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Image quality of late gadolinium enhancement in cardiac magnetic resonance with different doses of contrast material in patients with chronic myocardial infarction

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Abstract

Background: Contrast-enhanced cardiac magnetic resonance (CMR) is pivotal for evaluating chronic myocardial infarction (CMI). Concerns about safety of gadolinium-based contrast agents favour dose reduction. We assessed image quality of scar tissue in CMRs performed with different doses of gadobutrol in CMI patients.

Methods: Informed consent was waived for this Ethics Committee-approved single-centre retrospective study. Consecutive contrast-enhanced CMRs from CMI patients were retrospectively analysed according to the administered gadobutrol dose (group A, 0.10 mmol/kg; group B, 0.15 mmol/kg; group C, 0.20 mmol/kg). We calculated the signal-to-noise ratio for scar tissue (SNR_{scar}) and contrast-to-noise ratio between scar and either remote myocardium ($CNR_{scar-rem}$) or blood ($CNR_{scar-blood}$).

Results: Of 79 CMRs from 79 patients, 22 belonged to group A, 26 to group B, and 31 to group C. The groups were homogeneous for age, sex, left ventricular morpho-functional parameters, and percentage of scar tissue over whole myocardium ($p \geq 0.300$). SNR_{scar} was lower in group A (46.4; 40.3–65.1) than in group B (70.1; 52.2–111.5) ($p = 0.013$) and group C (72.1; 59.4–100.0) ($p = 0.002$), $CNR_{scar-rem}$ was lower in group A (62.9; 52.2–87.4) than in group B (96.5; 73.1–152.8) ($p = 0.008$) and in group C (103.9; 83.9–132.0) ($p = 0.001$). No other significant differences were found ($p \geq 0.335$).

Conclusions: Gadobutrol at 0.10 mmol/kg provides inferior scar image quality of CMI than 0.15 and 0.20 mmol/kg; the last two dosages seem to provide similar LGE. Thus, for CMR of CMI, 0.15 mmol/kg of gadobutrol can be suggested instead of 0.20 mmol/kg, with no hindrance to scar visualisation. Dose reduction would not impact on diagnostic utility of CMR examinations.

Keywords: Contrast media, Gadobutrol, Gadolinium, Magnetic resonance imaging, Myocardial infarction

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Key points

- Late gadolinium enhancement is pivotal in assessing chronic myocardial infarction.
- Safety issues of gadolinium-based contrast agents advocate for dose reduction.
- Gadobutrol at 0.10 mmol/kg showed lower scar quality compared to higher doses.
- Gadobutrol at 0.15 mmol/kg provides comparable image quality to 0.20 mmol/kg.
- Gadobutrol at 0.15 mmol/kg can be suggested for assessing chronic myocardial infarction.

Background

Coronary heart disease is one of the main causes of morbidity and mortality, especially in developed countries, where it causes around 20% of all deaths [1]. The most common presentation of coronary heart disease is myocardial infarction, which is defined as the occurrence of necrosis in the setting of myocardial ischaemia [2].

Contrast-enhanced cardiac magnetic resonance (CMR) is a multi-parametric, multi-planar imaging technique, which represents the current non-invasive standard of care for assessing cardiac volumes, function and tissue characterisation through late gadolinium enhancement (LGE) [3, 4]. The importance of LGE may be found, among other reasons, in its prognostic potential [5]. Given its capability to monitor cardiac conditions, contrast-enhanced CMR may be useful in the evaluation of patients with chronic myocardial infarction, especially when the latter is transmural and of greater clinical relevance [6, 7]. Moreover, automatic scar quantification is growing in popularity due to the increase in numbers of examinations and the development of increasingly more reliable methods [8]. Scar recognition is most often based on image characteristics of the scarred area, such as signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) [9].

However, especially in the latest years, concerns about the safety of gadolinium-based contrast agents (GBCA) have arisen. In addition to the well-known issue of nephrogenic systemic fibrosis [10], gadolinium deposits of yet unknown clinical relevance have been shown in the brain of patients, adults and children, who underwent repeated GBCA-enhanced magnetic resonance examinations [11, 12]. This led to a growing attention concerning the possibility to reduce GBCA doses in such examinations, provided that scar quality is not hindered.

Patients with chronic myocardial infarction hence represent a population where GBCA dose reduction would lead to a lower chance of contrast-related adverse events. At present, GBCA doses used in these patients are variable among countries and centres, usually between 0.1 (single dose) and 0.2 (double dose) mmol/kg [13]. While in some countries, such as Japan, the single dose is

recommended, in most cases there are no specific indications [14]. All doses seem to provide diagnostic quality to examinations, albeit a reduction in scar visualisation corresponding to a lower contrast dosage might, for instance, hinder post-processing applications.

The purpose of our study was to analyse image quality of the scar tissue in CMR examinations performed with different GBCA doses in patients with chronic transmural myocardial infarction, to investigate the impact of gadolinium dose variation on the visibility of myocardial LGE quantified as SNR and CNR.

Methods

Ethical statement and study design

The local Ethics Committee approved this study (Ethics Committee of IRCCS Ospedale San Raffaele; protocol code “Cardioretro Ricerca Spontanea”; approved on September 14, 2017, and amended on July 18, 2019). This study was supported by local research funds of IRCCS Policlinico San Donato, a clinical research hospital partially funded by the Italian Ministry of Health. This research received no specific grant from funding agencies in the public, commercial, or non-profit sector. Due to the retrospective nature of this study, specific informed consent was waived.

Study population

All patients who had undergone a contrast-enhanced CMR examination with administration of gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany), at our institution between March 2014 (the introduction of our newer magnetic resonance unit) and May 2018, and who were diagnosed with chronic myocardial infarction from clinical findings and CMR, were included in our study. Exclusion criteria were the presence of oedema, indicating acute phase of infarction, presence of relevant artefacts which rendered differentiation of the myocardial scar difficult, and non-transmural, thin infarcts which were either only subendocardial ($\leq 50\%$ of wall thickness) or too small (scar $\leq 10\%$ of the myocardium), as such conditions do not allow the calculation of SNR and CNR of the scarred region [15]. Moreover, in patients with subendocardial infarction, image contrast may vary according to acquisition timing, and thus this may provide data that are not compatible with those of transmural scars [16].

Patients were then divided into three subgroups, depending on the contrast dose administered during their CMR: the first group (A) received 0.10 mmol/kg, the second (B) 0.15 mmol/kg, and the third (C) 0.20 mmol/kg. These different doses were mainly due to choices of the physicians in charge of the examination during the study period, not related to a specific patient's condition.

Image acquisition

All subjects were imaged using one 1.5-T whole-body magnetic resonance unit (Magnetom Aera, Siemens Healthineers, Erlangen, Germany) with 45 mT/m gradient power and an 18-channel surface phased-array coil. The examined patient was lying supine and the coil was placed over the thorax. All images were acquired with breath-holding and ECG gating.

The imaging protocol of all patients included cine and LGE sequences.

Cine images were acquired in multiple short- and long-axis planes using an ECG-triggered bright-blood steady-state free-precession pulse sequence.

LGE images were acquired after intravenous administration of 0.10, 0.15, or 0.20 mmol/kg of gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany) and were performed using a 2D segmented inversion-recovery fast gradient-echo sequence covering the entire left ventricle. Earlier exams utilised higher-contrast doses, which were then lowered over time. Nevertheless, the sequence for LGE imaging remained the same. The time of echo was 3.33 ms, while the time of repetition was adapted to patients' heart rates, and inversion time was progressively modified from 260 to 330 ms, to blacken cardiac muscle; flip angle was 25°, slice thickness 8 mm, and pixel size 3.6 mm². LGE images were reconstructed using magnitude reconstruction. From the R wave of the electrocardiogram, a delay period was used to ensure that image acquisition occurred in mid-diastole, when the heart is relatively motionless, therefore reducing motion artefacts. Data were acquired every other heartbeat, although in tachycardic patients data were acquired every third heartbeat, while in bradycardic patients and in patients with difficulties in breath holding acquisition was performed every heartbeat. Timing between contrast administration and acquisition of delayed enhancement scans was tailored to the contrast dose that was utilised in each case, according to literature recommendations [14].

Image analysis

Image analysis was performed using QMass 7.6 (Medis Medical Imaging Systems, Leiden, The Netherlands). The epicardial contour of the left ventricle was manually traced for all short-axis slices at end-diastolic and end-systolic phases in cine sequences. Afterwards, a blood-thresholding technique (Mass-K mode) was applied to automatically segment myocardium and blood pool. The software then calculated end-diastolic and end-systolic volumes, both indexed and non-indexed to body surface area, myocardial mass, stroke volume, and ejection fraction.

For LGE quantification, manual segmentation of endocardium and epicardium of the left ventricle was

performed in inversion recovery sequences after contrast agent injection. Then the software automatically detected the myocardial scar as being 6 standard deviations above average myocardial intensity [17]. Manual corrections were made when the software erroneously detected additional scarred areas, or when it failed to properly detect the scar. LGE was quantified as percentage over the whole myocardium. Two regions of interest were automatically placed in the scarred and healthy myocardium. An example of LGE segmentation is shown in Fig. 1.

SNR and CNR were calculated using data provided by automatic LGE quantification, namely intensities from the two ROIs automatically placed in the scarred and healthy myocardium, and two additional ROIs traced in the left ventricular blood pool and in the background air. SNR was calculated as $SNR = 0.655 \cdot \frac{\text{signal intensity}}{SD_{\text{background}}}$ according to a study by Kaufman et al. [18], while CNR was calculated as $CNR_{1/2} = \frac{|\text{signal intensity}_1 - \text{signal intensity}_2|}{SD_{\text{background}}}$. SNR was calculated on the scar tissue (SNR_{scar}), while CNR was calculated between scar tissue and remote myocardium ($CNR_{\text{scar-rem}}$), and between scar tissue and blood ($CNR_{\text{scar-blood}}$). Timings between contrast injection and acquisition of LGE sequences were also reported.

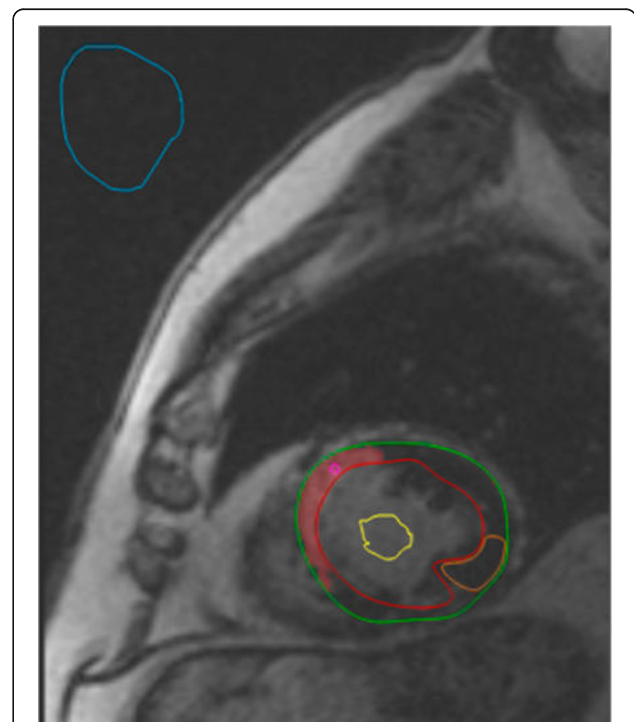


Fig. 1 Figure showing segmentation of the scarred myocardium in a 49-year-old male patient. Scarred myocardium is shown in red and is automatically segmented at 6 standard deviations above average signal intensity. Regions of interest placement is also depicted: those in the scarred (pink) and healthy (orange) myocardium are automatically placed during scar segmentation, while the ones in the blood pool (yellow) and air (blue) are manually placed on the same image

Subjective image quality was also analysed, using a 4-point Likert scale, defining score as follows: 0: non-diagnostic; 1: diagnostic exam, sufficient quality; 2: diagnostic exam, good quality; 3: diagnostic exam, excellent quality. The quality definition was based on the visual contrast differences between blood pool signal and LGE.

Statistical analysis

Data were reported as median and interquartile range (IQR). Differences between groups were appraised with Kruskal-Wallis test for numerical variables, and post hoc tests when a significant difference was appraised by Kruskal-Wallis test, or Fisher χ^2 tests for non-numerical variables.

Statistical analysis was performed with MATLAB R2018b (Mathworks, Natick, MA, USA), and p values ≤ 0.05 were considered statistically significant.

Results

Study population

Out of 124 patients who had undergone contrast-enhanced CMR at our institution, with gadobutrol as GBCA, 79 were included. The flowchart of exclusion is shown in Fig. 2. Out of the 79 included patients, 22 belonged to the group being administered 0.10 mmol/kg of gadobutrol (group A), 26 to the group being administered 0.15 mmol/kg of gadobutrol (group B) and 31 to the last group, which was administered 0.20 mmol/kg of gadobutrol (group C). There were no significant differences in either age or sex among the three groups ($p \geq 0.300$). Group demographics are summarised in Table 1.

The median acquisition time of LGE sequences was 9 min (IQR 8–13 min) for group A, 14 min (IQR 9–17 min) for group B and 17 min (IQR 14–20 min) for group C. Acquisition time showed a significant difference ($p < 0.001$) among groups; in particular, it did not differ

between group A and group B ($p = 0.105$), but was shorter in group B than group C ($p < 0.018$), and shorter in group A than in group C ($p < 0.001$).

Cardiac morphology and function

Left ventricular volumetric and functional data are reported in Table 1, along with myocardial scar burden quantified as percentage of scar tissue volume over the whole left ventricular volume. There were no significant differences in volumetric, functional or scar data.

Image quality

Images of LGE in patients belonging to the three different groups are shown in Fig. 3.

SNR_{scar} was 46.4 (IQR 40.3–65.1) in group A, 70.1 (IQR 52.2–111.5) in group B, and 72.1 (IQR 59.4–100.0) in group C. There was a significant difference in SNR_{scar} among groups ($p = 0.002$), in particular SNR_{scar} in group A was lower than both that of group B ($p = 0.013$) and group C ($p = 0.002$), while there was no significant difference in SNR_{scar} between group B and group C ($p = 0.884$).

$CNR_{scar-rem}$ was 62.9 (IQR 52.2–87.4) in group A, 96.5 (IQR 73.1–152.8) in group B, and 103.9 (IQR 83.9–132.0) in group C. There was a significant difference in $CNR_{scar-rem}$ among groups ($p < 0.001$), in particular $CNR_{scar-rem}$ in group A was significantly lower than both that of group B ($p = 0.008$) and group C ($p = 0.001$), while there was no significant difference in $CNR_{scar-rem}$ between group B and group C ($p = 0.871$).

$CNR_{scar-blood}$ was 25.5 (IQR 14.4–35.0) in group A, 32.7 (IQR 17.9–60.8) in group B, and 29.6 (IQR 18.2–53.5) in group C. There were no significant differences in $CNR_{scar-blood}$ among groups ($p = 0.335$).

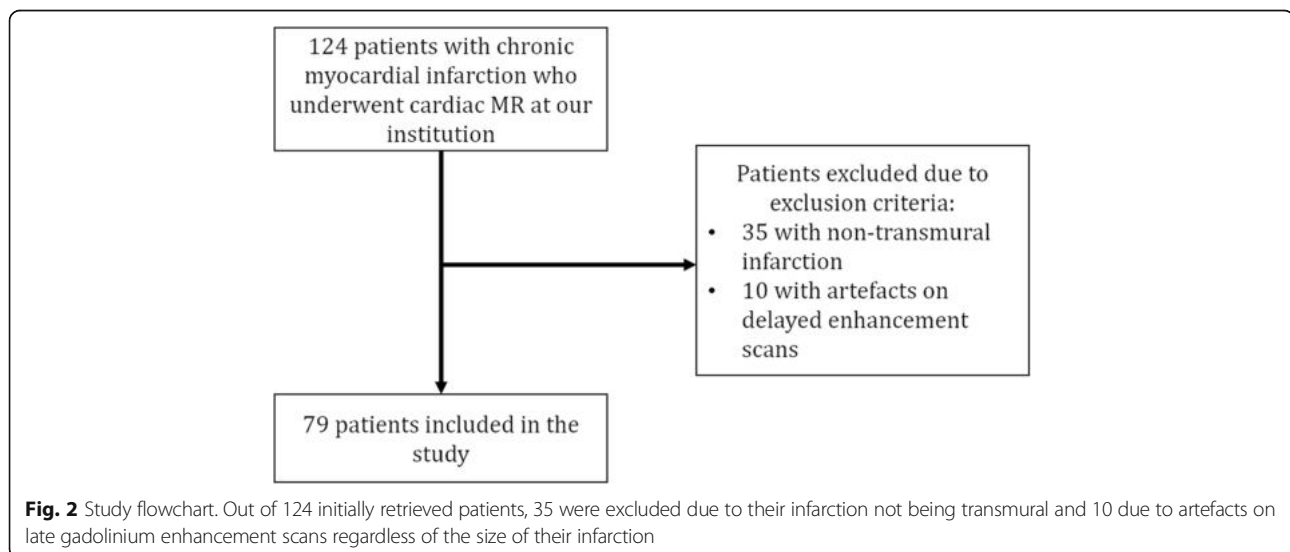


Table 1 Demographics, left ventricular function and volume, and scar data from the three study subgroups

	Group A	Group B	Group C	<i>p</i>
Number	22	26	31	–
Age (years)	68 (58–71)	62 (51–72)	60 (51–68)	0.300
Males (%)	95	92	90	0.811
LV EDVi (ml/m ²)	94 (75–118)	93 (73–107)	100 (80–126)	0.319
LV ESVi (ml/m ²)	58 (31–77)	56 (46–74)	63 (46–87)	0.472
LV SV (ml)	66 (46–78)	69 (60–86)	70 (62–83)	0.410
LV EF (%)	38 (28–46)	38 (31–47)	37 (30–45)	0.800
LV Mi (g/m ²)	89 (81–116)	91 (77–114)	92 (77–102)	0.961
LGE (%)	32.5 (21.7–38.1)	30.9 (23.0–42.4)	31.1 (25.5–44.0)	0.594

EDVi End-diastolic volume indexed to body surface area, EF Ejection fraction, ESVi End-systolic volume indexed to body surface area, LGE Percentage of scar represented as late gadolinium enhancement over the myocardial mass, Mi Myocardial mass index, SV Stroke volume. Kruskal-Wallis test was used

Box plots of SNR_{scar} , $\text{CNR}_{\text{scar-rem}}$, and $\text{CNR}_{\text{scar-blood}}$ across the three groups are depicted in Fig. 4, and data are reported in Table 2.

Concerning subjective image quality, no exams were non-diagnostic (Likert score 0), 7 exams displayed sufficient quality (Likert score 1), 24 exams good quality (Likert score 2), and 48 exams excellent quality (Likert score 3). In group A, 4 exams displayed sufficient quality, 7 good quality, and 11 excellent quality. In group B, 3 exams displayed sufficient quality, 7 good quality, and 16 excellent quality. In group C, 10 exams displayed good quality and 21 excellent quality. There were no significant differences in subjective image quality among groups ($p = 0.250$).

Discussion

The issue of GBCA dose reduction has become crucial in the last few years [19]. Among patients who undergo contrast-enhanced CMR, one of the main groups is represented by patients with chronic myocardial infarction, especially when the infarct is transmural and of greater clinical relevance [20]. In this study, we wished to ascertain whether lower GBCA doses resulted in lower scar image quality, or if there was room for dose reduction while preserving scar visibility. Even lower GBCA doses

guarantee diagnostic quality; however, especially given the rise of automatic post-processing methods, it may be important to preserve the highest possible scar discernment to ensure images can be utilised for such purposes. In fact, the quantification of LGE using standard deviations may be influenced by SNR and CNR, as lower SNR and CNR may signify that background noise has a higher impact on intrinsic signal intensity variations, and this may lead to less accurate scar detection, for instance using standard deviation-related systems.

Acquisition time was optimal in all groups, never exceeding 30 min as recommended by the literature [21]. Moreover, the differences in acquisition timings reflect the recommendations to obtain adequate image contrast according to the dose of contrast agent used [14]. Among our study groups, there were no significant differences in demographics or volumetric or functional left ventricle data and scar percentage over the whole myocardium. This would imply that none of these variables should have influenced the results of our research.

Concerning scar visibility, a lower SNR_{scar} (see Table 2) in group A than in both group B and group C could be due to the fact that a 0.10 mmol/kg GBCA dose was not sufficient to enhance the scarred myocardium in the same way as the two other doses, even though timing

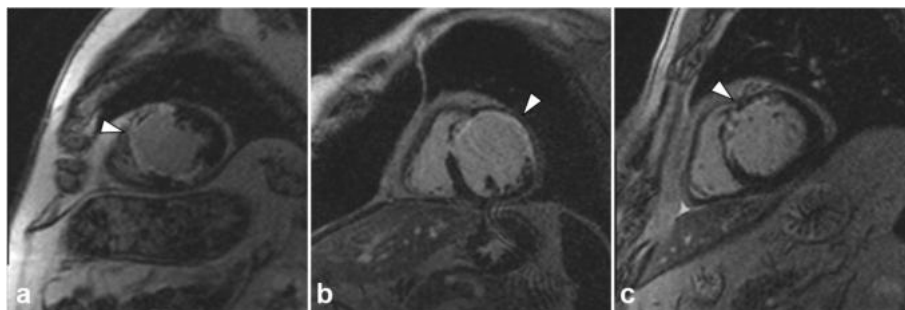


Fig. 3 Inversion recovery sequences for late gadolinium enhancement performed using 0.10 (a), 0.15 (b), or 0.20 (c) mmol/kg of gadobutrol, in male patients of 76, 54, and 49 years of age, respectively, matched for percentage infarct size

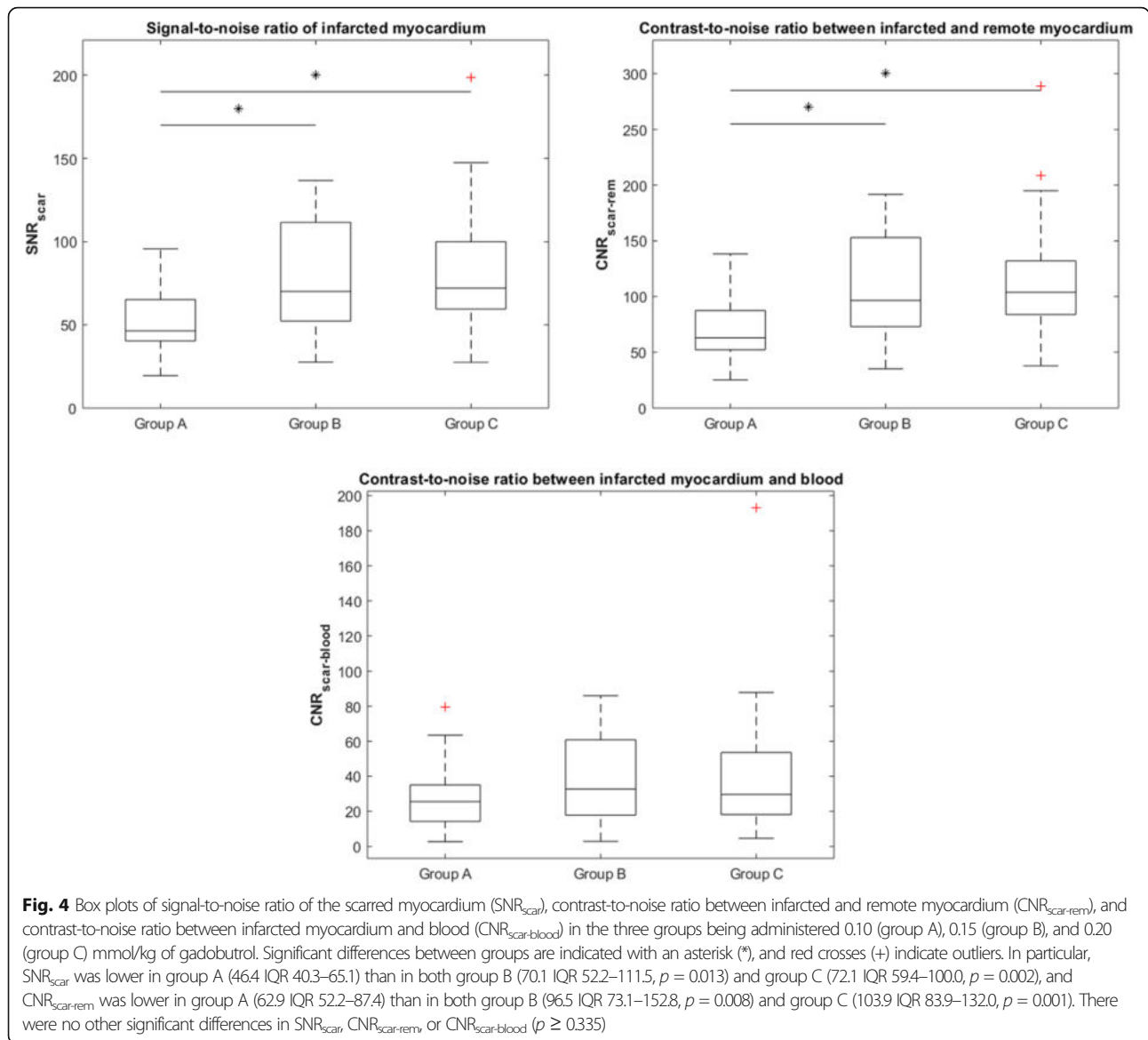


Table 2 Image quality and differences among the three groups according to the dose of gadobutrol used for late gadolinium enhancement

	Group A	Group B	Group C	<i>p</i> value (global)	<i>p</i> value (A versus B)	<i>p</i> value (B versus C)	<i>p</i> value (A versus C)
SNR_{inf}	46.4 (40.3–65.1)	70.1 (52.2–111.5)	72.1 (59.4–100.0)	0.002*	0.013*	0.884	0.002*
$CNR_{scar-rem}$	62.9 (52.2–87.4)	96.5 (73.1–152.8)	103.9 (83.9–132.0)	< 0.001*	0.008*	0.871	0.001*
$CNR_{scar-blood}$	25.5 (14.4–35.0)	32.7 (17.9–60.8)	29.6 (18.2–53.5)	0.335	–	–	–

Group A received 0.10 mmol/kg, group B 0.15 mmol/kg, and group C 0.20 mmol/kg of gadobutrol. $CNR_{scar-blood}$ Contrast-to-noise ratio between myocardial scar and blood, $CNR_{scar-rem}$ Contrast-to-noise ratio between scarred and remote healthy myocardium, SNR_{inf} Signal-to-noise ratio of the myocardial scar. Kruskal-Wallis and Fisher χ^2 tests were used

*Indicates statistical significance

was appropriate for LGE (median 9 min, IQR 8–13 min) [22]. This hypothesis is also supported by a lower $CNR_{scar-rem}$ (see Table 2) in group A than in both group B and group C. $CNR_{scar-blood}$ showed no differences (see Table 2) between group A and group B, in accordance with our hypothesis, since both the scarred myocardium and blood are enhanced by the same contrast dose and are still enhanced at the time of LGE acquisition. SNR_{scar} was not significantly different between group B and group C, neither did $CNR_{scar-rem}$ and $CNR_{scar-blood}$, suggesting that image quality between the two doses of 0.15 mmol/kg and 0.20 mmol/kg of gadobutrol is comparable.

Our results concerning SNR and CNR were not always similar to those obtained by other authors using the same doses of gadobutrol. At 0.10 mmol/kg, our SNR_{blood} was lower than that obtained for by De Cobelli et al. [23] using gadobutrol 0.10 mmol/kg on a group of patients with mixed pathologies exhibiting LGE. Our $CNR_{scar-rem}$ was on average slightly lower than theirs but overlapping to a certain degree due to the wide range of distributions; conversely, our $CNR_{scar-blood}$ was higher. Their method of calculating SNR was equal to ours except for the lack of the 0.655 adjusting factor which would indeed lower our SNR compared to theirs. Their method of calculating CNR was equal to ours. Concerning 0.15 mmol/kg, both $CNR_{scar-rem}$ and $CNR_{scar-blood}$ were higher than those obtained by Durmus et al. [24] utilising gadobutrol at 0.15 mmol/kg with a 15-min delay to LGE scan. Durmus et al. used the same method for calculating CNR as our study. However, we should consider that our study only included transmural infarctions, while these authors did not exclude patients by scar size. Concerning the comparison of objective image quality parameters, while studies have assessed the differences between different contrast agents at different doses [25, 26], to our knowledge none have yet compared different gadobutrol doses.

This study has some limitations, the first being its retrospective design. Results refer to the specific sequence for LGE used at our centre, and to gadobutrol. However, fast inversion-recovery gradient-echo sequences are widely used in clinical practice, and our timings for LGE are aligned to recommendations [21]. On the other hand, gadobutrol is commonly used in CMR [13], it has a double concentration (1.0 M) in comparison with all other vascular/interstitial GBCAs and exhibits an r1-relaxivity relatively higher. However, the double molarity should not impact on LGE findings (obtained after about 10 min after injection), especially concerning SNR and $CNR_{scar-rem}$, as observed by Wildgruber et al. [26], while the clearance of each single GBCA might impact on $CNR_{scar-blood}$. Conversely, since the relatively higher relaxivity of gadobutrol may have positively impacted objective image quality of

LGE imaging, as also reported by Schlosser et al. [27], the results obtained for gadobutrol may not be generalizable to GBCAs with a lower relaxivity. Another potential limitation could be posed by the variability of the placement of the regions of interest in the different areas. Nevertheless, the two regions of interest in scarred and healthy myocardium, which were the ones that could carry more issues, were automatically placed by the scar quantification software, and the ones in the air and the blood pool, which were hand-drawn, brought less difficulties. One further limitation, related to the retrospective nature of the study, is represented by the method used for SNR and CNR calculation. In fact, with the only availability of LGE sequences for the assessment of such parameters, the lone viable method for SNR and CNR calculation depended on the use of ROIs placed on the desired structures and background. However, this method has shown to provide the highest variability on SNR in a study by Dietrich et al. [28]. An ideal method for SNR and CNR calculation would perhaps be the one presented by Holtackers et al. [29], who utilised subsequent acquisitions of the same sequence using different inversion times. Nevertheless, we utilised the same sequence for all patients, thus variations in SNR and CNR should be of a systematic nature, thus preserving statistical significance of the observed differences.

In conclusion, results from our study suggest that, while 0.10 mmol/kg of gadobutrol provides inferior scar image quality of CMI than 0.15 and 0.20 mmol/kg, the last two dosages seem to provide similar LGE. In view of a global trend of standardisation and reduction of GBCA doses, 0.15 mmol/kg of gadobutrol could be suggested instead of 0.20 mmol/kg, with no hindrance to image quality. Further studies should be conducted to evaluate whether lower GBCA dosages provide a high enough scar quality for clinical evaluations. This would pave the way for further GBCA dose reduction which may impact on image quality, but not on diagnostic utility of CMR examinations.

Abbreviations

CMR: Cardiac magnetic resonance; CNR: Contrast-to-noise ratio; $CNR_{scar-blood}$: Contrast-to-noise ratio between scar tissue and blood; $CNR_{scar-rem}$: Contrast-to-noise ratio between scar tissue and remote myocardium; GBCA: Gadolinium-based contrast agents; IQR: Interquartile range; LGE: Late gadolinium enhancement; SNR: Signal-to-noise ratio; SNR_{scar} : Signal-to-noise ratio of scar tissue

Authors' contributions

FSa, FSe, and MC contributed to the study design. CM, AC, LS, and FSe performed and reviewed image post-processing. CM, MC, and MA performed statistical analysis. All authors participated to manuscript drafting and reviewing. All authors read and approved the final manuscript.

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Availability of data and materials

All data obtained or analysed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of IRCCS Ospedale San Raffaele (protocol code "Cardioretro", approved on September 14, 2017, and amended on July 18, 2019). Due to the retrospective nature of this study, specific informed consent was waived.

Consent for publication

As stated in the "Ethics approval and consent to participate" section, consent for publication was also waived due to the retrospective nature of this study.

Competing interests

Caterina Beatrice Monti, Marina Codari, Andrea Cozzi, Marco Ali, Lorenzo Saggiante, and Francesco Secchi all declare that they have no competing interests. Francesco Sardanelli has received research grants from and is a member of the speakers' bureau and of the advisory group for General Electric, Bayer, and Bracco. In addition, Francesco Sardanelli is the Editor-in-Chief of *European Radiology Experimental*; for this reason, he was not involved in any way in the revision/decision process, which was completely managed by the Deputy Editor, Dr. Akos Varga-Szemes (Medical University of South Carolina, Charleston, SC, USA).

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