 92.9%, positive predictive value of 94.73%, negative prediction value of 76.47%, and diagnostic accuracy of 86.11%.

MR INFORM trial was conducted with participants recruited from the UK, Germany, Australia, and Portugal.**[15]** Hypertension and diabetes were the most common risk factors, the mean BMI of patient's was 29 ± 4.7, and all patients were on multi-drug therapy (66.1 % were on statins and 75 % were on platelet inhibitors). The present study showed similar BMI, with most of the participants on multiple drug therapy for existing comorbidities treatment.

Lipinski MJ et al conducted a study in 2013 on the USA population,**[16]** and concluded that negative stress CMRI was associated with a very low risk of cardiovascular mortality, or MI. Stress CMRI has excellent prognostic characteristics, and may help to guide risk stratification of patients, presenting with known or suspected CAD. In the present study also, risk stratification of patients was done, based on findings on stress CMRI.

Coronary revascularization has a central role in the management of patients with stable CAD; however, despite extensively published literature, the appropriate selection of patients and lesions for revascularization in stable CAD, continues to be an area of controversy. Stress CMRI is not commonly used in India, which can be explained by the following factors: a) unawareness, b) limited availability of CMRI machines, and c) availability of few cardio-radiologists.

The present study highlights the importance of stress CMRI, in patients with moderate coronary artery disease; especially for risk stratification, and for advising PCI. It can not only improve morbidity and mortality but also the quality of life of these patients.

Even though only 30 patients were recruited in this pilot study (Due to ongoing COVID 19 Pandemic) the results of this study have far-reaching implications, especially for advocating the use of stress CMI in patients with 50-69% CAS, for guiding PCI. 24 out of 30 patients showed inducible ischemia on Stress CMRI and were advised to undergo PCI. The current study is limited by a small sample size, with follow-up for only one month.

Highlights

- A total of 30 patients underwent stress CMRI, with the youngest participant being 32 years old, and the oldest patient being 76 years old.
- 14 (46.7%) patient's were in the age group of 51-60 years; 6 (20.0%) patient's were in the age group of 31-40 years; 4 (13.3%) patient's were in the age group of 41-50 years; 4 (13.3%) patient's were in age group of 61-70 years; and 2 (6.7%) patient's were in the age group of 71-80 years.
- 24 (80.0%) patient's were male, and 6 (20.0%) patients were female. Multiple risk factors were observed in participants. 22 (73.3%) patient's had a history of hypertension; 18 (60.0%) patients had diabetes mellitus; 14 (46.7%) patients had a history of smoking; 12 (40.0%) patient's had a previous history of CAD. All 30 (100%) patient's had a history of chest pain, and 16 (53.3%) patient's had a history of dyspnea.
- All participants were on multiple drug therapy for existing comorbidities. 30 (100.0%) patient's were taking aspirin, 30 (100.0%) patient's were taking statins, 24 (80.0%) patient's were taking beta-blockers, 12 (40.0%) patient's were taking angiotensin-converting enzyme inhibitors, and 18 (60.0%) patient's were taking oral hypoglycemic medication.
- Mean Heart Rate (BPM) was 74.07 ± 7.81; mean Systolic BP was 121.87 ± 10.32 mm Hg; and Diastolic BP was 71.33 ± 10.05 mm Hg.
- A total of 90 coronary vessels were assessed, out of which 18 were excluded due to a history of previous coronary artery stenting.
- The final study included 72 coronary vessels (Table 2). CMRI showed normal findings in 44 (61.1%) coronary vessel territories and inducible ischemia in 28 (38.8%) coronary vessel territories.
- Following was the distribution of 44 coronary vessels with less than 50 % stenosis: 8 left anterior descending (LAD) territory, 18 left circumflex (LCX) territory, and 18 right coronary artery (RCA) territory. Following was the distribution of 28 coronary vessels which showed inducible ischemia: 18 LAD territory, 6 LCX territory, and 4 RCA territory.
- We retrospectively correlated stress CMRI with findings of invasive catheter angiography. LVEF was calculated by CMRI using cardiac VX software. The mean (SD) of left ventricular ejection fraction (LVEF) (%) (MRI) was 49.80 (10.46), with LVEF (%) (MRI) ranging from 35 - 70. Mean (SD) of LVEF (%) (Echocardiography) was 50.80 (9.47), with LVEF (%) (Echocardiography) ranging from 40 - 65.
- There was a very strong correlation between LVEF (%) (Echocardiography) and LVEF (%) (MRI), and this correlation was statistically significant (Interclass Correlation Coefficient = 0.92, p = <0.001).
- Adverse effects experienced by patient's during stress CMRI were recorded. 24 (80%) patient's experienced no adverse event, 4 (13.33%) patients experienced palpitation, and 2 (6.66%) patients experienced chest pain as an adverse event.
- During analysis of images, 3 patterns were found: a) Normal finding on rest, stress, and delayed sequence (Figure 5-7), b) Reversible hypointense area suggestive of stress-induced reversible ischemia (Figure 8-10), and c) Late gadolinium enhancement suggestive of an old infarct (Figure 11-13).
- 36 (81.8%) patient's had <50% CAS, and normal findings on CMRI (Table 3). 8 (18.2%) patients had 50-69% CAS, and normal findings on CMRI. 2 (7.1%) patient's had <50% CAS, and inducible ischemia on CMRI. 26 (92.9%) of patient's had 50-69% CAS and inducible ischemia on CMRI. There was a significant difference between various groups in terms of the distribution of vessel stenosis ($\chi 2 = 19.143$, p = <0.001).
- In the present study, sensitivity was 81.81%, specificity was 92.9%, positive predictive value was 94.73%, negative prediction value was 76.47%, and diagnostic accuracy was 86.11% when we compared imaging findings on conventional coronary angiography (excluding <50% and >70% CAS) with imaging findings on stress CMRI.
- Based on the above findings, risk stratification was done, and patients were advised PCI if they had 50-69% CAS on conventional coronary angiography, and inducible ischemia on stress CMRI.
- We hereby conclude that Stress CMRI is an excellent prognostic tool, which can detect inducible ischemia in patients with 50-69% CAS, for guiding PCI.
- CMRI can also be used as one test to assess multiple things at the same time, like inducible ischemia, LVEF, and infarct tissue.
- However, a large multicentre trial involving populations from different geographical regions, and with follow-up of at least 6 months, is needed to truly advocate the role of stress CMRI in patients with moderate CAS.

Main Points

- Functional imaging is becoming the guiding imaging modality for the management of patients with CAD.
- Stress CMRI is one one-stop tool, that helps in both diagnostic and therapeutic management of patients with CAD.
- Out of all stress-inducing agents, adenosine (rather than regadenoson) is a well-suited drug for countries like India, as it is cheap and widely available.
- The inclusion of stress CMRI in the management of patients with CAD, has the potential to improve prognosis in this patient.

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Conclusion

We hereby conclude that Stress CMRI is an excellent prognostic tool, which can detect inducible ischemia in patients with 50-69% CAS, for guiding PCI. **[17,18]** CMRI can also be used as one test to assess multiple things at the same time, like inducible ischemia, LVEF, and infarct tissue. However, a large multicentre trial involving populations from different geographical regions, and with follow-up of at least 6 months, is needed to truly advocate the role of stress CMRI in patients with moderate CAS.

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