creative commons
COMMONS DEED

저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:

저작자표시. 귀하는 원저작자를 표시하여야 합니다.

비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.

변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 이용허락규약(Legal Code)을 이해하기 쉽게 요약한 것입니다.

Disclaimer

dCollection

의학석사 학위논문

단일 용량 조영제를 사용한 3 T 자기공명 지연 조영 영상

-고식적 이중용량 1.5 T 자기공명 지연 조영 영상과의 비교-

Single Dose Gadolinium Contrast for 3 T Late Gadolinium Enhancement MRI

-Intra-individual Comparison with Conventional Double Dose at 1.5 T MRI-

2015년 2월

서울대학교 대학원

의학과 영상의학 전공

임 지 연

A thesis of the Master's degree

단일 용량 조영제를 사용한 3 T 자기공명 지연 조영 영상

-고식적 이중 용량 1.5 T 자기공명 지연 조영 영상과의 비교-

Single Dose Gadolinium Contrast for 3 T Late Gadolinium Enhancement MRI

-Intra-individual Comparison with Conventional Double Dose at 1.5 T MRI-

February 2015

The Department of Radiology
Seoul National University
College of Medicine
Jiyeon Lim

단일 용량 조영제를 사용한 3 T 자기공명 지연 조영 영상

-고식적 이중 용량 1.5 T 자기공명 지연 조영 영상과의 비교-

지도교수 이 활

이 논문을 의학석사 학위논문으로 제출함

2014년 10월

서울대학교 대학원

의학과 영상의학과 전공

임 지 연

임지연의 의학석사 학위논문을 인준함

2015년 1월

위 원 장 김 용 진 (인)

부위원장 이 활 (인)

위 원 박 은 아 (인)

Single Dose Gadolinium Contrast for 3 T Late Gadolinium Enhancement MRI

-Intra-individual Comparison with Conventional Double Dose at 1.5 T MRI-

by

Jiyeon Lim

A Thesis Submitted to the Department of Medical Science in Partial Fulfilment of the Requirements for the Degree of Master of Science in Medical Science (Major in Radiology) at the Seoul National University College of Medicine

January 2015

Approved by thesis committee:

Professor Yong-Jin Kim Chairman

Professor Whal Lee Vice Chairman

Professor Eun-Ah Park

ABSTRACT

Single Dose Gadolinium Contrast for 3 T Late Gadolinium Enhancement MRI

− Intra-individual Comparison with Conventional Double Dose at 1.5 T MRI −

Jiyeon Lim
Medical Science (Major in Radiology)
Seoul National University College of Medicine

Purpose: 3 T late gadolinium enhancement (LGE) imaging is expected to provide comparable image quality to 1.5 T even with reduction of gadolinium contrast, thanks to superior signal to noise ratio and longer T1 relaxation time of normal myocardium. This prospective study was designed to perform intra-individual comparison of 3 T MR with use of 0.1 mmol/kg of gadoterate meglumine to 1.5 T MR with use of 0.2 mmol/kg of the same gadolinium contrast for the assessment of myocardial infarction.

Materials and Methods: In this prospective study, a total of ten patients (M:F = 8:2; mean age, 62.5 ± 11.8 years) diagnosed as old myocardial infarction were examined at 3 T MR with single dose within two weeks after 1.5 T conventional double dose MR. A single representative short-axis image was acquired at three-time point temporal scans (10 minute, 15 minute and 20 minute) after

administration of gadolinium agent (Uniray, gadoterate meglumine, Dongkook Pharmaceutical Co., Ltd). Two contrast to noise ratios (CNRs) between infarcted and normal myocardium and between infarcted and left ventricular (LV) cavity were calculated and compared intra-individually at each temporal scan. Two independent readers assessed infarct size semiautomatically by using a threshold of 6 standard deviations above the mean signal intensity of the remote myocardium. The interobserver reproducibility was also evaluated using intraclass correlation coefficient (ICC).

Results: Despite the usage of single dose of gadolinium, the mean values of infarcted myocardium tended to be higher at 3 T MR than 1.5 T MR with double dose at each time scan. 3 T LGE images with the single dose of gadolinium showed no significant difference in CNR between infarcted and normal myocardium at each time scan (all, $p > 0.05$). The CNR between infarcted myocardium and LV cavity was significantly better at 10 minute scan, compared to that of 1.5 T double dose (12.4 ± 8.2 vs. 7.6 ± 4.5, $p = 0.049$) but there were no differences at 15 and 20 minute scan. The measurement of relative infarct size was not significantly different between 1.5 T and 3 T MR by both observers 1 and 2 (all, $p > 0.05$). Interobserver reproducibility was excellent at 3 T single-dose MR (ICC range: 0.962-0.968) and good or excellent at 1.5 T double-dose MR (ICC range: 0.769-0.866).

Conclusions: LGE imaging at 3 T with single-dose contrast is as effective as 1.5 T conventional double-dose MR for the delineation of infarcted myocardium from non-infarcted myocardium and is superior for detection of infarcted myocardium from blood cavity at 10 minute scan. Therefore, 3 T LGE imaging using a single dose of gadolinium is expected to not only reduce risk of nephrogenic systemic fibrosis but also help to delineate subendocardial infarction.

Keywords: Myocardial infarction, magnetic resonance imaging, 3 Tesla, contrast agent, gadolinium, image quality, infarct size

Student Number: 2013-21695

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CMR - cardiac magnetic resonance imaging

CNR - contrast-to-noise ratio

IR - inversion recovery

LGE - late gadolinium enhancement

LV - left ventricle

ROI - region of interest

SD - standard deviation

SI - signal intensity

INTRODUCTION

Cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) is widely considered as a gold standard for assessment of myocardial viability with high spatial resolution and has been proven to accurate correlation in comparison to the histopathologic results by triphenyltetrazolium chloride (TTC) stain in animal experiments (1-7). Recovery of contractibility of the hypokinetic segments of the ischemic myocardium can be predicted by CMR imaging by estimating transmurality of myocardial infarction, which is critical to guide revascularization therapy and prognostic prediction. Gadolinium-based agents have been generally used for delayed enhancement images of CMR. In acute or chronic condition of myocardial infarction, extracellular space is relatively increased and therefore, nonspecific extracellular gadolinium chelates could be more accumulated within the extracellular space, compared to the intact normal myocardial area. While the concentration of gadolinium in normal myocardium is washed out earlier, greater amount of gadolinium stays longer in the infarcted tissue. Consequently, it provides an opportunity for optimal visualization of the infarcted areas (1, 8-10). Up to now, CMR imaging has been predominantly performed at 1.5 Tesla (T), yielding clinically acceptable image quality. However, all of those studies with LGE were validated at 1.5 T MR with a conventional double-dose (0.2 mmol/kg) or more of gadolinium contrast agents, which exceeded the label-recommended dose (11). Unfortunately, the free gadolinium ions, released from gadolinium complexes, are known to have a high level of potential toxicity. Many current publications have proven dose-related association between

gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF) (12-17).

In recent years, commercially available MR systems with a higher magnetic field strength (3 T) and dedicated multi-element coils have become available for clinical applications. CMR imaging with LGE aided by the advantages of high-field strength imaging is expected to provide the capability to distinguish between the viable, hibernating and infarcted myocardium with high sensitivity and with strong pathophysiologic correlation (7). Although the problems derived from high field strength exist at 3 T, concerning amplified susceptibility artifacts, increased radiofrequency field inhomogeneity, dielectric resonance effects and higher specific absorption rate (SAR), 3 T CMR is currently considered as a promising tool for many clinical applications (18-20). Most of all, the major advantage in imaging at a higher field strength is attributed to an improvement in signal to noise (SNR). The signal intensity (SI) of MR generally shows quadratic increase as the static magnetic field strength (B_0) increases, while the noise exhibits the linear B_0 dependence. Therefore, a gain of doubled SNR would be expected when increasing the main magnetic field strength from 1.5 T to 3 T (18, 21). With an increase in the field strength from 1.5 T to 3 T, the longitudinal relaxation time (T1) of most tissues increases with the third root of the field strength (22). As normal myocardium at 3 T recovers more slowly, requiring longer TI, particularly on LGE imaging, the absolute signal difference between normal and infarcted myocardium can be maximized (22, 23). Hence, even with the reduced dose of gadolinium contrast 3 T MR with LGE is anticipated to provide comparable image quality to 1.5 T as well as to decrease the risk of NSF.

Many prior studies assessing image quality of LGE imaging at 1.5 T MR with the reduced dosage (0.1 mmol/kg or 0.15 mmol/kg) have achieved comparable image quality, owing to better delineation between the LV cavity and the infarcted myocardium compared to that with conventional double dose (11, 24-31). Until now, however, there has been very few study with 3 T MR using a single dose to evaluate either image quality or even infarct area quantification (32). In previous animal and human studies with 3 T CMR, various dosage of gadolinium contrast agents (ranging from 0.05 mmol/kg to 0.2 mmol/kg) (19, 32-35) have been empirically used. Feasibility of single dose of gadolinium at 3 T has not been validated yet.

Therefore, we hypothesized that 3 T CMR imaging with single-dose gadolinium agents would provide comparable CNR between infarcted and normal myocardium and better CNR between LV cavity and normal myocardium, and also the quantification of infarcted area would present high reproducibility subsequently due to better CNR between LV cavity and normal myocardium.

This prospective study was designed to perform intra-individual comparison of 3 T MR with use of 0.1 mmol/kg of gadoterate meglumine to 1.5 T MR with use of 0.2 mmol/kg of the same gadolinium contrast agent for assessment of myocardial infarction.

MATERIALS AND METHODS

The institutional review board of our hospital approved this prospective study and written informed consent was obtained from all patients before enrolment in the study.

Patients

All patients who were diagnosed as old myocardial infarction proven by the previous CMRs (32, 36) and referred to the Department of Radiology of our hospital for CMR were eligible for recruitment into this prospective study. Exclusion criteria were any renal impairment (glomerular filtration rate under 60 mL/min), known hypersensitivity to gadolinium agents, and general contraindications to MR imaging, including cardiac pacemaker, metal clips, and claustrophobia. A total of ten patients (M:F = 8:2; mean age, 62.5 ± 11.8 years; age range, 44-77 years) have been successfully enrolled, who underwent imaging at 1.5 T MR with conventional double dose first, followed by imaging at 3 T with single dose within two weeks.

MRI Protocol

All MR examinations were performed in both 1.5-Tesla MR scanner (Magnetom Sonata; Siemens Medical solutions, Erlangen, Germany) and 3-Tesla MR scanner (Trio; Siemens Medical Solutions, Erlangen, Germany) for all patients. All MR images were acquired during repeated end-expiratory breath-holds and were electrocardiographically retrospective gated.

After performing the scout images, LGE images were obtained with an inversion recovery (IR) turbo fast low-angle shot (FLASH) sequence that produces both magnitude-reconstructed and phase-sensitive images in both 1.5 T and 3 T MR scanners. We adjusted the scan parameters to be identical between two examinations for optimal comparison and the parallel imaging technique was not applied on both scans. The detailed scan parameters are listed in the Table 1. A single dose (0.1 mmol/kg) of gadolinium agent (Uniray, gadoterate meglumine, Dongkook Pharmaceutical Co., Ltd) for 3 T MR and double dose (0.2 mmol/kg) of for 1.5 T MR were injected at a flow rate of 2.0 ml/s followed by a saline flush of 20 ml at the same flow rate. After reviewing the each patient's previous CMRs, one radiologist (J.Y.L) selected the single representative short axis slice that best presented LGE of the infarcted myocardium in advance, and the selected short axis slice was identically performed at both 3 T and 1.5 T MR at 10, 15 and 20 minutes after contrast administration. The optimal inversion time (TI) was determined using a TI scout (TR/TE, 25/1.1 msec; flip angle, 50°; slice thickness, 8 mm; matrix: 192 × 72; in-plane resolution 4.8-1.4 mm^2; different TIs from 80-804 msec, 31 images for 1.5 T, TR/TE, 29/1.5 msec; flip angle, 35°; slice thickness, 8 mm; matrix: 192 × 78; in-plane resolution 3.8-1.2 mm^2; different TIs from 100-1007 msec, 26 images for 3 T), adjusted to obtain the maximal contrast between viable and infarcted myocardium at each temporal scan (TI range, 10 minute: 250-290 msec, 15 minute 250-310 msec, 20 minute: 300-330 msec for 1.5 T, 10 minute: 400-450, 15 minute: 420-470 msec, 20 minute: 450-480 msec for 3 T).

MR Image Analysis

Image Quality Assessment

On the short axis magnitude images, circular regions of interest (ROIs) were defined by one observer (J.Y.L) within the infarcted myocardium, remote normal myocardium and LV cavity. The mean values of SI values were measured within these regions. Noise was derived from the standard deviation (SD) of the SI of an ROI located in the background air (Figure 1). These ROIs were placed at the corresponding locations on the representative short axis images of both MR examinations. The CNR between the infarcted myocardium and normal myocardium ($CNR_{infarct\text{-}normal}$) was calculated using the following equation: $CNR_{infarct\text{-}normal} = SI_{infarcted\ myocardium} - SI_{normal\ myocardium}$ / noise. The CNR between the infarcted myocardium and LV cavity ($CNR_{infarct\text{-}LVC}$) was calculated using this following equation: $CNR_{infarct\text{-}LVC} = SI_{infarcted\ myocardium} - SI_{LV\ cavity}$ / noise), in which SI indicates the mean SI of an ROI located in each anatomic region. All processes were performed on a picture archiving and communication system (PACS; Infinitt, Seoul, Korea) workstation.

Infarct Quantification

Two experienced observers (E.A.P. and J.Y.L with 10 and 4 years of experience in CMR interpretation, respectively), blind to the field strength and the dosage of gadolinium contrast agent independently measured the area of LGE on the magnitude images in a random order by using the dedicated semiautomatic analysis program (CMR[42] Version 4.1, Circle Cardiovascular Imaging Inc., Calgary, Canada). As Figure 1 depicted, epicardial and endocardial contours and a ROI placed in remote, unenhanced myocardium were outlined manually twice by two observers, and the LGE area are defined by means of a threshold of 6 SD above the mean SI of remote, non-enhanced myocardium according to the previous studies

(26, 36-38). The papillary muscles and trabeculations were equally excluded on all ROIs. Based on the LGE measurements, the software program calculated the relative infarct size, which was expressed as percentage of the total left ventricular myocardium.

Statistical Analysis

The quantitative results of the two examinations were compared with each other using paired two-tailed Student *t* test after data distributions were examined for normality using the Kolmogorov-Smirnov test. Normally distributed data were expressed as the mean ± standard deviation. Interobserver reproducibility for the measurement of relative infarct size was evaluated by intraclass correlation coefficient (ICC) generated by a two-way random-effects model with an absolute agreement definition (0.0-0.40, poor; 0.41-0.60, moderate; 0.61-0.80, good; and 0.81-1.00, excellent correlation) (39) and Bland-Altman analysis. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Differences were considered significant when the *p* value was less than 0.05.

RESULTS

Details of demographic and clinical characteristics of all patients are listed in the Table 2. Scanning at both field strengths was well tolerated by all patients, and all images were acquired of sufficient quality for analysis. No problems with breath holding nor electrocardiographic gating were encountered.

Image Quality Assessment

The results of SI of the infarcted and normal myocardium and LV cavity are demonstrated in Table 3 in detail. Despite the usage of single dose of gadolinium, mean values of SIs of infarcted regions tended to be twice higher at each time scan at 3 T MR than 1.5 T MR with double dose but the statistical significance did not reach (all, $p > 0.05$). Also, all of the SIs of normal myocardium and LV cavity tended to be higher at 3 T than 1.5 T MR (Table 3 and Figure 2).

3 T LGE images with the single dose of gadolinium showed no significant difference in CNR between infarcted and normal myocardium at each time scan (all, $p > 0.05$). At 3 T MR with the single dose of gadolinium, the CNR between infarcted myocardium and LV cavity was significantly better at 10 minute scan, compared to double-dose 1.5 T MR. Even though they were statistically insignificant, 3 T LGE images also showed a tendency toward higher CNR between infarcted myocardium and LV cavity at both 15 minute and 20 minute (Table 4 and Figure 2). The representative two cases are exhibited in Figures 3 and 4.

Infarct Quantification

There was no difference in relative infarct size between 1.5 T with double-dose and 3 T with single-dose images (Table 5). Bland-Altman analysis (Figure 5) indicated that both MR exams had good agreement in measuring relative infarct size by observer 1 (mean bias, -0.8% ± 10.8, range -21.9 to 20.3%) and observer 2 (mean bias, 5.8% ± 10.0, range -13.9 to 25.5%). Table 6 summarized the ICC values between observers 1 and 2 regarding interobserver reproducibility for the quantification of relative infarct size. Interobserver agreement was excellent in all three time point scans at 3 T single-dose MR with statistical significance. On the other hand, interobserver reproducibility at 1.5 T with double-dose MR, was good or excellent.

Table 1. Scan parameters of MR

	1.5 T	**3 T**
FOV (mm)	271 x 300	271 x 300
Pixel size (mm)	1.2 x 1.8	1.2 x 1.8
Section thickness (mm)	6	6
Repetition time (msec)	8.8	5.3
Echo time (msec)	4.2	2
Flip angle (degree)	25	13
Scan time (sec)	12-17	7-13
Parallel imaging	Not applied	Not applied

Table 2. Patient characteristics

Patient characteristics	**n = 10**
Age (years)	62.5 ± 11.8
Gender (M/F)	8/2
Risk factors	
Hypertension	3
Diabetes mellitus	2
Hypercholesterolemia	1
Smoking	6
Coronary artery disease classification	
One vessel	1
Two vessels	2
Three vessels	7
Prior coronary artery bypass graft	9
Ejection fraction (%)	38.1 ± 8.6
End-diastolic volume (ml/m^2)	120.9 ± 32.0
End-systolic volume (ml/m^2)	76.3 ± 26.0
Average LV myocardial mass (g)	138.0 ± 51.0

Note. LV = left ventricle

Table 3. Signal intensity of 1.5 T double-dose and 3 T single-dose images (n = 10)

	1.5 T Double-dose	3 T Single-dose	*p* value
$SI_{infarct}$			
10 minute	47.9 ± 15.8	82.5 ± 29.0	0.992
15 minute	45.1 ± 14.8	88.3 ± 36.0	0.459
20 minute	48.1 ± 17.2	85.9 ± 30.4	0.469
SI_{normal}			
10 minute	6.6 ± 1.7	12.8 ± 7.4	0.084
15 minute	6.6 ± 1.4	11.5 ± 5.9	0.523
20 minute	6.9 ± 1.8	12.2 ± 7.3	0.368
SI_{LVC}			
10 minute	39.0 ± 13.4	59.6 ± 31.2	0.223
15 minute	32.1 ± 13.2	56.3 ± 28.4	0.598
20 minute	34.4 ± 14.4	50.2 ± 26.1	0.858

Note. Data are presented as means ± standard deviations.
SI = Signal intensity
LVC = Left ventricular cavity

Table 4. Comparison of CNR between 1.5 T double-dose and 3 T single-dose images (n = 10）

	1.5 T Double-dose	3 T Single-dose	*p* value
$CNR_{infarct\text{-}normal}$			
10 minute	35.4 ± 12.1	37.7 ± 10.9	0.592
15 minute	36.9 ± 12.2	37.6 ± 12.4	0.898
20 minute	40.6 ± 14.5	34.1 ± 11.0	0.187
$CNR_{infarct\text{-}LVC}$			
10 minute	7.6 ± 4.5	12.4 ± 8.2	0.049
15 minute	12.4 ± 5.9	16.1 ± 9.2	0.244
20 minute	14.3 ± 7.3	17.3 ± 8.3	0.257

Note. Data are presented as means ± standard deviations.
CNR = Contrast to noise ratio
LVC = Left ventricular cavity

Table 5. Quantification of relative infarct size (%) measured by observer 1 and 2 (n = 10)

	1.5 T double-dose	3 T single-dose	*p* value
Observer 1			
10 minute	27.7 ± 10.4	27.1 ± 11.7	0.820
15 minute	28.5 ± 13.2	30.9 ± 14.4	0.609
20 minute	28.1 ± 8.1	28.8 ± 8.1	0.838
Observer 2			
10 minute	33.8 ±10.7	29.0 ± 11.6	0.095
15 minute	37.2 ± 10.5	31.2 ± 12.8	0.069
20 minute	36.1 ± 12.0	29.5 ± 10.1	0.149

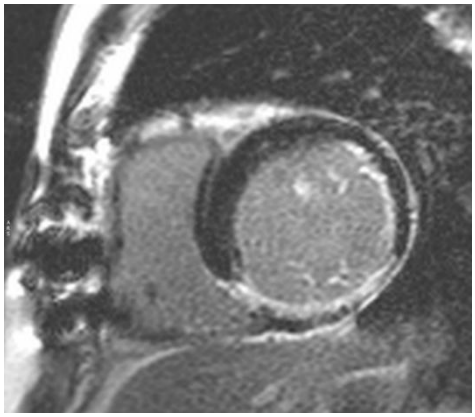
Note. Data are presented as means ± standard deviations.

Table 6. Interobserver reproducibility between 1.5 T double-dose and 3 T single-dose exams

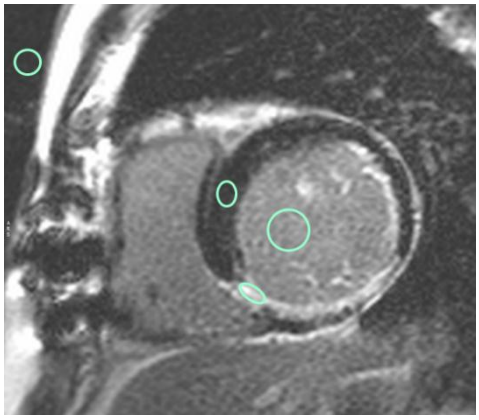
	Intraclass correlation coefficient (95% CI)			
	1.5 T double-dose	*p* value	3 T single-dose	*p* value
10 minute	0.866 (0.473-0.966)	0.003	0.962 (0.962-0.990)	< 0.001
15 minute	0.769 (0.024-0.943)	0.024	0.968 (0.873-0.992)	< 0.001
20 minute	0.796 (0.256-0.948)	0.010	0.967 (0.875-0.991)	< 0.001

Note. CI = Confidence interval

(A)



(B)



(C)

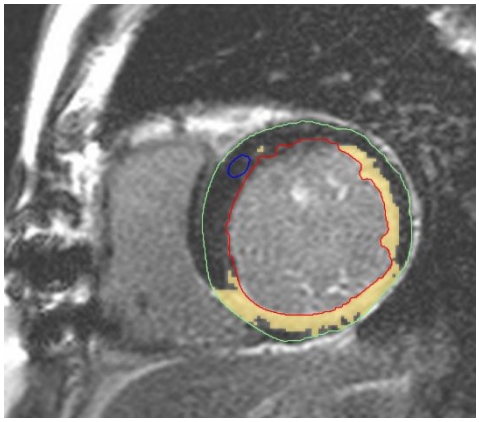
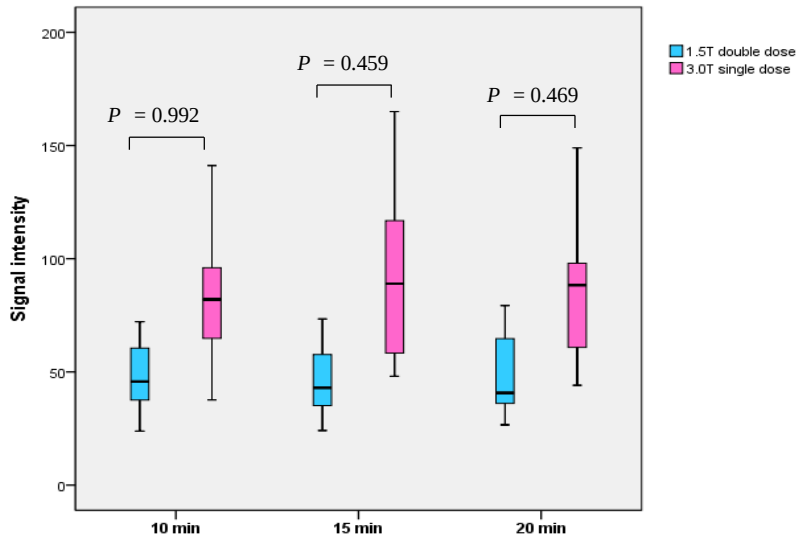
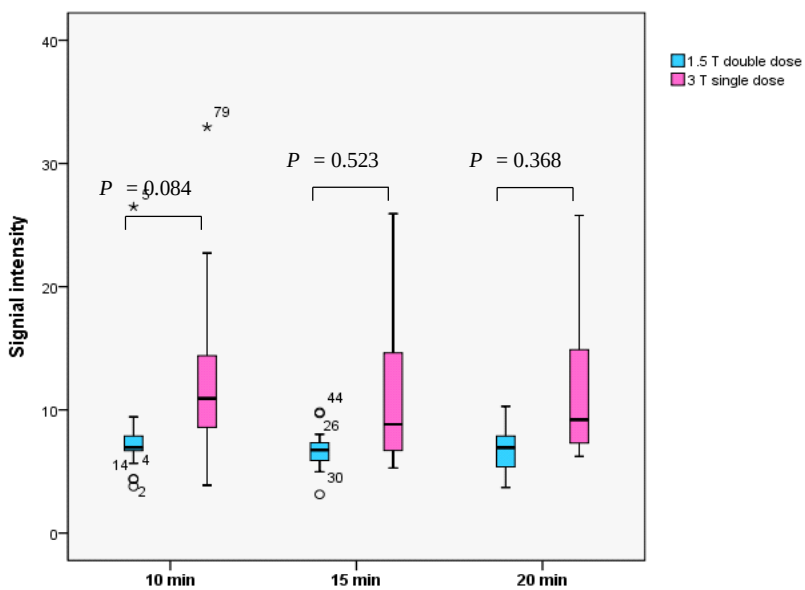


Figure 1. Assessment of SIs, CNR and infarct size on magnitude images. (A, B) SIs were determined in circular ROIs placed in remote normal and infarcted myocardium, and LV cavity. Noise was derived from the ROI located in the background air. (C) Assessment of infarct size of LGE by using the semiautomatic analysis software. A small blue circle indicates reference myocardium as normal remote myocardium. The infarct size was quantified by identifying myocardial areas with LGE, overlaid with yellow color, by means of a threshold of 6 SD above the mean SI of the remote, non-enhanced myocardium.

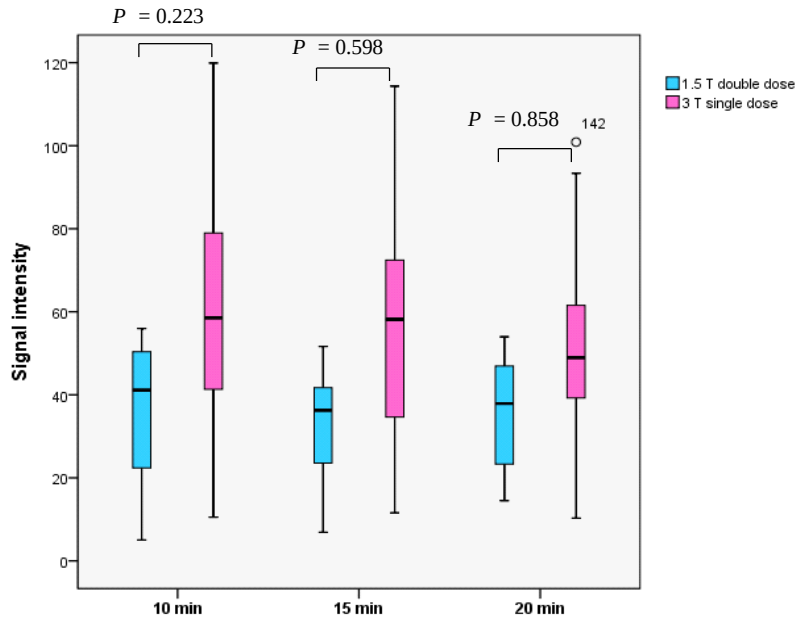
(A)


Signal intensity
200
150
100
50
0
P = 0.992
P = 0.459
P = 0.469
10 min
15 min
20 min
1.5T double dose
3.0T single dose

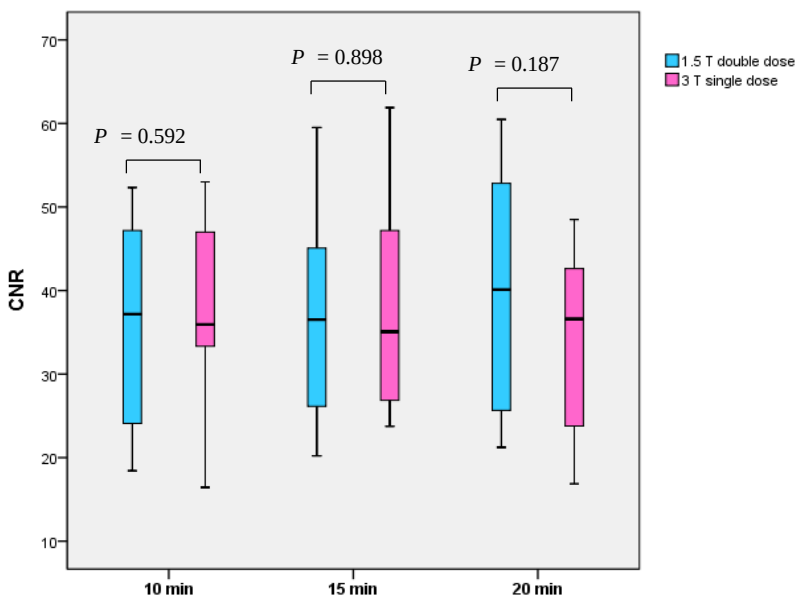
(B)


Signial intensity
40
30
20
10
0
P = 0.084
P = 0.523
P = 0.368
79
44
26
30
14
4
2
10 min
15 min
20 min
1.5 T double dose
3 T single dose

(C)


P = 0.223
P = 0.598
P = 0.858
142
1.5 T double dose
3 T single dose
Signal intensity
120
100
80
60
40
20
0
10 min
15 min
20 min

(D)


P = 0.592
P = 0.898
P = 0.187
1.5 T double dose
3 T single dose
CNR
70
60
50
40
30
20
10
10 min
15 min
20 min

(E)

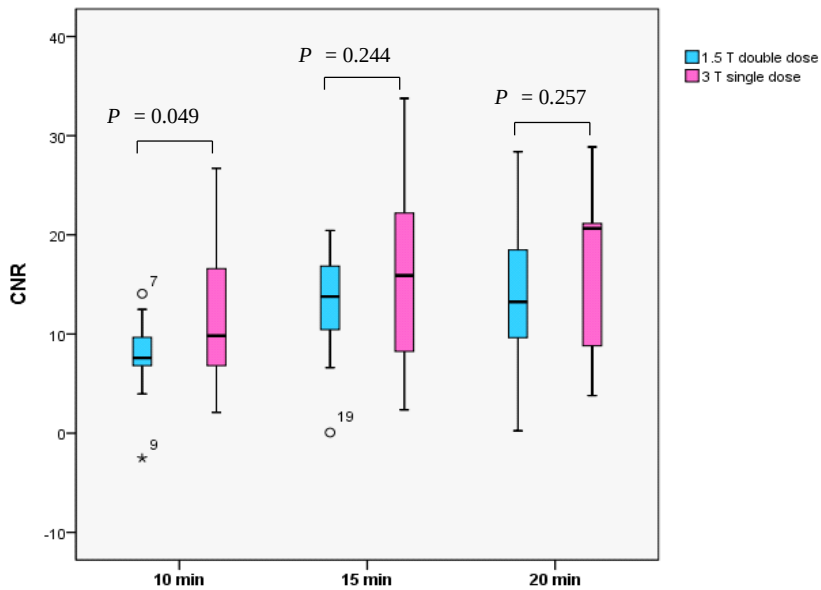


Figure 2. Box and Whisker plot shows the SIs of infarcted myocardium (A), remote unenhanced myocardium (B), LV cavity (C), $CNR_{infarct\text{-}normal}$ (D) and $CNR_{infarct\text{-}LVC}$ (E), comparing 1.5 T double-dose with 3 T single-dose images.

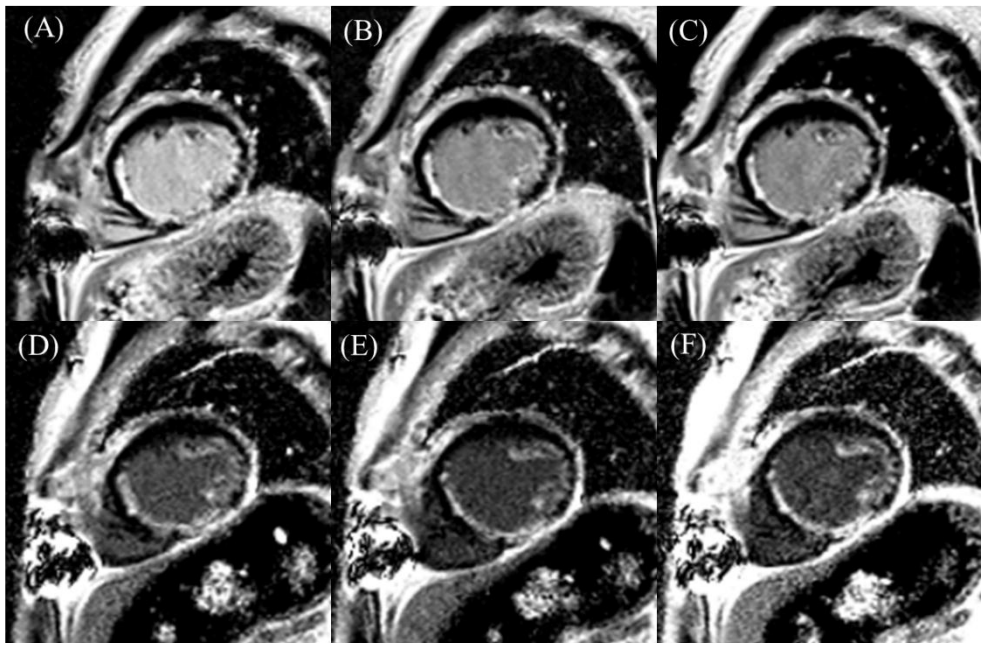


Figure 3. 71-year-old man. Delineation of the subendocardial infarction on LGE images with a 1.5 T double dose (A, B, C) and 3 T single dose (D, E, F) of gadolinium contrast agent. It is hard to delineate the border between subendocardial infarction and LV cavity because the bright blood cavity obscures subendocardial infarction at 1.5 T. On the other hand, delineation of endocardial border of infarction was much more improved at 3 T with single dose.

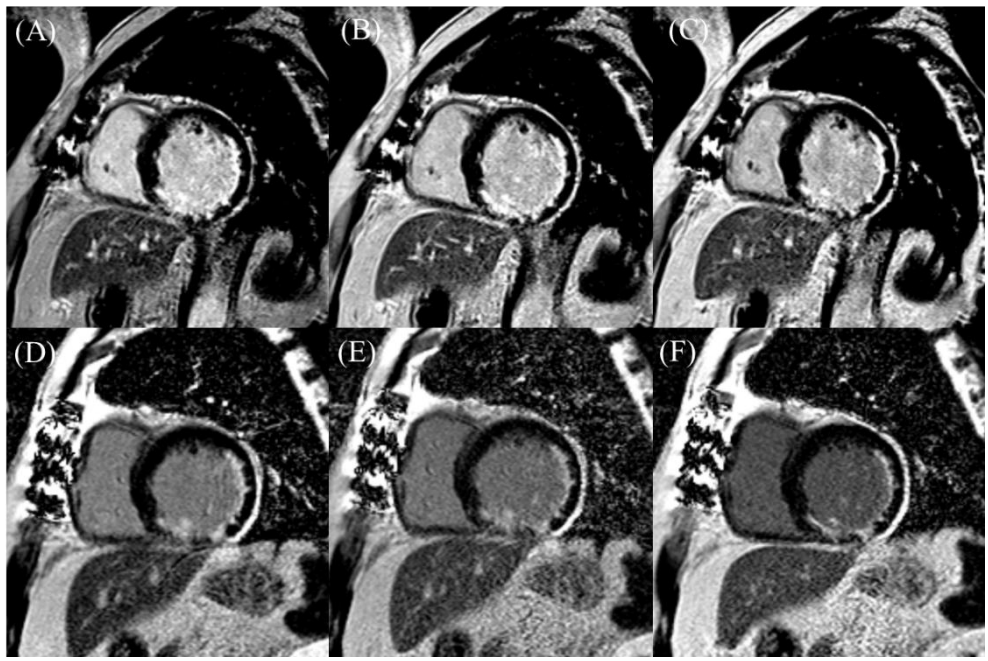
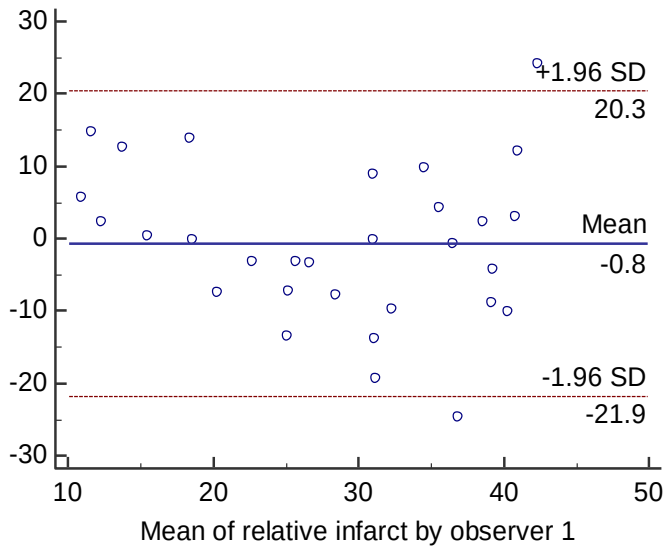


Figure 4. 59-year-old man. Delineation of the subendocardial infarction on LGE images with a 1.5 T double dose (A, B, C) and 3 T single dose (D, E, F) of gadolinium contrast agent. The greater signal difference between LV cavity and the subendocardial infarcted region on 3 T MR (D, E, F) enables to better delineation the infarcted myocardium, compared to 1.5 T MR (A, B, C).

(A)



(B)

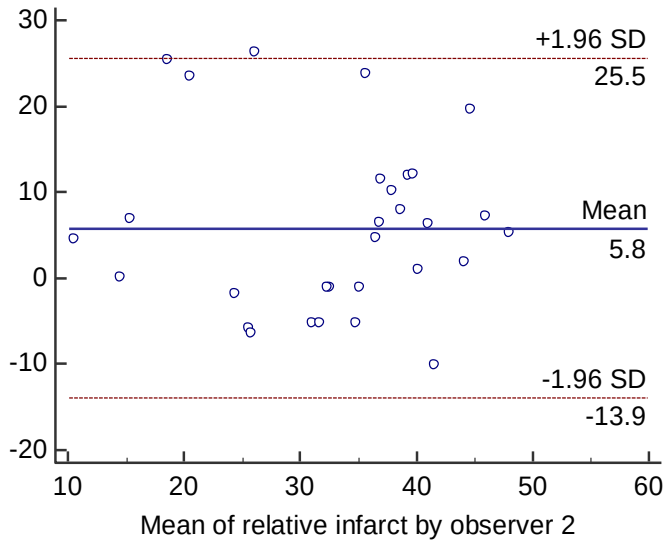


Figure 5. Bland-Altman analysis of relative infarct size measured by observer 1 and 2. Solid line = mean difference. Dashed lines = upper and lower limits of agreement.

DISCUSSION

This study is the first to demonstrate the feasibility of single dose 3 T MR, compared to double dose 1.5 T MR. The principal findings from our results can be summarized as follows: (a) CNR between the infarcted and normal myocardium at 3 T with single dose MR was comparable to that of 1.5 T. (b) CNR between infarcted myocardium and blood cavity was significantly higher at 10 minute scan of 3 T with single dose contrast than 1.5 T with double dose. (c) Regarding quantitatitive assessment of relative infarct size, 3 T MR showed excellent ICC values, while ICC values were good or excellent at 1.5 T MR.

Currently, technical advances that enhance the ability of MRI after administration of gadolinium based contrast agents have allowed to visualize pathological changes in the heart with enhanced spatial and temporal resolution and can improve the diagnostic capability of this modality for the diagnosis and characterization of myocardial infarction (1). Furthermore, CMR with LGE at higher magnetic field strength is a promising tool, which is beneficial for evaluation of myocardial viability, with a growing number of 3 T MR scanners being installed worldwide. In fact, recent studies have demonstrated notable improvement in image quality, SNR and CNR of LGE MR imaging at 3 T over 1.5 T (19, 40). One of the most appealing advantage of imaging at 3 T MR is a substantial gain in SNR (18), which may also be interpreted into an improvement in CNR between enhancing blood pool and non-enhancing background (41).

As the longitudinal relaxation time of unenhanced blood or background tissue substantially increases with field strength the signal recovery of those tissue

occurs more slowly at higher magnetization field, the T1 shortening effect of gadolinium agents may become more heightened, because the relaxivity of those contrast agents is only minorly affected between 1.5 T and 3 T magnetic fields. Accordingly, the increased efficacy of administrated gadolinium agents at 3 T allows to reduce the amount contrast agents without deteriorating the image quality, in theory. MR studies using single-dose gadolinium at 3 T have been validated in the field of angiography but there was no validation study for the evaluation of myocardial infarction to date. Similar to the design of our study, Herborn et al. (42) compared between single-dose contrast-enhanced MR renal angiography at 3 T and double-dose MR angiography at 1.5 T intraindividually and they proved that the difference in mean image quality was not statistically significant. Also, Kramer et al. (43) also demonstrated the feasibility of single-dose, time-resolved contrast-enhanced 3D MR angiography in assessment of the abdominal aorta and its major branches at 3 T. In particular, of our results, even though we reduced the dose of gadolinium contrast agent by half when performing 3 T MR imaging, all of the SIs of the infarcted and normal myocardium and the LV cavity in each time scan tended to be higher than those of 1.5 T double dose images. The major elements affecting these results can be explained as follows; (a) a gain of doubled SNR at 3 T (18), and (b) prolonged T1 relaxation time of the normal myocardium and increase in the efficacy of T1 shortening effect of gadolinium agents may result in maximizing the signal difference between the normal and infarcted myocardium (22, 23).

Conventionally, a double dose of contrast agent has been used because LGE was originally validated by animal experimental studies using a double dose of gadolinium contrast agent and the subsequent clinical studies were performed

using the same dose establishing substantially high image quality and diagnostic accuracy (1, 7, 10, 31, 44-47). However, it is an important issue in fact that gadolinium-based contrast agents may trigger the development of an extremely rare but serious complication, nephrogenic systemic fibrosis (NSF). In 2010, the U.S. FDA announced that label-recommended dose of the conventional gadolinium based-contrast agent (generally 0.1 mmol/kg) should not be exceeded in any patients (11). As gadolinium has to be chelated with appropriate ligands to be allowed to clinical use, these gadolinium complexes are linear or macrocyclic. Of various gadolinium-based contrast agents, gadoterate meglumine (Gd-DOTA) has the highest thermodynamic stability ($\log_{10} K_{THERM} = 25.6$), apparent stability ($\log_{10} K_{cond} = 19.3$), pharmacokinetic stability, and decomplexation of all available gadolinium-chelate agents (48, 49). Uniray (gadoterate meglumine, Dongkook Pharmaceutical Co., Ltd.), used for LGE in our study, is a macrocyclic ionic gadolinium-based contrast agent as well as a generic agent of Dotarem (gadoterate meglumine, Guerbet, Roissy CdG, France). It has been proven very safe even in the high-risk patients with impaired renal function and so far, to our knowledge, no validated cases of NSF have been documented yet, solely attributed to Gd-DOTA (48, 50-51). In this study, none of all patients have shown any sign of NSF and other adverse effects up to now.

There is another major concern in terms of the usage of a double dose of gadolinium contrast agents: brightened blood cavity may lead to obscure subendocardial infarction (8). This is a critical obstacle in detection of subendocardial infarction and in estimation of the exact infarct size some parts of subendocardial infarction may be misinterpreted as the LV cavity. According to a recent study reported by Kim et al. (24), they compared LGE images at 1.5 T MR

with single dose versus double dose, and found that CNR between the infarcted myocardium and LV cavity exhibited negative value when a double dose of gadolinium agent was used, which indicated that the LV cavity blood was much brighter than the infarcted myocardium. Also in our results, as we initially hypothesized, the CNR between the infarcted myocardium and the LV cavity was significantly higher at 10 minute exam at 3 T with single dose than at 1.5 T with a double dose of contrast agent. On the other hand, at 15 and 20 minute scans, CNR between the infarcted myocardium and the LV cavity was not significantly different, even though it showed a tendency to be higher at 3 T MR than 1.5 T MR. It suggests that bright blood cavity could be overcome by more delayed scan at double-dose 1.5 T but this can be a disadvantage due to longer scan time in clinical practice. Our results from the measurement of relative infarct size did not show any significant difference between two observers at both field strengths. Particularly, using 3 T MR, the quantification of infarcted area presented excellent interobserver agreement at each temporal scan. We suggested that it is because the more decrease in brightness of the LV cavity at 3 T MR with single dose than 1.5 T with double dose allowed accurate demarcation of the endocardial contour of infarcted area. Therefore, we finally suggest that the 3 T CMR imaging with single dose gadolinium agents can be feasible in clinical practice and has sufficient capability of the detection and precise quantitative measurement of myocardial infarction.

We recognize that the present study has several limitations. Major limitation is a small number of population for an adequate statistical work-up. Second, this study is a single center study. Third, to maintain the patent cohort uniformly, we only included the patients who diagnosed as old myocardial infarction confirmed by previous MR studies. Because the pathologic and patient

status are different between acute and chronic myocardial infarction, our results cannot be extrapolated in a group of acute myocardial infarction. Fourth, we did not evaluated diagnostic accuracy and detectability of LGE, because in all patients recruited in our study the presence of LGE regions was already confirmed on previous MR exams. Lastly, we only analyzed the magnitude images for the evaluation of the image quality. As the magnitude-reconstructed image is highly sensitive to the inversion recovery time, an error in selecting the precise nulling time can lead to a reduction in contrast between normal myocardium and enhancing tissue. Therefore, we determined the optimal nulling time of normal myocardium according to the TI scout performed only a few seconds before every temporal scan. We believe that optimal adjustment of TI could avoid any significant bias on the contrast of the magnitude images. In addition, since the phase-sensitive inversion recovery (PSIR) reconstruction fundamentally implements the process of spatial smoothing, applied to reduce the noise of reference image, the value of noise on PSIR images is known to not to indicate the true value (45).

CONCLUSION

LGE imaging at 3 T with single dose contrast is as effective as 1.5 T conventional double dose MR for delineation of the infarcted myocardium from the non-infarcted myocardium and is superior for detection of the infarcted myocardium from the blood cavity. Therefore, 3 T LGE imaging using a single dose of gadolinium is expected to not only reduce the risk of NSF but also might help to delineate subendocardial infarction by reducing the SI of the blood cavity.

ACKNOWLEDGEMENTS

This research was supported by grant no 06-2013-1390 from Dong-Kook Pharmaceutical Research Fund

REFERENCES

1. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med. 2000;343(20):1445-53.

2. Tillisch J, Brunken R, Marshall R, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. N Engl J Med. 1986;314(14):884-8.

3. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium". Journal of the American College of Cardiology. 1986;8(6):1467-70.

4. Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. Circulation. 1997;96(3):793-800.

5. Perrone-Filardi P, Pace L, Prastaro M, et al. Assessment of myocardial viability in patients with chronic coronary artery disease. Rest-4-hour-24-hour 201Tl tomography versus dobutamine echocardiography. Circulation. 1996;94(11):2712-9.

6. Chaudhry FA, Tauke JT, Alessandrini RS, Vardi G, Parker MA, Bonow RO. Prognostic implications of myocardial contractile reserve in patients with coronary artery disease and left ventricular dysfunction. Journal of the American College of Cardiology. 1999;34(3):730-8.

7. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999;100(19):1992-2002.

8. Kim RJ, Shah DJ, Judd RM. How we perform delayed enhancement imaging. J Cardiovasc Magn Reson. 2003;5(3):505-14.

9. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J. 2005;26(15):1461-74.

10. Fieno DS, Kim RJ, Chen EL, Lomasney JW, Klocke FJ, Judd RM. Contrast-enhanced magnetic resonance imaging of myocardium at risk: distinction between reversible and irreversible injury throughout infarct healing. Journal of the American College of Cardiology. 2000;36(6):1985-91.

11. Nacif MS, Arai AE, Lima JA, Bluemke DA. Gadolinium-enhanced cardiovascular magnetic resonance: administered dose in relationship to United States Food and Drug Administration (FDA) guidelines. J Cardiovasc Magn Reson. 2012;14:18.

12. Thomsen HS, Marckmann P, Logager VB. Nephrogenic systemic fibrosis (NSF): a late adverse reaction to some of the gadolinium based contrast agents. Cancer imaging : the official publication of the International Cancer Imaging Society. 2007;7:130-7.

13. DeHoratius DM, Cowper SE. Nephrogenic systemic fibrosis: an emerging threat among renal patients. Seminars in dialysis. 2006;19(3):191-4.

14. Cowper SE. Nephrogenic fibrosing dermopathy: the first 6 years. Current opinion in rheumatology. 2003;15(6):785-90.

15. Scheinfeld N. Nephrogenic fibrosing dermopathy: a comprehensive review for the dermatologist. American journal of clinical dermatology. 2006;7(4):237-47.

16. Abujudeh HH, Kaewlai R, Kagan A, et al. Nephrogenic systemic fibrosis after gadopentetate dimeglumine exposure: case series of 36 patients. Radiology.

2009;253(1):81-9.

17. Grobner T. Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2006;21(4):1104-8.

18. Wieben O, Francois C, Reeder SB. Cardiac MRI of ischemic heart disease at 3 T: potential and challenges. Eur J Radiol. 2008;65(1):15-28.

19. Klumpp B, Fenchel M, Hoevelborn T, et al. Assessment of myocardial viability using delayed enhancement magnetic resonance imaging at 3.0 Tesla. Invest Radiol. 2006;41(9):661-7.

20. Schar M, Kozerke S, Fischer SE, Boesiger P. Cardiac SSFP imaging at 3 Tesla. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine. 2004;51(4):799-806.

21. Fenchel M, Kramer U, Nael K, Miller S. Cardiac magnetic resonance imaging at 3.0 T. Topics in magnetic resonance imaging : TMRI. 2007;18(2):95-104.

22. Bottomley PA, Foster TH, Argersinger RE, Pfeifer LM. A review of normal tissue hydrogen NMR relaxation times and relaxation mechanisms from 1–100 MHz: dependence on tissue type, NMR frequency, temperature, species, excision, and age. Medical physics. 1984;11(4):425-48.

23. Haacke EM, Brown RW, Thompson MR, Venkatesan R. Magnetic resonance imaging. Physical principles and sequence design. 1999.

24. Kim YK, Park EA, Lee W, Kim SY, Chung JW. Late gadolinium enhancement magnetic resonance imaging for the assessment of myocardial infarction: comparison of image quality between single and double doses of contrast

agents. The international journal of cardiovascular imaging. 2014.

25. Balci NC, Inan N, Anik Y, Erturk MS, Ural D, Demirci A. Low-dose gadobenate dimeglumine versus conventional-dose gadopentate dimeglumine for delayed contrast-enhanced cardiac magnetic resonance imaging. Academic radiology. 2006;13(7):833-9.

26. De Cobelli F, Esposito A, Perseghin G, et al. Intraindividual comparison of gadobutrol and gadopentetate dimeglumine for detection of myocardial late enhancement in cardiac MRI. AJR American journal of roentgenology. 2012;198(4):809-16.

27. Bauner KU, Reiser MF, Huber AM. Low dose gadobenate dimeglumine for imaging of chronic myocardial infarction in comparison with conventional dose gadopentetate dimeglumine. Invest Radiol. 2009;44(2):95-104.

28. Wagner A, Mahrholdt H, Thomson L, et al. Effects of time, dose, and inversion time for acute myocardial infarct size measurements based on magnetic resonance imaging-delayed contrast enhancement. Journal of the American College of Cardiology. 2006;47(10):2027-33.

29. Durmus T, Schilling R, Doeblin P, et al. Gadobutrol for magnetic resonance imaging of chronic myocardial infarction: intraindividual comparison with gadopentetate dimeglumine. Invest Radiol. 2012;47(3):183-8.

30. Nacif MS, Kawel N, Lee JJ, et al. Interstitial myocardial fibrosis assessed as extracellular volume fraction with low-radiation-dose cardiac CT. Radiology. 2012;264(3):876-83.

31. Kim RJ, Albert TS, Wible JH, et al. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded,

randomized trial. Circulation. 2008;117(5):629-37.

32. Cheng AS, Robson MD, Neubauer S, Selvanayagam JB. Irreversible myocardial injury: assessment with cardiovascular delayed-enhancement MR imaging and comparison of 1.5 and 3.0 T--initial experience. Radiology. 2007;242(3):735-42.

33. Huber A, Bauner K, Wintersperger BJ, et al. Phase-sensitive inversion recovery (PSIR) single-shot TrueFISP for assessment of myocardial infarction at 3 tesla. Invest Radiol. 2006;41(2):148-53.

34. Gebker R, Jahnke C, Paetsch I, et al. Diagnostic performance of myocardial perfusion MR at 3 T in patients with coronary artery disease. Radiology. 2008;247(1):57-63.

35. Kino A, Zuehlsdorff S, Sheehan JJ, et al. Three-dimensional phase-sensitive inversion-recovery turbo FLASH sequence for the evaluation of left ventricular myocardial scar. AJR American journal of roentgenology. 2009;193(5):W381-8.

36. Flett AS, Hasleton J, Cook C, et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. JACC Cardiovasc Imaging. 2011;4(2):150-6.

37. Beek AM, Bondarenko O, Afsharzada F, van Rossum AC. Quantification of late gadolinium enhanced CMR in viability assessment in chronic ischemic heart disease: a comparison to functional outcome. J Cardiovasc Magn Reson. 2009;11:6.

38. Harrigan CJ, Peters DC, Gibson CM, et al. Hypertrophic cardiomyopathy: quantification of late gadolinium enhancement with contrast-enhanced cardiovascular MR imaging. Radiology. 2011;258(1):128-33.

39. Song YS, Choi SH, Park CK, et al. True progression versus

pseudoprogression in the treatment of glioblastomas: a comparison study of normalized cerebral blood volume and apparent diffusion coefficient by histogram analysis. Korean journal of radiology : official journal of the Korean Radiological Society. 2013;14(4):662-72.

40. Gutberlet M, Noeske R, Schwinge K, Freyhardt P, Felix R, Niendorf T. Comprehensive cardiac magnetic resonance imaging at 3.0 Tesla: feasibility and implications for clinical applications. Invest Radiol. 2006;41(2):154-67.

41. Schmitt F, Grosu D, Mohr C, et al. [3 Tesla MRI: successful results with higher field strengths]. Der Radiologe. 2004;44(1):31-47.

42. Herborn CU, Runge VM, Watkins DM, Gendron JM, Naul LG. MR angiography of the renal arteries: intraindividual comparison of double-dose contrast enhancement at 1.5 T with conventional dose at 3 T. AJR American journal of roentgenology. 2008;190(1):173-7.

43. Kramer U, Fenchel M, Laub G, et al. Low-dose, time-resolved, contrast-enhanced 3D MR angiography in the assessment of the abdominal aorta and its major branches at 3 Tesla. Academic radiology. 2010;17(5):564-76.

44. Hillenbrand HB, Kim RJ, Parker MA, Fieno DS, Judd RM. Early assessment of myocardial salvage by contrast-enhanced magnetic resonance imaging. Circulation. 2000;102(14):1678-83.

45. Kellman P, Arai AE, McVeigh ER, Aletras AH. Phase-sensitive inversion recovery for detecting myocardial infarction using gadolinium-delayed hyperenhancement. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine. 2002;47(2):372-83.

46. Ingkanisorn WP, Rhoads KL, Aletras AH, Kellman P, Arai AE. Gadolinium

delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. Journal of the American College of Cardiology. 2004;43(12):2253-9.

47. Setser RM, Chung YC, Weaver JA, Stillman AE, Simonetti OP, White RD. Effect of inversion time on delayed-enhancement magnetic resonance imaging with and without phase-sensitive reconstruction. Journal of magnetic resonance imaging : JMRI. 2005;21(5):650-5.

48. Ishiguchi T, Takahashi S. Safety of gadoterate meglumine (Gd-DOTA) as a contrast agent for magnetic resonance imaging: results of a post-marketing surveillance study in Japan. Drugs in R&D. 2010;10(3):133-45.

49. Idee JM, Port M, Raynal I, Schaefer M, Le Greneur S, Corot C. Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. Fundamental & clinical pharmacology. 2006;20(6):563-76.

50. Deray G, Rouviere O, Bacigalupo L, et al. Safety of meglumine gadoterate (Gd-DOTA)-enhanced MRI compared to unenhanced MRI in patients with chronic kidney disease (RESCUE study). European radiology. 2013;23(5):1250-9.

51. Herborn CU, Honold E, Wolf M, et al. Clinical safety and diagnostic value of the gadolinium chelate gadoterate meglumine (Gd-DOTA). Invest Radiol. 2007;42(1):58-62.

국 문 초 록

목적: 3 T 자기공명 영상 장치는 1.5 T 와 비교하여 우월한 신호 대 잡음 비와 더 길어진 정상 심근의 T1 이완 시간 덕분에 조영제의 양을 줄이더라도 고식적인 이중 용량을 쓴 1.5 T 자기공명 지연 조영 영상과 대등한 정도의 영상의 질을 제공할 수 있을 것이라는 예상이 되고 있다. 그러므로 이 연구에서는 단일 용량의 조영제를 사용하여 시행한 3 T 자기공명 지연 조영 영상을 고식적 이중 용량 조영제를 사용하여 시행한 1.5 T 자기공명 지연 조영 영상과 영상의 질을 비교하였다.

방법: 이 전향적 연구에서는 만성 심근 경색으로 진단 받은 총 10명의 환자 (남:여= 8:2; 평균연령, 62.5 ± 11.8 세) 를 대상으로 이중 용량의 조영제를 쓴 1.5 T 자기공명 영상을 획득한 후 이주일 이내에 단일 용량의 조영제를 사용한 3 T 자기공명 영상 검사를 시행하였다. 가돌리늄 조영제 (유니레이, 동국제약) 를 주입한 후 대표적인 한 개의 단축면 영상에 대해서 세 시점에서 (10분, 15분, 20분) 영상을 획득하였다. 경색 심근과 정상 심근의 대조 잡음 비와 경색 심근과 좌심실 내강 사이의 대조 잡음 비를 각각의 촬영 시점에서 개인 내에 비교를 하여 산출 하였다. 또한 두 관찰자가 각각 반자동 정량분석 프로그램으로 정상 심근과 6-표준편차 기준으로 심근경색 크기를 정량화 하였고, 급내 상관 계수 측정을 통하여 관찰자 간의 재현성을 평가하였다.

결과: 3 T 자기공명 영상에서 단일 조영제만을 사용하였음에도 모든

정상 또는 경색 심근과 심실 내강의 신호 강도가 이중 용량의 조영제를 사용하였을 때 보다 두 배 가량 높은 신호 강도를 보였다. 3 T 단일 조영제를 사용한 지연 조영 증강 영상에서 경색 심근과 정상 심근 간의 대조 잡음 비는 모든 촬영 시간 대에서 유의한 차이가 없었다. (모두, $p > 0.05$). 경색 심근과 좌심실 내강 사이의 대조 잡은 비는 10분 촬영에서 3 T 자기공명 지연 영상이 이중 용량을 사용한 1.5 T 영상 보다 유의하게 높은 결과를 보여주었으나(12.4 ± 8.2 대 7.6 ± 4.5, $p = 0.049$) 15분과 20분 촬영 영상에서는 유의한 차이가 없었다. 경색 크기의 정량화 결과는 두 관찰자 간에 1.5 T 와 3 T 에서 유의한 차이가 없었다 (모두, $p > 0.05$). 관찰자 간의 재현성은 3 T 단일 용량 조영제 급내 상관계수 범위: 0.962−0.968) 를 사용하였을 때 통계적으로 유의하게 모든 시간 대에서 이중용량을 사용한 1.5 T MR (급내 상관계수 범위: 0.769−0.866) 에 비해 우수하였다.

결론: 단일 용량의 조영제를 사용하여 시행한 3 T 자기공명 지연 조영 영상은 좌심실 내강 또는 정상 심근으로부터 경색 심근의 윤곽을 구분하는 데에는 이중 용량 조영제를 사용하여 시행한 1.5 T 자기공명 지연 조영 영상보다 우월하다는 결과를 보여주었다. 그러므로 3 T 자기공명 지연 조영 영상은 신원성 전신 섬유증의 위험을 감소시킬 뿐만 아니라 경색 심근의 감별에 도움을 줄 수 있을 것으로 기대한다.

주요어: 심근경색, 자기공명 영상, 3 테슬라, 조영제, 가돌리늄, 영상의 질, 경색 크기

학 번: 2013-21695