Semi-quantitative Analysis of Adenosine Perfusion Magnetic Resonance Imaging Outperforms Visual Analysis in Identifying Fractional Flow Reserve-Altered Intermediate-grade Coronary Artery Stenosis: A Pilot Study

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Original Article

Abstract

Purpose

To evaluate the diagnostic accuracy of semi-quantitative adenosine perfusion magnetic resonance imaging(MRI) to determine fractional flow reserve(FFR)≤0.80 intermediate-grade coronary stenoses as compared to visual analysis.

Methods

Forty-six patients (mean age 61±9 years;33 males) with 49 intermediate-grade stenoses underwent adenosine perfusion MRI and FFR measurement within 4 months between 2010 and 2013. Retrospective interpretation of all prospectively acquired data was performed. MRI was visually assessed by 2 experienced readers twice with one-year interval, the second time with the knowledge of the diseased artery. All myocardial enhancement maximal upslopes were evaluated distal to the coronary stenosis (=RISK) and in remote myocardium supplied by normal arteries (=REMOTE); stress subendocardial relative myocardial perfusion index (RMPI; RISK/REMOTE upslopes) was assessed in predicting FFR≤0.80 stenoses. Deep learning boosting models including all RISK and REMOTE upslopes were fitted to confirm the added value of accounting for perfusion changes in remote myocardium for FFR prediction.

Results

The average FFR value was 0.84±0.09 and 15/49 (31%) stenoses were FFR≤0.80. Both readers had moderate accuracy (range: 36/49(73%)-38/49(78%)) in predicting FFR≤0.80 stenoses, even with the knowledge of the stenosis location. At a cutoff value of 0.84, stress subendocardial RMPI had higher accuracy (43/49(88%)) than individual visual readings to predict FFR≤0.80 stenoses. The best FFR prediction using the boosting model occurred when accounting for REMOTE myocardial perfusion parameters, leading to diagnostic accuracy of 44/49(90%) for FFR≤0.80.

Conclusion

Semi-quantitative adenosine perfusion MRI accounting for stress perfusion in remote myocardium predicts FFR≤0.80 intermediate-grade coronary stenoses with a higher accuracy than individual visual analysis.

Introduction

Coronary computed tomography angiography and catheter coronary angiography poorly predict flow limitation, especially for stenoses in the intermediate-grade range (i.e. 40%-70% diameter reduction) [1, 2] that may represent up to 42% of coronary stenoses [3]. Additional functional assessment is often required to guide therapeutic management as approximately only one-third of patients with intermediate-grade stenoses suffer from ischemia and would benefit from revascularization [4, 5].

Invasive fractional flow reserve (FFR) measurement is the standard of reference for the functional significance (ischemia) of coronary stenoses. However, its use as a first step in intermediate-grade lesions is prevented by its invasiveness, the use of ionizing radiation, time and the costs of pressure wires [6, 7]. Moreover, the use of invasive FFR varies widely depending on the practice of interventional cardiologists.

While single-photon emission computed tomography [8] and dobutamine stress echocardiography [9] have moderate accuracy (66%-72%) for identifying FFR-altered (i.e. FFR≤0.8) intermediate-grade stenoses, no study has specifically addressed this subgroup of stenoses using stress perfusion magnetic resonance imaging (MRI). Though it has a higher accuracy for the detection of myocardial ischemia as compared to other non-invasive imaging modalities [10], visual analysis of adenosine perfusion MRI in daily clinical practice may be misleading compared to FFR. Actually, MRI

assesses perfusion defects, interrogating both the epicardial coronary artery stenosis and the downstream microvasculature, whereas the FFR value is inherently corrected for the microvascular resistance [11]. The relative myocardial perfusion index (RMPI), recently-described on MRI as the ratio of the maximal enhancement upslope distal to a coronary artery stenosis to that of a normally perfused area during stress perfusion is similar to the FFR approach [12].

As this semi-quantitative index better correlated with the FFR value than the uncorrected enhancement upslope [12], we hypothesized that RMPI could provide high diagnostic accuracy for the detection of FFR-altered intermediate coronary stenoses. Accordingly, the aim of this study was to evaluate the diagnostic accuracy of stress RMPI to determine FFR≤0.80 intermediate-grade coronary stenoses as compared to individual visual analysis.

Material And Methods

Patients and study protocol

This study protocol was approved by the local institutional ethics committee, and patients provided written informed consent. Between 2010 and 2013, consecutive patients with an intermediate-grade stenosis on computed tomography angiography involving one or two major epicardial coronary vessels >1.5mm in diameter were eligible for a study requiring both catheter coronary angiography with FFR measurements and adenosine perfusion MRI within 4 months as previously reported [12]. MRI examinations were performed on a 1.5T MR scanner (Avanto, Siemens Healthineers), as previously reported [12]. In short, the examination consisted in performing stress and resting perfusion on dynamic contrast-enhancement imaging (each using 0.1 mmol/kg Gadodiamide, Omniscan$^{\mathrm{O}}$), and late-gadolinium enhancement (LGE) in the same three short-axis positions (see the supplementary materials for more details). These prospectively acquired data were analyzed retrospectively as follows: visually twice with one-year interval, the second reading with knowledge of the diseased coronary artery; semi-quantitatively and using machine learning analysis to confirm the added value of accounting for perfusion changes in remote myocardium in predicting the FFR value.

MRI analysis

Visual analysis

Two readers (AN, JND) with more than 10-years of experience in cardiac MRI, blinded to patient's characteristics, history and coronary angiography and FFR findings, performed twice an individual visual analysis of perfusion MRI, using dedicated software (Syngo Via$^{\mathrm{O}}$, Siemens Health). First, splenic switch-off was qualitatively assessed to evaluate the appropriateness of the vasodilatation response after adenosine administration [13] . Myocardial ischemia was defined as stress-induced myocardial perfusion defect in the absence of LGE in the same segment, as previously reported [3]. The readers had no common training before the study and had freedom to adjust the display window level and width. In a final step, all reading discordances were solved by consensus. Twelve months after the first readings, a second round of individual and consensus visual analysis was performed by the same readers who then were provided with full knowledge of the coronary stenosis location, but still blinded to the FFR data.

Semi-quantitative analysis

Semi-quantitative analysis was performed under the supervision of an expert in cardiac MRI using dedicated software (MOCO, Syngo ViaVA30$^{\mathrm{O}}$, cardiac Engine-perfusion module, Siemens Healthineers). This operator had full knowledge of

the location of the stenosis, but was blinded to the FFR data. He performed a visual analysis using the same scheme as the 2 other readers to determine areas of myocardial perfusion defects.

As previously described [12], equally divided subendocardial (END) and subepicardial (EPI) regions of interest and time-signal intensity curves were obtained during adenosine stress in the myocardium distal to the stenosis (=RISK). When the RISK area involved more than one segment of the left ventricle representation, the myocardial segment with the greatest lateral and transmural extent of the perfusion defect was used for further measurements. Then, similar curves were obtained for a remote myocardial segment without a stenosis ≥40% diameter reduction on the supplying artery on QCA (=REMOTE) (Figure 1).

When no myocardial perfusion defect was visualized, the RISK segment was defined distal to the anatomic location of the coronary stenosis and the remaining steps were performed as when a perfusion defect could be visually detected. In patients with more than one intermediate-grade stenosis, each corresponding area of myocardial supply was assessed separately. Subsequently, these regions of interest were copy-pasted on the resting perfusion images. If necessary, manual correction was made to adjust the region of interest placement.

The stress subendocardial RMPI (i.e.: RISK/REMOTE mean maximal enhancement upslopes) of each stenosis was assessed for the diagnosis of FFR≤0.80 stenosis, as previously reported [12].

Maximal enhancement upslopes derived from subendocardial and subepicardial time-signal intensity curves per RISK and REMOTE areas (n=8, Figure 1) for each of the stenoses were normalized to the respective left ventricle cavity enhancement maximal upslope and used for Boosting machine learning.

Statistical analysis

Statistical analyses were performed using R (version 3.2.3, with the model-based boosting package 2.6-0). Normally distributed continuous variables are expressed as mean +/- standard deviation (SD). Comparisons between continuous variables were performed using two-tailed Student t-tests, and comparisons of proportions were performed using χ^2 tests.

A regression model was fitted to determine the best cut-off value for stress subendocardial RMPI in predicting FFR≤0.80. Then, boosting models including all semi-quantitative parameters collected in the RISK and REMOTE myocardium were used to predict FFR-related outcomes and to validate the added value of accounting for perfusion parameters in REMOTE myocardium in the prediction of these outcomes. As more extensively described in the supplementary materials, the Boosting models were assessed with the Akaike Information Criterion (AIC) value. Subsequently, the best model was optimized for a categorical outcome (i.e.: predicting FFR≤0.80). The diagnostic values were expressed as sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios and accuracy. The diagnostic accuracies were compared between visual readings, stress subendocardial RMPI and the boosting predictive model for FFR≤0.80, using binomial exact tests. P-values<0.05 were considered to express a statistically significant difference.

Results

Patient and intermediate-grade coronary stenoses characteristics

One hundred and thirty-seven patients fulfilled inclusion criteria, fifty-four were excluded because of consent refusal (n=32), pacemaker (n=1) and recent stress imaging (n=21). Additionally, 7 patients were excluded after MRI because of

poor image quality (n=2) and a segmental transmural myocardial infarct on LGE (n=5); 30 patients were excluded after quantitative coronary angiography because actual stenosis was <40% (n=12) or >70% (n=12) minimal diameter reduction, because there were multiple intermediate-grade stenoses on the same artery (n=3) (Figure 2), and >70% stenosis on another vessel (n=3). In total, 46 patients were included (mean age 61±9 years): 33 men (mean age 59±9 years) and 13 women (mean age 67±8 years). The demographics and cardiovascular risk factors are given in Table 1. Three of the 46 patients (6.5%) presented 2 intermediate-grade stenoses on distinct coronary arteries. Therefore, a total number of 49 intermediate-grade stenoses (59±7.6% (range, 42–70%) diameter reduction) were evaluated in this study (Table 2). The mean FFR value was 0.84±0.09, with a range of 0.60 to 0.98; 31% (15/49) were ≤0.80.

Table 1
Patient demographics and cardiovascular risk factors

Patient characteristics	Non ischemic (n=31)	Ischemic (n=15)
Age (years)*	61±9 [44-80]	62±9 [48-80]
Ratio M/F	22/9	11/4
BMI (kg/m^2)*	29 ± 5 [21-39]	27±3 [24-35]
Resting heart rate (beats per minute)*	68±13 [51-100]	67±8 [54-81]
Family history of coronary disease	9 (29%)	3 (20%)
Personal history of coronary disease	3 (10%)	5 (33%)
Diabetes mellitus	10 (32%)	2 (13%)
Current tobacco smoker	10 (32%)	7 (47%)
Elevated blood lipid profile	23 (74%)	13 (87%)
Systemic hypertension	25 (80%)	8 (53%)
Agatston coronary calcium score**	225 [139- 480]	465 [109-578]
* Mean ± standard deviation [range].		
** 4 males with coronary stenting excluded		

Table 2
Segmental topography of 49 intermediate-grade
coronary artery stenosis

Location	n (%)
Right coronary artery	12 (24.5)
Proximal segment	3 (6.1)
Mid segment	7 (14.3)
Distal segment	2 (4.1)
Left main trunk	1 (2)
Left anterior descending coronary artery	28 (57.2)
Proximal segment	14 (28.6)
Mid segment	14 (28.6)
Left circumflex coronary artery	7 (14.3)
Proximal segment	3 (6.1)
Mid segment	2 (4.1)
Distal segment	2 (4.1)
Marginal branch	1 (2)
First branch	1 (2)

Visual analysis

Of the 46 examinations, the spleen was not visible in one case. Splenic switch-off on stress imaging was absent in 2 cases while present in the remaining patients (43/46; 93%). The diagnostic values of perfusion MRI for FFR ≤ 0.80 are given on table 3, including individual readers' visual analyses. On the first reading session, there was no significant difference in diagnostic accuracy between Reader 1 and Reader 2 (respectively 37/49, 78% vs 36/49, 73%); p = 0.289). The consensus reading yielded a sensitivity of 73% (11/15) and a specificity of 85% (29/34) with an overall higher diagnostic accuracy compared to individual readings, although not statistically significant (all p-values > 0.05). Even with the knowledge of stenosis location on the second reading, the diagnostic accuracy of the visual readings remained in the same range for individual readers and the consensus reading.

Semi-quantitative analysis: RMPI and Boosting predictive models

The values of myocardial time-signal intensity maximal upslope in RISK and REMOTE areas, normalized to the respective left-ventricle cavity enhancement upslope are summarized in Table 4, both in patients with ischemic and

non-ischemic intermediate coronary artery stenosis. The stress subendocardial RMPI ranged between 0,57 and 1,39 (0,81± 0,17). Using the cutoff value of 0.84, the stress subendocardial RMPI had higher diagnostic accuracy (43/49, 88%) than all the visual readings to detect FFR ≤ 0.80 intermediate-grade coronary stenoses (Table 3).

Bringing in information from the perfusion in remote myocardial areas on top of information in the RISK areas beyond the stenosis was suggested to improve the predictive performance (AIC from -100 to -140). The boosting model computing all semi-quantitative perfusion MRI parameters confirmed their importance with a significantly higher diagnostic accuracy (44/49, 90%) compared to all individual visual readings in predicting FFR ≤ 0.80 stenoses, regardless of the prior knowledge of the stenosis localization (all p-values <0.05). Furthermore, this model tends to fulfill the criteria for a good diagnostic test, with positive and negative likelihood ratios of 9.82 and 0.15, respectively (Table 3).

Table 3
Diagnostic values of visual and semi-quantitative analysis of adenosine perfusion MRI for FFR ≤0.80 intermediate-grade coronary artery stenoses

Intermediate stenoses (n= 49)	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Accuracy
Visual reading 1 R1	13	24	10	2	(13/15) 87%	(24/34) 71%	(13/23) 57%	(24/26) 92%	2.95	0.19	(37/49) 76%
Visual reading 1 R2	7	29	5	8	(7/15) 47%	(29/34) 85%	(7/12) 58%	(29/37) 78%	3.17	0.63	(36/49) 73%
Visual reading 1 Consensus	11	29	5	4	(11/15) 73%	(29/34) 85%	(11/16) 69%	(29/33) 87%	4.99	0.31	(40/49) 82%
Visual reading 2 R1	8	30	4	7	(8/15) 53%	(30/34) 88%	(8/12) 67%	(30/37) 81%	4.53	0.53	(38/49) 78%
Visual reading 2 R2	10	26	8	5	(10/15) 67%	(26/34) 76%	(10/18) 56%	(26/31) 84%	2.83	0.44	(36/49) 73%
Visual reading 2 Consensus	9	31	3	6	(9/15) 60%	(31/34) 91%	(9/12) 84%	(31/37) 84%	6.80	0.44	(40/49) 82%
Relative myocar- dial perfusion	12	31	3	3	(12/15) 80%	(31/34) 91%	(12/15) 80%	(31/34) 91%	4.56	0.11	(43/49) 88%
Boosting model	13	31	3	2	(13/15) 87%	(31/34) 91%	(13/16) 81%	(31/33) 94%	9.82	0.15	(44/49) 90%

The proportions by which the percentages were calculated are given in parentheses.

R1 = reader 1; R2 = reader 2; TP = true positive; TN = true negative; FP = false positive; FN = false negative; MRI = magnetic resonance imaging; FFR = fractional flow reserve; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; relative myocardial perfusion = stress subendocardial relative myocardial perfusion index

Table 4
Semi-quantitative subendocardial stress enhancement parameters in RISK and REMOTE myocardium during adenosine perfusion in patients with ischemic and non-ischemic intermediate coronary artery stenosis (as defined by 0.80 FFR cut-off value)

Subendocardial stress enhancement parameter	Ischemic (FFR £0.80, n=15)	Non-ischemic (FFR > 0.80, n=31)
Mean maximal upslope in RISK myocardium*	0.16±0.04 [0.11-0.24]	0.18±0.05 [0.07-0.29]
Mean maximal upslope in REMOTE myocardium*	0.20±0.04 [0.13-0.26]	0.18±0.04 [0.09-0.28]
RMPI	0.79 ± 0.14 [0.57-1.05]	1.01±0.13 [0.81-1.39]
Values are given as mean ± standard deviation [range].		
* Maximal upslopes are normalized by the corresponding left ventricle cavity enhancement upslope;		
RISK = myocardium beyond stenosis; REMOTE = remote myocardium; RMPI = relative myocardial perfusion index; FFR = fractional flow reserve		

Discussion

The current study heralds important findings regarding the workup for intermediate-grade stenoses via adenosine perfusion MRI: namely the weakness of single-observer visual analyses and the importance of accounting for distant territories to better predict FFR.

Single-observer visual analysis identified FFR≤0.80 intermediate-grade stenosis with a moderate accuracy and highly variable sensitivities and specificities, likely owing to the freedom in image setting adjustment and dark-rim artifact assessment. The agreement would have been higher, but less representative of the "real life" if a pre-study training of the readers would have been organized [14]. These potential reading pitfalls suggest that the interpretation of myocardial signal abnormality depends on many more factors beyond the reader's experience.

Consensus reading resulted in higher diagnostic accuracy for FFR≤0.80 stenosis while keeping sensitivity and specificity close to the individual reader's highest levels. These results are lower than previous perfusion MRI studies [3, 15, 16], which can be explained by the exclusive inclusion of intermediate-grade stenoses in our study. It is also in line with the reported lower sensitivity of MRI in identifying FFR≤0.80 lesions in a subanalysis of intermediate-grade stenoses from a larger series [17]. Only few studies have specifically addressed coronary flow-limitation in intermediate-grade stenoses using other non-invasive techniques such as stress dobutamine MRI [18], dobutamine stress echocardiography [9], and single-photon emission tomography [8, 19, 20], with respective sensitivity and specificity ranges of 62%-95% and 69%-90%, all confirming the challenge posed by this range of stenoses. Even the knowledge of the area-at-risk did not increase the accuracy of visual readings. Indeed, the perfusion defects induced by intermediate-grade stenoses are likely to be shallower and less extended, thus more difficult to perceive and to distinguish from subendocardial dark-rim artefacts, than those caused by high-grade stenoses [21, 22]. This implies that beyond encouraging consensus reading of perfusion MRI to mitigate the reader's perception biases, diagnostic use of MRI as a gatekeeper to predict functional significance of intermediate-grade stenoses demands improvement. Actually, visual analysis assesses only perfusion defects beyond a coronary stenosis, and does not account for perfusion in normal perfusion areas, in contrast to the FFR value [23]. As expected, the accuracy of the FFR prediction using deep-learning statistics was higher when accounting for perfusion parameters in remote, normal myocardium than when these parameters were not included. These predictive models were used as proof of concept of the added value of accounting for perfusion parameters in remote myocardium for FFR prediction. It supports the need of an

integrative interpretation of the entire myocardium for improved perfusion MRI assessment in determining FFR≤0.80 stenoses, but is difficult to implement in clinical practice.

In this setting, the reported stress subendocardial RMPI [12] provides a simplified and more useful semi-quantitative parameter for clinical practice, with a high diagnostic accuracy to determine FFR≤0.80 intermediate-grade stenoses, in line with those of previous meta-analyses, including mainly semi-quantitative and quantitative MRI analyses [10]. This approach has also been reported in stress dynamic computed tomography perfusion showing better accuracy to identify flow-limiting stenoses than the myocardial blood flow in the area-at-risk [24]. Nevertheless, using RMPI three false-negative and three false-positive cases remained for the FFR≤0.8 cutoff, owing to image artifacts and the existence of the so-called gray-zone of FFR values (0.75-0.80) [25]. In addition, Ghekiere et al. reported in their series that all three false-negatives for RMPI exhibited splenic switch-off on adenosine imaging (i.e. did not receive appropriate adenosine vasodilatation) [12].

Our study has certain limitations including the relatively low number of patients and FFR≤0.80 stenosis. Second, the MRI studies were performed between 2010 and 2013 with an older generation equipment. Both visual and deep learning results could have been improved using a higher resolution adenosine perfusion MRI as it improves the detection of subendocardial ischemia [26]. Third, substantial amount of dropouts occurred after QCA to maintain stenoses within the intermediate-grade range and to control the possible bias related to the hemodynamic interactions between distinct coronary territories and that of successive stenosis. We nevertheless included a sufficient number of patients regarding the sample estimation for statistical significance, and approximately one-third of the intermediate-grade stenoses had an FFR≤0.80, as reported in the literature. Larger cohorts of patients will be suitable to confirm and validate the results of our study. Finally, in spite of epicardial stenosis, several confounders may alter myocardial perfusion on MRI [27] and, therefore, its diagnostic values in predicting flow-limitation as defined by the FFR value. Systematic bias such as cardiac-phase variability of the myocardial perfusion was not taken into account [28, 29], but can be ignored as long as a single-slice frame is evaluated, as it was done in this study. Patient-related confounders inherently limit the validity of our data to a population of individuals with similar cardiovascular risk factors for microvascular disease.

In conclusion, consensus reading should be encouraged in clinical practice to improve the diagnostic accuracy of visual analysis of adenosine perfusion MRI in predicting FFR≤0.80 intermediate-grade coronary stenoses. Semi-quantitative analysis using RMPI has a higher diagnostic accuracy than individual visual analysis, but further studies with larger patient samples are needed to confirm its clinical value as a gatekeeper for invasive FFR in patients with intermediate-grade stenoses.

Declarations

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Conflicts of interest/Competing interests

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Availability of data and material

All authors confirm that all data and materials as well as software application comply with field standards.

Code availability

NA

Authors' contributions

This study is part of a PhD project of the first author at the Hasselt University, Belgium. Experts from different sites substantially contributed to the setup and the design of the study, statistical analyses and manuscript writing. Patients were included in one site, the CHC hospital Liège, Belgium.

Ethics approval

The study protocol was approved by the local ethics committee (Comité d'éthique médicale N° d'agrément: OM87) with reference "Etude n° 09/12/473".

Consent to participate

Written informed consent was obtained from all patients to participate in this study.

Consent for publication

Written informed consent was obtained from all patients to publish their data in a journal article.

Study subjects or cohorts overlap:

Some study subjects or cohorts have been previously reported in AJR Am J Roentgenol. 2019; 212:1–8 "The value of relative myocardial perfusion at MRI for FFR-defined ischemia: a pilot study" and Int J Cardiovasc Imaging 2019;35:559-568 "Correlation of FFR-derived from CT and stress perfusion CMR with invasive FFR in intermediate-grade coronary artery stenosis". See also the attached PDF.

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Figures
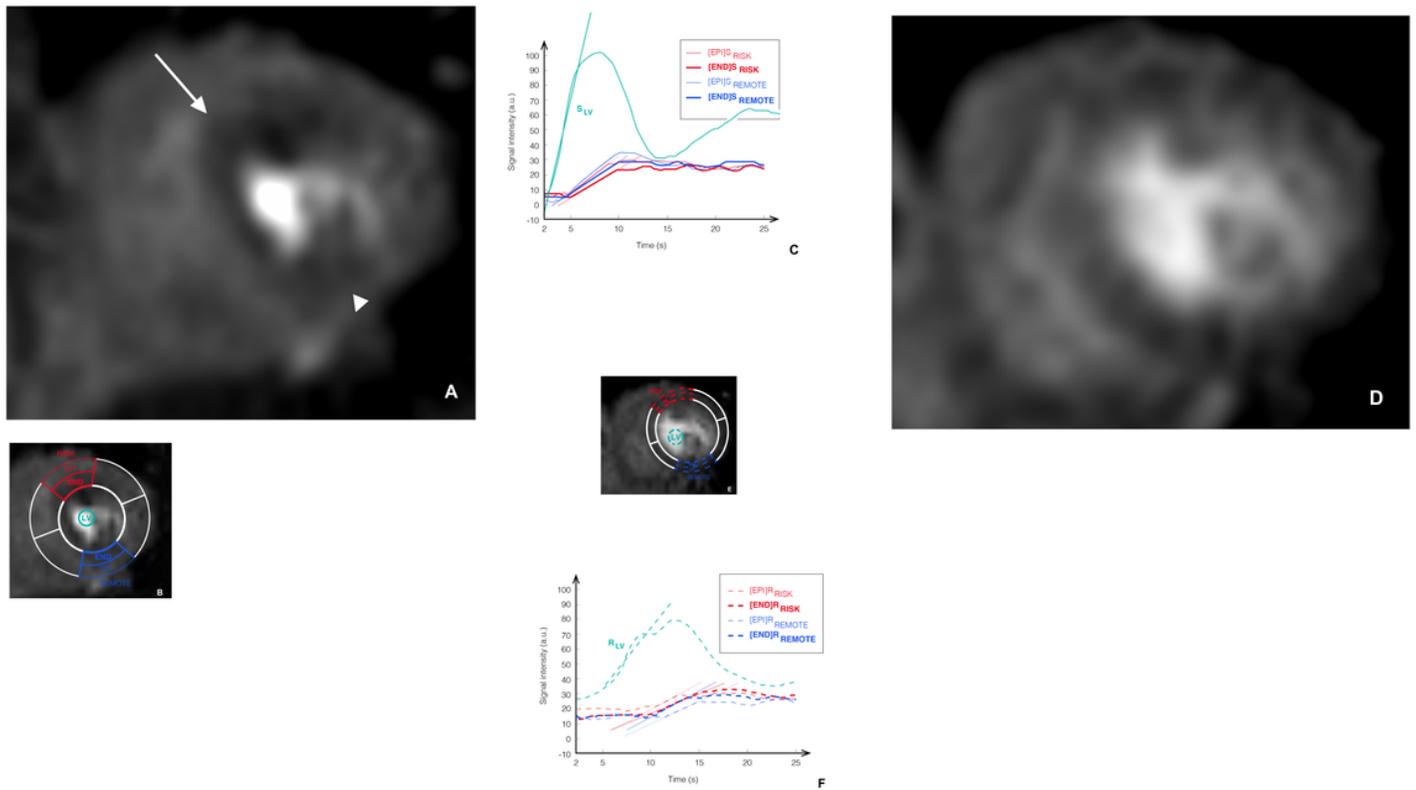
Figure 1

Semi-quantitative myocardial perfusion magnetic resonance imaging analysis Detailed steps for semi-quantitative perfusion magnetic resonance imaging (MRI) analysis in a 69-year-old patient with intermediate-grade stenosis of the mid portion of the left anterior descending artery on both coronary computed tomography angiography and catheter coronary angiography (not shown). Peak myocardial enhancement on adenosine perfusion MRI showed a septal and anterior wall mid-left ventricular area of low signal intensity (white arrow, segment 7 in figure 1A) in the area-at-risk (RISK), whereas the remote area (REMOTE) (arrowhead, segment 10 in figure 1A) and both areas on rest perfusion (figure 1D) were homogenously enhanced. Note the more systolic phase during stress perfusion, while the rest perfusion was performed during the diastolic phase of the cardiac cycle. No abnormal enhancement was present on late-enhancement imaging (not shown). Equally divided subendocardial (bold lines, END) and subepicardial (thin lines, EPI) regions of interest are drawn in the RISK (red color) and REMOTE segments (blue color) after outlining the endocardial and epicardial borders of the myocardium during maximal hyperemia (Figure 1B). The same indicators are present (dashed lines, same colors) on the rest peak myocardial enhancement images (figure 1E). After extending these regions of interest to the whole frames, corresponding time-signal intensity curves and the maximal upslope value of the contrast enhancement were obtained (Figures 1C and 1F). RISK = myocardium beyond stenosis; REMOTE = remote myocardium; [END] = subendocardial; [EPI] = subepicardial; R= rest imaging; S= adenosine stress imaging

Image not available with this version

Figure 2

Study flowchart CCTA = coronary computed tomography angiography; CCA = catheter coronary angiography; QCA = quantitative coronary angiography; FFR = fractional flow reserve; MRI = magnetic resonance imaging.

Supplementary Files

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- Supplementalmaterials.pdf