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Original article

Diagnostic accuracy of combined dipyridamole stress perfusion and delayed enhancement cardiovascular magnetic resonance imaging for detection of coronary artery disease

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Background: The diagnosis of coronary artery disease (CAD) is one of the most common clinical issues that face medical practitioners. Myocardial ischemia can be noninvasively assessed with cardiovascular magnetic resonance imaging (CMRI), which has become an emerging modality.
Objective: Determine the accuracy of dipyridamole stress CMRI by using stress and rest perfusion combined with delayed enhancement imaging for detecting CAD.
Methods: Thirty-nine patients (24 men, 15 women; mean age 64±11.4 years) who had experienced prior myocardial infarction or had suspected CAD were enrolled. Dipyridamole stress CMRI with subsequent coronary angiography was performed within a mean time interval of 16 days (range: 1-30 days). The dipyridamole stress CMR protocol included stress and rest perfusion followed by delayed enhancement imaging. Per-vessel analysis was done according to 17-segment model recommendation by the American Heart Association.
Results: Coronary angiography depicted significant coronary artery stenosis (≥70% stenosis of major epicardial artery) in 26 patients (55 coronary arteries). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the combined stress and rest perfusion with delayed enhancement imaging for detection of significant coronary artery stenosis were 76-96%, 79-96%, 87-93%, 83-96%, and 85-95%, in left anterior descending, left circumflex, and right coronary arteries, respectively. Without delayed enhancement imaging, stress and rest perfusion produced slightly lower sensitivity (69-92%), specificity (73-96%), positive predictive value (79-93%), negative predictive value (80-92%), and accuracy (79-92%).
Conclusion: Dipyridamole stress CMRI combined with delayed enhancement imaging yielded high diagnostic accuracy for the detection of coronary artery disease. This modality allows the clinical application for detection of CAD in selected group of patients.

Keywords: Cardiovascular magnetic resonance imaging, coronary angiography, coronary artery disease, delayed enhancement imaging, dipyridamole stress

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide. Dipyridamole stress cardiovascular magnetic resonance (CMRI) has been utilized as a non-invasive modality for detection of coronary artery stenosis. After dipyridamole administration, contrast-enhanced perfusion CMRI can demonstrate areas of hypoperfusion which represents abnormal myocardial blood flow due to coronary artery obstruction in contrast with areas of normal myocardial perfusion [1, 2]. Prior stress perfusion CMRI studies reported sensitivity of 58-97% and specificity of 68-85% by using coronary angiography as the reference standard [3-5]. The accuracy of the test is dependent on the type of magnetic resonance machine, patient

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cooperation, regular heart rate, and experience of the interpretator. We performed a prospective study of the accuracy of dipyridamole stress CMRI in patients with suspected CAD compared with conventional coronary angiography.

Materials and methods

The study protocol was approved by the Ethics Committee of King Chulalongkorn Memorial Hospital, and all subjects gave informed written consent. Thirty-nine patients with suspected CAD who were referred for invasive coronary angiography were enrolled. Both dipyridamole stress CMRI and subsequent coronary angiography were performed within a mean time interval of 16 days (range: 1-30 days). Patients who had hemodynamic instability, previous coronary artery bypass grafting, contraindication for CMRI, and dipyridamole injection were excluded.

Dipyridamole stress CMRI

All patients were examined in supine position with a 1.5-Tesla MR scanner (Signa Excite HD; GE Medical Systems, Berkshire, USA). An eight-channel cardiac coil was placed over the anterior chest wall. Dipyridamole stress CMRI time-line protocol is shown in **Fig. 1**.

Dipyridamole 0.56 mg/kg was administrated intravenously over four minutes. Two minutes later, stress perfusion was performed using two dimensional (2D) fast gradient echo-planar pulse sequence during a bolus injection of 0.065 mmol/kg of gadolinium contrast agent with flow rate of 5 mL/sec, followed by a 20-mL saline flush [6]. This pulse sequence yielded five to eight sections of short-axis view covering the entire left ventricle every other heart beat. Aminophylline 100 mg was given intravenously to all patients for antidote. Rest perfusion was acquired after 20 minutes of dipyridamole injection with the same sequence, gadolinium dose, and injection rate. Standard cardiac views (2-chamber, 3-chamber, 4-chamber, and multislice short axis views) of steady state free precession white blood imaging was obtained before and during stress and rest perfusion for functional analysis. Delayed enhancement imaging was performed with total dose of 0.13-0.2 mmol/kg of gadolinium contrast agent in 2-chamber, 3-chamber, 4-chamber, and multi-slice short axis views for assessment of myocardial infarction [7].

During scanning, electrocardiography, heart rate, blood pressure, and oxygen saturation were monitored continuously. All patients underwent the complete stress CMRI examination without severe complications or early termination. Only two patients (5.1%) had minor side effects of dyspnea and chest pain those resolved after administration of aminophylline.

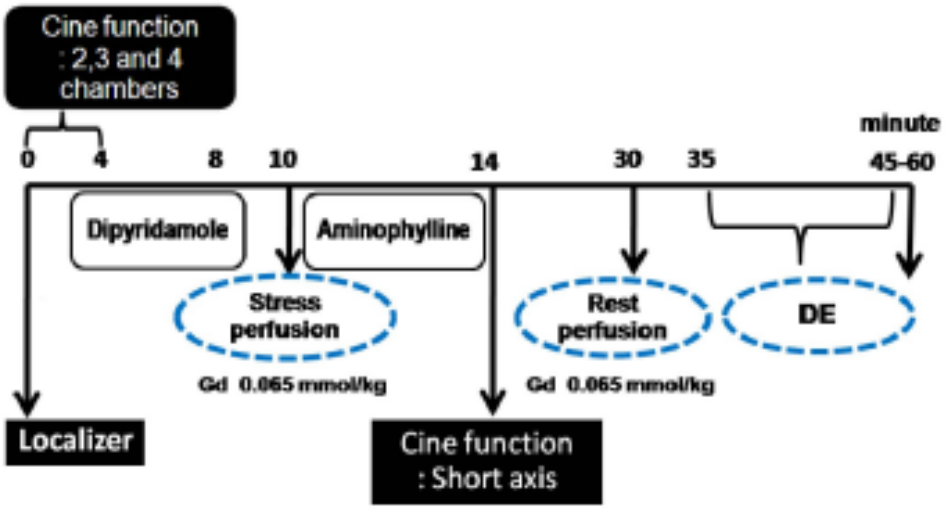

Fig. 1 Dipyridamole stress CMRI time-line protocol. Gd: gadolinium, DE: delayed enhancement.

Coronary angiography

Coronary angiography was performed and interpreted independently by two experienced cardiologist without knowing clinical data and the CMRI results. Luminal narrowing was estimated visually. Significant CAD was defined as ≥70% narrowing of the luminal diameter of the epicardial coronary artery (diameter ≥2.5 mm) or ≥50% narrowing of the left main coronary artery [8]. On average, six projection planes were obtained (four views of the left coronary artery and two views of the right coronary artery). Patients were classified as having one-, two-, or three-vessel disease.

CMRI analysis

CMRI data were reviewed by experienced cardiovascular radiologists by visual analysis. Stress and rest perfusion was compared slice-by-slice on a PACS (picture archiving communication system) monitor. Perfusion defects were identified in terms of subendocardial hyposignal intensity during contrast enhanced myocardial perfusion. Myocardial ischemia was defined as a segment of perfusion deficit on stress and not demonstrable on rest in at least three consecutive temporal images and at least two contiguous myocardial segments [5]. Myocardial infarction was defined as an area of subendocardial or transmural delayed enhancement consistent with coronary distribution. Each abnormal myocardial segment was assigned into 17-segment model to represent three major coronary arteries according to the recommendation by the American Heart Association [9] (see **Fig. 2)**. Stress CMRI was considered positive if there was myocardial ischemia or infarction or both ischemia and infarction (see **Fig. 3**). CMRI data was reviewed three months later by the same cardiovascular radiologist for assessment of intraobserver reliability.

Statistical analysis

Results are expressed as sensitivity, specificity, and overall accuracy with the angiographic result serving as the reference standard. All measures of diagnostic accuracy were calculated on a per-vessel basis. Diagnostic accuracy was calculated from results of combined stress-rest perfusion with additional delayed enhancement imaging. Descriptive statistic e.g., continuous variables were described as mean ± standard deviation (SD) and categorical variables were described as count and percentages. Inter-and intra-observer reliability of the coronary angiography was assessed by kappa statistic.

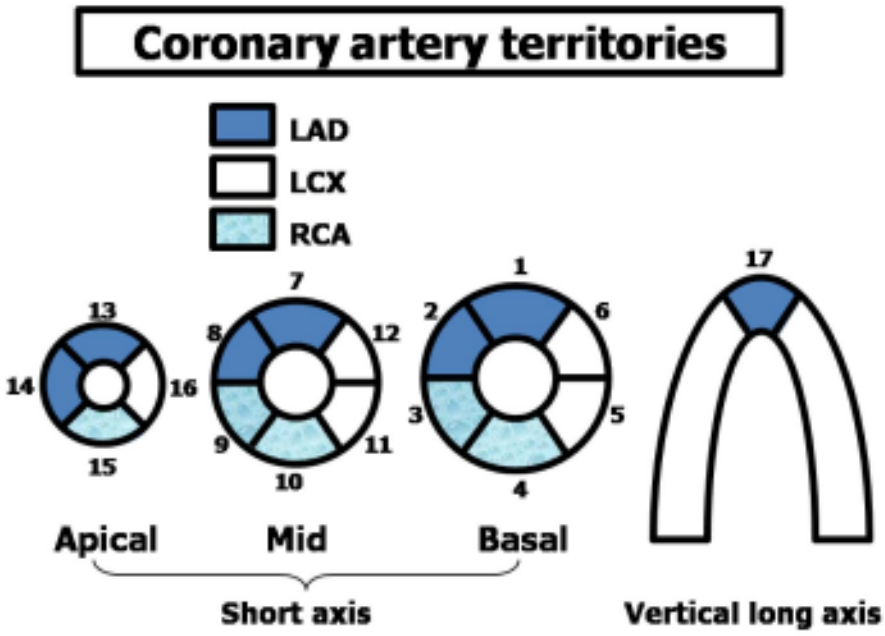

Fig. 2 Seventeen segment model to represent three major coronary arteries. Note assignment of the 17 myocardial segments to the territories of the left anterior descending (LAD), right coronary artery (RCA), and the left circumflex coronary artery (LCX).

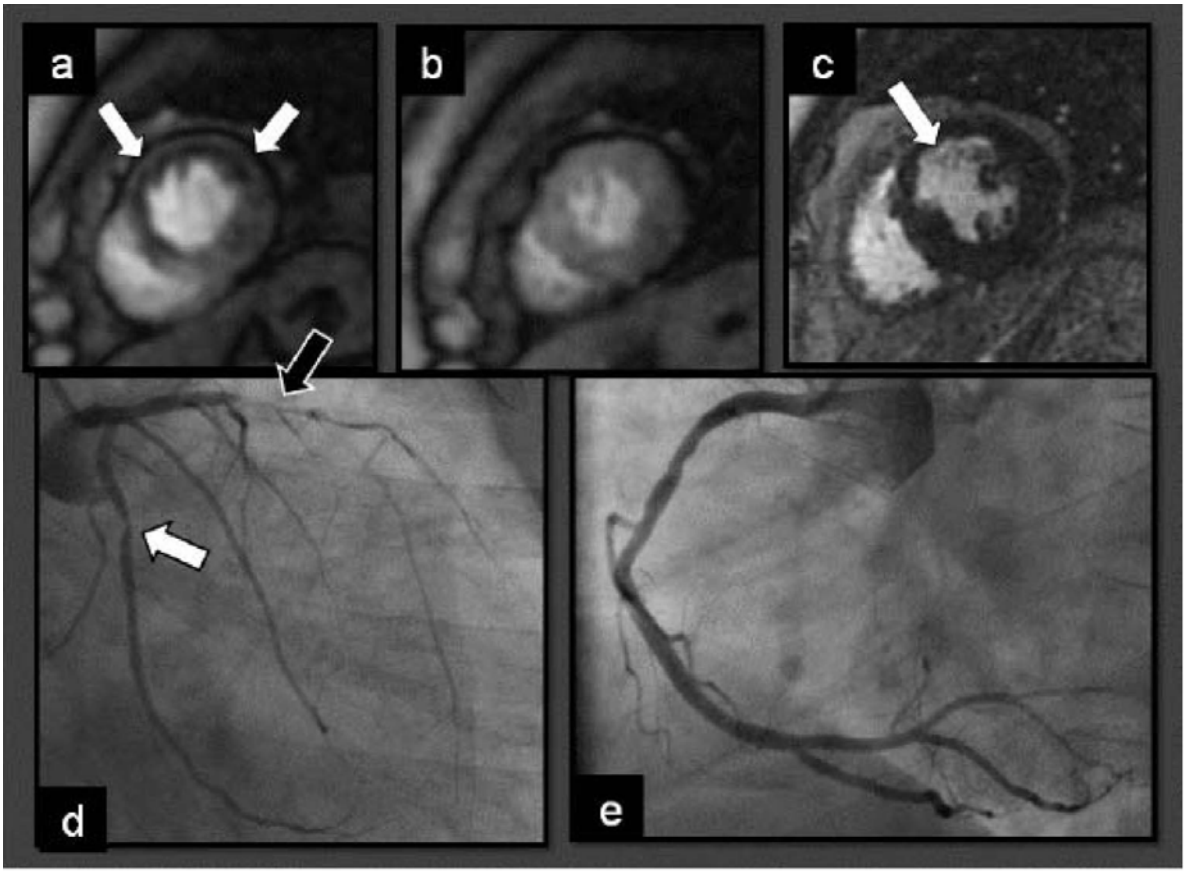

Fig. 3 Patient with previous myocardial infarction and inducible ischemia. Stress perfusion image (**a**) depicts a hypoperfused area in LAD and LCX territories (indicated by white arrows). This is not seen on rest perfusion image (**b**). Delayed enhancement (DE) image (**c**) shows hyperenhancement in LAD territory (indicated by white arrows). Coronary angiographic CAG images (**d, e**) reveal a 85% stenosis of mid LCX (indicate dy white arrow) along with subtotal occlusion of mid LAD (indicated by black arrow). This corresponds with the DE area and Q-wave on surface electrocardiogram confirming myocardial infarction. LAD: left anterior descending artery, LCX: left circumflex coronary artery, RCA: right coronary artery.

Results

Out of 39 patients (24 men and 15 women; mean age 59 years˜1 1.4 [SD]), nine patients had prior myocardial infarction. All patients gave written informed consent. Patient characteristics and indications by coronary angiography are shown in **Table 1.**

CMRI images showed adequate quality for interpretation in all patients. No patient experienced serious adverse reactions during pharmacologic stress. Coronary angiography showed clinically significant disease in 26 patients (55 coronary arteries) calculated as 67% for the prevalence of CAD (**Table 2**). Inter-observer agreement of coronary angiography was excellent between two cardiologists (Kappa = 0.96). Likewise, the analysis of CMRI showed good intra-observer agreement (Kappa = 0.76).

Diagnostic performance of combined stress-and rest-perfusion with delayed-enhancement for detection of CAD is shown in **Table 3**.

Twenty patients had myocardial infarction on delayed enhancement images, which correlated well with significant disease in 24 coronary arteries. Eleven patients had no history of previous myocardial infarction. Nine patients with history of myocardial infarction demonstrated myocardial scars on delayed-enhancement image in at least one coronary artery territory, confirming the presence and location of previous myocardial infarction.

Two patients had only myocardial infarction without evidence of myocardial ischemia.

Table 1. Baseline demographic data.

Characteristics	Value
Age (year): mean±SD (range)	59.0±11.4 (37-80)
Male gender: number (%)	24 (61)
Body mass index (mean±SD)	24.9±3.2
median (kg/m^2)	24.5
<19 kg/m^2: number (%)	1 (5.1)
>25 kg/m^2: number (%)	16 (41)
Hypertension: number (%)	21 (54)
Diabetes: number (%)	15 (39)
Hypercholesterolemia: number (%)	20 (51)
Smoking: number (%)	10 (26)
Family history of CAD: number (%)	11 (28)
Previous cerebrovascular accident: number (%)	6 (15)
Previously known myocardial infarction: number (%)	9 (23)
Prior percutaneous coronary intervention: number (%)	1 (3)
Indication by coronary angiography	
Clinical symptoms: number (%)	11 (28)
Positive stress nuclear study: number (%)	5 (13)
Positive exercise stress test: number (%)	10 (26)
Chronic left ventricle systolic dysfunction: number (%)	8 (20)
Inconclusive result from prior test: number (%)	5 (13)

Table 2. Distribution of significant diseases by coronary angiography.

Distribution of significant diseases	Value
None: number (%)	13 (33)
Isolated left main disease: number (%)	1 (3)
One-vessel: number (%)	7 (18)
Two-vessels: number (%)	8 (20)
Three-vessels: number (%)	10 (26)

Table 3. Diagnostic performance of combined stress and rest perfusion with delayed enhancement for detection of CAD. (LAD: left anterior descending artery, LCX: left circumflex coronary artery, RCA: right coronary artery).

	All	LAD	LCX	RCA
Sensitivity	85.7	94.4	68.8	93.3
Specificity	88.5	78.6	91.3	91.7
Accuracy	87.2	87.2	82.1	92.3

Discussion

Area of myocardial ischemia represented areas of abnormal coronary artery blood flow during stress due to coronary artery obstruction, whereas myocardial infarction represented area of myocardial scar due to prior infarction [10-12]. Both findings presumably resulted from CAD. Our study showed the high sensitivity, specificity, and accuracy of the combined stress-rest perfusion, and delayed enhancement, which were similar to prior studies [3-5]. LAD had high sensitivity and low specificity due to false positives from susceptibility artifacts at

anterior wall and anteroseptal wall. LCX had relatively low sensitivity compared to LAD and RCA. This is explained by the fact that most patients had a right dominant coronary artery system and a long posterolateral branch that partially supplied the lateral wall. False positive stress tests may be caused by arterial hypertension and diabetes, which may lead to ''small vessel disease'' without relevant coronary macroangiopathy [13].

Eleven out of 20 patients with identified myocardial scar from delayed enhancement imaginghad no history of previous myocardial infarction. This outcome demonstrated the benefit of delayed enhancement imaging in the detection of unsuspectedprevious myocardial infarction. This information may have clinical implications for therapy and clinical management as reported by Kim et al. [14] in that segments with greater than 50% transmural scar were unlikely to recover after revascularization.

There are several limitations in this study. Firstly, the quantitative measurement of stress-rest perfusion and delayed enhancement, which was reported to increased specificity [15] of the test, was not used in our study. Quantitative analysis is more time consuming and requires specific software, and thus has limited used in clinical practice. However, previous studies showed good correlation between quantitative and visual assessments of myocardial perfusion [16]. Secondly, our study was done in patients who had relatively high pretest probability for CAD, thus, it is difficult to generalize these results using with low disease prevalence population.

Conclusion

Dipyridamole stress CMRI combined with delayed enhancement imaging yielded high diagnostic accuracy for the detection of coronary artery disease. This modality allows the clinical application for detection of CAD in selected group of patients.

The authors have no conflict of interest to report.

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