Combination of magnetic resonance imaging and targeted contrast agent for the diagnosis of myocardial infarction

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Abstract. Myocardial infarction is one of the most common human cerebrovascular conditions and frequently leads to ischemic stroke. Evidence has indicated that magnetic resonance imaging (MRI) is a potential method for the diagnosis of patients with cardiovascular injury. However, the efficacy of MRI in diagnosing patients with myocardial infarction requires to be improved. In the present study, a novel nano-size contrast agent, a chitosan/Fe_3O_4-enclosed albumin (CFEA), was introduced that was used to quantify blood volume and permeability in the infarcted myocardium. A total of 68 patients with suspected myocardial infarction were recruited to analyze the efficacy of MRI combined with CFEA (MRI-CFEA). All patients received diagnosis by MRI and MRI-CFEA. It was revealed that MRI-CFEA provided a higher signal intensity than MRI in the same patients. It was demonstrated that the diagnostic efficacy of MRI-CFEA for patients with myocardial infarction was higher than that of MRI ($P<0.05$). By MRI-CFEA, 50/68 of cases with myocardial infarction were diagnosed, providing a significantly higher diagnostic rate compared with the 38/68 of cases diagnosed by contrast-enhanced MRI ($P<0.01$). MRI-CFEA successfully discriminated the infarcted regions based on a decreased fractional blood volume and increased permeability-surface (PS) area product in the infarcted myocardium. A pharmacodynamics analysis indicated that CFEA was eliminated within 24 h in all individuals. In conclusion, the present study provided a novel method to diagnose infarcted myocardium for patients with myocardial infarction, providing an imaging biomarker for the assessment of endothelial dysfunction in the clinic.

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Introduction

Acute myocardial infarction (AMI) is a leading cause of mortality and morbidity in the world, despite the rates having significantly declined over the past decade (1). Numerous risk factors, including age, sex, social deprivation, smoking, use of anti-hypertensives or lipid-lowering drugs and diabetes mellitus, are associated with myocardial infarction (2-4). In the clinic, the treatment of AMI includes blood transfusion and a previous study has reviewed the risks and benefits of thrombolytic, anti-platelet and anti-coagulant therapies for myocardial infarction (5). In recent years, early diagnosis of myocardial infarction has been widely applied for patients with recent myocardial infarction or suspected or known coronary artery disease (6).

At present, ultrasound, positron emission tomography (PET) with fludeoxyglucose (FDG)/computed tomography and MRI are widely used for the diagnosis and staging of human cardiovascular diseases (7-9). Among these diagnostic methods, MRI provides a higher sensitivity and accuracy in the diagnosis of myocardial infarction in the clinic (10,11). The clinical utility of cardiac MRI in patients with myocardial infarction has a high reproducibility and accuracy, allowing for detailed functional assessment and characterization of myocardial tissue determined by infarct size (IS), transmural extent of necrosis (TEN) and microvascular obstruction (MVO) (12). A previous study also reported that simultaneous assessment of late gadolinium enhancement (LGE) and FDG uptake using a hybrid PET/MRI system is feasible, which accurately predicted the regional outcome of wall motion after AMI (13). In addition, although numerous studies have reported on the diagnosis of myocardial infarction by using MRI (14,15), the diagnostic accuracy of MRI in diagnosing patients with early-stage myocardial infarction requires to be improved.

In the present study, a novel contrast agent, chitosan/Fe_3O_4-enclosed albumin (CFEA), was introduced and the efficacy of MRI with CFEA (MRI-CFEA) in the diagnosis of patients with early-stage myocardial infarction was assessed. The results indicated that MRI-CFEA not only improved

the signal intensity in the localized area of the myocardial infarction, but also enhanced the diagnostic efficacy of MRI in the diagnosis of clinical patients with suspected myocardial infarction.

Materials and methods

Ethics statement. The present clinical trial was performed in strict accordance with the recommendations for clinical study in China (approval number, 20140521TJ) (16). The present study was also approved by the Ethics Committee of Tongji Medical College (Wuhan, China). Written informed consent was obtained from all patients or their relatives prior to their inclusion within the study.

Targeted contrast agent. The CFEA nano-size contrast agent was used for the diagnosis of patients with suspected early-stage myocardial infarction as previously described (17). Nano-size CFEA was produced using a covalent bond with albumin as previously described (18). The CFEA was administrated by intravenous injection. The nano-particle contrast agent to be visualized by the MRI system was administered by intravenous injection at 30 min prior to MRI.

Patients. A total of 68 patients (males, n=36; females, n=32) with suspected myocardial infarction were enrolled in the present study. In addition, 32 healthy individuals (males, n=15; females, n=9) were enrolled in the present study. The mean age was 45.6 and 42.8 years in patients with suspected myocardial infarction and healthy individuals, respectively. The present study included 68 patients consecutively registered between January 2015 and May 2016 at Tongji Medical College (Wuhan, China) with suspected myocardial infarction who wished to be included in the study. A total of 32 healthy individuals were recruited between January 2015 and May 2016 following a routine health check. All patients with suspected myocardial infarction were subjected to MRI scanning for the detection of early-stage myocardial infarction using conventional LGE-cardiovascular magnetic resonance (MRI) and MRI-CFEA. Patients with chest pain (which was rated using the rapid emergency medical scoring system (19)) and/or abnormities in the electrocardiograph and heart color ultrasound were included in the present study. Patients with a personal or family history of heart disease and/or myocarditis were also excluded from the study. All measurements were performed at the diastole status for patients with myocardial infarction.

ELISA. The serum levels of marker proteins were analyzed by commercialized ELISA kits [C-reactive protein (CRP; cat. no. DY1707), tumor necrosis factor (TNF-α; cat. no. DTA00C), interleukin (IL-1; cat. no. DLB50) and creatine phosphokinase (CPK; cat. no. DYDTA02P); all from R&D Systems, Inc., Minneapolis, MN, USA). The operational procedures were performed according to the manufacturer's instructions. The results were performed by an ELISA reader system (1775xMark™, Bio-Rad Laboratories, Inc., Hercules, CA, USA).

MRI scanning. An MRI diagnosis system (Ingenia 1.5T CX; Philips Medical Systems, Cleveland, OH, USA) was used to diagnose patients with suspected myocardial infarction using pre-programmed settings. These settings were optimized to reach the optimal image formation. The whole heart in all of the patients was subjected to MRI scanning according to the manufacturer's protocol. The details of principles and settings of MRI were described in a previous study (20). MRI processes included T1 and T2 parametric mapping. Imaging parameters were set as follows: Flip angle, 46˚; repetition time, 3.2 msec; echo time, 1.40 msec; typical field of view, 340x260 mm^2; matrix, 250x210; slice thickness, 6 mm; slice gap, 3 mm; receiver bandwidth, 977 Hz/pixel; and cardiac phases, n=25. The necessary dose of CFEA for optimal signal intensity for MIR detection was determined by analyzing MRI images following increasing doses of CFEA (0-0.5 mg/kg). Images were collected 10-15 min after the administration of 0.30 mg/kg CFEA or 0.1 mmol/kg contrast agent (Gadovist; Bayer, Leverkusen, Germany).

Image analysis. The MRI image sets were analyzed using the software included in the MRI system, based on which the presence and location of myocardial infarction was determined. Signal enhancement of MRI by CFEA was also measured with this preparatory program. Planimetric analysis of the myocardial infarction size was performed using the software included in the system (SyngoMR A30; Philips Medical Systems) and ImageJ 1.38x software (National Health Institute, Bethesda, MD, USA).

Statistical methods. Values are expressed as the mean ± standard deviation. SPSS version 19.0 (IBM Corp., Armonk, NY,

Table I. Characteristics of patients with myocardial infarction.

Characteristic	Males (n=36)	Females (n=32)
Age (years)	50±17.8	54.3±18.1
Chest pain	36	32
Heart rate (beats/min)	122	130
Diagnostic method		
MRI	36	32
MRI-CFEA	36	32

Values are expressed as n or mean (range). MRI, magnetic resonance imaging; CFEA, chitosan/Fe_3O_4-enclosed albumin; SD, standard deviation. Chest pain was determined using the rapid emergency medical scoring system.

Table II. Diagnostic rates of myocardial infarction by MRI and MRI-CFEA in suspicious patients.

Gender	MRI (%)	MRI-CFEA (%)	P-value
Male	21 (58.33)	26 (72.22)	0.0404
Female	17 (53.13)	24 (75.00)	0.0362

MRI, magnetic resonance imaging; CFEA, chitosan/Fe_3O_4-enclosed albumin.

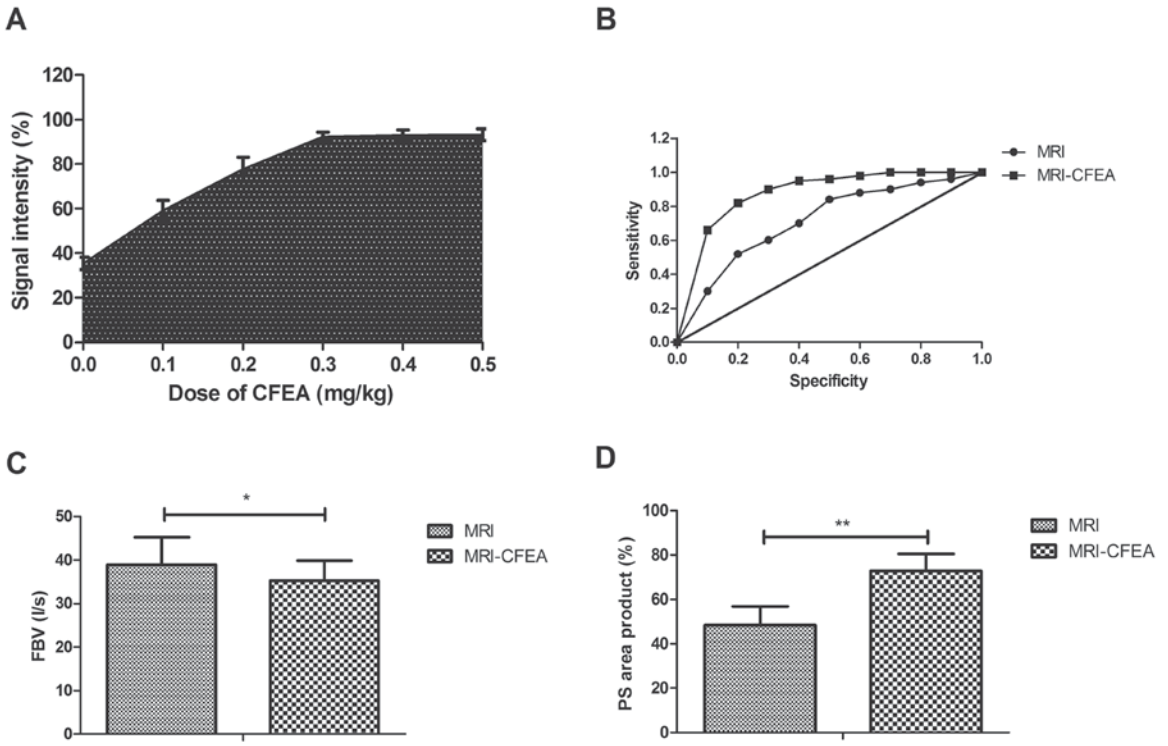

Figure 1. Efficacy of MRI-CFEA in early clinical diagnosis of patients with suspected myocardial infarction. (A) Dose of CFEA for optimum signal intensity for MIR detection. (B) Specificity of MRI-CFEA in diagnosing patients with myocardial infarction. (C and D) Capacity of MRI-CFEA to discriminate the infarcted regions by (C) FBV and (D) PS area product compared with MRI. *P<0.05, **P<0.01. MRI, magnetic resonance imaging; CFEA, chitosan/Fe_3O_4-enclosed albumin; FBV, fractional blood volume; PS, permeability surface.

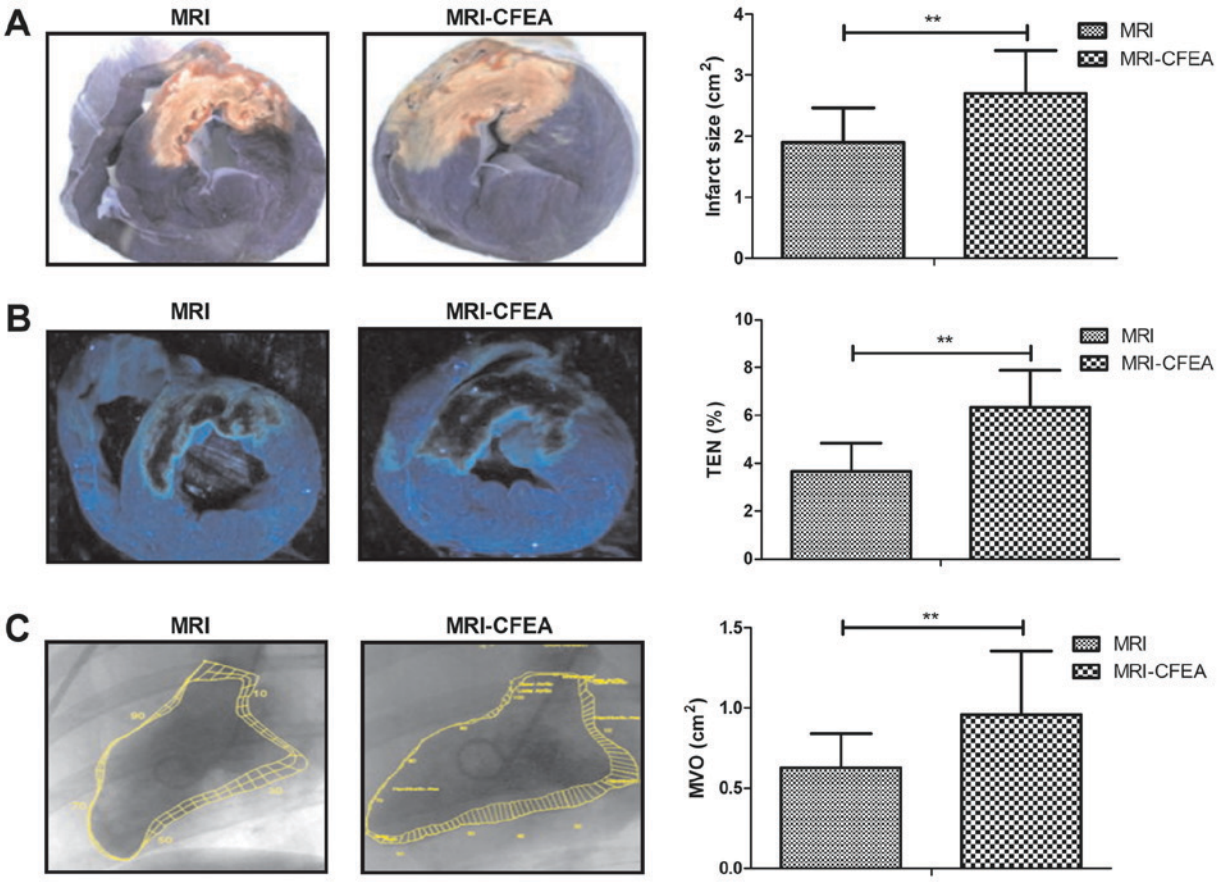

Figure 2. Morphological analysis of myocardial infarction by MRI-CFEA compared with MRI. MRI-CFEA clearly presents (A) the infarct size, (B) TEN and (C) MVO for patients with myocardial infarction. **P<0.01. MRI, magnetic resonance imaging; CFEA, chitosan/Fe_3O_4-enclosed albumin; TEN, transmural extent of necrosis; MVO, microvascular obstruction.

Table III. Serum levels of inflammatory factors in patients with suspected myocardial infarction.

Factor	Myocardial infarction	No myocardial infarction	Normal range	P-value
CPK (U/dl)	6.130±2.300	2.752±1.248	4.240±1.240	0.0052
CRP (mg/l)	4.290±4.110	11.225±4.495	10.000±3.000	0.0088
TNF-α (g/l)	1.770±0.540	1.220±0.320	1.000±0.300	0.0072
IL-1 (μg/l)	26.100±10.700	14.200±6.200	15.000±5.000	0.0028

TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; CPK, creatine protein kinase.

USA) was used to perform all statistical analyses. All statistical analyses were performed using one-way analysis of variance followed by Dunnett's post hoc test. P<0.05 was considered to indicate a statistically significant difference.

Results

Characteristics of patients. A total of 68 patients with suspected myocardial infarction were enrolled in the present study. Baseline characteristics all patients are summarized in Table I. The median period between the index events, including chest pain or abnormities in the electrocardiograph and heart color ultrasound and MRI or MRI-CFEA examination was 2 days with an interquartile range of 1-4 days (21). The cohort included 36 male patients and 32 female patients and the mean age was 50±17.8 (range, 32.2-67.8) years and 54.3±18.1 (range, 36.2-72.4) years in male and female patients, respectively.

Specificity of MRI-CFEA in the early clinical diagnosis of patients with suspected myocardial infarction. The dose of CFEA to achieve the optimum signal intensity for MIR detection was identified as 0.30 mg/kg (Fig. 1A). The diagnostic efficacy of MRI-CFEA in patients with suspected myocardial infarction was then further analyzed. It was demonstrated that MRI-CFEA is more specific than MRI, as more patients were diagnosed with myocardial infarction (P<0.05; Fig. 1B). By MRI-CFEA, 50/68 myocardial infarction cases were diagnosed, which is significantly higher than the 38/68 myocardial infarction patients diagnosed by MRI (P<0.05; Table II). It was also indicated that MRI-CFEA was able to discriminate the infarcted regions based on a decreased fractional blood volume (FBV) and increased permeability-surface (PS) area product in the infarcted myocardium (Fig. 1C and D). A total of 42 patients were confirmed as having myocardial infarction and 20 patients were without myocardial infarction. These outcomes suggest that MRI-CFEA is a reliable method for early clinical diagnosis of patients with suspected myocardial infarction.

Morphological analysis of myocardial infarction. Next, the efficacy of the clinical utilization of cardiac MRI-CFEA in patients with myocardial infarction was assessed. It was observed that MRI-CFEA displayed the IS and transmural extent of necrosis more clearly than MRI for patients with myocardial infarction (Fig. 2A and B). It was also indicated that MRI-CFEA was able to detect the MVO for patients with myocardial infarction (Fig. 2C). These results suggest that MRI-CFEA is more accurate than MRI in detecting pathological features of myocardial infarction in suspicious patients.

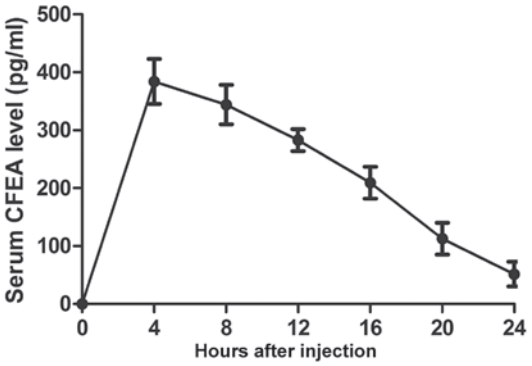

Figure 3. Pharmacodynamics of CFEA. Time-dependent plasma concentration of CEFA in patients with myocardial infarction. CFEA, chitosan/Fe_3O_4-enclosed albumin.

Serology confirms the diagnosis of MRI-CFEA for patients with suspected myocardial infarction. Assessment of serological biomarkers of myocardial infarction demonstrated that serum levels of CPK were increased in patients with myocardial infarction compared with those in healthy individuals (P<0.05; Table III). Furthermore, it was demonstrated that the serum levels of CRP, TNF-α and IL-1 were increased in patients with myocardial infarction (P<0.05; Table III). Of note, MRI-CFEA is efficient in diagnosing patients with myocardial infarction along with high levels of CRP, CPK, TNF-α and IL-1.

Pharmacodynamics of CFEA in patients with myocardial infarction. Finally, the pharmacodynamics of CFEA were assessed after administration to the patients with myocardial infarction. It was demonstrated that CFEA was eliminated from the plasma within 24 h after intravenous injection (Fig. 3). This result indicates that CFEA may be easily eliminated from patients with myocardial infarction. No adverse effects were observed in the present study.

Discussion

Early diagnosis of myocardial infarction is an efficient method to decrease the mortality and morbidity of affected patients (22,23). At present, MRI is widely used for diagnosing

myocardial infarction (14,15). Evidence has indicated that contrast agents increase the diagnostic efficacy in patients with AMI undergoing coronary angiography (24). In the present study, the diagnostic efficacy of the nano-size contrast agent CFEA combined with MRI was investigated to quantify the blood volume and permeability in the infarcted myocardium in a total of 68 patients with suspected myocardial infarction. It was indicated that MRI-CFEA is an efficient method for diagnosing patients with suspected myocardial infarction. Of note, a pharmacodynamics analysis demonstrated that CFEA was easily eliminated from patients with myocardial infarction within 24 h.

A previous study summarized the current knowledge of the pharmacokinetic principles of gadolinium chelates for enhancing the diagnostic value of cardiac MRI in the diagnosis of complications of myocardial infarction (25). In addition, delayed-enhancement 3.0T MRI with 0.15 mmol/kg of contrast agent superparamagnetic iron oxide provides more accuracy in the assessment of chronic myocardial infarction (26). The present study identified that the optimal dose of CFEA was 0.30 mg/kg to achieve the maximum signal intensity for MIR detection, which enhanced the diagnostic efficacy of MRI for patients with suspected myocardial infarction. A previous study also revealed that early assessment of myocardial contractility by contrast-enhanced magnetic resonance imaging is inversely associated with the contractility after revascularization in patients after AMI (27). It was demonstrated that the nano-size contrast agent CFEA improves the signal intensity for the localization of the myocardial infarction area and the accuracy of MRI in the diagnosis of clinical patients with early-stage myocardial infarction.

The pathological characteristics of myocardial infarction patients include IS, TEN and MVO (28). The present study reported that MRI-CFEA clearly indicated the IS, TEN and MVO in patients with early-stage myocardial infarction. It was also demonstrated that MRI-CFEA was able to discriminate the infarcted regions based on a decreased FBV and increased PS area product in the infarcted region. Observation of these parameters facilitates the selection of a targeted therapy for patients with myocardial infarction.

Inflammatory responses are included in the pathogenesis of atherosclerosis and its clinical result, myocardial infarction (29). CRP and CPK-MB may act as mortality predictors in patients with AMI (30). The present study reported that the serum levels of CRP and CPK were upregulated in clinical myocardial infarction patients. According to previous studies, the serum levels of TNF-α and IL-1 were increased in patients with previous myocardial infarction (31,32). The present study demonstrated that the serum levels of TNF-m and IL-1 were increased in patients with myocardial infarction. The present results suggested that MRI-CFEA is efficient in diagnosing patients with myocardial infarction who also presented with elevated levels of CRP, CPK, TNF-α and IL-1.

In conclusion, the present study reported that MRI using CFEA as a contrast agent improved the sensitivity and accuracy of MRI in diagnosing patients with early-stage myocardial infarction. It was reported that MRI-CFEA was able to detect pathological characteristics of myocardial infarction. The present study may contribute to the development of methods for the early diagnosis of myocardial infarction, and may be used for evaluating the degree of myocardial infarction.

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Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

JQ and SZ performed the experiments. TA designed the experiments for the study and ZL, YC and QQ analyzed the experimental data. The final version of the manuscript has been read and approved by all authors.

Ethics approval and consent to participate

The present study was also approved by the Ethics Committee of Tongji Medical College and written informed consent was obtained from all patients or their relatives prior to their inclusion within the study.

Consent for publication

Written informed consent was obtained from all patients for the publication of their data.

Competing interests

The authors confirm that they have no competing interests.

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