

## SHORT COMMUNICATION

# Quantitative analysis of cardiac left ventricular variables obtained by MRI at 3 T: a pre- and post-contrast comparison

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**ABSTRACT.** Short-axis cine images are acquired during cardiac MRI in order to determine variables of cardiac left ventricular (LV) function such as ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and LV mass. In cardiac perfusion assessments this imaging can be performed in the temporal window between first pass perfusion and the acquisition of delayed enhancement images in order to minimise overall scanning time. The objective of this study was to compare pre- and post-contrast short-axis LV variables of 15 healthy volunteers using a two-dimensional cardiac-gated segmented cine true fast imaging with steady state precession sequence and a 3.0 T MRI unit in order to determine the possible effects of contrast agent on the calculated cardiac function variables. Image analysis was carried out using semi-automated software. The calculated mean LV mass was lower when derived from the post-contrast images, relative to those derived pre-contrast (102 vs 108.1 g,  $p < 0.0001$ ). Small but systematic significant differences were also found between the mean pre- and post-contrast values of EF (69.4% vs 68.7%,  $p < 0.05$ ), EDV (142.4 vs 143.7 ml,  $p < 0.05$ ) and ESV (44.2 vs 45.5 ml,  $p < 0.005$ ), but no significant differences in SV were identified. This study has highlighted that contrast agent delivery can influence the numerical outcome of cardiac variables calculated from MRI and this was particularly noticeable for LV mass. This may have important implications for the correct interpretation of patient data in clinical studies where post-contrast images are used to calculate LV variables, since LV normal ranges have been traditionally derived from pre-contrast data sets.

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Cardiac MRI (CMRI) is a reproducible [1], non-invasive tool which provides a rapid and accurate [2, 3] cardiac assessment in any desired imaging plane without the use of ionising radiation. CMRI is considered by many to be the reference standard for the assessment of left ventricular (LV) variables [4] such as volumes, mass and function, with steady-state free precession (SSFP) currently being considered as the sequence of choice for carrying out such assessments [5].

It is possible to obtain cardiac images of good diagnostic quality in high-field MRI without the need for gadolinium (Gd)-based contrast agents; however, contrast agents are required during cardiac perfusion to aid the evaluation of different patterns of myocardial scarring seen in myocardial infarctions and cardiomyopathies [6]. In such cardiac studies, the short-axis images used to derive ventricular volumes and mass

measurements are usually acquired before the administration of contrast agent. In studies where perfusion analysis is required, there is a temporal window of approximately 10–15 min available between “first pass” and “delayed enhancement” acquisitions. This provides the opportunity to obtain short-axis LV data sets during this period, thus minimising the length of time that the patient is in the scanner.

Results of previous studies have identified that the contrast conditions at the left ventricle can influence the magnitude of the resulting LV parameters. For example, a previous comparison of spoiled-gradient echo and steady-state gradient echo sequences for the assessment of LV function identified significant differences in the resulting LV variables [7]. Other studies have also investigated the use of inversion recovery gradient-echo (IR-GRE) techniques for combined post-contrast perfusion and LV mass analysis in patients [8, 9] and these have been compared with pre-contrast SSFP methods. In the latter of these reports, significant LV mass differences were identified between IR-GRE and SSFP for pre- and post-contrast LV mass assessment, with SSFP being

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validated as the more accurate measure of LV mass using *ex vivo* methods.

To date, previous assessments of pre- and post-contrast LV variables have been undertaken using different pulse sequences. With this information in mind, our aim was to establish if differences between LV variables might exist on the basis of whether the data were collected before or after the delivery of a Gd contrast agent, using a single pulse sequence only (SSFP). This study specifically addresses LV analysis at 3 T in order to determine what effect the administration of contrast agent has on the calculated measurement of ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and LV mass. A correct understanding of any such differences is deemed important, since MRI-derived normal human left and right ventricular ranges are routinely defined from pre-contrast short-axis images [10]. Identifying and acknowledging such differences may also allow the most appropriate post-scan clinical management of patients with LV dysfunction.

## Methods and materials

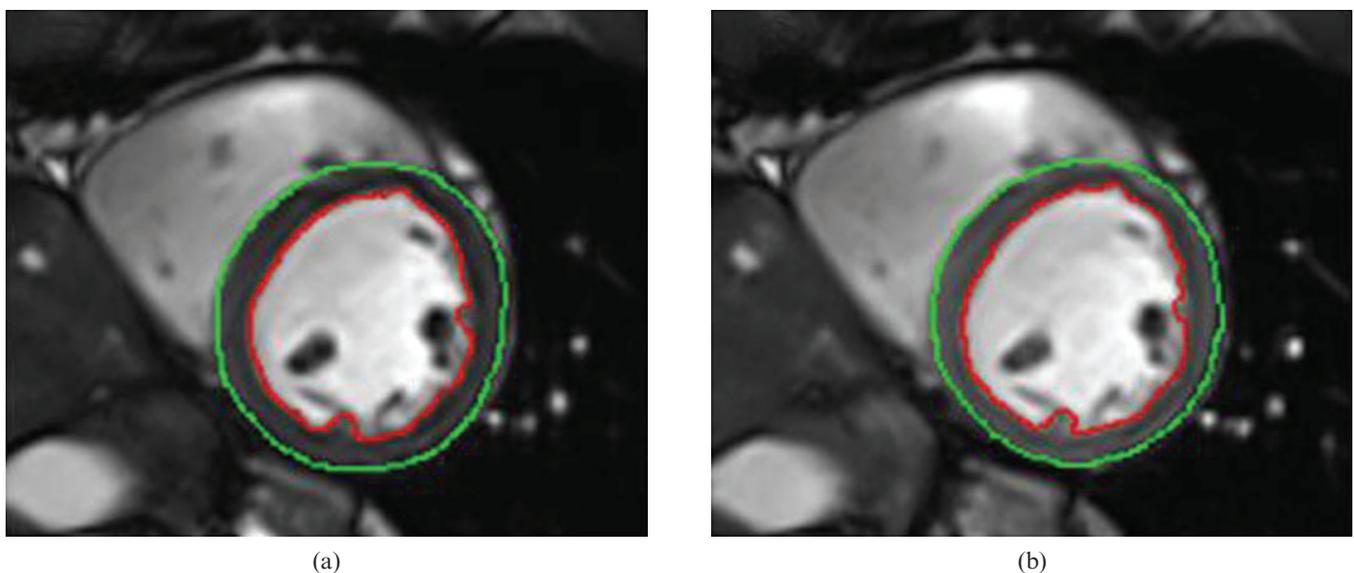
15 healthy volunteers [8 females (average age 48 years, range 41–61 years) and 7 males (average age 59 years, range 48–71 years)] with no history of atherosclerotic disease, primary muscle disease, statin therapy or serious illness were selected for imaging from a large database of individuals who were participating in a separate local MRI cardiovascular screening study. Exclusion criteria included age of less than 40 years, known alcohol abuse, pregnancy, claustrophobia and any other known contraindication to MRI. Approval for this study was obtained from the local ethics committee and volunteers provided written informed consent.

The sample size calculation for our investigation was based on information obtained from previous CMRI studies. For example, Grothues et al [11] studied various

clinical subject groups using CMRI and the typical minimum sample size required to detect a clinically significant 10 g change in LV mass with a power of 90% and an  $\alpha$  error of 0.05 was 13. Our initial hypothesis was that the influence of the contrast agent on the myocardial blood pool signal in our work might result in similar LV parameter differences. Based on this, a decision was taken to optimise our statistical power by increasing recruitment slightly to include 15 healthy volunteers.

This study was completed over a 5-month period with the pre- and post-contrast stacks of short-axis images (slice thickness 6 mm, interslice gap 4 mm) for each volunteer being obtained during a single imaging session using a 3 T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany). Initially, pre-contrast images were acquired (during end-expiration breath-hold) from the atrioventricular ring to the apex of the heart using a two-dimensional cardiac-gated segmented cine true fast imaging with steady state precession sequence with spine matrix and six-element body-array matrix radio frequency coils. One or two slices were imaged per breath-hold, depending on the ECG R–R wave interval of the volunteer. Imaging parameters included an in plane data acquisition matrix of  $173 \times 256$ , a field of view ranging from 320 to 420 mm (depending on patient size), repetition time 3.4 ms, echo time 1.5 ms and flip angle  $50^\circ$ . Post-contrast images (using the same imaging parameters) were subsequently obtained after iv injection of 10 ml of Gd-based contrast agent (Dotarem, Villepinte, France) via a power injector (Spectris Solaris EP, MedRad Inc., Warrendale, PA) followed by a saline flush of 20 ml. Contrast was administered at a consistent rate ( $1.5 \text{ ml s}^{-1}$ ) for all volunteers. The elapsed time between the administration of contrast agent and the acquisition of the mid-slice at end-diastole in the post-contrast short-axis stack consistently fell between 4 and 5 min for each volunteer.

Image analysis was performed on a remote Siemens multi-modality workstation using ARGUS software [v. VB15 (Siemens, Erlangen, Germany)]. An MRI physicist with 4 years' experience of quantitative CMRI analysis



**Figure 1.** A comparison of pre- and post-contrast short-axis images (at end diastole) of one volunteer showing (a) pre-contrast administration and (b) post-contrast administration.

**Table 1.** Results of analysis performed on pre- and post-contrast data sets by Segmenter 1

Parameter	Pre-contrast	Post-contrast
EF (%)	69.4 ± 5.3	68.7 ± 5.0 <sup>a</sup>
EDV (ml)	142.4 ± 34.5	143.7 ± 33.7 <sup>a</sup>
ESV (ml)	44.2 ± 14.9	45.5 ± 14.6 <sup>a</sup>
SV (ml)	98.3 ± 22.6	98.2 ± 21.9
LV mass (g)	108.1 ± 26.5	102.0 ± 26.6 <sup>a</sup>

Mean values ± standard deviation for all pre- and post-contrast cardiac parameters of ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and left ventricular mass (LV mass).

<sup>a</sup>Denotes significant difference at  $p < 0.05$ .

(Segmenter 1) performed semi-automated placement of endocardial and epicardial myocardial borders, from base to apex, on all slices pertaining to end-diastole (Figure 1) and end-systole. Each contour was defined by manually placing a circular region of interest over each myocardial border and then invoking an automated edge-detection algorithm to optimise the placement of these contours. Finally, manual adjustment of each epicardial and endocardial contour was undertaken where required to ensure optimised precision and consistency of contour placement. Papillary muscles and trabeculae were included in the LV mass when they were indistinguishable from the endocardial border, but otherwise they were assigned to the blood pool volume. Care was taken to ensure that slice selection at end-diastole and end-systole was consistent between the pre- and post-contrast images of each volunteer selected for this study, and images were retrospectively reviewed to ensure that the inclusion or exclusion of papillary muscles was consistent between the pre- and post-contrast images of each volunteer.

Segmenter 1 repeated the analysis of 10 randomly selected short-axis data sets (4 pre-contrast and 6 post-contrast) to establish intraobserver reproducibility. A second MR physicist segmenter with 6 years of cardiac MRI analysis experience (Segmenter 2) repeated the analysis on seven pre-contrast data sets from the study in order to establish interobserver reproducibility. Segmenter knowledge/memory effects were minimised by ensuring that no individual segmentations were repeated within a 1 month period.

Statistical testing for normality of data was undertaken using the Shapiro–Wilks test (SPSS; IBM Corporation, Somers, NY) and subsequently the pre- and post-contrast values of each parameter were compared using a paired

$t$ -test (assuming equal variances) (Sigma Plot, v. 10; Systat Software, Inc., San Jose, CA). Results of the  $t$ -tests were deemed significant if  $p < 0.05$ . Bland–Altman analysis was implemented in order to investigate and highlight intra- and interobserver repeatability differences for each of the cardiac MRI measurements utilised.

## Results

All images were acquired successfully, resulting in 15 pairs of pre- *vs* post-contrast data sets for comparison. Initial inspection of the images showed subtle qualitative differences to the contrast between the myocardium, the blood pool and other surrounding tissues (Figure 1).

A significant reduction to the mean EF and LV mass parameters was noted following delivery of Gd contrast agent (Table 1). Additionally, a small but significant increase in the mean EDV and ESV parameters was also noted after contrast agent delivery. Individual values (*i.e.* on a per-volunteer basis) for LV mass were consistently lower for every volunteer following contrast agent, with values ranging from  $-1.6$  to  $-11.3$  g (mean  $-6.1$  g, median  $-5.0$  g). The EF in 12 out of 15 volunteers was also reduced, with values ranging from  $-2.4\%$  to  $1.3\%$ , (mean  $-0.7\%$ , median  $-1.0\%$ ). In contrast, the majority of calculated EDV ( $n=10$ ) and ESV ( $n=12$ ) parameters displayed a small increase with the administration of contrast agent, with values ranging from  $-4.3$  to  $4.1$  ml (mean  $1.3$  ml, median  $2.1$  ml) and  $-2.5$  to  $3.7$  ml (mean  $1.3$  ml, median  $1.7$  ml), respectively. Stroke volume was found to be particularly stable; no mean pre- *vs* post-contrast change of any significance was noted.

No correlations were identified between the age, sex and body mass index of the volunteers and the extent of change between the calculated pre- and post-contrast values obtained for each cardiac parameter.

## Reproducibility

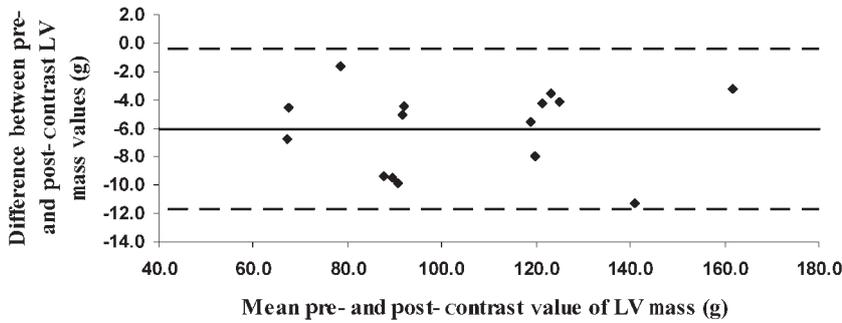
Intra- and interobserver assessments of single time point, test re-test and repeated measures for each LV parameter made by Segmenters 1 and 2 are highlighted in Table 2.

Bland–Altman plots are displayed for the LV mass data, illustrating the variation between pre- and post-contrast LV mass variables (Figure 2), as well as the variation

**Table 2.** Intra- and interobserver reproducibility of pre- and post-contrast data sets

Parameter	Intraobserver analysis ( $n=10$ )		Interobserver analysis ( $n=7$ )	
	1st analysis	2nd analysis	Segmenter 1	Segmenter 2
EF (%)	70.0 ± 6.2	69.0 ± 5.4	71.9 ± 4.4	72.1 ± 4.8
EDV (ml)	141.6 ± 28.5	142.1 ± 28.0	126.7 ± 25.3	128.5 ± 27.6
ESV (ml)	44.3 ± 13.0	44.4 ± 12.2	35.7 ± 8.5	35.9 ± 9.7
SV (ml)	97.3 ± 19.8	97.8 ± 19.9	91.2 ± 19.4	92.6 ± 20.1
LV mass (g)	108.7 ± 19.7	108.4 ± 19.6	103.7 ± 23.0	105.0 ± 20.7

Segmenter 1 analysed 10 data sets twice whereas Segmenter 2 performed repeat analysis on seven data sets previously analysed by Segmenter 1. Data are presented for ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and left ventricular mass (LV mass) as mean ± standard deviation. No significant differences between the means of any of the parameters were identified.



**Figure 2.** Variations between pre- and post-contrast left ventricular (LV) mass values obtained by segmenter 1. The mean “shift from zero” highlights the consistent post-contrast reduction in LV mass values.

between intraobserver repeated measures (Figure 3). It can be seen that the spread of data in Figure 2 is greater than that in Figure 3, with the mean “shift from zero” in Figure 2 highlighting the consistent post-contrast reduction in the LV mass values.

### Discussion

This study has demonstrated significant changes to pre- vs post-contrast cardiac MRI values of EF, EDV, ESV and LV mass in this cohort of healthy volunteers, with the calculated values of EF and LV mass decreasing after contrast delivery and EDV and ESV increasing after contrast delivery. By far the largest of these changes was found for LV mass.

These data appear to be consistent with the hypothesis that the administration of contrast agent leads to a change in the visual detection of the endocardial and epicardial borders during image analysis. The presence of contrast agent in the left ventricle improves the high-contrast detection of the endocardial border and this appears to result in an LV mass reduction together with increased blood pool volumes during segmentation. However, we do acknowledge that this has not been independently measured.

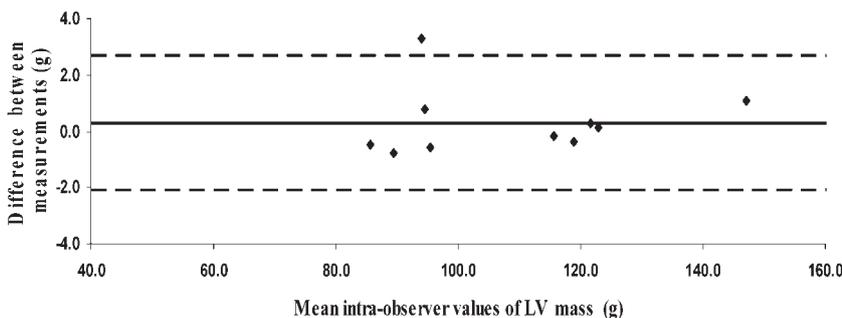
Every effort was made to address possible covariate effects such as minor image slice positioning differences and segmenter reproducibility variations. Care was taken to minimise systematic errors and maintain consistency in the acquisition and analysis of all data sets, resulting in minimal intra- and interobserver variation. Experienced radiographic technicians participated in order to ensure standardised data acquisition methods and a single

experienced segmenter carried out the analysis of all data sets since cardiac analysis (in particular LV mass) is known to be more reproducible for intraobserver assessments [12].

The relative differences between our pre-contrast and post-contrast LV mass measurements are similar to those reported by Stephensen et al [9]. This is reassuring from the point of view of study consistency, although in this study our data imply that LV mass differences have arisen from the presence of the contrast agent as opposed to the particular pulse sequence used.

The clinical significance of the parameter differences noted in this work is most likely to be dependent upon the wider context of the particular cardiac MRI investigation under question. For example, if precise follow-up data are being assessed as part of a quantitative longitudinal study, then a 7 g drop in LV mass is highly likely to be regarded as significant. However, if the data are being used for a quick single time-point quantitative assessment of a particular cardiac condition then these differences may be less important. It is accepted that the pre- and post-contrast differences between the parameters of EF, EDV and ESV are far smaller and as such we have reported these from the perspective of an interesting and consistent observation.

It is acknowledged that this study has some limitations. It is possible that a larger sample size might have resulted in the detection of more clear-cut changes to each parameter since the systematic differences reported in our work were rather small. It would also be advantageous to see whether the changes found could be replicated in defined patient groups. However our sample size is consistent with other cardiac MRI studies of a similar nature [11, 13] and this was



**Figure 3.** Variation of intraobserver measurements obtained by segmenter 1 for left ventricular (LV) mass. It can be seen that the spread of data is less than that of Figure 2 and that the variation is spread around zero.

carefully considered during the design phase of this work.

Finally, our “standard dose” approach for contrast agent delivery is different from routine clinical practice in CMRI perfusion where a weight-corrected dose would normally be delivered. The reason for this design compromise was that our cardiac imaging was performed within the framework of a larger whole-body MRA investigation where a standard dose approach was required as part of this work. However, from a clinical perspective the inclusion criteria for our subjects (see methods and materials) was such that a formal clinical assessment of cardiac perfusion involving weight-corrected dose was not deemed essential for this cohort.

## Conclusion

This pilot study has demonstrated that the administration of contrast agent in this cohort of healthy volunteers has significantly altered the calculated cardiac parameters of EF, EDV, ESV and particularly LV mass. Future studies involving cardiac patients are warranted since systematic differences in LV mass may need to be considered carefully in the context of clinical decision-making. It is also recommended that image analysis is undertaken on either pre- or post-contrast data sets and that this choice is kept consistent for the case of repeat scans or longitudinal studies.

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