Journal of Cardiovascular Magnetic Resonance (2005) **7,** 815–822

ISSN: 1097-6647 print / 1532-429X online
DOI: 10.1080/10976640500287877

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PERFUSION

Interstudy reproducibility of quantitative perfusion cardiovascular magnetic resonance

ANDREW G. ELKINGTON, B.SC., M.R.C.P.,[1] PETER D. GATEHOUSE, PH.D.,[1] NICHOLAS A. ABLITT,[2] GUANG-ZHONG YANG, PH.D.,[2] DAVID N. FIRMIN, PH.D.,[1] and DUDLEY J. PENNELL, M.D., F.R.C.P., F.A.C.C.[1,*]

[1]*Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, London, UK*
[2]*Medical Image Computing Laboratory, Imperial College, London, UK*

Purpose. To determine the interstudy reproducibility of quantitative first-pass perfusion cardiovascular magnetic resonance with comparison of 2 previously described analysis techniques. There is no published data on the interstudy reproducibility of perfusion cardiovascular magnetic resonance which can be used to determine the significance of longitudinal changes in myocardial perfusion after pharmacologic or therapeutic interventions with defined sample sizes. *Methods.* Sixteen subjects (7 normal volunteers, 9 patients with coronary artery disease) had rest and adenosine stress perfusion cardiovascular magnetic resonance studies on two separate visits. A short axis slice was studied on each visit using a fast low-angle shot sequence. The global and regional myocardial perfusion reserve indices were calculated using 2 methods: model based constrained deconvolution with the Fermi function, and normalized upslopes. Reproducibility was defined as the standard deviation of the measurement differences, divided by the mean (coefficient of variation). *Results.* The reproducibility of global myocardial perfusion reserve indices was 21% in normal volunteers, which was similar to that in patients with coronary artery disease (CAD) (23%, p = .88). The reproducibility of regional myocardial perfusion reserve indices was 28% (p = .45 vs. global analysis). The reproducibility of global MPRi was superior with Fermi deconvolution compared with normalized upslopes (21% vs. 41%, p = .02). *Conclusion.* At this stage of clinical development, the reproducibility of quantitative perfusion cardiovascular magnetic resonance is good, and superior using Fermi deconvolution in preference to upslope analysis.

Key Words: MR; Heart; Perfussion; Coronary artery disease; Gadolinium

1. Introduction

The assessment of myocardial perfusion is integral to the practice of clinical cardiology. Single-photon emission computed tomography (SPECT) is the most widely used test while positron emission tomography (PET) is currently regarded as the gold standard. Perfusion cardiovascular magnetic resonance (CMR) has potential advantages over these techniques. Perfusion CMR is free of ionizing radiation, has good spatial resolution (~ 2 mm), and can be readily combined with cardiac function (1), anatomy, viability (2), and coronary angiography (3). Studies show first-pass perfusion CMR gives comparable clinical results to PET (4) and SPECT (5) for the non-invasive detection of coronary artery disease (CAD). The technique has also already provided new insight into difficult conditions (6) and has demonstrated perfusion changes in response to therapeutic interventions (7, 8).

Previous studies have reported the interstudy reproducibility of SPECT (9, 10) and PET (11, 12). To our knowledge, there are no published studies on the interstudy reproducibility of contrast echocardiography. The only previously published work on the reproducibility of perfusion CMR has been on inter- and intraobserver reproducibility (13). There is no published work on the interstudy reproducibility of perfusion CMR which needs to be determined before it can be used to determine the significance of longitudinal changes in myocardial perfusion after pharmacologic or therapeutic interventions in defined sample sizes.

The majority of perfusion CMR work has been with the first-pass bolus tracking technique (14), using fast low-angle shot (FLASH) (8, 15–18). Therefore, we aimed to measure the interstudy reproducibility of first-pass perfusion CMR with a FLASH sequence. In addition, we aimed to compare the influence on reproducibility of two previously

Received 7 February 2005; accepted 20 July 2005.
This work was supported by CORDA, The British Heart Foundation and Siemens Medical Solutions. The CMR unit at the Royal Brompton Hospital receives research support from Siemens. Professor Pennell is a consultant to Siemens and has served on an advisory board for Nycomed Amersham. Professor Pennell and Professor Yang are Directors of Cardiovascular Imaging Solutions.
*Address correspondence to Professor Dudley J. Pennell, M.D., F.R.C.P., F.A.C.C., Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; Fax: +44-207-351-8816; E-mail: d.pennell@ic.ac.uk

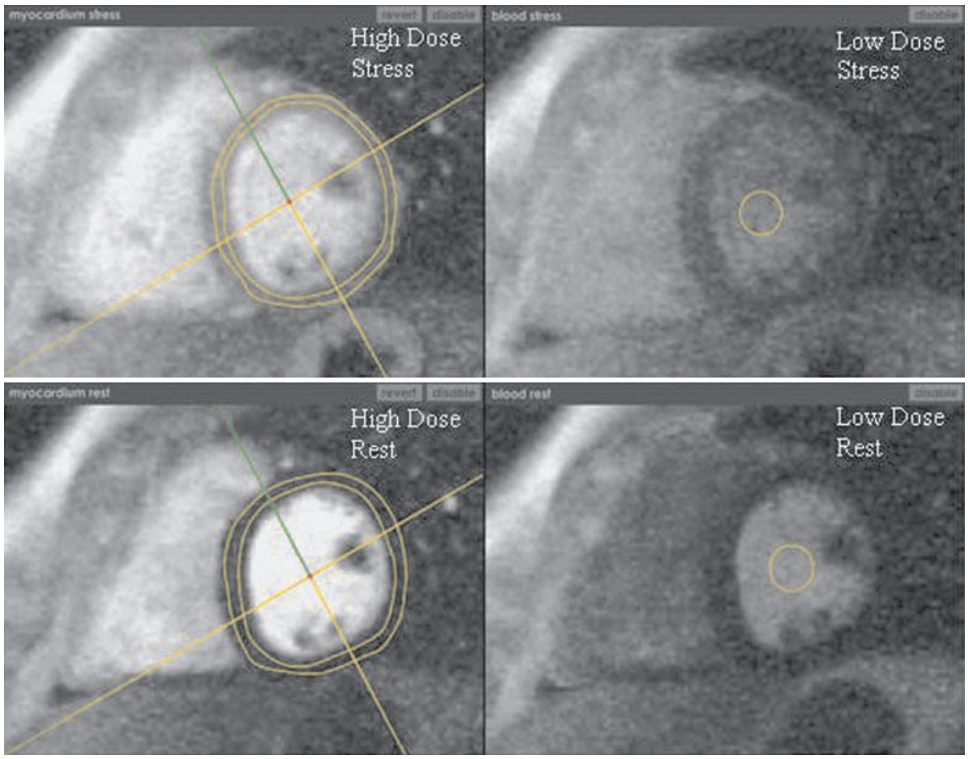

Figure 1. Analysis of the perfusion studies. A short axis (SA) slice is shown with the stress study (top row) and the rest study (lower row). The SA slice is split into 4 regions (anterior, lateral, inferior and septal), and the software package allows the low dose arterial input function (small circle in the left ventricular blood pool) and high dose myocardial signal (larger circles outlining the myocardium) to be separately acquired.

described analysis techniques—model-based deconvolution using the Fermi function (19, 20) and normalized up-slopes (21).

2. Methods

2.1. *Subjects*

The study was approved by the local ethics committee, and each volunteer gave written informed consent. The study group consisted of 7 normal subjects (mean age 37 years, 6 males, 1 female) and 9 patients with known CAD (mean age 65 years, 8 males, 1 female). Entrance criteria for the normal patients included normal examination, resting blood pressure (BP) and electrocardiogram (ECG). All patients with CAD had previously undergone a coronary x-ray angiogram. Four had three vessel disease, four had two vessel disease, and one had one vessel disease. Any subjects with contra-indications to receiving adenosine or undergoing a CMR study were excluded from the study.

2.2. *CMR*

All studies were performed on a 1.5T scanner (Siemens Sonata, Erlangen, Germany) with a 4-channel body array coil. Each subject underwent rest and adenosine stress first-pass myocardial perfusion CMR study on 2 separate visits (mean period between the 2 studies 13 ± 8 days). All subjects were

Table 1. Haemodynamics

	Baseline 1	Baseline 2	p	Ado 1	Ado 2	p
SBP	138 ± 14	143 ± 28	ns	146 ± 29	141 ± 21	ns
DBP	81 ± 15	77 ± 15	ns	82 ± 15	78 ± 15	ns
HR	67 ± 14	63 ± 12	ns	88 ± 16	84 ± 18	ns
RPP	8500 ± 1410	8250 ± 780	ns	12300 ± 2620	11300 ± 810	ns

Haemodynamic measurements on visit 1 and 2 at rest and during adenosine stress in all 16 subjects. Values are mean ± SD. Ado = adenosine; DBP = diastolic blood pressure (mm Hg); HR = heart rate (beats per minute); ns = not significant; RPP = rate pressure product (SBP × HR); SBP = systolic arterial blood pressure (mm Hg).

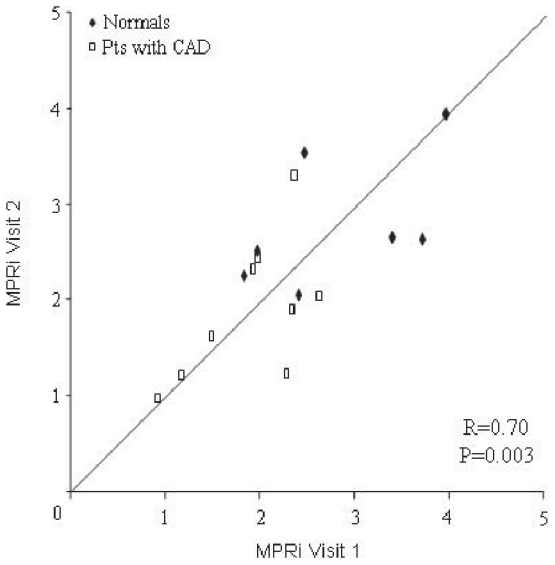

Figure 2. Global, transmural, MPRi with Fermi deconvolution. Scattergram of the repeat global, transmural, MPRi measurements in all 16 subjects by Fermi deconvolution. The line of identity is superimposed and the linear regression coefficient (R) for the linear regression line is quoted. MPRi = myocardial perfusion reserve index.

asked to abstain from coffee, tea and other adenosine antagonists for 12 hours prior to each study. In none of the subjects with CAD was there any change in their symptoms or medication between the two studies. A high resolution non-selective saturation-recovery FLASH sequence was used (FoV read 320–400 mm, FoV phase 75–100% of the FoV read, acquired voxel size 1.3–1.6 × 1.3–1.6 × 10 mm

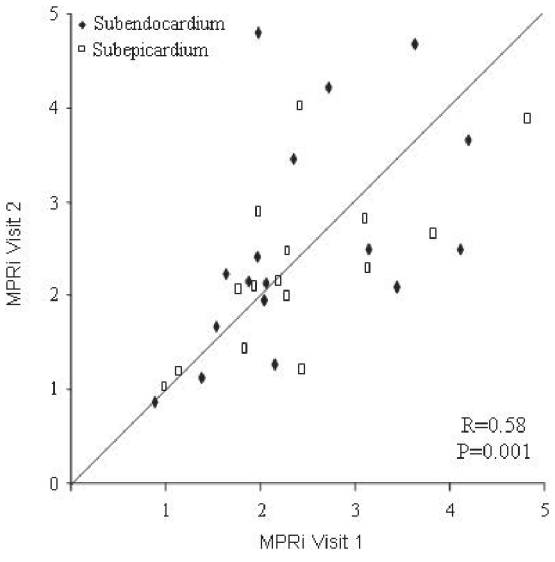

Figure 3. Subendo- and subepicardial MPRi with Fermi deconvolution. Scattergram of the repeat subendo- and subepicardial MPRi measurements in all 16 subjects by Fermi deconvolution. Format same as Fig. 2.

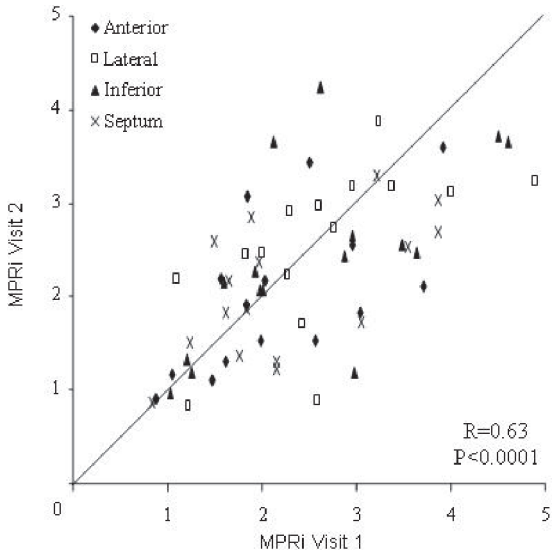

Figure 4. Regional, transmural, MPRi with Fermi deconvolution. Scattergram of the repeat regional transmural MPRi measurements in all 16 subjects by Fermi deconvolution. Format same as Fig. 2.

without interpolation, flip angle 10°, image duration 295 ms, TE 1.11 ms, time from saturation pulse to beginning of imaging 63 ms, linear phase-encode order covering central raw data halfway through image duration). Gadolinium-DTPA-BMA (Gd) was injected as a bolus at 7 mL/s by power injector (Medrad) via an 18G cannula in the right antecubital fossa. Images were acquired over 50 cardiac cycles, and the volunteers were asked to hold their breath in end-expiration for as long as was comfortable. One mid-ventricular short axis

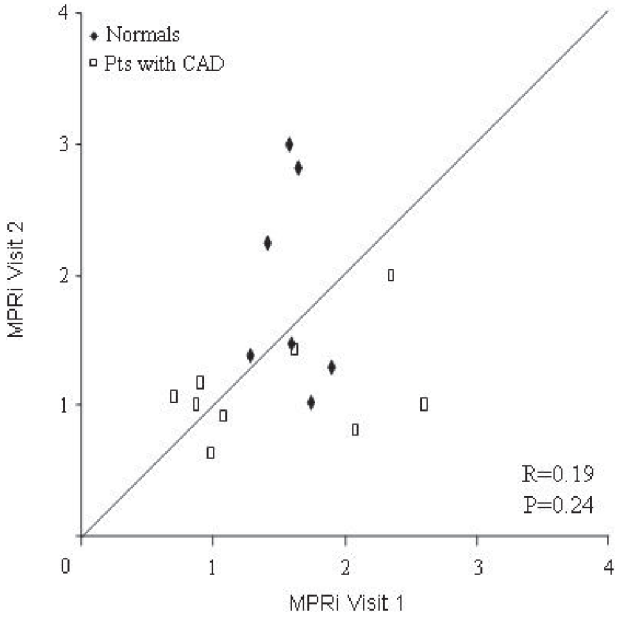

Figure 5. Global, transmural, MPRi with normalized up-slopes. Scattergram of the repeat global transmural MPRi measurements in all 16 subjects by normalized up-slopes. Format same as Fig. 2.

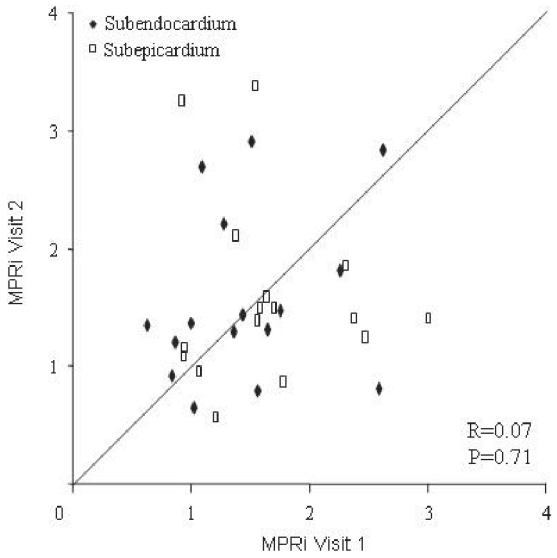

Figure 6. Subendo- and subepicardial MPRi with normalized up-slopes. Scattergram of the repeat subendo- and subepicardial MPRi measurements in all 16 subjects by normalized up-slopes. Format same as Fig. 2.

(SA) slice was acquired each cardiac cycle in diastole. Adenosine was infused for 4 minutes at 140 μg/kg/min prior to the stress images being acquired. The stress study was performed at least 20 minutes after the rest study. On the volunteer's second visit, the SA slice planned to be imaged was compared with the SA slice from the first visit, to ensure similar slices were studied. As far as possible, the two studies were performed at the same time of day, to try to limit the effect of any diurnal variations in myocardial perfusion or other physiological parameters.

As the studies were to be analyzed quantitatively, a 'dual bolus' protocol was used (22). For both the rest and stress study, the volunteer received a low dose (0.01 mmol/kg at 0.05 M) bolus of Gd (Omniscan, GE Healthcare, UK), followed by a high dose bolus of Gd (0.1 mmol/kg at 0.5 M). The low-dose was injected approximately 2 minutes before the high-dose injection. The power injector had two syringes (designed for contrast agent and saline), which were used for 0.05 M and 0.5 M Gd in this work. The 5 mL line volume was pre-loaded with saline and an additional 5 mL injection volume to that required for the dose was programmed to ensure complete dose delivery. Therefore, each subject received a total of 0.22 mmol/kg of Gd on each visit. Each bolus was of equal volume and the lines were flushed with normal saline between each injection. By injecting a low dose bolus, followed by a high dose bolus, both an accurate arterial input function (AIF) and optimized signal in the myocardium was achieved (22). Blood pressure and heart rate were monitored throughout each study.

2.3. *Image analysis*

Each study was analyzed using customized software (CMRtools, Cardiovascular Imaging Solutions, London, UK). The subendocardial and subepicardial myocardial borders were drawn, and adjusted if necessary to compensate for cardiac and respiratory motion. The software package allowed regional and non-transmural myocardial perfusion analysis, once the subendo- and subepicardial borders had been drawn (Fig. 1). AIF and myocardial tissue response curves were corrected by baseline subtraction then assumed to be linearly proportional to Gd concentration. The myocardial perfusion reserve index (MPRi; a measure of the ratio between stress and rest myocardial perfusion) was calculated using two methods: model-based deconvolution using the Fermi function and normalized up-slope analysis, using the same regions of interest (ROI).

2.4. *Statistical analysis*

Differences between haemodynamic parameters were assessed by using the paired two-tailed student's *t*-test. Coefficients of variation (CoV) were calculated as the standard deviation of the differences between the 2 measurements divided by the mean value. Comparison of reproducibility of techniques was calculated using a technique developed by Bland (23). A p value of less than .05 was considered to indicate statistical significance.

3. Results

3.1. *Haemodynamics*

There was no significant difference in systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product

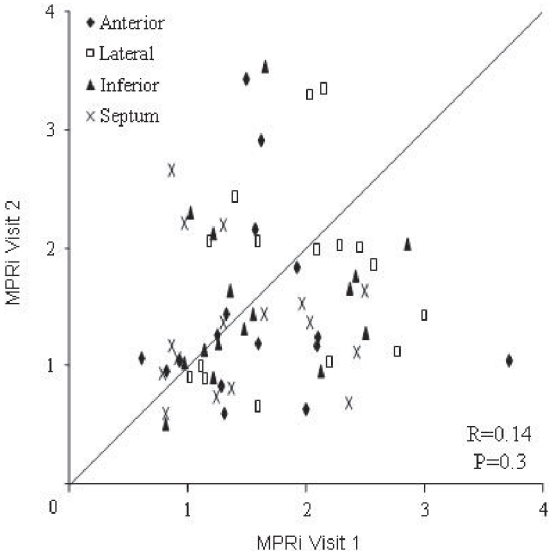

Figure 7. Regional, transmural, MPRi with normalized up-slopes. Scattergram of the repeat regional transmural MPRi measurements in all 16 subjects by normalized up-slopes. Format same as Fig. 2.

Table 2. Myocardial perfusion reserve index

	Fermi			Normalised up-slope			
	MPRi 1	MPRi 2	CoV (%)	MPRi 1	MPRi 2	CoV (%)	p
Global							
Transmural	2.3 ± 0.8	2.3 ± 0.8	21	1.8 ± 1.1	1.5 ± 0.7	41	0.02
Subendocardial	2.3 ± 0.9	2.4 ± 1.1	31	1.7 ± 1.1	1.6 ± 0.7	47	0.55
Subepicardial	2.5 ± 1.0	2.4 ± 1.0	23	1.8 ± 1.0	1.6 ± 0.8	50	0.11
Regional							
Anterior	2.2 ± 0.9	2.0 ± 0.8	26	1.8 ± 1.1	1.4 ± 0.8	55	0.50
Lateral	2.6 ± 1.0	2.5 ± 0.9	34	2.1 ± 1.0	1.7 ± 0.8	45	0.11
Inferior	2.6 ± 1.1	2.4 ± 1.0	28	1.8 ± 1.2	1.5 ± 0.7	39	0.46
Septum	2.3 ± 0.9	2.1 ± 0.7	28	1.7 ± 1.2	1.3 ± 0.6	53	0.01

MPRi ± SD and CoV (%) in all 16 subjects on visit 1 and 2 calculated with Fermi deconvolution and normalised up-slopes, by global and regional analysis. p value shown is for comparison of CoV values by Fermi and normalised up-slopes. CoV = coefficient of variation; MPRi = myocardial perfusion reserve index.

(heart rate × systolic blood pressure) between the two studies (Table 1).

3.2. *MPRi analysis*

Figures 2–4 show scattergrams of the global (transmural and by myocardial layer) and regional MPRi measurements, calculated by Fermi deconvolution. The reproducibility of MPRi was similar in normal volunteers and in patients with CAD (21% vs. 23%, p = .88). The reproducibility of the regional analysis was 28%, and the difference compared with the global analysis fell short of statistical significance (p = .45). Figures 5–7 show analogous scattergrams of the global (transmural and by myocardial layer) and regional MPRi measurements, calculated by normalized up-slopes. All the reproducibility values were superior using the Fermi deconvolution compared with normalized slopes and this was significant for global MPRi (21% vs. 41%, p = .02). The comparison for all subjects is shown in Table 2, with breakdown into patients and normals in Table 3.

4. Discussion

4.1. *Fermi deconvolution vs. normalized up-slope analysis*

This study demonstrates that quantitative single-slice first-pass myocardial perfusion FLASH CMR has reasonable interstudy reproducibility for the measurement of MPRi at its current stage of development and that the reproducibility using Fermi deconvolution was superior to normalized up-slope analysis to calculate global MPRi. Both Fermi deconvolution and normalized up-slopes have been previously shown to be useful techniques to measure MPRi. However, there has been no previous direct comparison of the two analysis techniques. The superior interstudy reproducibility of the Fermi deconvolution MPRi measurements suggests that this is the superior analysis technique. It is also of note that the mean MPRi calculated by Fermi deconvolution was higher than that by normalized slopes (2.3 ± 0.8 vs. 1.5 ± 0.6 respectively, p < .001). This might be explained by the fact that the Fermi deconvolution utilizes more of the

Table 3. Coefficient of variation (%) with Fermi deconvolution and normalised up-slopes

	Fermi		Normalised up-slope	
	Normals (n = 7)	CAD (n = 9)	Normals (n = 7)	CAD (n = 9)
Global				
Transmural	21	23	39	41
Subendocardial	25	37	37	50
Subepicardial	28	21	64	31
Regional				
Anterior	29	24	45	62
Lateral	19	42	40	46
Inferior	26	32	51	24
Septum	29	29	62	42

CoV, as a percentage, between the MPRi values on visit 1 and 2 by Fermi deconvolution and normalised up-slopes, in the normal volunteers and patients with CAD. CAD = coronary artery disease; CoV = coefficient of variation; MPRi = myocardial perfusion reserve index.

characteristics of the SI-time curve than just the few points on the up-slope. There are no previous published studies on the interstudy reproducibility of quantitative perfusion CMR, nor a direct comparison of two analysis techniques. This is the first study to our knowledge to look at the interstudy reproducibly of any technique at measuring MPR in patients with CAD and non-transmural MPR.

4.2. *Global vs. regional analysis with Fermi deconvolution*

Regional MPRi was similar in the four left ventricular segments, with comparable CoV in all regions. However, compared to the global MPRi values, the agreement between these two measurements in each segment was lower (CoV 21% for global analysis; mean CoV 28% for regional analysis, although the difference fell short of statistical significance, $p = .45$). This difference is mainly due to methodological reasons because ROIs of a smaller size yield data with greater standard deviations. However, it is important to consider that spatial and temporal heterogeneity of myocardial perfusion may have influenced the reproducibility (24–27).

4.3. *CMR vs. PET*

To the best of our knowledge, there have only been two previous studies on the reproducibility of myocardial perfusion measurements with PET (11, 12). Nagamachi et al. studied a total of 30 healthy volunteers. In this study, the correlation for global rest perfusion ($r = 0.63$, $p < .005$) and hyperemic perfusion ($r = 0.69$, $p < .005$) was reasonable. However, this study had a number of limitations. The CoV was not given for data obtained on different days, and no MPR values were quoted. Only 13 of the volunteers had two resting and hyperemic PET studies, the others having either only rest or hyperemic studies; the interventricular septum was excluded from quantitative analysis because of prominent biventricular spill over. In the study by Kaufmann et al., 21 healthy volunteers had rest and hyperemic perfusion measured twice within one hour. The repeatability coefficient for global coronary vasodilator reserve was 1.32 (33% of the mean). The equivalent repeatability coefficient in our study with perfusion CMR was 1.49 (53% of the mean MPRi). However, in our study, the gap between visits was on average 13 days, which more accurately reflects the likely gap between studies in clinical trials. In this study, the term quantitative perfusion CMR has been used, reflecting the measurement of MPRi. However, it showed be noted that absolute myocardial perfusion was not measured (for example as mL/g/min) as can be by PET. Therefore, the measurement of perfusion by the CMR in this study is semi-quantitative.

4.4. *CMR vs. SPECT*

To the best of our knowledge, there have been two previous studies on the interstudy reproducibility of SPECT (9, 10). Both these studies showed good reproducibility for the detection of defects. However, SPECT is not able to give a measure of MPR; thus, it is not directly analogous to quantitative perfusion CMR.

4.5. *Study limitations*

Although we required our volunteers to avoid caffeine for 12 hours before each perfusion study, it is possible that some patients had caffeine, which would have influenced their hyperaemic response to the adenosine. If we had measured caffeine levels in the bloodstream to ensure for each study the volunteers were caffeine free we may have been able to improve perfusion reproducibility. ROI and slice acquisition positioning variations between the two visits, especially in the CAD patients, may have affected reproducibility. In this study, as such a high resolution, long acquisition, sequence was used, only one SA slice was acquired per cardiac cycle; therefore, only myocardium corresponding to 6 segments of the 17 segment model were studied (28). This is in contrast to the PET studies, where the entire myocardium was analyzed. However, sequences have now become available (29) which have greater temporal resolution, and thus allow comprehensive myocardial coverage while maintaining the similar spatial resolution to the sequence used in this study. The reproducibility of the assessment of global MPRi may improve with more comprehensive myocardial perfusion imaging. These new sequences also offer higher signal to noise ratio and reduced motion artifacts, which may improve regional MPRi reproducibility (30). In this study, a fairly complex, dual bolus protocol was used. We used this protocol to achieve both an accurate AIF while also achieving good myocardial signal. However, this protocol has its own limitations. The complex nature of the set up in comparison to a single bolus technique may lessen its reproducibility. Derivation of the AIF from the second low dose bolus of Gd may be affected by the residual Gd from the first rest study (31). The degree of this effect may vary from study to study, and this will influence the reproducibility of the technique. While the low dose arterial input and the high dose myocardial response bolus injections were given as close together as practical, there was an inevitable gap between the two injections (usually $\sim$ 2 minutes). This is a weakness in the dual bolus protocol, with a potential, variable dissimilarity between the arterial input and myocardial response boluses. A new technique has been proposed (31) which would avoid the problems associated with the dual bolus technique.

5. Conclusion

Quantitative first-pass FLASH perfusion CMR, using the Fermi model for constrained deconvolution has reasonable reproducibility for the assessment of MPRi, and this is superior to normalized up-slope analysis. As this rapidly

developing technique improves, it is anticipated that its reproducibility will improve.

6. Abbreviations

AIF	arterial input function
BP	blood pressure
CAD	coronary artery disease
CMR	cardiovascular magnetic resonance
CoV	coefficient of variation
ECG	electrocardiogram
FLASH	fast low-angle shot
FoV	field of view
Gd	gadolinium-DTPA-BMA
MPRi	myocardial perfusion reserve index
PET	positron emission tomography
SA	short axis
SPECT	single-photon emission tomography

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