Evaluation of myocardial ischemia in coronary artery disease with cardiac MR perfusion method: comparison with the results of catheter or CT angiography

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ABSTRACT

Aim To evaluate the efficacy of the Cardiac Magnetic Resonance Perfusion (CMRP) method in detection of Coronary Artery Disease (CAD) by comparing CMRP findings with the results of Coronary Computed Tomography Angiography (CCTA) or Catheter Coronary Angiography (CCA).

Methods Thirty one patients in whom CMRP was performed along with CCTA or CCA within a month after CMRP between December 2009 and November 2010 were selected for the study. In CMRP, after adenosine administration as a stress agent Balanced TFE sequences were used to gather dynamic images that include the myocardial first pass of contrast media. Image analysis was performed visually. CMRP findings were compared to CCTA or CCA results for each coronary artery territories and for all territories.

Results Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of CMRP test in the identification of patients with significant (≥70%) coronary artery stenosis were 94.7%, 83%, 90.3%, 90%, and 90.9% for all coronary arteries, respectively; 94.4%, 84.6%, 90.3%, 89.4%, and 91.6% for left anterior descending artery, respectively; and 100%, 100%, 100%, 100%, and 100% for circumflex and right coronary artery, respectively. There was no statistically significant difference between angiography methods (CCTA/CCA) and CMRP (p>0.05). Methods had good to perfect consistency (k = 0.79-1.00).

Conclusion CMRP test seems to be a reasonable alternative for catheter angiography, which is considered the gold standard for evaluation of CAD and exclusion of significant coronary artery obstruction.

Key words cardiac catheterization, computed tomography, coronary angiography, perfusion magnetic resonance imaging
INTRODUCTION
The major cause of Ischemic Heart Disease (IHD) is reduction of blood flow through coronary arteries due to atherosclerosis. Detection of coronary atherosclerosis and evaluation of myocardial hypoperfusion is important for decisions regarding an appropriate and effective therapeutic approach, including catheter based interventions or surgical options (1).

Myocardial perfusion, defined as blood volume flowing through a given myocardial area in a determined time, is one of the first steps of the ischemic cascade and may be detected prior to electrocardiogram (ECG) alterations, clinical symptoms, or myocardial wall motion abnormalities (2). The most common clinical method performed for detecting perfusion abnormalities is single photon emission computerized tomography (SPECT) (2). The validity of this method is evident in a number of multi-center trials, however, low spatial and temporal resolution, exposure to ionising radiation, and attenuation artifacts are its significant limitations (2). In contrast, stress Cardiac Magnetic Resonance Perfusion (CMRP) does not emit ionising radiation, has high spatial and temporal resolution, is able to evaluate subendocardial perfusion, and is a non-invasive modality; therefore it is the preferred method for myocardial perfusion evaluation (2,3). In 2006, a consensus panel from the American College of Cardiology Foundation (ACCF) deemed the following indications as appropriate uses of stress perfusion MRI: evaluating chest pain syndromes in patients who have intermediate probability of coronary artery disease (CAD) and ascertaining the physiologic significance of indeterminate coronary artery lesions (4). Recent studies have shown that stress CMRP has high sensitivity and specificity for IHD diagnosis, and negative stress CMRP was considered a perfect test for ruling out a major cardiac event (2,3,5).

In light of this information, the present study aims to compare the findings of CMRP with the results of CCTA or CCA and to evaluate the efficacy of CMRP in detection of CAD.

PATIENTS AND METHODS
Patients
Thirty one patients were selected at the Department of Radiology, Dokuz Eylul University Hospital between December 2009 and November 2010 in whom CMRP, as well as CCA or CCTA, were performed within one month after CMRP. All patients were investigated for the criteria that are contraindicated for the Magnetic Resonance Imaging (MRI) including claustrophobia, cardiac pacemaker, and inappropriate surgical and prosthetic materials for MRI. Perfusion MRI was performed after 12-hour fasting. For maximum response to vasodilatory effect of adenosine, if patients were using calcium channel blockers, beta-blockers and nitrates these were discontinued 24 hours before the procedure. Also consumption of foods and beverages containing caffeine was discontinued 12 hours prior to the procedure. Patients with conditions that are contraindicated for adenosine administration including significant valvular stenosis, unstable angina, obstructive pulmonary disease, severe arterial hypertension, and history of myocardial infarction within 3 days prior to the procedure were excluded. An anesthesia team was ready during the procedure in order to address any potential adverse effects of adenosine. All patients provided written informed consents before the procedure. This retrospective study was approved by the Ethics Committee of Dokuz Eylul University School of Medicine.

Cardiac MR perfusion techniques
Although the present study was retrospective, the standard sequences of adenosine-stress CMRP imaging were used in each patient. Cardiac Magnetic Resonance Perfusion imaging was performed with 1.5 Tesla MRI device (Philips Intera Achieva; Philips Medical Systems, Holland) with ECG, respiratory pad and 5-phased array cardiac coil that was applied to the anterior chest of the patient in the supine position. In stress perfusion imaging, 140 microgram/kg/min dosing of adenosine was administered for 4 minutes via IV infusion as a vasodilator (Adenosin-L.M., Apoteket AB, Sweden). At the end of the 4th minute, 0.08 mmol/kg gadobutrol (Gadovist, Bayer Schering, Germany) followed by 20-50 ml saline (4-5 ml/sec) IV bolus was administered. In the mean time, through the short axis perpendicular to the long axis of left ventricle, 3-4 slices with slice thickness of 10 mm and interval of 10 mm from the left ventricle basal, midventricular layer, and apex were displayed at each heart beat. From these slices, 60 heart beat long dynamic images were gathered that included myocardial first pass of con-
trast media with Balanced Turbo Field Echo (TFE) sequence. Imaging parameters for Balanced TFE sequences were as follows: TR: 2.4 msec; TE: 1.2 msec; Flip Angle: 50 degrees; FOV: 350-400 mm; matrix: 128x256; Sense factor: 2; Slice width: 10 mm and Slice Interval: 10 mm. For higher quality images, patients were asked to hold breath at the end of the expirium during dynamic assessment.

In rest perfusion imaging, after waiting 10 minutes for clearance of gadolinium from the blood pool, dynamic images were taken with the same parameters that were used before without adenosine infusion. During this 10-minute waiting period, dynamic images including the entire left ventricle through the short axis with Steady-state Free Precession (SSFP) sequence were taken (functional imaging). The myocardial perfusion MRI protocol used in our study is summarized in Figure 1.

**Image analysis**

For each coronary artery territory, CMRP findings were evaluated retrospectively by two radiologists separately (one of them was experienced on cardiac imaging) and they were blinded to the results of CCTA and CCA assessment of perfusion defect. Perfusion defect is defined as hypointense subendocardial regions in comparison with the normal myocardium at early myocardial signal enhancement. If discordance occurred in the results, the radiologists re-examined the findings and reached a consensus.

Then, CMRP results were compared to that of angiography techniques (CCTA or CCA). Obstructions of 70% or greater detected at angiography were considered positive for significant stenosis.

**Statistical analysis**

Cardiac Magnetic Resonance Perfusion imaging results of 31 patients were compared to those of angiography (CCTA or CCA) according to the coronary artery territories.

Angiography findings were considered as gold standard, and then CMRP findings were compared to angiography with respect to perfusion defects for each case and also each coronary artery perfusion territory. Then sensitivity, specificity, accuracy, positive predictive value and negative predictive value were calculated. Analysis of diagnostic differences for all comparisons mentioned above was performed using the McNemar test. P<0.05 value was considered significant for the McNemar test. The Kappa test was used for harmonization between analyses. For the Kappa test, ≤ 0.20, 0.21 - 0.40, 0.41 - 0.60, 0.61 - 0.80 and 0.81 - 1.00 values were considered bad, weak, moderate, good and perfect harmonization, respectively.

**RESULTS**

Twenty five of 31 patients were males (80.6%) and six of 31 (19.4%) were females (age range, 22-88 years). All patients had chest pain. The interval between CMRP imaging and angiography methods varied 0 to 18 days (mean 4.2 days). Two patients had a history of coronary artery bypass surgery, nine had coronary artery stents. Five patients with stent had obstruction or occlusion.

A total of 93 coronary artery territories consisting of left anterior descending artery (LAD), circumflex artery (Cx) and right coronary artery (RCA) territories were evaluated and it was revealed that 32 of these included perfusion defects.

Twenty of 31 patients had perfusion defect in at least one of the coronary artery territories. Five patients had perfusion defects at all three LAD, Cx and RCA territories (Figure 2), one patient...
had perfusion defects at LAD and RCA territories, one had perfusion defects at LAD and CX territories. One patient had a perfusion defect at the CX artery territory and the remainder (12 patients) had perfusion defect at LAD artery territory (Figures 3, 4).

Angiography studies (CCTA or CCA) revealed that 18 of 20 patients with perfusion defects had 70% or greater obstruction in at least one of the three coronary arteries (LAD, CX or RCA) or their branches. One patient had no coronary artery obstruction in CCA, the other patient had no coronary artery obstruction in CCTA, however, there was myocardial bridging at the middle segment of LAD artery (Figure 4). During the evaluation of both coronary arteries and perfusion territories, angiography detected significant luminal narrowing (≥70%) or occlusion in LAD arteries of 17 of 19 patients who had perfusion defect in LAD artery territory, and in all RCA and/or CX arteries who had a perfusion defect in RCA and/or CX artery territories. Stenosis of 90% was detected at the D1 branch of LAD artery in one of 11 patients who did not have perfusion defects (Figure 5). In this case, stenosis of 60% at the distal LAD artery and 30% obstruction at the RCA were also observed. No significant stenosis (≥70%) was detected in the coronary arteries of 10 patients who did not have perfusion defect. Similarly, coronary arteries associated with normal perfusion areas of the patients with perfusion defect were not significantly narrowed. Only five patients had stenosis with up to 50% obstruction in coronary arteries or branches.

The overall sensitivity, specificity, accuracy, positive predictive value and negative predictive value of CMRP imaging in detecting significant coronary artery stenosis (≥70%) at angiography were 94.7%, 83%, 90.3%, 90% and 90.9%, respectively. There was no statistical difference between the two methods (p>0.05). Harmonization between the two groups was “good” (κ=0.79).

When evaluating each separate coronary artery territory; sensitivity, specificity, accuracy, positive predictive value and negative predictive value of cardiac MR perfusion test in detecting significant (70% or greater) obstruction at CCA-CCTA

<table>
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<th>LAD AT</th>
<th>94.4</th>
<th>84.6</th>
<th>90.3</th>
<th>89.4</th>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>none</td>
<td>perfect</td>
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<tr>
<td>RCA AT</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>none</td>
<td>perfect</td>
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<tr>
<td>All ATs</td>
<td>94.7</td>
<td>83</td>
<td>90.3</td>
<td>90</td>
<td>90.9</td>
<td>none</td>
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CCA, catheter coronary angiography; CCTA, coronary computed tomography angiography; LAD, left anterior descending artery; CX, circumflex artery; RCA, right coronary artery; AT, artery territory.
and negative predictive value of CMRP imaging for detecting significant obstruction in associated coronary artery indicated at angiography (CCTA or CCA) were 94.4%, 84.6%, 90.3%, 89.4% and 91.6% respectively for LAD; 100%, 100%, 100%, 100% and 100% respectively for Cx; and 100%, 100%, 100%, 100% and 100% respectively for RCA. There was no diagnostic difference between methods (p>0.05). Harmonization of two methods resulted in k values of 0.80, 1.00 and 1.00 for LAD artery, Cx and RCA territories, respectively and harmonization was “good”, “perfect” and “perfect”, respectively (Table 1).

**DISCUSSION**

This study evaluates the efficacy of CMRP imaging in detecting CAD in comparison to CCTA or CCA results, revealing high sensitivity and specificity. This is the first adenosine-stress CMRP study on this subject in Turkey.

Hamon et al. (6) completed a meta-analysis of articles that had been published up to July 2009. This analysis included 20 trials and a total of 1678 patients in whom CMRP imaging was performed with adenosine as the pharmacological stress agent and another 5 trials with a total of 417 patients in whom dipiridamol was used as the pharmacologic stress agent in CMRP imaging. Sensitivity and specificity for detecting CAD were 90% and 81% respectively in the first group and 86% and 76% respectively in the latter. We used adenosine as the stress agent and found both high sensitivity (94.7%) and high specificity (83%). Semi-quantitative analysis requires additional time; it is not appropriate for daily practice and there is no consensus in post-processing protocol. Therefore, we preferred the visual method.

It is stated that as a stress test, CMRP imaging should be avoided in patients with significant valvular stenosis, unstable angina, obstructive pulmonary disease, recent myocardial infarction, and severe arterial hypertension because of the hemodynamic disruption and possible side effects of adenosine (7), whereas, Greenwood et al (8) suggest that adenosine-stress CMRP imaging is a safe method in early after ST elevated myocardial infarction (STEMI) patients. In our study, the patients in whom adenosine usage may be hazardous were excluded from MRI perfusion examination.

Plein et al. (9) evaluated cardiac MRI tests that include 4 parameters: perfusion imaging, myocardial function, late enhancement, and coronary artery anatomy. In this study, CMRP imaging itself is sufficient for detecting coronary artery stenosis with high sensitivity and specificity (88% and 83%, respectively). But in cases of equivocal results or cases with insufficient evaluation resulting from artifacts (motion artifact, respiratory artifact, ring artifact) other cardiac MRI methods may be combined to increase sensitivity.

Klem et al. (10,11) stated that the combination of CMRP imaging with late enhancement would increase specificity and accuracy. Moreover, according to the results of another study this combination did not seem to affect sensitivity and specificity (12). We evaluate only the efficacy of CMRP in detecting significant coronary artery stenosis at angiography and found high sensitivity, specificity and accuracy. These results are similar to that of literature, with the exception of the studies by Klem et al. (10,11).

Merkle et al. (13) stated that CMRP imaging had low positive predictive value (59%) in the primary diagnosis of CAD. They thought that the higher rate of risk factors in these patients supported the idea that those patients more frequently had non-vascular conditions like hypertensive heart disease, syndrome X, or coronary endothelial dysfunction, which might be the cause of false positive results and ischemic pain. Burgstahler et al. (14) found severe myocardial hypertrophy in 2 patients with false positivity. Hamon et al. (6) stated that the reason for higher sensitivity than specificity was the high rate of false positives. We also found that sensitivity was higher than specificity. Our two cases had MR perfusion defects in the LAD artery territory, but there were no significant coronary artery stenosis. One had LIMA-LAD and AO-OM-SVG bypass grafts with patent vascular lumen and sufficient flow on CCA. In this case, perfusion defect is considered to be due to microvascular disease or persistent microvascular obstruction. The other case was not observed to have significant coronary artery stenosis in CCTA, however, there was myocardial bridging at the middle segment of LAD artery and this is thought to explain the perfusion defect.

Cheng et al. (15) reported that 3 T CMRP imaging was superior to 1.5 T CMRP imaging. Meyer et
al. (16) used 3 T MR device and performed adenosine-stress CMRP test. When they compared the results to those in the literature at 1.5 T based on a visual analysis, they found that their protocol was at least as efficacious as those at 1.5 T. Our results are similar to the study by Meyer et al. with 3 T MR Devices.

Merkle et al. (13) found that the sensitivity of CMRP imaging for diagnosis of coronary artery stenosis was higher in LAD artery territory than that of Cx and RCA territories. They stated that a possible explanation might be the use of surface coil leading to lower signal intensities at lateral and inferior segments in especially obese population.

In our study, we evaluated efficacy of CMRP method for detection of significant coronary artery stenosis in each coronary artery territory separately. Sensitivity, specificity, and accuracy were higher than the values in literature. These higher values, especially for Cx artery and RCA territories, are thought to be due to fewer perfusion defects in these territories in comparison to LAD artery territory, and relatively low number of patients with Cx artery and RCA obstruction.

In our study, one of the patients without perfusion defects in CMRP imaging had an obstruction of 90% at D1 branch of LAD in CCA and it was noted as a thin vessel (Fig. 5). Lack of perfusion defect in this patient may be explained because of thin structure of obstructed artery and possible collateral blood flow.

One of the major limitations of our study is that we did not compare the CMRP method with an accepted test for evaluating perfusion defects such as SPECT. Another limitation was the use of angiography methods for comparison in a perfusion study. CCA is the standard diagnostic method for detecting significant coronary artery obstruction in daily practice. However, it is not appropriate to evaluate the hemodynamic significance of coronary artery obstruction and the functional significance of obstruction is more important than morphological obstruction in the prognosis of CAD. The invasive gold standard method in detecting functional significance of obstruction is measurement of pressure dependent fractional flow reserve (FFR) (17). Rieber et al. (18) compared CMRP imaging to CCA and FFR in accordance with detecting functional status of CAD and found a strong correlation between CMRP method and FFR measurement. FFR was not measured in patients included in our retrospective study. We considered angiography as the reference method, similar to most studies in the literature. Another limitation of our study was the absence of a single angiography method. Coronary artery evaluation was performed with CCA in 21 patients and CCTA in 10 patients in our study. However, recent advances in CCTA with the development of Multi-Detector Computed Tomography technology provide high sensitivity, specificity, and accuracy for detection of CAD (19). Because of its high negative predictive value, we used CCTA as an alternative method to catheter angiography, especially in patients without perfusion defects. Small study sample and retrospective design are two additional factors that decrease statistical power. Further prospective studies with larger sample size are needed.

Cardiac MR Perfusion test has high sensitivity and specificity in detecting significant coronary artery stenosis when compared to catheter coronary angiography. We used adenosine as a pharmacologic stress agent in this technique. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value in detecting 70% or greater obstructions of coronary arteries in catheter coronary angiography or coronary CT angiography were high, similar to literature. There was no significant diagnostic difference between these methods and the harmonization was good-to-perfect.

In conclusion, cardiac MR perfusion test seems to be a reasonable alternative for catheter angiography, which is considered the gold standard for evaluation of CAD and exclusion of significant coronary artery obstruction. We suggest that as a non-invasive method, CMRP imaging could be used more commonly in clinical practice in order to decrease the use of invasive procedures like catheter angiography.

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TRANSPARENCY DECLARATIONS
Competing interests: none to declare.
REFERENCES


