

# Cardiac magnetic resonance perfusion imaging for the functional assessment of coronary artery disease: a comparison with coronary angiography and fractional flow reserve

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## KEYWORDS

CMRI;  
Coronary artery disease;  
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**Aims** Cardiac magnetic resonance perfusion imaging (CMRI) is a promising technique for non-invasive measurement of myocardial perfusion reserve. Fractional flow reserve (FFR) is an established invasive method for functional assessment of coronary artery disease (CAD). To prospectively assess the diagnostic value of CMRI for the detection of haemodynamically significant coronary lesions, compared with coronary angiography (CA) and FFR.

**Methods and results** Forty-three patients with suspected or known CAD underwent CA, CMRI, and FFR measurement. First pass magnetic resonance perfusion examination was performed during hyperaemia (140 µg/kg/min adenosine over 6 min) and at rest. One hundred and twenty-nine perfusion territories were assessed by semi-quantitative evaluation of signal intensity–time curves using the myocardial perfusion reserve index (MPRI) [ $\text{upslope}_{\text{stress}(\text{corrected})} / \text{upslope}_{\text{rest}(\text{corrected})}$ ]. Perfusion territories were categorized as normal (coronary stenosis  $\leq 50\%$ ), intermediate (stenosis  $> 50\%$  and FFR  $> 0.75$ ), or severe (stenosis  $> 50\%$  and FFR  $\leq 0.75$  or total occlusion). MPRI values ( $\pm$ SD) were significantly different between the three categories [normal,  $2.2 \pm 0.5$  vs. intermediate,  $1.8 \pm 0.5$  ( $P = 0.005$ ) and intermediate vs. severe,  $1.2 \pm 0.3$  ( $P < 0.001$ )]. An MPRI cut-off value of 1.5 (derived from receiver operating characteristics analysis) distinguished haemodynamically relevant (severe) from non-relevant (normal and intermediate) stenoses with a sensitivity of 88% (CI 74–100%) and a specificity of 90% (CI 84–96%).

**Conclusion** In contrast to earlier studies that compared CMRI with morphological examination (CA) alone, the present study compared CMRI with CA plus a standard invasive functional assessment (FFR) and demonstrated that CMRI is able to distinguish haemodynamically relevant from non-relevant coronary lesions with a high sensitivity and specificity and may therefore contribute to clinical decision-making.

## Introduction

Despite recent advances in non-invasive imaging techniques, coronary angiography (CA) remains the standard method for morphological assessment of coronary artery disease (CAD). Patient prognosis, however, is more closely related to the functional significance of the disease.<sup>1–3</sup> For example, patients with no evidence of myocardial ischaemia have low cardiac event rates, despite demonstrating coronary

artery lesions of intermediate severity.<sup>4–6</sup> To assess the functional severity of coronary stenoses, measurement of the pressure-derived fractional flow reserve (FFR) has become a well-established invasive standard of reference.<sup>4,7</sup> FFR represents the ratio of maximal coronary blood flow in the presence of a stenosis to the maximum achievable blood flow if all epicardial obstructions were absent.<sup>8</sup> Measurement of FFR has the disadvantage of being invasive and associated with radiation exposure. Conversely, cardiac magnetic resonance perfusion imaging (CMRI) offers the possibility to assess myocardial blood flow non-invasively and without radiation exposure, recording the myocardial signal intensity over time characteristics of the first pass of a T1-shortening contrast agent.<sup>9–13</sup> CMRI

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has been extensively validated in animals and healthy volunteers;<sup>10,11,14</sup> also CMRI has shown promising results when compared with CA or positron emission tomography (PET).<sup>15,16</sup> Ishida *et al.*<sup>17</sup> found that in 104 patients without myocardial infarction, stress enhancement as measured by dynamic MR imaging correlates more closely with quantitative CA results than does stress enhancement as measured by SPECT. The aim of this study was to estimate the sensitivity and specificity of CMRI and to determine the optimal cut-off for the detection of haemodynamically relevant coronary lesions, using the combination of CA and FFR as the reference standard.

## Methods

### Patients

Of 79 patients, referred for diagnostic CA for clinically suspected CAD or progression of existing CAD, 50 patients met the inclusion criteria and were willing to participate. Exclusion criteria included contraindications to CMRI, intolerance to the used pharmacological agents, or refusal to participate as well as the presence of acute coronary syndromes within the preceding 30 days. Of these 50 patients, seven had to be excluded due to technical reasons (MRI,  $n = 4$ ; FFR measurement,  $n = 2$ ) or claustrophobia ( $n = 1$ ). The remaining 43 patients were included in the data analysis. Demographic and clinical characteristics were recorded [hypertension ( $\geq 140/\geq 90$  mmHg), diabetes (non-insulin-dependent or insulin-dependent), angina class, family history of CAD]. All patients underwent CMRI and CA within 4 weeks. FFR measurement was performed if angiography indicated a coronary stenosis of  $>50$ – $99\%$  (100% stenosis does not allow a pressure wire to be passed). The study protocol was approved by the local Ethics Committee and written informed consent was obtained.

### Coronary angiography

All patients underwent CA by the femoral approach. At least two orthogonal views were obtained with the projection showing the most severe narrowing used for quantitative coronary measurements (Philips DCI, Eindhoven, The Netherlands). An intracoronary bolus of 0.25 mg nitroglycerine was administered for maximum dilatation of the epicardial vessels. Using the guiding catheter as a scaling device, lesion length, minimal lumen diameter, and proximal and distal reference diameter were calculated (CAAS II, Pie Medical, Maastricht, The Netherlands). If more than one coronary artery stenosis was present within the same perfusion territory, the most severe stenosis was used. For subsequent analysis, the coronary tree was divided into 15 segments<sup>18</sup> [right coronary artery (RCA) 1–4, LM and left anterior descending artery (LAD) 5–10, and left circumflex artery (LCx) 11–15]. The segments 1, 2, 5, 6 and 11 were defined as proximal and the remaining segments as distal segments.

### FFR measurement

FFR was measured with a sensor-tipped 0.014 in. angioplasty guide-wire (PressureWire™, Radi Medical Systems, Uppsala, Sweden). After crossing the target lesion with the wire, hyperaemia was induced by an infusion of 140  $\mu\text{g}/\text{kg}/\text{min}$  adenosine (Adrekar™, Sanofi, Munich, Germany). The maximum pressure gradient was used to calculate FFR, defined as the ratio of mean post-stenotic pressure vs. mean aortic pressure (measured via the guiding catheter) during maximum hyperaemia.

### Cardiac magnetic resonance perfusion imaging

Patients were examined in the supine position with a 1.5 T whole body MR-tomograph (Sonata, Siemens Medical Solutions, Erlangen, Germany) equipped with eight independent receiver channels

using a 12-element body-phased array cardiac surface coil. During the examination, blood pressure and ECG were continuously recorded. After two rapid surveys to determine the exact position of the heart, three parallel short-axis views (basal, mid-papillary, and apical) were chosen for perfusion imaging. We used a T1-weighted saturation recovery turbo flash sequence (flip angle  $12^\circ$ , TE 1.0 ms, acquisition window 192 ms, inversion time 100 ms, 128 phase-encoding lines) with prospective ECG triggering. Slice thickness was 10 mm. With a typical field-of-view of  $340 \times 265 \text{ mm}^2$ , the in-plane spatial resolution was  $2.7 \times 2.1 \text{ mm}$ . Hyperaemia was induced with a continuous (6 min) intravenous injection of 140  $\mu\text{g}/\text{kg}/\text{min}$  adenosine (Adrekar) via a venous line. A bolus of gadodiamide (Omniscan, GE Healthcare, Buckinghamshire, UK) 0.05 mmol/kg body weight with a flow rate of 5 mL/s followed by 20 mL saline solution using an MR-compatible automatic injector (Spectris, Medrad, Indianola, PA, USA) was administered via a separate cannula in the opposite arm while the adenosine injection was continued. To minimize breathing artefacts, care was taken to achieve breath-holding during the first pass of the contrast agent through the myocardium. The resting perfusion examination was performed 10 min after the stress examination and discontinuation of the adenosine infusion, using a second bolus of contrast agent. Flow rates, dosage, slice position, and pulse sequence parameters were identical to those used for the stress examination.

### Image analysis

Data was analysed off-line by means of a commercially available dedicated software tool (Dynamic Signal Analysis, Argus, Siemens Medical Solutions). Subendocardial and subepicardial borders were positioned on each slice on a frame with high contrast between left ventricular (LV) cavity and myocardium. The borders were propagated by the software on all frames with a semi-automated contour correction. An interactive correction was done if necessary. The LV myocardium was divided into six equiangular segments per slice, according to the modified standardized nomenclature for tomographic imaging of the heart,<sup>19</sup> resulting in a total number of 36 segments per patient (18 for the stress examination and 18 for the resting examination).

Mean signal intensity for each myocardial segment was registered over time and signal intensity-time curves were obtained. Signal intensity in different myocardial segments may be somewhat variable-dependent on the coil sensitivity profile. In order to eliminate signal inhomogeneities caused by the location of the segment and the surface coil, a baseline and coil normalization was performed using the following equation:

$$\text{Signal}_{\text{corrected}} = \frac{\text{Mean}_{\text{Baseline/Segment}}}{\text{Mean}_{\text{Baseline/All segments}}} * \text{Signal}_{\text{Source data}} - \text{Mean}_{\text{Baseline/Segment}}$$

$\text{Mean}_{\text{Baseline/Segment}}$  is the mean value of the consecutive signal values of the baseline in the individual segment.  $\text{Mean}_{\text{Baseline/All segments}}$  is the mean value of the consecutive signal values of the baselines of all segments in three slices.  $\text{Signal}_{\text{Source data}}$  is the signal intensity value at one time point of the signal intensity curve within one segment without any correction.  $\text{Signal}_{\text{corrected}}$  is the resulting value of signal intensity at one time point of the signal intensity curve within one segment with completed correction. Using this equation, a normalization of the curves and a subtraction of the baseline was performed. For each signal intensity-time curve, the foot point and the point of signal maximum were determined by the software. A straight-line model was used for a linear fit of the data. The linear fit was based on the least-squares regression line, the most commonly used method. Signal maximum was defined as the data point with the highest value of signal intensity. Both data points (foot point, signal maximum) were corrected interactively if necessary. The downslope data points were excluded from the

evaluation to avoid the effect of contrast material diffusion into the interstitial space.

The upslope values of the line were used for further calculations. The upslope values of all segments ( $US_{\text{segment}}$ ) were divided by the upslope value of the signal intensity–time curve in the LV cavity ( $US_{\text{LV cavity}}$ ) obtained from the same slice as the myocardial segment's curve was. The signal intensity–time curve of the LV cavity served as input function.<sup>15</sup> After normalization by the  $US_{\text{LV cavity}}$  ( $US_{\text{corrected}} = US_{\text{segment}}/US_{\text{LV cavity}}$ ),<sup>15,20</sup> the myocardial perfusion reserve index (MPRI) was calculated by division of the corrected upslope of the stress examination by the corresponding segment's corrected upslope value of the rest examination [MPRI:  $\text{upslope}_{\text{stress (corrected)}}/\text{upslope}_{\text{rest (corrected)}}$ ]. The MPRI served as a semi-quantitative estimation of the perfusion reserve. According to the coronary dominance, the segments were assigned to the respective perfusion territory<sup>19</sup> and the mean value of the two lowest scoring segments for each perfusion territory was used for further analysis.

## Statistical analysis

All perfusion territories were classified as normal, intermediate, or severe, according to the coronary angiogram and FFR measurements. A perfusion territory was classified as normal if CA showed no significant stenosis ( $\leq 50\%$ ). A perfusion territory was classified as intermediate if it encompassed a lesion with a stenosis of  $>50\%$  and an FFR  $> 0.75$ . A territory was classified as severe if there were lesions of  $>50\%$  and an FFR  $\leq 0.75$  or a total occlusion. A dichotomous classification was also defined to allow for analysis of sensitivity and specificity: normal and intermediate results were considered negative and severe results as positive.

Descriptive analysis for categorical and continuous parameters was performed using the software package SPSS version 13.0 (SPSS, Chicago, IL, USA) and SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). All data are presented as mean  $\pm$  standard deviation for continuous data and as proportions for binary data.

As three territories have been measured in each patient, data on the territory level may not be independent. We accounted for this fact by using generalized estimation equations (GEEs) methods for statistical tests. All statistical tests were two-sided. We used an alpha level of 0.05 and adjusted for pairwise comparisons using the Bonferroni method.

We estimated the area under the receiver operating characteristics (ROC) curve using the approach by Liu and Wu<sup>21</sup> For exploratory purposes, the optimal cut-off for MPRI value was defined as the value that maximized the sum of sensitivity and specificity. Confidence intervals for sensitivity and specificity were calculated according to the approach of Zhou *et al.*<sup>22</sup>

## Results

A total of 129 perfusion territories were analysed: three territories in each of the 43 consecutive patients. The patients were 88% male, average age of  $65.5 \pm 8$  years (Table 1). Twenty-three patients (53%) experienced stable angina and the remaining 20 patients (47%) had no typical angina but had inconclusive stress tests or were scheduled for control angiography for clinical reasons. Characteristics of the perfusion territories are given in Table 2. Seventy-six (59%) territories were normal, 29 (22%) were intermediate, and 24 (19%) were severe according to the previously defined criteria. No significant differences were noted regarding the clinical characteristics (sex, hypertension, diabetes, familial history, angina class).

### Coronary angiography

CA was carried out in all 43 patients. An overview of all angiographic characteristics is provided in Table 2. A

**Table 1** Patient clinical characteristics

Clinical characteristics	
Male	38 (88)
Smoking	15 (35)
Hypertension	37 (86)
Diabetes	10 (23)
Familial history	7 (16)
Angina present	23 (53)
Prior MI	8 (19)
Prior coronary intervention	12 (28)
Mean age (years)	$65.5 \pm 8.1$
LVEF (%)	$58 \pm 9$
Angiographic characteristics	
No relevant CAD	14 (33)
Single-vessel disease	12 (28)
Multi-vessel disease	17 (39)
At least one stenosis $>30\%$ in any coronary artery	43 (100)

Values are numbers of patients or mean  $\pm$  SD (per cent of all 43 patients). Coronary single-vessel disease was defined as the presence of one vessel with a diameter stenosis  $> 50\%$ . Multi-vessel disease was defined as the presence of diameter stenosis of  $>50\%$  in at least two vessels.

normal angiography was noted in 30 (23%) perfusion territories. Angiographic stenosis of  $\leq 50\%$  was present in 46 (36%) cases. Fifty-three (41%) perfusion territories revealed an angiographic stenosis  $>50\%$ . Stenoses were located: LAD = 38 (38%), LCx = 32 (32%), and RCA = 29 (29%). Fifty-seven (58%) lesions were proximal and 42 (42%) distal. The overall mean diameter stenosis was  $43 \pm 30\%$  and was significantly different between the three categories ( $P < 0.001$ ). Eleven coronary arteries were totally occluded, six proximal and five distal. However, at least partial collateral filling ( $\geq$  Rentrop grade 2)<sup>23</sup> was present in seven (64%) of the occluded arteries (Table 3).

### FFR measurement

FFR measurement was performed in 42/129 territories. FFR values ranged from 0.38 to 1.0 with a mean FFR of  $0.79 \pm 0.1$ . In 11 territories, an FFR measurement could not be performed due to a complete occlusion of the coronary vessel. In 13/42 (31%) territories, the FFR was significantly reduced (FFR  $\leq 0.75$ ), whereas 29 (69%) territories revealed an FFR above 0.75.

The degree of angiographic stenosis correlated only moderately with the FFR ( $r = 0.64$ ,  $P < 0.001$ ).

### Cardiac magnetic resonance perfusion imaging

CMRI was successfully performed in all 43 patients giving 129 perfusion territories. The mean MPRI was  $1.9 \pm 0.6$  (range: 0.6–4.4). The MPRI was highest in the normal category and significantly different between the remaining categories [normal,  $2.2 \pm 0.5$  vs. intermediate,  $1.8 \pm 0.5$  ( $P = 0.005$ ) and intermediate vs. severe,  $1.2 \pm 0.3$  ( $P < 0.001$ )] (Figure 1). A moderate inverse correlation was observed between diameter stenosis and MPRI ( $r = -0.53$ ;  $P < 0.001$ ) (Figure 2). Correlation between FFR and MPRI was higher ( $r = 0.77$ ,  $P < 0.001$ ). The MPRI values of perfusion segments in patients with diabetes but without a critically reduced FFR were significantly lower than perfusion segments in patients without diabetes ( $1.67 \pm 0.48$  vs.  $1.97 \pm 0.44$ ,  $P = 0.02$ ).

**Table 2** Clinical and procedural characteristics of perfusion territories

	Normal territories (n = 76)	Intermediate territories (n = 29)	Severe territories (n = 24)	P-value
<b>Clinical characteristics</b>				
Male	67 (88)	25 (86)	22 (92)	0.91
Smoking	26 (34)	8 (28)	11 (46)	0.44
Hypertension	66 (87)	26 (90)	19 (79)	0.80
Diabetes	12 (16)	12 (41)	6 (25)	0.12
Familial history	11 (15)	5 (17)	5 (21)	0.78
Angina class	1.82 ± 0.9	1.72 ± 0.8	1.92 ± 1.0	0.79
<b>Angiographic characteristics</b>				
Single-vessel disease	24 (32)	8 (28)	4 (17)	0.024
Multi-vessel disease	10 (13)	21 (72)	20 (83)	0.024
RCA	26 (34)	9 (31)	8 (33)	0.94
LAD	22 (29)	11 (38)	10 (42)	0.55
Left CX	28 (37)	9 (31)	6 (25)	0.60
Proximal segment	25 (54 <sup>a</sup> )	17 (59)	15 (63)	0.74
Distal segment	21 (46 <sup>a</sup> )	12 (41)	9 (38)	0.74
Diameter stenosis (%)	24 ± 21	59 ± 6	84 ± 17	<0.001
<b>Functional characteristics</b>				
FFR	n.a.	0.87 ± 0.07	0.61 ± 0.1	
MPRI	2.2 ± 0.5	1.8 ± 0.5	1.2 ± 0.3	<0.001

Values are numbers of territories or mean ± SD (per cent of the respective number of territories). P-values are those between different categories by GEEs.

<sup>a</sup>Per cent of territories with visible stenoses.

**Table 3** Collateralization of occluded vessels

Sample	Vessel	Location	MPRI	Rentrop grade
0603	RCA	Prox	0.83	0
1501	LAD	Dist	0.93	1
1602	LCx	Dist	1.06	1
5101	LAD	Prox	1.28	1
0103	RCA	Prox	1.48	2
0302	LAD	Dist	1.29	2
1303	RCA	Prox	1.32	2
1403	RCA	Prox	1.48	2
2501	LAD	Dist	1.35	2
2801	LAD	Dist	1.14	2
3202	LCx	Prox	1.75	3

Prox, proximal location; Dist, distal location; Rentrop grades, collateral filling grades: 0, none; 1, filling of branches of the artery to be dilated via collateral channels without visualization of the epicardial segment; 2, partial filling of the epicardial segments via collateral channels; 3, complete filling of the epicardial segment of the artery being dilated via collateral channels.

There was also a trend observed towards lower MPRI values in patients with hypertension and without critically reduced FFR (1.78 ± 0.46 vs. 1.97 ± 0.79,  $P = 0.65$ ).

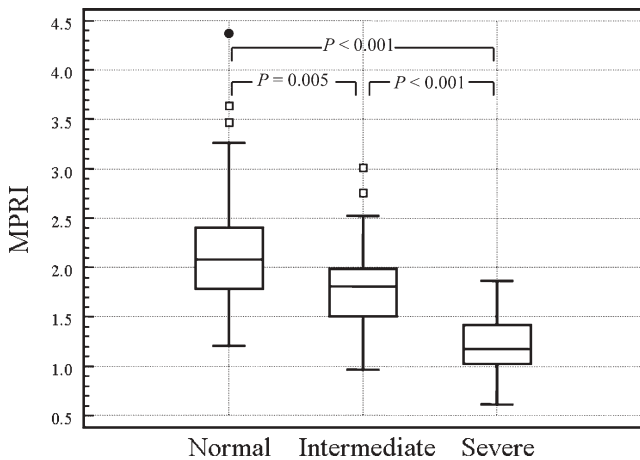
ROC analysis for distinguishing the 'severe' category from the 'normal' and 'intermediate' category revealed an AUC derived from the ROC curves of 0.93. The sum of sensitivity (88%, CI 74–100%) and specificity (90%, CI 84–96%) was maximized (Figures 3 and 4) using an MPRI cut-off value of 1.5 (Figure 5).

## Discussion

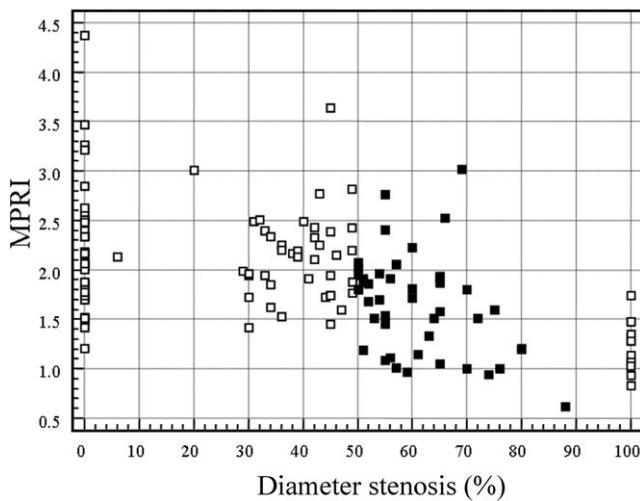
The primary objectives of this study were to prospectively assess the diagnostic value of CMRI (compared with the

invasive reference standard FFR) and to determine the optimal cut-off value for distinguishing haemodynamically relevant from non-relevant coronary stenoses. For the measurement of absolute blood flow, PET remains the method of choice.<sup>24</sup> However, PET is expensive and, due to the short half-lives of the typical tracers, limited to few specialized centres.<sup>25</sup> In the presence of epicardial coronary artery stenoses, the coronary blood flow under stress is closely correlated to the FFR.<sup>26,27</sup> In addition, FFR has been shown to predict outcomes in patients with CAD,<sup>6,7,28,29</sup> but FFR measurement is invasive, limited to coronary catheterization procedures, and therefore associated with radiation exposure. In contrast, CMRI offers the potential to accurately measure the myocardial blood flow non-invasively and without radiation exposure.<sup>14</sup> Contrast agent is administered in a bolus technique increasing the signal intensity of the perfused myocardium during the first pass. The MPRI values observed in the present study showed a very broad range but did not achieve values typically reported for the myocardial perfusion reserve in healthy subjects<sup>20</sup> even in patients without evidence of epicardial stenoses. Also the high prevalences of diabetes and hypertension (seen even in the patients without relevant epicardial coronary stenoses) might contribute to this. Diabetes and hypertension often result in an endothelial microvascular dysfunction not detectable by FFR<sup>30</sup> but potentially reducing MPRI.<sup>31</sup> Mean MPRI was found to be significantly different between the three study categories: none, intermediate, and severe. ROC analysis gave a cut-off value of 1.5 for optimal discrimination between haemodynamically significant and non-significant lesions. Similar cut-off values have been reported in other myocardial perfusion imaging studies.<sup>15,32,33</sup> These studies, however, used only CA as a reference examination; CA is a morphological method that seems inappropriate to evaluate





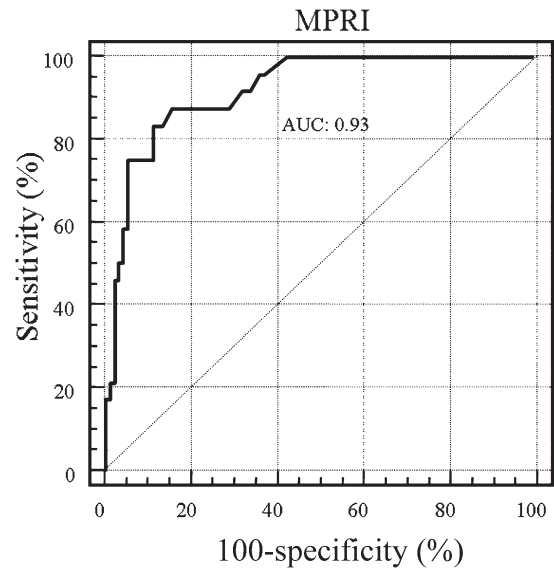
**Figure 1** Comparison of MPRI by category. Boxplots showing the median, quartiles, extreme values, and values out of range for each category.



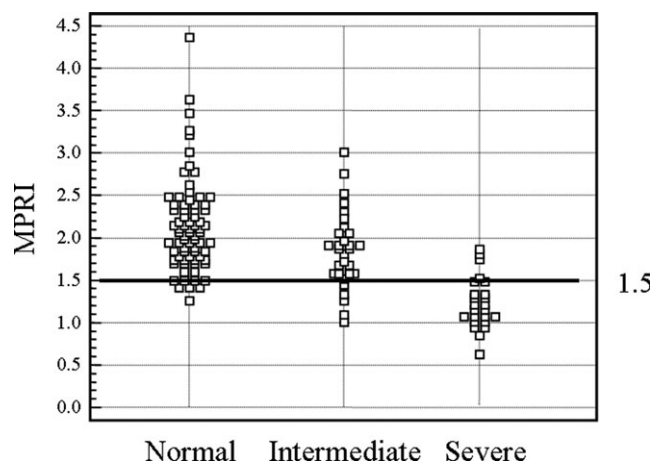
**Figure 2** Correlation of MPRI and diameter stenosis. This chart shows a moderate inverse correlation of the MPRI and the diameter stenosis by angiography. The filled markers indicate the perfusion territories where FFR measurement was performed.

a functional method like CMRI. Only a moderate correlation was observed between CMRI and diameter stenosis. FFR was also only moderately correlated to diameter stenosis, consistent with the published literature.<sup>34</sup> FFR and MPRI, both functional methods, tend to show a higher correlation. Using the MPRI cut-off value of 1.5, we estimated CMRI test characteristics (sensitivity of 88% and specificity of 90%), comparable to earlier studies of Al-Saadi *et al.*<sup>15,20</sup> that used only a single-slice technique and dipyridamole for pharmacological stress. Sensitivity of CMRI for the detection of ischaemic CAD was, in this limited number of patients, at least equal to the reported sensitivities of commonly used imaging techniques like dobutamine stress echocardiography (DSE) or SPECT (reported sensitivities between 67 and 82%).<sup>35,36</sup> When sensitivity and specificity were determined for separate perfusion areas, CMRI remained at least equal to SPECT and DSE (sensitivity decreased markedly to levels of 44%<sup>35</sup>).

Mean MPRI was also significantly different between stenoses <50% and stenosis above 50% diameter, whereas FFR



**Figure 3** Comparison of sensitivity and specificity for MPRI. This ROC curve provide the sensitivity and specificity of the MPRI to distinguish perfusion territories with a haemodynamically significant coronary stenosis.

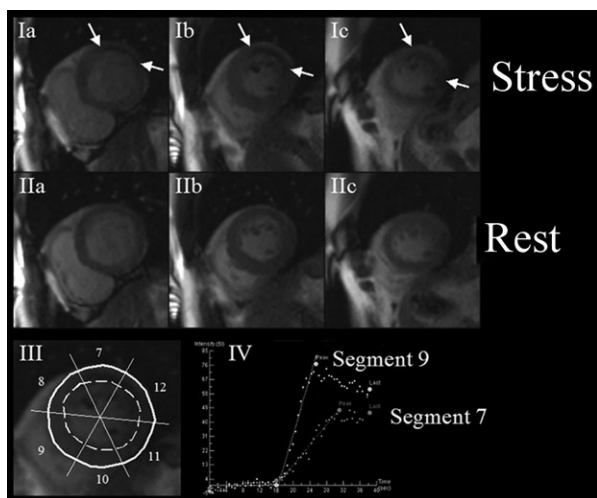


**Figure 4** Individual values of MPRI by category. This chart shows the individual MPRI values for the perfusion territories with normal, intermediate, and severe coronary stenosis. The optimal cut-off value for MPRI (1.5) is indicated.

was not significantly changed. However, FFR values exhibited such a large overlap that no clear discrimination between groups was possible. One possible explanation for this is the differential effects of microvascular disease on MPRI vs. FFR: patients with perfusion areas with stenoses above 50% diameter tended to have a higher prevalence of microvascular dysfunction than patients with no epicardial narrowing.<sup>37-39</sup> In fact, perfusion segments in patients with diabetes and not critically reduced FFR revealed significantly lower MPRI values than in patients without.

**Limitations**

Our study has several limitations. First, FFR measurement was not performed in all coronary arteries; therefore, the reference standard is a combination of angiographic diameter stenosis measurements with and without



**Figure 5** Example of a CMRI study. This figure shows a CMRI study at stress (top row: Ia–c) and at rest (second row: IIa–c). The images represent a basal (a), mid-papillary (b), and apical (c) short-axis view. A stress-induced hypoperfusion was found in the antero-lateral wall (segments 7 and 12; indicated by arrows) with complete replenishment at rest. Exemplary, the corresponding time-intensity curves (IV) of segments 7 and 9 (III) at stress are provided.

corresponding FFR values. Coronary arteries with a diameter stenosis  $<50\%$  were not assessed for cost reasons and to avoid potential iatrogenic complications. It is generally believed that lesions below  $50\%$  diameter stenosis are unlikely to cause ischaemia.<sup>40</sup> Although care was taken to assess the coronary artery by several orthogonal projections, flow-limiting stenoses with a diameter reduction of  $<50\%$  by CA cannot be fully ruled out. Coronary arteries with a total occlusion were not evaluated as the pressure wire is not designed to cross total occlusions. These lesions were all defined as functionally severe. Nevertheless, MPRI was only mildly decreased in some of such patients due to good collateralization (Rentrop grades 2 and 3).

A second limitation was the potential for case mix and spectrum biases. Our study population had high prevalence of CAD relative to the general population, so our reported values of sensitivity and specificity of CMRI have to be interpreted within this context. Thirdly, the assessment of the optimal cut-point was based on the criterion of maximizing the sum of sensitivity and specificity. However, the optimal cut-off depends on the tradeoff of the consequences (both clinical and economic) vs. a false-negative and a false-positive test result.<sup>41,42</sup> Therefore, after validation of this cut-off value using an independent patient population, one of the next research tasks should be a full clinical and economic decision analysis evaluating different cut-off values.

## Conclusion

On the basis of the results of this study, CMRI demonstrates good correlation with the invasive reference standard FFR in the functional assessment of coronary stenosis. An MPRI cut-off value of 1.5 distinguished haemodynamically significant from non-significant coronary lesions with a sensitivity of  $88\%$  (CI 74–100%) and a specificity of  $90\%$  (CI 84–96%),

using conventional CA and FFR measurement as a reference examination. Because of this high sensitivity and specificity as well as the absence of ionizing radiation, CMRI may have the potential to contribute to non-invasive assessment of the haemodynamic relevance of coronary artery lesions.

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**Conflict of interest:** all contributing authors have nothing to disclose.

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