ORIGINAL RESEARCH PAPER

Radiology

ROLE OF STRESS CARDIAC MRI IN THE EVALUATION OF SUSPECTED CORONARY ARTERY DISEASE.

KEY WORDS: Cardiac Magnetic Resonance, Coronary Artery Disease

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ABSTRACT

Background: Cardiovascular magnetic resonance (CMR) has emerged in recent years as an essential tool in the imaging of coronary artery disease(CAD) and its preclinical detection. Our study aims at describing CMR imaging features of CAD, including CINE and perfusion imaging. **Methods:** We performed Stress perfusion CMR with pharmacologic stress(Adenosine) in 26patients of suspected CAD with intermediate cardiac chest pain. **Results:** All patients showed maintained wall thickness.The mean wall thickness of LV was 7.3mm ± 0.6 SD. 5 (6.4%) coronary territories showed regional wall motion abnormality on CINE imaging. No patient had hyperintensity on T2/STIR images. 9 patients (34.6%)showed subendocardial perfusion defect in coronary distribution on stress imaging, without matched defect on rest perfusion or LGE on delayed imaging (reversible inducible ischemia). 17 patients (73.4%) showed no perfusion defect on stress imaging. Out of 26, only 15 patients underwent catheter coronary angiography (CCA). This included all the 9 patients with stress inducible perfusion defect, of which 7(78%) showed significant CAD (>70% stenosis) in the corresponding artery and 2(22%) showed no significant CAD and 6 patients without stress inducible perfusion defect of which 5(83%) patients showed no significant CAD and 1(17%) showed significant CAD. Using CCA as a gold standard, the sensitivity of stress perfusion CMR in our study was 87.5%, specificity was 71.4% and accuracy was 80%. **Conclusion:** Stress Perfusion CMR is a noninvasive technique capable of detecting obstructive CAD with excellent diagnostic accuracy. It has high sensitivity and moderate specificity for diagnosing significant obstructive CAD compared with CCA.

INTRODUCTION

Significant CAD is considered in the presence of a more than 70% diameter stenosis in a major vessel on CCA and often results in referral for intervention[1]. Although CCA provides valuable information about a wide variety of indices, it has significant limitations. Mild or non-stenotic CAD is not visualised and no information about the plaque composition and degree of vascular remodelling is provided. Thus, a normal CCA does not exclude CAD, and a stenotic plaque may be just the tip of the iceberg in some CAD patients. In most patients with an acute MI, the episode is instigated by rupture of a non or minimally stenotic plaque[2].The use of CCA is limited to symptomatic patients with high pre-test likelihood of obstructive CAD due to its invasive nature, the use of iodinated contrast and radiation exposure.

Further, the inter-relationship between CAD and myocardial ischaemia is not straight-forward, and many patients fulfilling the criteria of significant CAD do not have a flow-limiting stenosis when their fractional flow reserve is measured (FFR, the ratio of maximum blood flow distal to a stenotic lesion to normal maximal flow in the same vessel).[3,4]

While treatment should be reserved for patients with myocardial ischaemia, the oculostenotic reflex (tendency to overestimate the functional importance of intermediate coronary artery lesions) risks the overuse of revascularisation.[5] Also in some patients with typical anginal chest pain and ST-segment depression on exercise testing, CCA detects no abnormalities. In such cases, stress perfusion imaging has shown diffuse subendocardial perfusion defects, implying that microvascular dysfunction may be the cause of myocardial ischaemia and anginal chest pain.

Management of CAD is very challenging as numerous studies have shown that revascularisation does not improve mortality over medical treatment in randomised trials.[6,7]This is most likely due to the poor relation between stenosis severity in diffuse CAD and coronary flow physiology.[3,4] While anatomical techniques like CCA provide limited information regarding the impact of a stenosis on the coronary flow, stress testing assesses the extent of myocardial ischaemia.

MATERIALS AND METHODS

The study was conducted at a tertiary care institute in North India over a period of two years.

26 patients with suspected CAD were included in the study. Detailed informed consent was taken from the patients before inclusion in the study. Patients underwent Stress perfusion CMR and CCA. CMR findings were correlated with findings on CCA.

Study Design: Prospective study

Selection of subjects:

Inclusion Criteria:

Patients with Cardiac Chest Pain of Intermediate pretest probability.

Exclusion Criteria:

Patients with contraindications to Adenosine-asthma, high degree AV blocks, recent stroke (<1 month), bilateral carotid stenosis, arterial hypotension and patients with general contraindications to MRI.

Patient Preparation:

- Caffeine containing foods were avoided for 24 hours.
- In patients on beta blockers, last dose was skipped.
- 8 hours fasting.
- Preprocedure baseline vitals were checked (HR, BP, SpO2).
- 2 large bore, preferably 16 G cannulas were secured (one in either arm): one for contrast and one for adenosine.

CMR Protocol:
CMR was performed on 1.5T Magnetom Avanto (Siemens Healthcare). Our protocol included:

a) Trufi based short-axis cine images from the mitral valve to the apex, 4-chamber and 3-chamber (LVOT views).
b) T2/STIR sequences in short axis.
c) Trufi based dynamic first pass stress and rest perfusion: Perfusion imaging was performed using a heavily T1 weighted saturation-recovery GRE sequences.
d) Delayed enhancement images (inversion recovery free breath/ breath hold sequences). These were obtained 10 minutes after the administration of contrast (0.2 mmol/kg gadolinium-DTPA).

CINE Imaging: Global, regional wall thickening and functional assessment**.**

Stress Perfusion: Stress induced myocardial ischemia.

Rest Perfusion: Artefact assessment.

Delayed Enhancement: Myocardial infarct.

Timeline for Adenosine Stress Perfusion CMR:

1. Adenosine as pharmacological stress agent was administered as infusion @140mcg/kg/min for 6 minute after functional CINE imaging.
2. First dose of contrast was injected after 2 minutes of adenosine administration for stress perfusion, contrast dose was 0.075-0.10mmol/kg body weight @4-5ml/sec followed by 30 ml saline flush at the same rate.
3. After 10 minutes, 2nd dose of contrast was injected for rest perfusion as 0.1mmol/kg, after stress perfusion.

Interpretation and Reporting:
We used the American Heart Association recommended 17-segment model for reporting.[8] The left ventricle is divided into equal thirds named the basal, mid and apical thirds. The basal and mid thirds have 6 segments each, the apical third has 4 and the true apex has 1. The left ventricular systolic function was visually graded for each segment using a 5-point scale (normal wall motion to dyskinesis). We derived quantitative measures of left ventricular function from the short-axis SSFP images using ARGUS software. The left ventricular mass, end-diastolic volume, and end-systolic volume were derived from the customary method of manually outlining the contours of the ventricular borders (epicardial and endocardial), from which ejection fraction and stroke volume were calculated automatically.

The delayed enhancement (DE) images were also visually graded using a 5-point scale. For each segment, the area or transmural extent of hyperenhanced tissue was assessed. The DE images were interpreted with theimmediately adjacent cine images, which provided a reference of the diastolic wall thickness of each region.

We scored stress and rest perfusion images for perfusion defects in 16 segments (apex - segment 17 was not well visualized). Then a systematic approach was used to detect the presence or absence of CAD. We used DE imaging to improve the accuracy of detecting CAD over that of perfusion imaging alone. A CMR stress test was labelled "positive for CAD" if myocardial infarction was present on DE-MRI ***OR*** if perfusion defects were present during stress MR, but absent at rest imaging ("reversible" defect) in the absence of infarction.

The test was labelled "negative for CAD" if no aberrations were found (e.g. no MI and no stress/rest perfusion defects) ***OR*** if perfusion defects were seen at both stress and rest MRI ("matched" defect) in the absence of infarction. Matched defects were regarded as artifacts and not indicative of CAD. When both DE-MRI and stress perfusion MRI were abnormal, the test was deemed positive for ischemia if the perfusion defect was greater than the area of infarction.

OBSERVATIONS AND RESULTS
The study was conducted on 26 patients with suspected CAD.

CINE imaging:
All patients showed maintained wall thickness. Only 5 (6.4%) coronary territories (3 LAD, 1 LCX and 1 RCA) showed regional wall motion abnormality(hypokinesia) on CINE imaging. Regional left ventricular wall thickness was measured at end-diastole using computer-assisted calipers in the anterior septum, lateral wall, inferior septum, and any suspected regional wall motion abnormality. The mean wall thickness was 7.3mm ± 0.6 SD.

T2/STIR hyperintensities:
No patient had hyperintensity on T2/STIR images.

Perfusion Imaging:
9patients(34.6%) showed subendocardial perfusion defect in coronary distribution [LAD territory in 5(55.5%) patients, LCX territory in 2(22.2%) patients and RCA territory in 2(22.2%) patients]on stress imaging, without matched defect on rest perfusion.

Table 1: Dynamic first pass perfusion in patients with intermediate chest pain

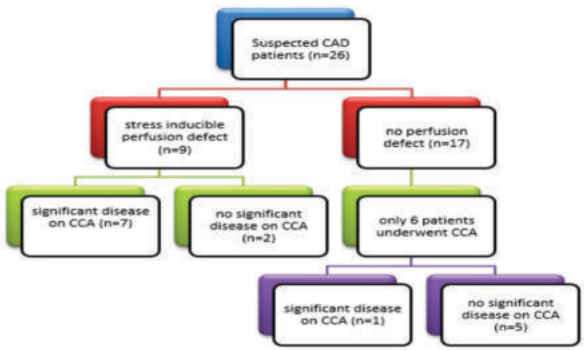
Stress		Number	Percentage
Perfusion defect	Present	9	35
	Absent	17	65
	Total	26	100

Invasive coronary angiography(CCA):
Out of 26, only 15 patients underwent CCA. These included the 9 patients with stress inducible perfusion defect of which 7 (78%) showed significant CAD i.e. >70% stenosis (true positives)in the corresponding artery [4 LAD, 2 LCX and 1 RCA] and 2 (22%) showed no significant CAD (false positives); and 6 patients without stress inducible perfusion defect (based on high clinical suspicion) of which 5 (83%) showed no significant CAD (true negatives) and 1 (17%) showed significant CAD in RCA (false negative).

Table 2 : Invasive coronary angiography (n=15)

CCA: significant disease	Number	Percentage
Present	8	53.3
Absent	7	46.7
Total	15	100

Flow-chart depicting the perfusion CMR and CCA findings in our study.



CCA correlation:
The anatomic QCA (based on 70% quantitative coronary analysis stenosis)was used as reference standard. Significant CAD was considered in the presence of a diameter stenosis of ≥ 70% in a major vessel or ≥ 50% in the left main.

Using CCA as a gold standard, the sensitivity of stress perfusion CMR in detection of CAD in these patients was87.5%, specificity was 71.4%and accuracy was 80%.

Table 3 : Diagnostic accuracy of adenosine stress perfusion MRI in diagnosis of stable CAD		
Variable	Value(%)	95% CI
Sensitivity	87.5	71.2-94.5
Specificity	71.4	61.2-86.9
PPV	77.8	64.6-88.9
NPV	83.3	67.5-93.6
Diagnostic accuracy	80	57.96-90.76

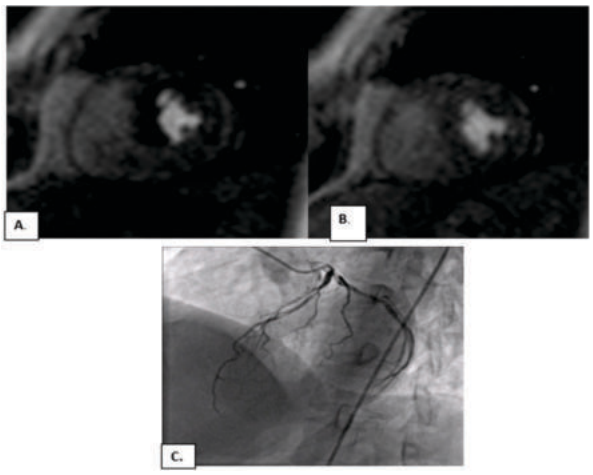


Figure 1: *showing an extensive perfusion deficit in the anteroseptal and anterior wall at the basal level on stress imaging (A) with no matched defect on rest imaging (B), CCA film reveals proximal LAD 70-80% stenosis (C).*

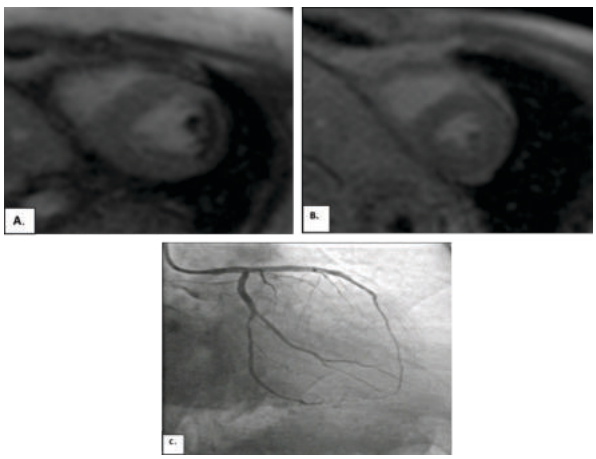


Figure 2: *showing a subendocardial perfusion defect extending into myocardium(anteriolateral) atmid-ventricular level (A), with no perfusion deficit under resting conditions(B). Corresponding CCA revealing 70-80% stenosis in mid-LCX (C).*

DISCUSSION

In our study, 26 patients with clinical, biochemical, electrocardiographic, echocardiographic features suspicious of CAD were studied for characterization of perfusion MR features and compared with CCA.

Cine Imaging: Ventricular Wall Motion And Thickness:

All patients showed maintained wall thickness (7.3mm ± 0.6). 6.4% coronary territories showed hypokinesia.

The advantage of Cine MRI is that it accurately assesses the Left Ventricular contractile function in patients with poor acoustic windows i.e. patients poorly suited for echo cardiography[9,10].

Regional wall motion thickness helps in viability assessment, as thin dysfunctional wall (end-diastolic wall thickness <6 mm) has a low likelihood of recovering function[11], however weakness of this approach is its poor performance to predict recovery in dysfunctional segments with preserved wall thickness.

T2/STIR hyperintensities:

T2-weighted imaging techniques such as STIR is an "edema-weighted" imaging, showing myocardial edema as bright while normal myocardial appears dark.[12,14] Myocardial edema is most evident in the first days post-infarction, and then slowly fades away due to process of infarct healing.

No patient in this study had such hyperintensities. These are present in acute infarcts and identifies myocardial area at Risk (AAR)[13,16,17] this includes the reversibly injured myocardium, which is capable of functional recovery (difference between T2 hyperintensity and LGE identifies salvageable myocardium). With increasing ischaemia time, salvageable myocardium decreases at the expense of increasing infarct size, while the myocardium at risk remains constant. Thus, early reperfusion may result in complete myocardial salvage (i.e. aborted infarction)[15,18]. Myocardial salvage is independently associated with early ST-segment resolution and is an independent predictor of adverse ventricular remodelling and major cardiac events[9,10].

Dynamic first pass perfusion:

We visually assessed the presence of a regional perfusion defect, and compared the corresponding coronary territories against CCA findings.

Results similar to our study were reported by Igor Klem et al. who prospectively enrolled 92 patients with suspected CAD scheduled for X-ray coronary angiography and found that 29 (31.5%) patients had subendocardial perfusion defect in coronary distribution on stress imaging.[19]

Stress perfusion CMR effectively and non-invasively defines and reclassifies stable CAD patients, into those without inducible ischemia and those with reversible inducible ischemia[20,21,22]. Patients without inducible ischemia will benefit from optimal medical therapy (OMT), and those with inducible ischemia will benefit from the invasive CCA and revascularisation procedures[23]. This will help to reduce negative CCA in stable CAD patients, improving the diagnostic yield of elective CCA in these patients. Stress perfusion CMR will serve as a functional imaging alternative to anatomical imaging Coronary CT angiography in patients with Stable CAD, with additional benefit of ischemia guided management.

CCA and Stress Perfusion CMR correlation:

Ricardo C. Cury et al. in their study "Diagnostic Performance of Stress Perfusion MR Imaging in Patients with Coronary Artery Disease" included 33 patients of suspected CAD and found stress perfusion CMR having a sensitivity of 81%, specificity of 90% and accuracy of 87%.

Compared to this study, a high false positive rate could be the reason forrelatively low specificity in our study group. This may be due to perfusion defects caused by the presence of microvascular disease as most of our study patients had diabetes and HTN. Spontaneous or therapeutic re-opening of a coronary artery supplying an area of myocardial infarction with persistent microvascular obstruction could be another cause. Moreover, because CCA detects luminal morphology rather than the functional impact of a stenosis, a false positive CMR result may actually represent a 'false negative' angiogram in the context of angiographically 'invisible' small vessel disease capable of causing subendocardial ischemia, as CCA only evaluates the epicardial part of the coronary circulation.

This could be minimised if the hemodynamic significance of

an epicardial coronary artery stenosis weredetermined by measuring the fractional flow reserve (FFR) during CCA.

Limitations of The Study

- Small sample size was available to reliably derive the sensitivity and specificity of stress perfusion CMR. Whether these results are pertinent to risk reclassification for all CAD patients requires further evaluation.
- Coronary physiology by invasive FFR was not available, so anatomic QCA [based on 70% stenosis] was used as reference standard (which has been shown to demonstrate functional mismatch in up to 50% of lesions).
- CCA with selective FFR is considered the gold standard for epicardial coronary stenosis, but not microvascular disease, which can be detected on stress testing and is associated with worse long-term prognosis.
- Estimation of the presence of perfusion defects on CMR was done by visual analysis, which provides a higher sensitivity but a lower specificity than semi-quantitative assessment. Although MRI allows semi-quantitative analysis, it is more time consuming andhence, is of limited use in clinical practice. Nevertheless, semi-quantitative assessment of first-pass perfusion MRI probably would have improved the results of this protocol.

Summary

- Stress Perfusion CMR is an emerging noninvasive technique capable of detecting obstructive CAD with excellent diagnostic accuracy. It has a high sensitivity and moderate specificity for diagnosing significant obstructive CAD compared with CCA.
- Although CCA is the established technique for diagnosing significant CAD in routine clinical practice, it remains an imperfect reference standard due to its inability to evaluate the hemodynamic significance of a stenosis.
- Detection of myocardial perfusion abnormalities can be used to identify patients with CAD, evaluate the hemodynamic significance of epicardial coronary stenosis, and enhance clinical decision making.
- Prior to an invasive CCA, stress CMR (non-invasive functional testing) can be a cost-effective gate-keeping tool in patients at risk for obstructive CAD. Anegative adenosine stress MR perfusion study obviates the need for CCA, as the negative study is associated with an extremely low risk for major adverse cardiac events in the year following the study.
- The decision to proceed to coronary revascularization in CAD patients must not be based on the coronary anatomy only, as is the usual clinical routine. As the oculostenotic reflex tends to overestimate the functional importance of coronary artery lesions, revascularisation should be reserved for patients with demonstratable myocardial ischemia, to limit the overuse of revascularisation.
- CAD is a complex disease entity with the need for continued focused investigation to meet several future challenges.

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