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Left Ventricular Infarct Size Assessed with 0.1 mmol/kg Gadobenate Dimeglumine (Gd-BOPTA) Correlates with 0.2 mmol/kg of Gadopentetate Dimeglumine (Gd-DTPA)

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Abstract

Objective—To determine myocardial infarct (MI) size during cardiovascular magnetic resonance (CMR) at 1.5 Tesla using 0.1 mmol/kg bodyweight of gadobenate dimeglumine (Gd-BOPTA) and 0.2 mmol/kg bodyweight of gadopentetate dimeglumine (Gd-DTPA).

Methods—Twenty participants (16 men, 4 women), aged 58 ± 12 years, with a prior chronic MI were imaged in a cross-over design. Participants received 0.2 mmol/kg bodyweight of Gd-DTPA, and 0.1 mmol/kg bodyweight of Gd-BOPTA on 2 occasions separated by 3 to 7 days

Results—The correlations were high between Gd-DTPA and Gd-BOPTA measures of infarct volume ($r=0.93$) and the percentage of infarct relative to LV myocardial volume ($r=0.85$). The size and location of the infarcts were similar ($p=0.9$) for the 2 contrast agents. Interobserver correlation of infarct volume ($r=0.91$) was high.

Conclusions—In chronic myocardial infarction, late gadolinium enhancement identified with a single 0.1 mmol/kg bodyweight dose of Gd-BOPTA is associated in volume and location to a double (0.2 mmol/kg body weight) dose of Gd-DTPA. Lower doses of higher relaxivity contrast agents should be considered for determining LV myocardial infarct size.

Keywords

myocardial infarction; contrast; ischemic heart disease

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INTRODUCTION

Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) imaging has been used to identify necrotic tissue or scar in the setting of chronic myocardial infarction (MI) (1,2). Currently, 0.2 mmol/kg (double-dose) per bodyweight of gadopentetate dimeglumine (Gd-DTPA) has been shown to have high histopathologic association with infarct size, and thus is used clinically at a CMR field strength of 1.5 T to identify infarcted tissue after chronic MI (3). Typically, voxels associated with infarcted tissue are defined as those exhibiting signal intensities >2 standard deviations above the average intensity observed in non-infarcted myocardium 10 to 20 minutes after Gd-DTPA administration (4).

Recently, concern has arisen related to the association of nephrogenic systemic fibrosis (NSF) and the administration of gadolinium chelates in patients with renal impairment. Some have suggested there may be an additional association between NSF and the amount of gadolinium administered (5,6,7). Gadobenate dimeglumine (Gd-BOPTA) is a relatively new paramagnetic contrast agent which produces two-fold higher T1 relaxivity compared with Gd-DTPA (8). For this reason, at 1.5 T, lower doses (0.1 mmol/kg) of Gd-BOPTA have been shown to be equivalent to higher doses of (0.2 mmol/kg) of Gd-DTPA in magnetic resonance angiography of the aorta and renal arteries (9). Importantly however, it is unknown whether a 0.1 mmol/kg dose would suffice for identifying LGE compared with 0.2 mmol/kg of Gd-DTPA. The purpose of this study was to determine the correlation between LGE observed after 0.1 mmol/kg bodyweight of Gd-BOPTA with that observed after a 0.2 mmol/kg bodyweight dose Gd-DTPA in participants with chronic infarcts.

MATERIALS & METHODS

Study Population and Design

This prospective study was approved by the Institutional Review Board at the home institution and met all criteria associated with the Health Insurance Portability and Accountability Act (HIPPA). Partial support for this study was provided by Bracco Diagnostics (Princeton, NJ), the manufacturer of Gd-BOPTA. All participants gave written informed consent. Twenty participants that sustained a prior MI of not < 3 months prior to enrollment were recruited between June and October of 2006. Myocardial infarction was defined according to previously published methods including: (a) an experience of chest pain, (b) an elevation of the cardiac enzyme creatine kinase (MB fraction) or cardiac Troponin I above the normal range for the assay, and (c) an ST-segment abnormality by electrocardiography consistent with an acute coronary syndrome (10). Exclusion criteria included pregnancy, age of < 18 years, New York Heart Association Class III or IV congestive heart failure, a serum creatinine value of > 2.0 mg/dl, or an implanted pacemaker, defibrillator, or intracranial metal.

A prospective, double-blind, cross-over design was implemented for the study. Each participant underwent a contrast-enhanced CMR study twice, with each exam separated by 3 to 7 days. During a single MRI exam, participants received either 0.2 mmol/kg bodyweight of Gd-DTPA (Magnevist, Berlex, USA), or 0.1 mmol/kg bodyweight of Gd-BOPTA (Multihance, Bracco Diagnostic., USA). A randomization code was used to ensure that 10 participants received Gd-DTPA at the first exam, and the other 10 participants received Gd-BOPTA during the first exam.

Imaging Procedure

Imaging was performed on a 1.5-Tesla MR system (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) with a phased-array receiver coil placed on the chest. Multislice coronal localizing images of the chest and the left ventricle were acquired. The apical long-

axis (3-chamber) view was then obtained using a cine white-blood steady-state free precession sequence with a 380 msec repetition time (TR), a 1.48 msec echo time (TE), and a 380mm field of view (FOV). Ten minutes following the contrast medium injection, an inversion time scout (TI Scout; Siemens Medical Solutions, Erlangen, Germany) sequence was performed, and an inversion time was selected that provided a uniform dark background in non-infarcted myocardium. Using this inversion time, multi-slice short-axis magnitude gradient-echo inversion recovery LGE images were obtained starting from the heart base to the LV apex (8 mm thick slices with 2 mm gap). Scan parameters included an 800 msec TR, a 4.18 msec TE, a flip angle of 25°, a 380 mm field of view, a 130 Hz bandwidth, a 256 × 192 matrix, and no flow compensation.

Infarct volume analysis

All images were reviewed and analyzed with a Cardiovascular Angiographic Analysis System (Pie Medical Imaging, Maastricht, Netherlands). The infarct volume was quantified by 2 investigators (with 4 years of experience in cardiovascular) blinded to results of one another by delineating regions of LGE across all of the multislice short axis acquisitions. Voxels defined as possessing LGE exhibited signal intensities that were >2 standard deviations above the average intensity observed in non-infarcted myocardium (1,4).

Signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR)

Signal-to-noise and CNR values were assessed by measuring the signal intensity (SI) in several regions of interest (ROI) on the magnitude LGE images. The ROI's were placed in normal myocardium (30 mm²), infarcted myocardium (10 mm²), the LV intracavitary space (100 mm²), and the air outside the body (500 mm²). Each ROI was placed on the same slice location acquired from both contrast studies. Noise was defined as the standard deviation of the SI of air outside the body.

Contrast to noise values were calculated using the following equations (11):

$$\begin{aligned}\text{CNR}_{\text{inf-normal}} &= (\text{SI}_{\text{inf}} - \text{SI}_{\text{normal}}) / N \\ \text{CNR}_{\text{inf-LVC}} &= (\text{SI}_{\text{inf}} - \text{SI}_{\text{LVC}}) / N\end{aligned}$$

in which $\text{CNR}_{\text{inf-normal}}$ was the CNR between infarcted myocardium and normal myocardium, SI_{inf} was the SI in infarcted myocardium, $\text{SI}_{\text{normal}}$ was the SI in normal myocardium, N was noise, $\text{CNR}_{\text{inf-LVC}}$ was the CNR between infarcted myocardium and the LV cavity, and SI_{LVC} was the SI in the LV cavity.

The SNR of infarcted tissue (SNR_{inf}) was calculated according to the following equation (11):

$$\text{SNR}_{\text{inf}} = \text{SI}_{\text{inf}} / N$$

Location of segments with LGE

Segments with LGE were correlated with those corresponding to coronary artery territories as defined by the American Heart Association (AHA) (12). Evidence of LGE within a coronary artery territory was defined as positive if LGE was evident in >1 segments within the respective territory. Agreement on the depiction of LGE achieved by the two contrast agents was determined using Cohen's kappa statistic.

Statistical Analysis

Continuous measures of overall infarcted volume and signal intensities, were assessed for the subjects using paired-analysis of acquired images with individuals blinded to the contrast agent administered. Paired t-tests were performed on the continuous measures of infarcted volume and signal intensities between the values measured at the first and second visits to identify any systematic mean changes between the two visits. If the mean values between the two visits were not significantly different, measures of agreement between the values measured using the two different contrast agents were not adjusted for a visit effect. For the continuous measures of infarcted volume and signal intensity, correlation and reliability coefficients were used to assess the agreement between values obtained using different contrast agents and between values obtained using the LGE technique. Also, the methods of Bland and Altman were used to compare differences between infarct volume and infarct volume as a percentage of LV volume between the two contrast agents (13). Pearson correlation coefficients were used to quantify whether one value could be predicted from another value (e.g., the value obtained using the first contrast agent versus the value obtained using the second contrast agent), and the degree of linear association between the two values obtained from the different agents. The degree that the two actual values agreed with each other was measured using the intra-class correlation coefficient of reliability (14). Agreement between three ordinal AHA defined territories of coronary artery disease using the two different contrast agents were summarized using Cohen's kappa statistic (15). The degree of agreement was defined as follow; Very Good = 0.81–1, Good = 0.61–0.80, Moderate = 0.41–0.60, Fair = 0.21–0.40, and Poor $\leq$ 0.20. To assess interobserver variability for identifying infarct size with the 2 contrast agents, 2 readers determined infarct volume and infarct volume as a percentage of LV myocardial volume during an unpaired reading of the images blinded to contrast agent, clinical data, and the results of each others analyses.

RESULTS

Twenty participants (16 men and 4 women) were enrolled (Table 1). The time from prior MI to CMR averaged 50 ± 65 months. Troponin levels and CKMB % at the time of each participant's infarct were 72.36 ± 101.85 U/L, and $15.79 \pm 15.53\%$, respectively. Upon review of the LGE images, the location of participant's prior MI was located into coronary artery territories ascribed by the AHA 17-segment model (12). This resulted in an infarct located in the distribution of the left anterior descending territory in 7 participants, the left circumflex coronary artery in 4 participants, and the right coronary artery in 8 participants.

The time of image acquisition after Gd-DTPA and Gd-BOPTA administration averaged 11.8 ± 3.7 , and 11.8 ± 3.4 minutes, respectively ($p = 1.0$). Mean inversion times of Gd-DTPA (244 ± 24 msec) were lower than that with Gd-BOPTA (263 ± 31 msec) ($p = 0.01$). Nineteen participants showed areas of LGE indicating prior MI. One subject with a clinical diagnosis of prior MI demonstrated no LGE by CMR with Gd-DTPA or Gd-BOPTA.

Infarcted volume analysis

On the CMR images, the mean ($\pm$ SD) for total (relative) infarcted volumes were not significantly different with values of 33.8 ± 20.2 mL ($20.6 \pm 10.0\%$) after administration of Gd-DTPA, and 32.8 ± 20.7 mL ($20.7 \pm 9.0\%$) after administration of Gd-BOPTA ($p = 0.68$ total volume, $p = 0.92$ relative volume). There was very good reliability with coefficients of 0.92 and 0.84 for total and relative volumes and a strong correlation was observed between the two contrast agents for the measurement of infarct volume in ml and as expressed as a percentage of the LV myocardial volume (Figures 1a and 1b). As shown in Figures 2a and 2b, the difference in infarct volume and infarct volume percent were small.

Signal to noise ratio (SNR) and contrast to noise ratio (CNR)

Images from participants with infarcted tissue are shown in Figure 3. The SI, SNR and CNR for both agents are shown in Table 2. No significant difference between contrast agents was noted for any quantitative enhancement parameter apart from the CNR determined between infarcted tissue and the blood pool within the LV cavity ($p=0.05$ as shown in Table 2).

Interobserver analysis

As shown in Figure 4, the correlation and reliability of assessment of LV infarct size was high between the 2 readers. Similarly, even though both readers had to account for the volume of 2 variables, infarct and LV myocardial volume, the relative infarct volume as a percentage of the total LV volume was also high for both readers. Importantly, both the correlation and reliability remained high regardless of the order of randomization in which the images were acquired.

Location of segments with DE

The agreement between the contrast agents for the identification of LV myocardial segments that corresponded to epicardial coronary artery territories as defined by the AHA model was good to very good. Kappa statistic values for the right coronary artery, left anterior descending artery and left circumflex territories were 1 ± 0 , 1 ± 0 and 0.60 ± 0.17 , respectively.

DISCUSSION

We compared a single 0.1 mmol/kg per bodyweight dose of Gd-BOPTA with a double (0.2 mmol/kg per bodyweight) dose of Gd-DTPA for the identification of LGE at 1.5 Tesla in subjects with chronic myocardial infarction. The results of our study show: a) that a single dose of Gd-BOPTA is highly associated with and similar ($p=0.68$) to a double dose of Gd-DTPA for the assessment of infarct volume in absolute (mL) and relative (% of LV myocardium) terms across a range of infarct volumes from small (2.7mL) to large (64.7mL); b) that measures of SNR and CNR between the infarct zones and normal myocardium are similar for the two agents at the administered doses; c) that in a blinded interobserver analysis, there is high correlation between 2 reader's assessment of infarct volume; and d) that a dose of 0.1 mmol/kg of Gd-BOPTA is similar to a dose of 0.2 mmol/kg of Gd-DTPA for the identification of myocardial segments with LGE across coronary artery territories defined by AHA criteria.

The relatively new paramagnetic contrast agent Gd-BOPTA exhibits partial hepatobiliary uptake and up to 2-fold higher T1 relaxivity in blood due to its relatively weak, transient interaction with serum albumin (16). Previously at 1.5T, Gd-BOPTA has been demonstrated to exhibit heightened delineation of liver tumors in adults, and visualization of central nervous system tumors in children when compared with Gd-DTPA (17,18). However, to date, there have been relatively few data at 1.5T utilizing single doses of Gd-BOPTA compared to double doses of Gd-DTPA for identifying the extent of necrotic tissue in patients who have sustained a chronic myocardial infarction.

A recent study by Schlosser, et al.(11), compared Gd-BOPTA at a double dose of 0.2 mmol/kg of bodyweight with an equivalent double dose of Gd-DTPA in 15 participants with myocardial infarction and found that in those with large infarcts, the size of the infarcts were similar between assessments made after Gd-BOPTA versus Gd-DTPA. Also however, their study concluded that delineation of subendocardial infarcts was more frequent with Gd-DTPA compared with Gd-BOPTA at a dose of 0.2 mmol/kg of bodyweight (11). This was secondary to the enhanced LV blood pool with Gd-BOPTA. A major criticism of Schlosser, et al.'s study was that the double dose of Gd-BOPTA that was utilized may have been excessive, resulting

in a paradoxical reduction of CNR (due to very high signal intensities within the blood pool) for the depiction of subendocardial infarcts (19).

This suggestion was further investigated by Balci, et al.(20), who compared a single 0.1 mmol/kg dose of Gd-BOPTA with a double 0.2 mmol/kg dose of Gd-DTPA in 23 participants with myocardial infarction and found no significant difference between the two agents in terms of the observed SNR, CNR, or SI enhancement of the infarcted myocardium (20). In contrast to Balci, et al.'s results, our data indicate a reduction ($p=0.05$) in CNR between the LV cavity and infarcted tissue exists at the lower dose (0.1mmol/kg) of Gd-BOPTA relative to the double dose of Gd-DTPA. This finding is similar to that noted by Schlosser, et al., using the double doses of Gd-BOPTA and Gd-DTPA. Although we have no data, we might speculate that the brightened blood pool occurs due to the transient interaction with albumen (causing increased bioavailability) rather than an increase in the total amount of gadolinium present as would occur in a double dose of contrast similar to that administered in Schlosser, et al.'s study. At present, the mechanism by which Gd-BOPTA retains its higher relaxivity in regions of myocardial fibrosis is not known.

Our findings have four possible clinical implications. First, it has recently been shown that identification of infarct volume is a strong predictor of recovery of LV systolic function after coronary arterial bypass grafting procedures in patients with a reduced LV ejection fraction due to chronic ischemic heart disease (21). Since our results indicate a high correlation between the two agents at their respective doses in measuring infarct volume, further studies should be performed to determine if 0.1 mmol/kg of Gd-BOPTA is efficacious for identifying improvement in LV systolic function after coronary arterial bypass grafting.

Second, infarct detection is frequently used with first-pass perfusion during adenosine stress testing (22). Typically, divided doses of contrast are administered during the stress and rest components of the study. Together, the total amount of contrast administered during both portions (rest and stress) of the study is used to identify LGE. If single dose Gd-BOPTA (0.1 mmol/kg bodyweight) were used to identify LGE in this setting, determination of the amount of contrast needed for the stress and rest perfusion components of the study needs clarification.

Third, because of the bright blood pool in the LV cavity associated with Gd-BOPTA administration, the potential exists to miss-identify small subendocardial regions of fibrosis. It is important to note that the potential clinical effect of this difference in CNR was negligible in this relatively small study. Further studies with larger numbers of participants with small subendocardial regions of fibrosis may clarify precisely the variance of Gd-BOPTA in identifying small, sub-endocardial infarcts. The results of our study show that a single dose of Gd-BOPTA correlates with a double dose of Gd-DTPA for determination of infarct volume (Figure 1), and that the agents are similar for appreciating the coronary artery territories in which prior myocardial infarction has occurred.

Finally, there is currently a great deal of concern among the medical community regarding the apparent association of NSF with the administration of gadolinium-based contrast agents to patients with renal failure (23). Both the type and dose of particular gadolinium contrast agents require further investigation. At present, it is recommended to limit the dose wherever possible (24). Although it has not yet been proven whether NSF is related to the dose or type of contrast agent administered, it is clear that if dose is an important factor in the pathophysiology of this disorder, the lower dose of Gd-BOPTA may be advantageous in individuals with chronic MI and marginally compromised renal function. In this regard, it should be noted that the 0.1mmol/kg dose of Gd-BOPTA is the FDA-approved dose for MR imaging of the central nervous system and related tissues. Conversely, the 0.2 mmol/kg dose of Gd-DTPA is not FDA approved for any indication.

This study has two principal limitations. First, there was no histopathologic data to serve as a reference standard for the determination of infarct size. However, given that 0.2 mmol/kg of Gd-DTPA has been validated in both animal and human studies for assessing infarct size (1, 4,25), it was felt that this agent at this dose could serve as the standard of reference for the current study. Based on the results of this study, it may also be worthwhile to perform further comparisons between single (0.1 mmol/kg) doses of Gd-BOPTA and Gd-DTPA. Second, long-term longitudinal follow-up for using LGE to identify prognosis with single dose of Gd-BOPTA during CMR is not available. This information requires additional study.

In conclusion, the size and location of a chronic myocardial infarction identified after administration of a single 0.1 mmol/kg dose of Gd-BOPTA correlates well with that observed after administration of a double 0.2 mmol/kg dose of Gd-DTPA. In situations where the amount of contrast is of concern, 0.1 mmol/kg Gd-BOPTA, rather than 0.2 mmol/kg of Gd-DTPA, may be sufficient for determining myocardial infarct size.

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Figure 1a: Infarct Volume

Figure 1b: Infarct volume percent

Figure 1. (Panels A & B). Scatterplots showing relation of total and relative infarcted volumes of gadopentate dimeglumine (Gd-DTPA – horizontal axes) and gadobenate dimeglumine (Gd-BOPTA-vertical axes). Each symbol represents data from 1 participant. The regression lines and equations are shown.

Figure 2a: Infarct volume using Bland/Altman analysis

Figure 2b: Infarct volume percent using Bland/Altman analysis

Figure 2. (Panels A & B). Scatterplots showing mean infarct volume (Panel A), and infarct as a percent of total LV myocardial volume (Panel B) identified after the administration of the 2 contrast agents. The mean values of the 2 agents are shown on the horizontal axes and the difference

between the 2 agents is shown on the vertical axes. Each symbol represents data from 1 patient. The mean difference (solid lines) and ± 2 standard deviations of the difference between the 2 agents (dashed lines) are shown.

Figure 3: Delineation of infarcts after gadolinium

Figure 3.

Late gadolinium enhancement (LGE) gradient-echo inversion recovery cardiovascular magnetic resonance images obtained in short axis planes of the left ventricle using a 800 msec TR, 4.2 msec TE, flip angle of 25°, a 38cm field of view and a 256 × 192 matrix. Inversion times were selected to provide a dark uniform background of non-infarcted myocardium.

Upper panels demonstrate a large transmural myocardial infarction involving the basal-anterolateral wall of the left ventricle (arrow heads). The top left panel demonstrates myocardial LGE after injection of 0.2 mmol/kg of Gd-DTPA; the top right panel demonstrates LGE after 0.1 mmol/kg of Gd-BOPTA.

Lower panels demonstrate small subendocardial LGE within the mid-inferolateral wall of the left ventricle (arrows). The lower left panel demonstrates myocardial LGE after injection of 0.2 mmol/kg of Gd-DTPA, and the lower right panel demonstrates the same after 0.1 mmol/kg of Gd-BOPTA.

Figure 4a: Correlation between Infarct Volume Measurements **Figure 4b: Reliability between Infarct Volume Measurements**

Figure 4.
(Panels A & B). Bar graphs of the correlation and reliability between Gd-DTPA and Gd-BOPTA infarct volumes for two separate readers blinded to the clinical data and results generated by one another.

Table 1**Participant Characteristics**

Women:Men	4:16	
Race - Cau:African/Amer.	18:2	
Age (years)	58 ±12 (range = 35 to 76)	
Height (cm)	171 ± 10.0 cm	
Weight (kg)	83.8 ± 17.5 kg	
Daily Medications	<u>No.</u>	<u>%</u>
• Aspirin	15	(.75)
• ACE inhibitor	12	(.60)
• β-blocker	13	(.65)
• Nitrate	4	(.20)
• Statin	15	(.75)
• Angiotensin II inhibitor	1	(.05)
• Diuretics	3	(.15)
Comorbidities	<u>No.</u>	<u>%</u>
• Diabetes	4	(.20)
• Hypertension	14	(.70)
• Hyperlipidemia	17	(.85)
• Tobacco	5	(.25)
• Obesity	1	(.05)

Table 2

Signal intensity (SI), contrast to noise ratio (CNR), and signal to noise ratio (SNR) values.

	Gd-DTPA	Gd-BOPTA	Difference	p-value
SI of normal myocardium	6.62 ± 1.28	6.54 ± 1.73	0.09 ± 1.86	0.84
SI of infarcted tissue	57.92 ± 17.59	55.10 ± 16.27	2.81 ± 10.86	0.27
SI of LVC	49.18 ± 15.22	55.10 ± 16.43	5.92 ± 13.62	0.54
SD of air (Noise)	1.67 ± 0.19	1.70 ± 0.23	0.03 ± 0.31	0.64
CNRinf-normal	31.61 ± 12.96	29.22 ± 10.66	2.40 ± 8.82	0.25
CNRinf-LVC	5.55 ± 7.12	2.40 ± 7.65	3.16 ± 6.62	0.05
SNRinf	35.63 ± 13.38	33.10 ± 11.13	2.53 ± 8.95	0.23

Abbreviations: LVC: Left ventricular cavity; SD : Standard deviation; CNRinf-normal: CNR between infarcted myocardium and normal myocardium; CNRinf-LVC: CNR between infarcted myocardium and the LV cavity; SNRinf: SNR of infarcted myocardium.