Original Research

Reproducibility of First-Pass Cardiovascular Magnetic Resonance Myocardial Perfusion

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Purpose: To assess the reproducibility of semiquantitative and quantitative analysis of first-pass myocardial perfusion cardiovascular magnetic resonance (CMR) in healthy volunteers.

Materials and Methods: Eleven volunteers underwent myocardial perfusion CMR during adenosine stress and rest on 2 separate days. Perfusion data were acquired in a single mid-ventricular section in two cardiac phases to permit cardiac phase reproducibility comparisons. Semiquantitative analysis was performed to derive normalized upslopes of myocardial signal intensity profiles (myocardial perfusion index, MPI). The quantitative analysis estimated absolute myocardial blood flow (MBF) using Fermi-constrained deconvolution. The perfusion reserve index was calculated by dividing stress by rest data. Two observers performed all the measurements independently. One observer repeated all first scan measurements 4 weeks later.

Results: The reproducibility of perfusion CMR was highest for semiquantitative analysis with an intraobserver coefficient of variability (CoV) of 3%–7% and interobserver CoV of 4%–10%. Semiquantitative interstudy comparison was less reproducible (CoV of 13%–27%). Quantitative intraobserver CoV of 10%–18%, interobserver CoV of 8%–15% and interstudy CoV of 20%–41%. Reproducibility of systolic and diastolic phases and the endocardial and epicardial myocardial layer showed similar reproducibility on both semiquantitative and quantitative analysis.

Conclusion: The reproducibility of CMR myocardial perfusion estimates is good, but varies between intraobserver, interobserver, and interstudy comparisons. In this study semiquantitative analysis was more reproducible than quantitative analysis.

Key Words: myocardial perfusion; myocardial blood flow; hyperemia; Fermi deconvolution; variability; reproducibility
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POSITRON EMISSION TOMOGRAPHY (PET) is currently regarded as the reference standard for myocardial perfusion quantification (1,2). With its advantages over nuclear imaging such as high spatial resolution (2–3 mm in-plane) and freedom from ionizing radiation, cardiovascular magnetic resonance (CMR) may represent a more suitable test for serial assessments of myocardial perfusion (3,4). CMR has demonstrated excellent reproducibility for the assessment of left and right ventricular function, mass, and volumes (5,6), but reproducibility data for first-pass myocardial perfusion CMR are relatively sparse (7–9). In clinical practice and research both "semiquantitative" and "quantitative" analysis methods have been used to calculate CMR indices of myocardial perfusion. Only one previous comparison of these analysis methods has been published (9). Data for the reproducibility of myocardial perfusion CMR in different myocardial layers are equally sparse and no previous studies have compared the effect of cardiac phase on the reproducibility of myocardial perfusion measurements.

The aim of this study was to assess the intraobserver, interobserver, and interstudy agreement of myocardial perfusion measurements from first-pass myocardial perfusion CMR in normal healthy volunteers at rest and during adenosine-induced hyperemia while also directly comparing the reproducibility of semiquantitative and quantitative analyses. In addition, we determined the reproducibility of acquisitions during systole and diastole, and in the endocardial and epicardial myocardial layers.

MATERIALS AND METHODS

Study Population

We enrolled 11 healthy volunteers (six males, mean age 33 ± 7 years) who underwent CMR studies on 2 separate days. Exclusion criteria for the study

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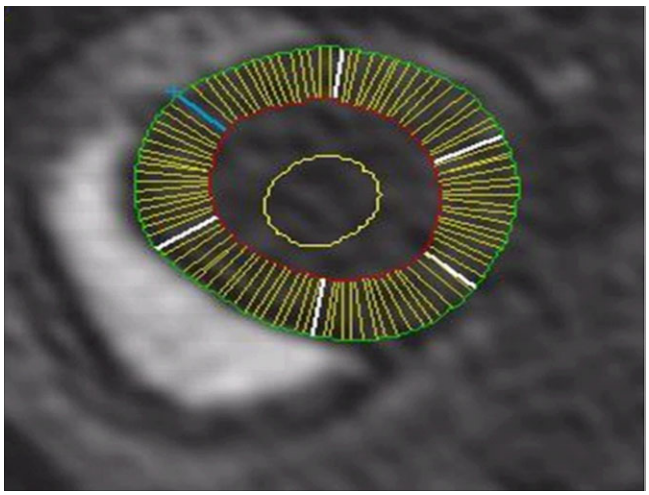

Figure 1. Example of contour delineation. Myocardial perfusion contours drawn on a systolic slice. One frame of the dynamic series is shown with both endocardial and epicardial contours drawn. A reference point put on the anterior insertion of RV with LV. A separate region of interest (inner circle) is placed in the LV blood pool to allow correction of myocardial perfusion parameters for the arterial input function. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

included symptoms or history of heart disease, diabetes mellitus, hyperlipidemia, abnormal resting blood pressure, and any history of nicotine or medication use. From CMR cine datasets, left ventricular (LV) volumes and LV mass index were calculated for each volunteer. All volunteer measurements were within previously published normal ranges (10). Informed consent was taken from all volunteers in accordance with a study protocol approved by the local Ethics Committee.

Anthropometric, LV Function, and Hemodynamic Measurements

All subjects had their height and weight measured. Body surface area was calculated using an online calculator implementing the Mosteller formula (11). Body mass index was calculated as the individual's body weight divided by the square of his or her height. LV mass, volumes, end systolic, and diastolic wall thicknesses were measured using a dedicated software package (Q Mass, v. 6.1.6, Medis, Leiden University, Leiden, The Netherlands). LV mass was also indexed to body surface area.

Scan Protocol

All volunteers were instructed to refrain from caffeine-containing food and beverages for at least 24 hours before the CMR examination and to eat a light breakfast on the day of the test. A 20G cannula was inserted in the antecubital vein of each arm. One cannula was used for administration of the vasodilating agent (adenosine) and a separate cannula for the administration of the contrast agent.

Imaging was performed in supine position on a 1.5T whole body magnetic resonance scanner (Intera, Philips Medical Systems, Best, The Netherlands) using a five-element cardiac phased array receiver coil and vectorcardiogram. Blood pressure and heart rate were monitored and recorded during the CMR examination. From scout CMR images the LV long and short axes were determined. Perfusion CMR was then planned in the mid LV short axis orientation. All perfusion imaging was carried out during a single breath-hold at end expiration. The first perfusion scan was performed during maximal vasodilatation, stimulated by intravenous infusion of adenosine at a dose of 140 μg/min/kg for 4 minutes. After a 15-minute delay a rest scan was performed. For each perfusion acquisition a contrast dose of 0.05 mmol/kg gadopentate dimeglumine (Magnevist, Bayer, Berlin, Germany) was administered with the use of a power injector (Spectris Solaris, Medrad, Indianola, PA) at a rate 5 mL/s followed by a 20-mL saline flush. The pulse sequence used was a saturation recovery fast gradient echo method accelerated by twofold sensitivity encoding (SENSE), repetition time (TR) / echo time (TE) / flip angle 2.7 msec / 1.0 msec / 15°, typical field of view (FOV) 380 × 380mm, acquired image matrix 160 × 160 (reconstructed to 256 × 256), in plane spatial resolution 2.4 × 2.4 mm, slice thickness 10 mm, preparation pulse delay (to the middle of *k*-space) 150 msec, readout shot duration 130 msec. Two slices were acquired. One was imaged in mid-systole and the other in mid-diastole, by choosing appropriate trigger delays from the cine images. Repeat studies were performed at a similar time of the day as the initial scan and using identical settings.

Image Analysis

Semiquantitative Analysis

Analysis was performed for the entire myocardial slice covered by the acquisition with a dedicated image analysis software package (Q Mass 6.1.6, Medis). The

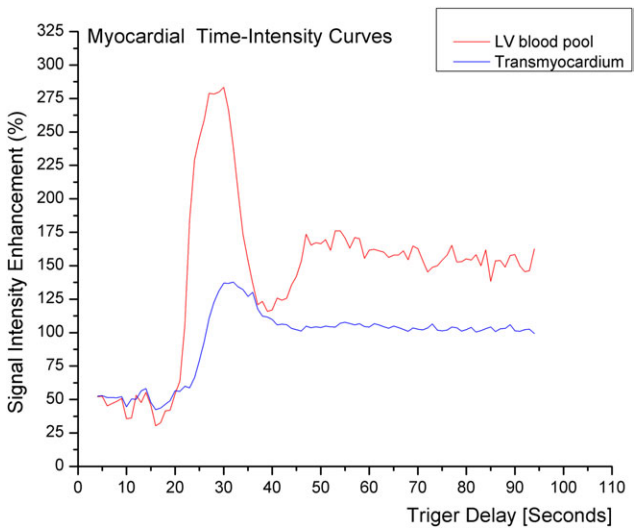

Figure 2. Myocardial and LV blood pool signal intensity–time profiles. Myocardial signal intensity–time profiles for the entire myocardial area of the systolic slice and the LV blood pool. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

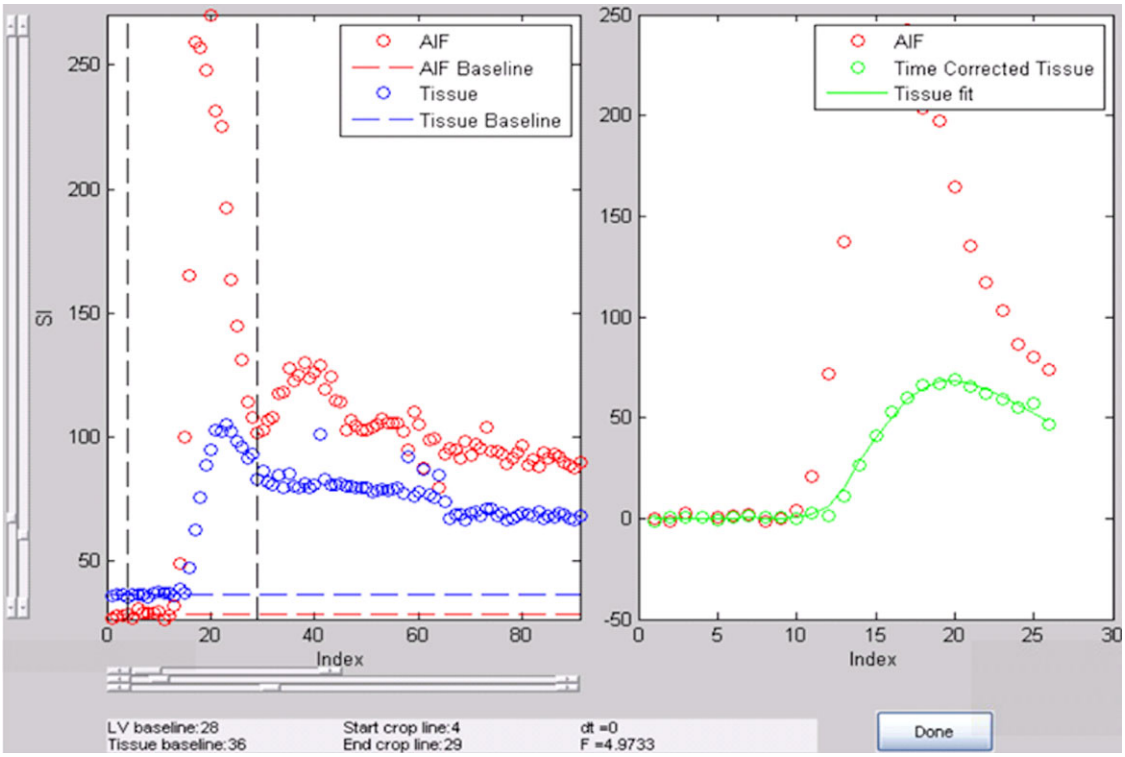

Figure 3. Fermi-constrained deconvolution analysis. The graph on the left shows the original data input for the left ventricular input function (red) and myocardial tissue signal intensity profiles (green). The dotted lines indicate the selected analysis window of the first pass of the contrast agent. On the right the time-corrected tissue curve and the fitted curve are shown. AIF = arterial input function; F = myocardial blood flow in mL/g/min; LV = left ventricle; SI = signal intensity.

endocardial and epicardial contours were outlined on the image with the best blood to myocardial contrast and copied to all other dynamic images. The position of individual contours was then manually corrected to account for any respiratory motion. In order to obtain an arterial input function (AIF), another region of interest was drawn inside the LV blood pool (Fig. 1). Signal intensity vs. time profiles were then generated for the mid LV myocardial slice as a whole without dividing into segments and the LV blood pool (Fig. 2). The maximal upslope of the profiles was generated using five-point fitting. These slope values were then divided by the maximal upslope of the AIF to calculate the myocardial perfusion index (MPI). Finally, the myocardial perfusion reserve index (MPRI) was calculated by dividing the MPI values at stress by the values at rest.

Absolute Myocardial Blood Flow Quantification

Signal-intensity vs. time data generated in QMass were analyzed with MatLab7 R2009b (MathWorks, Natick, MA). Fermi-constrained deconvolution (Fig. 3) was used to generate estimates of absolute myocardial blood flow (MBF) in mL/g/min (12). At doses of 0.05 mmol/kg the relationship between contrast agent concentration and signal intensity is nonlinear and can cause errors in MBF estimation. To minimise such errors, signal intensities were converted into concentration values using the equation for the imaging sequence (13,14) and an assumed T1 for blood of 1435 msec, which was derived from an average (weighted for study population) of the measurements published in Flacke et al (15), Klein et al (16), Messroghli et al (17), and Sharma et al (18).

As for the semiquantitative analysis, MBF was estimated for the entire myocardial slice, without division into segments. The MBF reserve was calculated by dividing hyperemic (stress) by rest MBF.

All measurements of semiquantitative and quantitative analysis were performed independently by two

Table 1
Anthropometric and Volumetric Measurements (n=11)

Parameter	Mean measurements
Age (years)	33 ± 7
Gender (male %)	55%
Body weight (kg)	75 ± 19
Body height (meter)	1.70 ± 0.08
Body surface area (m^2)	1.88 ± 0.26
Body mass index (kg/m^2)	26 ± 5.3
Ejection fraction (%)	58 ± 4
Stroke volume (mL)	92 ± 18.7
LV-EDV (mL)	162 ± 37
LV-ESV (mL)	71 ± 21
LV-mass (g)	87 ± 21
LV mass index (g/m^2)	46 ± 7.8
LV-ED wall thickness (mm)	5.3
LV-ES wall thickness (mm)	8.7

All measurements were obtained at the first visit.
LV-EDV: left ventricular end-diastolic volume; LV-ESV: left ventricular end-systolic volume; LV-ED wall thickness: left ventricular end-diastolic wall thickness; LV-ES wall thickness: left ventricular end-systolic wall thickness.

Table 2
Hemodynamic Measurements on Visit 1 and Visit 2 at Rest (Baseline) and During Adenosine-Induced Hyperemia (Mean ± SD)

	Rest study 1	Rest study 2	*P*-value	Hyperemia study 1	Hyperemia study 2	*P*-value
SBP	109 ± 9	106 ± 7	ns	112 ± 14	106 ± 12	ns
DBP	65 ± 12	59 ± 7	ns	63 ± 12	62 ± 8	ns
HR	66 ± 9	61 ± 10	ns	92 ± 16	89 ± 13	ns
RPP	7165 ± 1113	6388 ± 823	ns	10193 ± 1498	9434 ± 1502	ns

SBP = systolic arterial blood pressure (mmHg); DBP = diastolic arterial blood pressure (mmHg); HR = heart rate (beats /minute); RPP = rate pressure product (SBP x HR); ns = non-significant (ie, $P > 0.05$).

Table 3
Interscan Separation Time (IST)

Interscan time (days)	Volunteer frequency	Percent (%)	Cumulative %
7	5	45.5	45.5
9	1	9.1	54.5
14	1	9.1	63.6
139	1	9.1	72.7
189	1	9.1	81.8
259	1	9.1	90.1
280	1	9.1	100
Total	11	100	

IST Range = 273 days, Minimum IST = 7 days, Maximum IST = 280 days, Mode IST = 7 days, Mean IST = 84 days, SD IST = 111 days.

observers (3 years and 2 years experience in CMR). In addition, the first observer repeated the analysis of the first CMR scan after 4 weeks, being blinded to all previous results.

Statistical Analysis

All data were processed using Origin Pro software, v. 8.5 (Origin Lab, UK). Means and standard deviations (SDs) were calculated for all regions of interest using Excel software (Microsoft, 2007, Redmond, WA). The repeated measurements were compared using the two-tailed paired Student's *t*-test, assuming two equal variances. $P < 0.05$ was considered statistically significant. The coefficient of variability (CoV) was calculated as the SD of differences between the measurements divided by the mean value of the two observations or studies.

RESULTS

CMR Examinations and Hemodynamic Measurements

All 11 volunteers completed the two perfusion CMR examinations successfully. Anthropometric and LV volumetric measurements are shown in Table 1. Heart rate and rate pressure product were significantly different between rest and stress examinations at the same visit, but none of the interstudy hemodynamic variables showed any significant differences between the two visits as shown in Table 2. All volunteers experienced typical physiological side effects during the adenosine infusion. One volunteer experienced first-degree heart block during the first scan, which was terminated by reducing the infusion rate of the adenosine from 140 μg/kg/min to 115 μg/kg/min. For the repeat scan the same dose regime was used in this volunteer, but no heart block occurred. Table 3 shows the interstudy separation times (IST) between the two scans for the 11 volunteers.

Intraobserver Agreement

Tables 4 and 5 list the intraobserver, interobserver, and interstudy reproducibility results as mean

Table 4
Intraobserver, Interobserver, and Interstudy Variability for Semiquantitative and Quantitative Perfusion Estimates in Systole

	Semiquantitative (no units)			Quantitative (mL/g/min)		
	Rest MPI	Stress MPI	Reserve	Rest MBF	Stress MBF	Reserve
Intraobserver comparisons						
Mean ± SD	0.11 ± 0.02	0.18 ± 0.03	1.73 ± 0.3	1.24 ± 0.35	3.51 ± 0.89	2.93 ± 0.72
Mean% difference ± SD	0.46 ± 6.65	0.67 ± 3	0.7 ± 6	1.24 ± 13.59	5.78 ± 12.79	4.51 ± 13.22
Coefficient of variability	7%	3%	5.4%	10.4%	13.8%	12.7%
P-value	0.89	0.92	0.46	0.96	0.70	0.66
Interobserver comparisons						
Mean ± SD	0.11 ± 0.02	0.19 ± 0.03	1.7 ± 0.3	1.19 ± 0.34	3.41 ± 0.75	2.98 ± 0.67
Mean% difference ± SD	9 ± 8	4.8 ± 4	4 ± 8.6	9.89 ± 12.1	10 ± 13.34	0.22 ± 14.82
Coefficient of variability	9.8%	4.3%	8.6%	8.4%	14.5%	14.7%
P-value	0.18	0.45	0.63	0.52	0.31	0.92
Interstudy comparisons						
Mean ± SD	0.11 ± 0.02	0.19 ± 0.03	1.79 ± 0.36	1.15 ± 0.3	3.73 ± 1.03	3.35 ± 0.67
Mean% difference ± SD	3 ± 17	0.9 ± 12	3.8 ± 24	16.31 ± 23.13	3.18 ± 37.41	19.34 ± 35.33
Coefficient of variability	17.6%	13.6%	27%	20%	40.4%	35%
P-value	0.18	0.71	0.56	0.20	0.61	0.11

MPI: myocardial perfusion index; MBF: myocardial blood flow; SD: standard deviation.

Table 5
Intraobserver, Interobserver, and Interstudy Variability for Semiquantitative and Quantitative Perfusion Estimates in Diastole

	Semiquantitative (unit less)			Quantitative (mL/g/min)		
	Rest MPI	Stress MPI	Reserve	Rest MBF	Stress MBF	Reserve
Intraobserver comparisons						
Mean ± SD	0.11 ± 0.02	0.20 ± 0.03	1.89 ± 0.33	1.23 ± 0.29	4.77 ± 1.72	3.89 ± 1
Mean% difference ± SD	1.40 ± 6.27	0.50 ± 4.88	0.06 ± 4.84	5.56 ± 14.63	2.29 ± 13.5	7.78 ± 20.19
Coefficient of variability	5.7%	5.3%	4.5%	13.4%	14.1%	18.4%
P-value	0.88	0.96	0.98	0.60	0.93	0.58
Interobserver comparisons						
Mean ± SD	0.11 ± 0.02	0.21 ± 0.03	1.91 ± 0.37	1.13 ± 0.28	4.43 ± 1.52	3.95 ± 1.03
Mean% difference ± SD	2.67 ± 8.81	3.40 ± 6.50	0.82 ± 9.90	12.08 ± 17.8	16.64 ± 10.75	4.53 ± 12.83
Coefficient of variability	10.6%	6.9%	9.6%	15.2%	13.3%	13.3%
P-value	0.69	0.64	0.81	0.35	0.27	0.76
Interstudy comparisons						
Mean ± SD	0.11 ± 0.02	0.20 ± 0.03	1.85 ± 0.35	1.16 ± 0.29	4.77 ± 1.39	4.17 ± 0.82
Mean% difference ± SD	1.92 ± 12.90	3.16 ± 13.03	5.17 ± 18.32	8.21 ± 27.64	2.46 ± 39.11	5.83 ± 32.13
Coefficient of variability	13.7%	12.9%	19.4%	26.3%	41.2%	27%
P-value	0.72	0.65	0.69	0.61	0.93	0.49

MPI: myocardial perfusion index; MBF: myocardial blood flow; SD: standard deviation.

Table 6
Semiquantitative Perfusion Parameters: Coefficient of Variability (%) for Subendocardium and Subepicardium in Systole and Diastole

	Rest MPI		Stress MPI		Reserve	
Intraobserver	Systole	Diastole	Systole	Diastole	Systole	Diastole
Subendocardium	16.5	14.5	2.1	3.9	15.6	10.0
Subepicardium	7.0	11.1	6.9	10.8	8.6	15.1
Interobserver						
Subendocardium	11.3	17.3	5.5	4.9	12.8	17.8
Subepicardium	11.1	11.2	4.3	11.7	12.2	14.6
Interstudy						
Subendocardium	16.9	19.5	14.0	15.4	25	28.7
Subepicardium	17	16.2	17.3	13.8	30.4	19.8

MPI: myocardial perfusion index.

measurements with SD, mean percentage difference with SD, and CoV for systolic and diastolic measurements from the entire myocardial slices. Tables 6 and 7 list results for the endocardial and epicardial layers separately.

Semiquantitative Analysis

The intraobserver comparison showed no significant differences between the two observations for rest or stress MPI. The CoV was 7% vs. 5.7% at rest and 3% vs. 5.3% at stress for systole and diastole, respectively. The mean MPRI between the two observations was also not significantly different with a CoV of 5.4% vs. 4.5% for systole and diastole, respectively. For systolic reproducibility, see also Figs. 5a, 6a, and 7a (left panels). For the equivalent diastolic reproducibility data, see also Figs. 5b, 6b, and 7b (left panels).

Quantitative Analysis

A typical example of the enhancement curves used for quantitative analysis, with the Fermi response function and resulting fit to the myocardial tissue, curve

Table 7
Quantitative Perfusion Parameters: Coefficient of Variability (%) for Subendocardium and Subepicardium in Systole and Diastole

	Rest MBF		Stress MBF		Reserve	
Intraobserver	Systole	Diastole	Systole	Diastole	Systole	Diastole
Subendocardium	8.3	16.1	12.2	14.6	15.4	21.4
Subepicardium	22.6	10.7	14.7	17.3	21.1	19.4
Interobserver						
Subendocardium	11.9	21.8	13.1	24.9	19.6	24.9
Subepicardium	20.1	14.1	19.8	18.9	20.3	21.8
Interstudy						
Subendocardium	12.1	22.2	36.5	44	31.1	35.9
Subepicardium	25.1	20.6	44.3	37.1	40.7	32.0

MBF: myocardial blood flow.

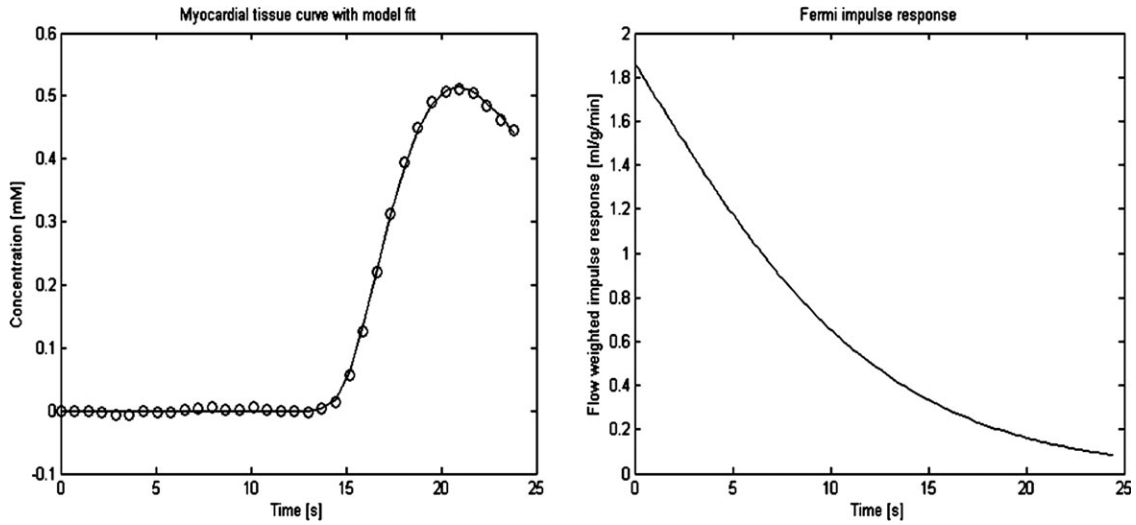

Figure 4. Example dataset showing enhancement curves used in quantitative analysis. Left panel: The myocardial tissue enhancement curve (dots) expressed in mM acquired from the MRI data with the fit to the data generated by deconvolution analysis (solid line). Right panel: The associated flow-weighted Fermi-constrained impulse response function.

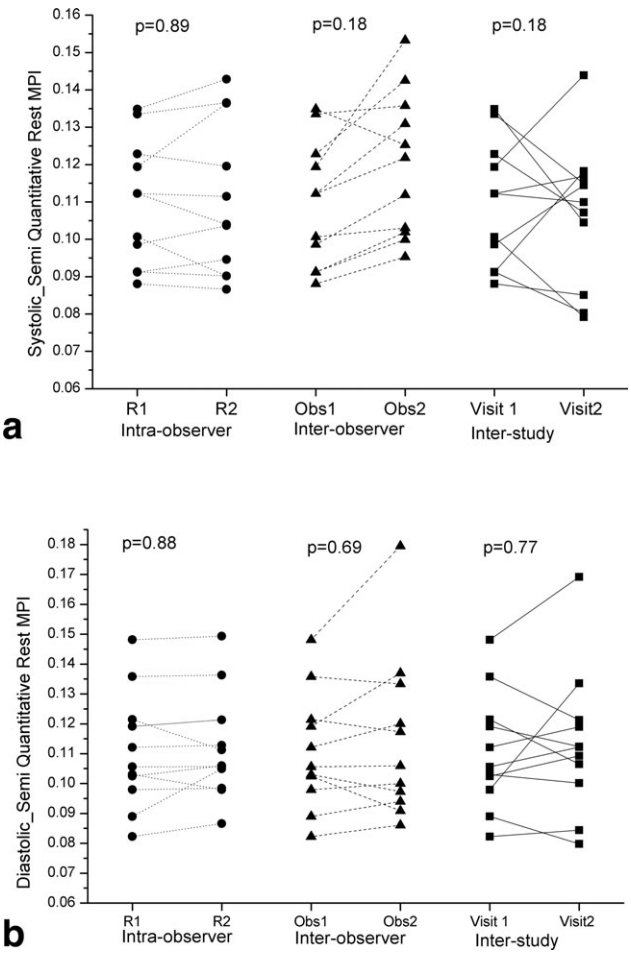

Figure 5. Variability of semiquantitative myocardial perfusion index measurements at rest in systole **(a)** and diastole **(b)**. R1 = first reading of the first observer, R2 = second reading of the first observer. Obs1 = first observer reading, Obs2 = second observer reading. Visit1 = first visit (first observer) reading, Visit2 = second visit (first observer) reading.

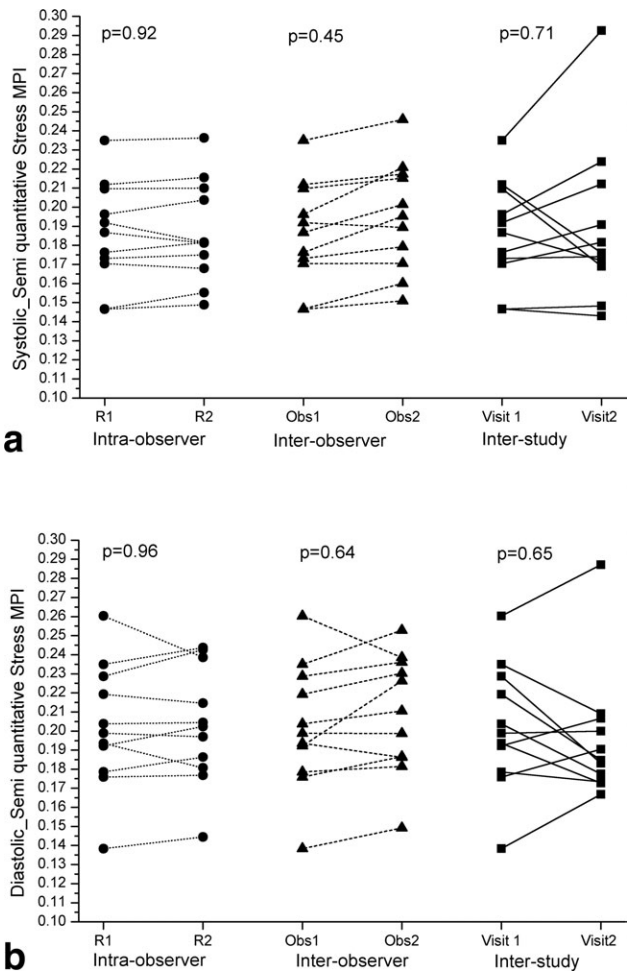

Figure 6. Variability of semiquantitative myocardial perfusion index measurements during hyperemia in systole **(a)** and diastole **(b)**. R1 = first reading of the first observer, R2 = second reading of the first observer. Obs1 = first observer reading, Obs2 = second observer reading. Visit1 = first visit (first observer) reading, Visit2 = second visit (first observer) reading.

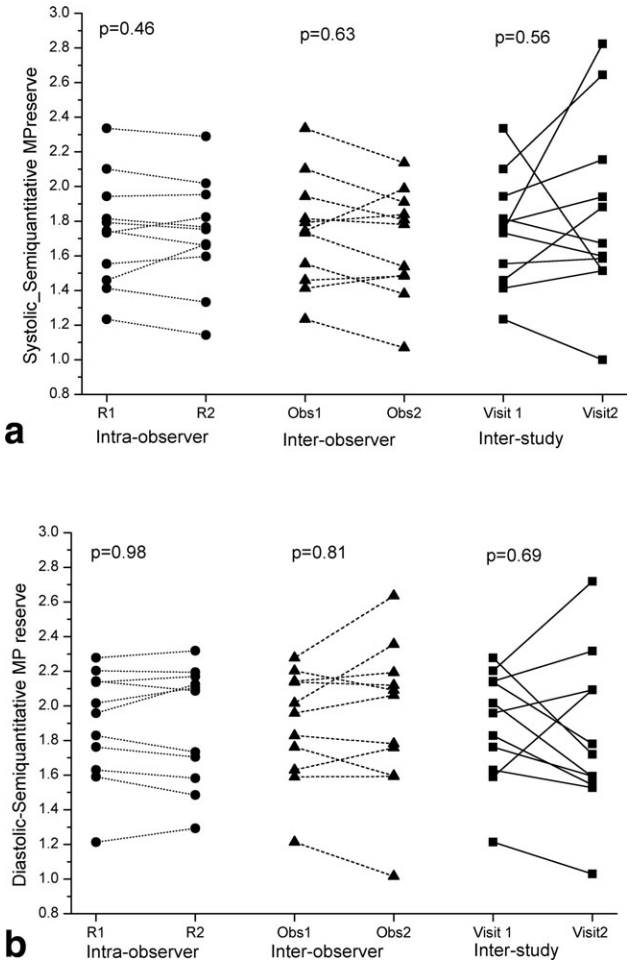

Figure 7. Variability of semiquantitative myocardial perfusion reserve index measurements in systole **(a)** and diastole **(b)**. R1 = first reading of the first observer, R2 = second reading of the first observer. Obs1 = first observer reading, Obs2 = second observer reading. Visit1 = first visit (first observer) reading, Visit2 = second visit (first observer) reading.

is shown in Fig. 4. Intraobserver variability of quantitative analysis was generally higher than the semiquantitative analysis. Although there were no statistically significant differences between the two observations for any measurement, the CoV was 10.4% vs. 13.4% for rest MBF, 13.8% vs. 14.1% for stress MBF, and 12.7% vs. 18.4% for MBF reserve for systole and diastole, respectively. Figures 8a, 9a, and 10a (left panels) show systolic data and Figs. 8b, 9b, and 10b (left panels) show diastolic data.

Interobserver Agreement

Semiquantitative Analysis

There were no statistically significant differences in any of the semiquantitative measurements between the two observers. CoVs were similar to those for intraobserver comparisons: 9.8% vs. 10.6% for rest MPI, 4.3% vs. 6.9% for stress MPI, and 8.6% vs. 9.6% for MPRI for systole and diastole, respectively. See Figs. 5a, 6a, and 7a (middle panels) for systolic and 5B, 6B, and 7B (middle panels) for diastolic data.

Quantitative Analysis

As for the intraobserver comparisons, no statistically significant differences were found between the means of the interobserver measurements on quantitative analysis. CoVs for quantitative analysis were higher than for semiquantitative analysis at 8.4% vs. 15.2% for rest MBF, 14.5% vs. 13.6% for stress MBF, and 14.7% vs. 13.3% for MBF reserve for systole and diastole, respectively. Figures 8a, 9a, and 10a (middle panels) show the systolic data and Figs. 8b, 9b, and 10b (middle panels) show the diastolic data.

Interstudy Agreement

Semiquantitative Analysis

For interstudy comparisons, the means of rest and stress MPI and the MPRI were not significantly different. However, the variability was higher than in intraobserver and interobserver comparisons. The coefficient of variability was 17.6% vs. 13.7% at rest, 13.6% vs. 12.9% at stress, and 27% vs. 19.4% for the MPRI for systole and diastole, respectively. See

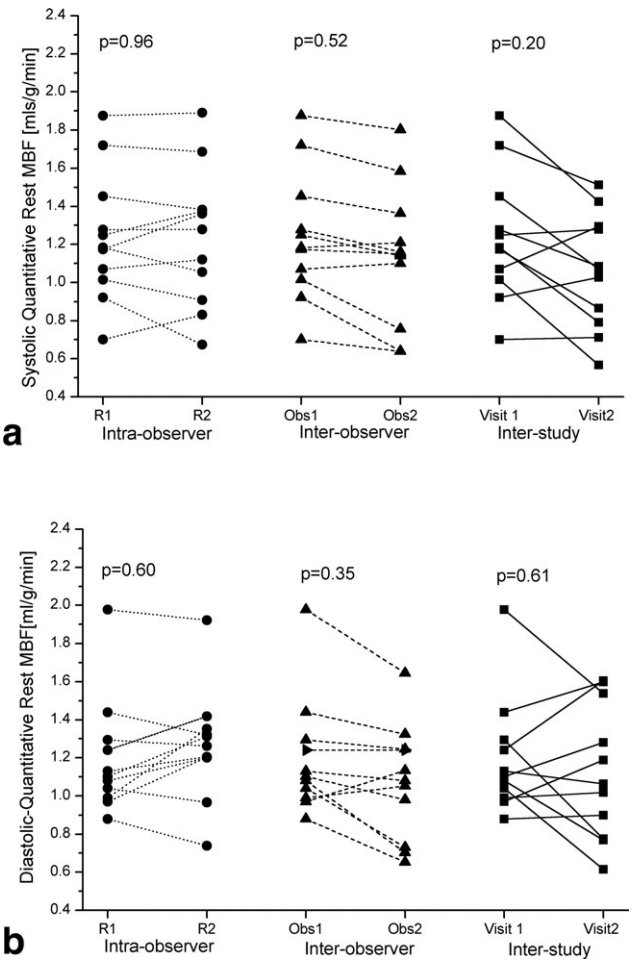

Figure 8. Variability of quantitative resting absolute myocardial blood flow estimates in systole **(a)** and diastole **(b)**. R1 = first reading of the first observer, R2 = second reading of the first observer. Obs1 = first observer reading, Obs2 = second observer reading. Visit1 = first visit (first observer) reading, Visit2 = second visit (first observer) reading.

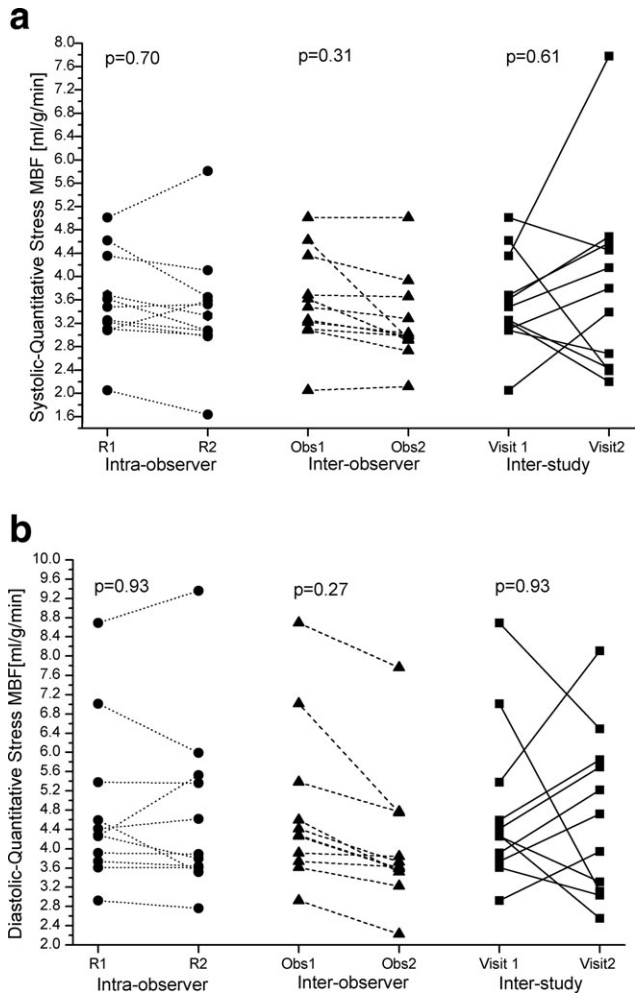

Figure 9. Variability of quantitative absolute myocardial blood flow estimates during hyperemia in systole **(a)** and diastole **(b)**. R1 = first reading of the first observer, R2 = second reading of the first observer. Obs1 = first observer reading, Obs2 = second observer reading. Visit1 = first visit (first observer) reading, Visit2 = second visit (first observer) reading.

Figs. 5a, 6a, and 7a (right panels) for the systolic data. For the equivalent diastolic reproducibility data see Figs. 5b, 6b, and 7b (right panels).

Quantitative Analysis

Again, no statistically significant differences were found between the means of measurements. The CoV was (20% vs. 26.3%) for rest MBF, (40.4% vs. 41.2%) for stress MBF, and (35% vs. 27%) for MBF reserve for systole and diastole, respectively. For systolic data refer to Figs. 8a, 9a, and 10a (right panels). For the equivalent diastolic reproducibility data see Figs. 8b, 9b, and 10b (right panels).

Endocardium vs. Epicardium

Tables 5 and 6 show the CoV for both subendocardium and subepicardium in systole and diastole using both methods. Epicardial variability tended to be higher than endocardial variability, but no statistical differences were found.

DISCUSSION

In this study, first pass myocardial perfusion CMR was shown to have good intraobserver, interobserver, and interstudy reproducibility. We found that reproducibility was higher for semiquantitative analysis than for quantitative analysis and better for interobserver and intraobserver analysis than for interstudy comparison. Analysis of systolic data and diastolic data and of endocardial versus epicardial layers was similar with both analysis strategies.

Comparisons with previous studies are in part limited by the fact that variability and repeatability are not uniformly expressed between studies. Interstudy variability of CMR perfusion was recently reported for 30 subjects recruited to the Multi Ethnic Study of Atherosclerosis (MESA). Estimates of MBF based on model-independent deconvolution showed a relative

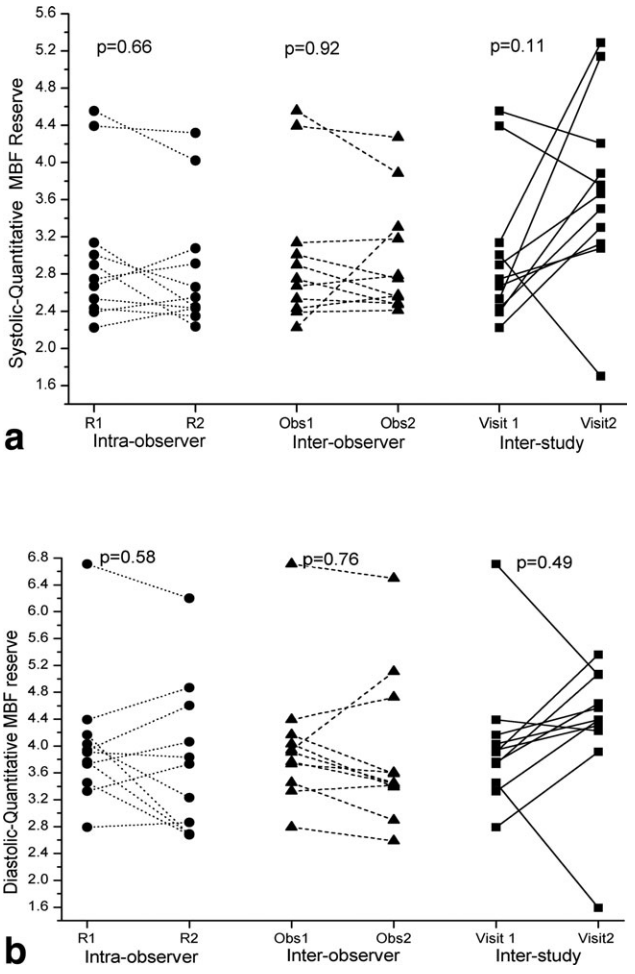

Figure 10. Variability of quantitative absolute myocardial blood flow reserve estimates in systole **(a)** and diastole **(b)**. R1 = first reading of the first observer, R2 = second reading of the first observer. Obs1 = first observer reading, Obs2 = second observer reading. Visit1 = first visit (first observer) reading, Visit2 = second visit (first observer) reading.

repeatability coefficient, expressed as a percentage of the MBF, of 30% at rest, and 41% during adenosine-induced hyperemia (7). These results are broadly in line with our interstudy data.

A study of 17 patients by Muehling et al (19) demonstrated better intraobserver than interobserver agreement of Fermi-constrained deconvolution analysis of CMR perfusion data and showed that variability was dependent on image quality. However, stress data were acquired in only three patients, so that comparison with our results and clinical relevance of this study are limited.

Only one previous study compared semiquantitative with quantitative analysis of CMR perfusion data. The study by Elkington et al (9) in seven volunteers showed superior reproducibility of quantitative analysis of myocardial perfusion CMR based on Fermi-deconvolution compared with semiquantitative analysis based on normalized upslopes of signal-intensity profiles. The CoV for global transmyocardial perfusion reserve was 21% vs. 39% for quantitative versus semiquantitative analysis, respectively. Our study yielded opposite results with higher variability of quantitative analysis compared with semiquantitative analysis. This apparent contradiction was mainly caused by better reproducibility of our semiquantitative analysis compared with the previous study, while the reproducibility of our quantitative analysis was similar. There are many methodological differences between the study by Elkington et al and ours, including different data acquisition schemes, different analysis strategies, for example for baseline correction, and the analysis software used. All of these differences may account for the low reproducibility of semiquantitative analysis in the previous study.

This study has added data to the existing literature comparing perfusion analysis in different cardiac phases and myocardial layers. The reproducibility of perfusion CMR was broadly similar between systole and diastole. We had anticipated that systole would be more reproducible, given the higher transmural thickness of the myocardium available for analysis in systole than diastole, which potentially minimizes sources of error. However, this was not confirmed in the present analysis. It is conventionally not feasible to choose the cardiac phase for perfusion CMR studies, but with the advent of 3D acquisition methods, cardiac phase will become a parameter open to choice. Our data support the use of either systole or diastole for such developments.

Our study also shows that reproducibility of myocardial perfusion measurements in the endocardial and epicardial layers is similar and does not differ from analysis of the entire myocardial extent.

The myocardial blood flow showed clear heterogeneity. The lower interstudy reproducibility compared with other reproducibility measurements probably reflects, at least in part, physiological temporal and spatial heterogeneity of myocardial blood flow rather than a methodological error alone (20,21). In this study we tried to minimize physiological factors by scheduling both scans at the same time of day and using identical preparation and set-up for both studies. This approach was aimed to correct, at least in part, for the effect of any circadian rhythm variability on hemodynamics (22,23). Another study has reported similar interstudy variability and also found it to be higher than the variability of repeated measurements of the same data (9).

Comparing perfusion CMR to other imaging modalities, PET is currently considered the reference standard for quantitation of myocardial perfusion (1,24). Nagamachi et al (24) reported an interstudy PET reproducibility (expressed as the mean percent difference ± SD between two scans) of 15.8% ± 15.8% at rest and 11.8% ± 9.4% at hyperemic stress. This compares with a mean percentage interstudy variability in our study of 3% ± 17% at rest and 0.9% ± 12% at stress with semiquantitative analysis and 16.3% ± 23.1% at rest and 3.18% ± 37.4% at stress using quantitative analysis. Kaufman et al (1) expressed reproducibility as the percentage coefficient of repeatability and reported 18% for rest and 25% for adenosine stress PET between baseline and follow-up studies. Our study yielded 17.6% vs. 13.6% for semiquantitative and 20% vs. 40.42% for quantitative analysis at rest and stress, respectively. Although not based on the same cohort of test subjects, these results suggest similar reproducibility of CMR and PET (25).

With regard to the study limitations, the relatively small number of subjects in this study may have precluded the detection of significant differences between measurements. However, most previous reproducibility studies of CMR perfusion and other modalities have had small numbers of participants, reflecting the complexity of such work and the time-intensive analysis. The use of an assumed blood T1 for the concentration conversion may increase the variability in the quantitative MBF estimates and might have been reduced by measuring patient-specific T1 values. However, the conversion method has been shown to be robust to errors in the assumed T1 value (26), and so this increase in variability should be small.

In conclusion, first-pass perfusion CMR with semiquantitative and quantitative analysis has comparable reproducibility to PET. In this study, semiquantitative analysis was more reproducible than quantitative analysis and interstudy reproducibility was lower than intraobserver and interobserver reproducibility. No differences were found between data acquired in diastole or systole and between separate myocardial layers.

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