Value of Relative Myocardial Perfusion at MRI for Fractional Flow Reserve-Defined Ischemia: A Pilot Study

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OBJECTIVE. Correcting the perfusion in areas distal to coronary stenosis (risk) according to that of normal (remote) areas defines the relative myocardial perfusion index, which is similar to the fractional flow reserve (FFR) concept. The aim of this study was to assess the value of relative myocardial perfusion by MRI in predicting lesion-specific inducible ischemia as defined by FFR.

MATERIALS AND METHODS. Forty-six patients (33 men and 13 women; mean [± SD] age, 61 ± 9 years) who underwent adenosine perfusion MRI and FFR measurement distal to 49 coronary artery stenoses during coronary angiography were retrospectively evaluated. Subendocardial time-enhancement maximal upslopes, normalized by the respective left ventricle cavity upslopes, were obtained in risk and remote subendocardium during adenosine and rest MRI perfusion and were correlated to the FFR values.

RESULTS. The mean FFR value was 0.84 ± 0.09 (range, 0.60–0.98) and was less than or equal to 0.80 in 31% of stenoses (n = 15). The relative subendocardial perfusion index (risk-to-remote upslopes) during hyperemia showed better correlations with the FFR value (r = 0.59) than the uncorrected risk perfusion parameters (i.e., both the upslope during hyperemia and the perfusion reserve index [stress-to-rest upslopes]; r = 0.27 and 0.29, respectively). A cutoff value of 0.84 of the relative subendocardial perfusion index had an ROC AUC of 0.88 to predict stenosis at an FFR of less than or equal to 0.80.

CONCLUSION. Using adenosine perfusion MRI, the relative myocardial perfusion index enabled the best prediction of FFR-defined lesion-specific myocardial ischemia. This index could be used to noninvasively determine the need for revascularization of known coronary stenoses.

Catheter-based fractional flow reserve (FFR) measurement is a reference for the functional significance of lesion-specific coronary artery stenosis, because FFR less than or equal to 0.8 identifies stenosis inducing ischemia and requiring revascularization in clinical practice. The concept of FFR was validated as a relative flow reserve—that is, the ratio of hyperemic flow in a stenotic coronary artery to the hyperemic flow in a normal coronary artery. Therefore, it standardizes inflow conditions, avoiding the confounding effects of microvascular disease and collateral flow [1–4].

Cardiac stress perfusion MRI assesses noninvasively the myocardial vascular sup-

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ply by visual, semiquantitative, and quantitative analyses (usually by analyzing the myocardial enhancement curves). Perfusion MRI has been validated on myocardial ischemia models using radiolabeled microspheres. Excellent correlation was shown between the mainstream perfusion defect during maximal hyperemia and microsphere deposition distal to coronary stenoses [5, 6]. In practice, quantitative perfusion MRI considers stress-only or stress-to-rest (myocardial perfusion reserve index) upslopes for the diagnosis of inducible perfusion defects. The correlations of these perfusion parameters and FFR value in the feeding artery, albeit significant, show dispersion [7–11].

The ratio of myocardial enhancement upslopes distal to a coronary stenosis (risk) to that of normally perfused (remote) areas defines the relative perfusion index, which also has shown good correlation with microsphere deposition in a seminal animal study [6]. Although this approach is similar to the FFR principle [2], to our knowledge, it has not been used in humans so far. Therefore, we hypothesized that this index will enhance the correlation with FFR, potentially reducing the need for invasive procedures to determine the suitability of coronary revascularization. The purpose of this study is to assess the value of the relative perfusion index on adenosine MRI in predicting inducible myocardial ischemia, as defined by impaired FFR, on a per-lesion basis.

Materials and Methods

Patient Selection and Study Protocol

This retrospective study protocol was approved by the institutional ethics committee of Centre Hospitalier Chrètien, and patients provided written informed consent. We selected all patients from our hospital database during a 3-year period who were older than 18 years with no history of myocardial infarction and who had undergone coronary angiography and FFR measurement as the final diagnostic tests for stable angina within 4 months of an adenosine perfusion MRI, without any endovascular or surgical intervention in the interim. All the usual contraindications to both examinations were considered. This initial search yielded 57 patients. A first round of review of the imaging data and patient charts was performed by a senior staff radiologist with 10 years of experience in cardiovascular imaging. Patients with transmural myocardial infarct on late gadolinium-enhanced MRI (n = 5), those with more than one stenosis with a greater than 70% diameter reduction in different vascular territories (n = 3), and those with more than one stenosis with a greater than 70% diameter reduction on the same artery (n = 3) on quantitative coronary angiography were excluded to avoid microvasculature heterogeneity, possible hemodynamic interactions between coronary territories, and confounding effects of successive stenosis on the flow patterns, respectively. These selection steps allowed the inclusion of 46 patients. Within the study period, three patients had FFR measurement on two stenoses in a different coronary artery. Therefore, a total of 49 stenoses (i.e., lesion-specific risk areas) were evaluated by adenosine perfusion MRI and FFR (Fig. 1).

MRI Protocol

MRI examinations were performed on a 1.5-T MRI scanner (Avanto, Siemens Healthcare) under continuous heart rate and blood pressure monitoring. All patients were asked to suspend the intake of β-blockers and competitive antagonists of adenosine (caffeinated beverages) 24 hours before the examination.

Stress perfusion MRI was performed during maximal vasodilatation (i.e., 3 minutes after beginning the injection of 140 μmol/kg/min of adenosine [Adenocor, Sanofi-Aventis]) using selective saturation-prepared T1-weighted steady-state free precession slices. Image acquisition started simultaneously with the injection of 0.1 mmol/kg of body weight of a gadolinium chelate (gadodiamide; Omniscan, GE Healthcare) and a 30-mL saline flush; both were given at an injection rate of 4 mL/s. During a single breath-hold, 50 measurements of the three slices per heartbeat were acquired using a linear sampling of the k-space. The preparation time for each slice, measured to the center of the k-space, was 110 milliseconds. Saturation was obtained with a simple hard pulse with a 90° nominal flip angle followed by a gradient crusher. Five dummy cycles with a linear flip angle were used to reduce the steady-state free precession signal oscillations. We used symmetric echoes with a TR/TE of 2.2/1.1 and a flip angle of 50°; the resulting acquisition time per image was 178 milliseconds. The bandwidth was 1371 Hz/pixel, and the matrix size was 192 × 115, resulting in an image resolution of 3.5 × 2.1 × 8.0 mm. The phase-encoding direction was left-to-right, and the FOV was adjusted to the subjects' size to avoid folding artifacts.

Approximately 10 minutes after the start of the injection of contrast agent, myocardial late gadolinium enhancement imaging was performed using breath-hold phase-sensitive inversion recovery sequences. Then, resting perfusion MR images were acquired under the same technical conditions as the adenosine perfusion MRI.

Semiquantitative Perfusion MRI Analysis

Semiquantitative analyses were performed using dedicated software (cardiac engine-perfusion module, syngo.via VA30, Siemens Healthcare) after correction of respiratory motion with navigator-guided motion correction (MOCO module, syngo.via VA30, Siemens Healthcare).

First, a visual analysis was performed in consensus by two observers who had full knowledge of the location of the coronary stenosis but were blinded to the FFR data. These observers determined the risk area, taking the coronary dominancy into account. The segment with the greatest transmural extent of the stress-induced myocardial perfusion defect was considered for further measurements when the risk area involved more than one segment of the left ventricle representation [12]. This segment was equally divided into subendocardial and subepicardial regions by outlining the endocardial and epicardial borders. Special emphasis was placed to avoid dark rim artifacts and adjacent tissue and blood from these tracings. Similar steps were performed for a remote myo-

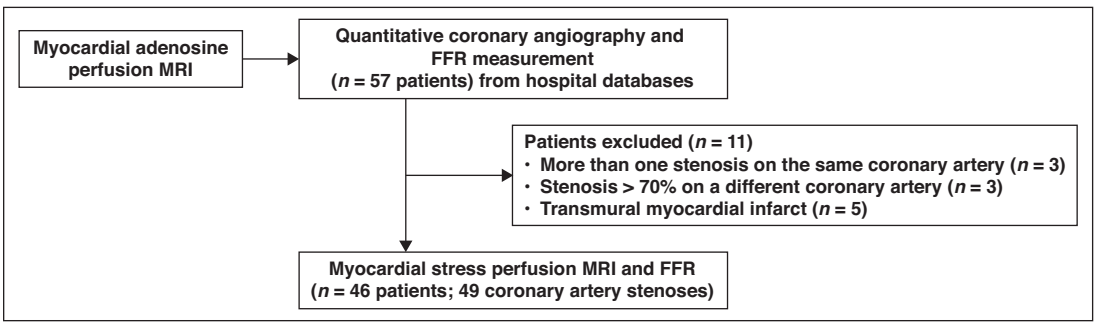


Fig. 1—Patient selection flowchart. FFR = fractional flow reserve.

cardial segment with no greater than 40% diameter reduction stenosis on the supplying artery.

Then, for each subendocardial risk and remote myocardial segment, the mean maximal initial upslope of the contrast enhancement phase was normalized by its respective left ventricle cavity upslope (measured under a circular ROI of 10 mm^2 in the center of the cavity) and recorded in both stress and rest conditions [13] (Fig. 2). If necessary, manual correction was made to adjust the ROI placement.

When no myocardial-inducible defect was visualized, the risk area 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 coronary stenosis, each perfusion defect was assessed separately.

The following three subendocardial upslope–derived perfusion indexes were stored for further analysis: the uncorrected risk upslopes during stress, the myocardial perfusion reserve index (stress-to-rest upslopes), and the relative myocardial perfusion index (risk-to-remote upslopes during stress), as described in Figure 1.

Coronary Angiography and Fractional Flow Reserve Measurements

Coronary angiography and FFR measurements were performed by an interventional cardiologist, using previously described standard procedures [14]. FFR measurement was performed after placement of a 0.014-inch pressure sensor–tipped coronary angioplasty guidewire across the diseased artery (FloWire Doppler Guide Wire, Volcano). FFR was determined as the ratio of the mean distal coronary to the mean aortic pressure during maximal myocardial hyperemia (i.e., 30–60 seconds after the intracoronary injection of 15–20 mg of papaverine [Sterop], 100 mg/3 mL).

Statistical Analysis

Statistical analyses were performed using R software (version 3.2.3, R Foundation for Statistical Computing). Continuous data with a normal distribution are expressed as mean ± SD. Where applicable, group comparisons for continuous variables were performed with paired two-tailed *t* tests and chi-square tests. Pairwise correlations were calculated between all maximal upslopes to investigate the extent to which multicollinearity must be handled. Pairwise correlations were calculated between the FFR value, the upslope in the risk area during stress, the subendocardial perfusion reserve index, and the relative subendocardial perfusion index. Correlation coefficients of 0–0.19, 0.20–0.39, 0.40–0.59, 0.60–0.79, and 0.80–1 indicated very weak, weak, moderate, strong and very strong correlations, respectively. Diagnostic values for FFR less than or equal to 0.80 of these perfusion MRI indexes are expressed as the sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, and accuracy. Diagnostic values are given with their 95% CIs. A $p < 0.05$ was considered to express a statistically significant difference.

Results

Patient and Coronary Stenosis Characteristics

In total, 46 patients with stable angina constituted the study group (mean age, 61 ± 9 years), including 33 men (mean age, 59 ± 9 years) and 13 women (mean age, 67 ± 8 years). The demographics and cardiovascular

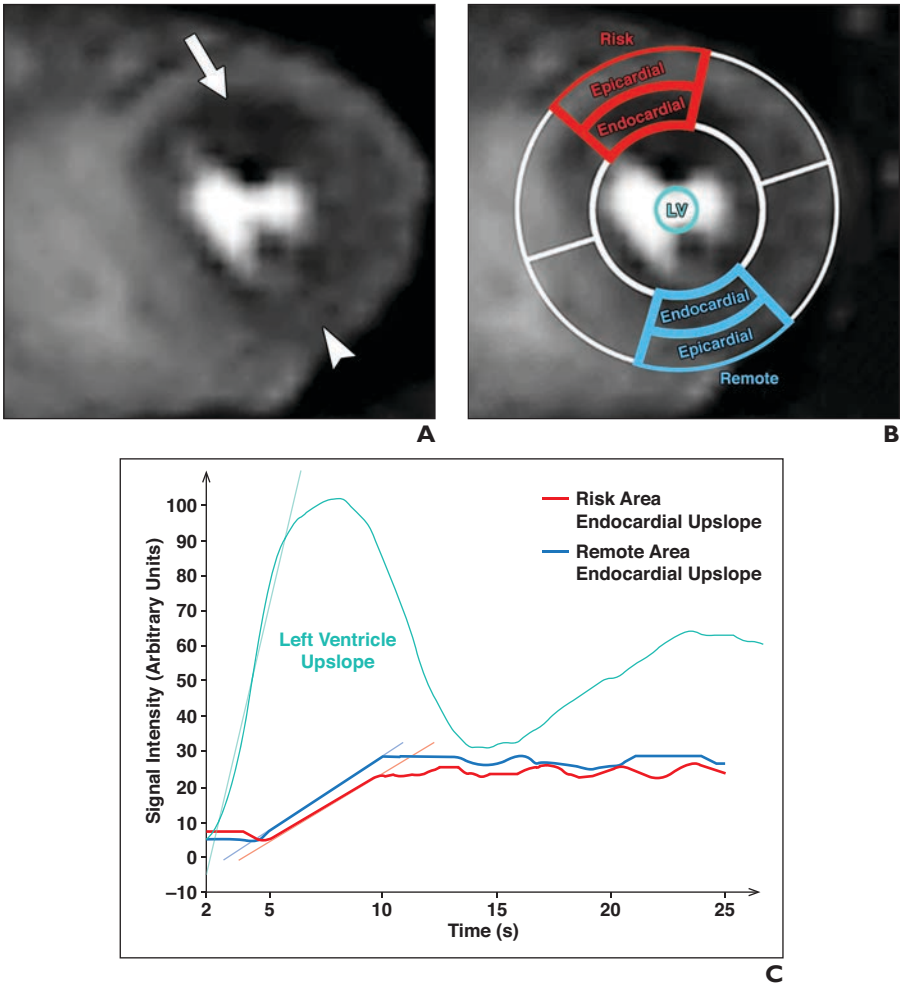
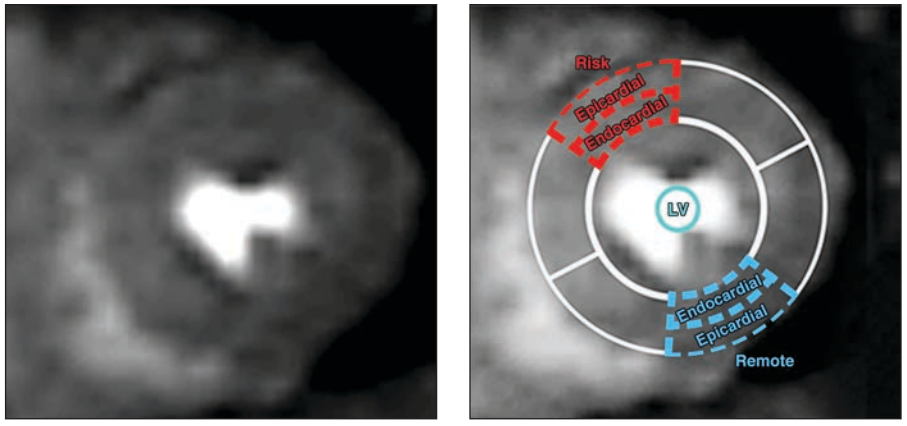


Fig. 2—64-year-old woman with stenosis of midportion of left anterior descending artery.
A–F, Peak myocardial enhancement on stress perfusion MR image shows low signal intensity in segment 7 (*arrow*, **A**) of anterior midleft ventricular (risk) myocardium, whereas inferior (remote) myocardium (*arrowhead*, **A**) and both areas on rest perfusion MR image (**D**) enhanced homogeneously. No abnormal enhancement was present on late-enhancement image (not shown). Equally divided subendocardial (*bold lines*) and subepicardial (*thin lines*) ROIs are drawn in risk (*red*) and remote (*blue*) myocardial segments of left ventricle (LV) after outlining endocardial and epicardial borders of myocardium on peak enhancement during maximal hyperemia (**B**). Same indicators are present (*dashed lines*; risk, *red*; remote, *blue*) on rest peak myocardial enhancement image (**E**). After extending these ROIs to whole frames, corresponding subendocardial dynamic contrast enhancement upslope curves (i.e., maximal upslope value of contrast enhancement) were obtained during adenosine (**C**) and rest (**F**) perfusion MRI. After normalization by respective left ventricle cavity upslopes, subendocardial upslope in risk myocardium during stress perfusion, perfusion reserve index (i.e., stress-to-rest upslopes), and relative perfusion index (i.e., risk-to-remote upslopes during stress perfusion) were available for further analysis. Lighter diagonal lines denote maximal enhancement upslopes.

(Fig. 2 continues on next page)



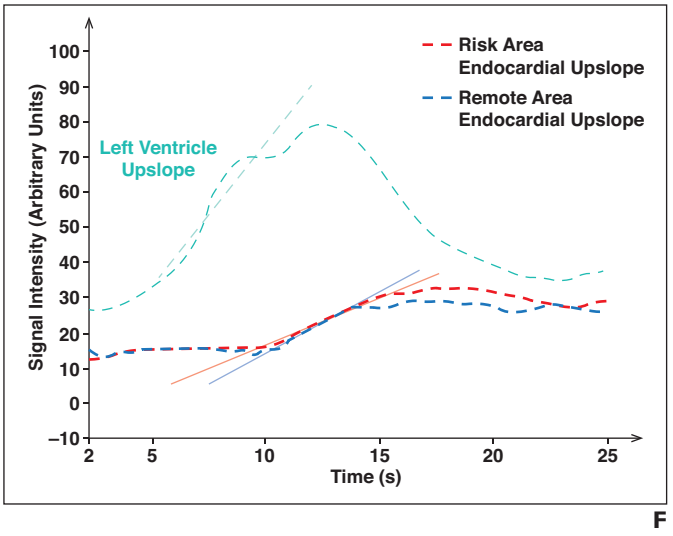


Fig. 2 (continued)—64-year-old woman with stenosis of midportion of left anterior descending artery.
A–F, Peak myocardial enhancement on stress perfusion MR image shows low signal intensity in segment 7 (*arrow*, **A**) of anterior midleft ventricular (risk) myocardium, whereas inferior (remote) myocardium (*arrowhead*, **A**) and both areas on rest perfusion MR image (**D**) enhanced homogeneously. No abnormal enhancement was present on late-enhancement image (not shown). Equally divided subendocardial (*bold lines*) and subepicardial (*thin lines*) ROIs are drawn in risk (*red*) and remote (*blue*) myocardial segments of left ventricle (LV) after outlining endocardial and epicardial borders of myocardium on peak enhancement during maximal hyperemia (**B**). Same indicators are present (*dashed lines*; risk, *red*; remote, *blue*) on rest peak myocardial enhancement image (**E**). After extending these ROIs to whole frames, corresponding subendocardial dynamic contrast enhancement upslope curves (i.e., maximal upslope value of contrast enhancement) were obtained during adenosine (**C**) and rest (**F**) perfusion MRI. After normalization by respective left ventricle cavity upslopes, subendocardial upslope in risk myocardium during stress perfusion, perfusion reserve index (i.e., stress-to-rest upslopes), and relative perfusion index (i.e., risk-to-remote upslopes during stress perfusion) were available for further analysis. Lighter diagonal lines denote maximal enhancement upslopes.

risk factors are given in Table 1. The mean interval between MRI and FFR measurement was 23.2 ± 25.9 days (range, 0–110 days). The 49 evaluated lesions had a mean percentage of diameter reduction of 56% ± 7% on quantitative coronary angiography, including 12 (24%) on the right coronary artery, one (2%) on the left main coronary artery, 28 (57%) on the left anterior descending artery, and eight (16%) on the left circumflex coronary artery. The mean FFR value in all stenoses was 0.84 ± 0.09 (range, 0.60–0.98); 31% (n = 15) of the lesions had an FFR less than or equal to 0.80, with a mean percentage diameter reduction of 59% ± 7.6% (range, 42–70%). No adverse events were observed during MRI, coronary angiography, and FFR measurements.

Correlations Between Fractional Flow Reserve and Adenosine Perfusion MRI

Table 2 and Figure 3 show the relationship between the FFR values and the three evaluated perfusion MRI indexes. Both the uncorrected risk subendocardial upslope (r = 0.27; p = 0.06) and the perfusion reserve (r = 0.29; p = 0.04) correlated very weakly with the FFR values. The relative perfusion index revealed a significantly improved correlation with the FFR values (r = 0.59; p < 0.001).

The AUC values were 0.69, 0.67, and 0.88 for the maximal uncorrected upslope, the subendocardial perfusion reserve index, and the relative subendocardial perfusion index, respectively (Fig. 4). The relative subendocardial perfusion index yielded a significantly higher diagnostic accuracy to predict FFR less than or equal to 0.80 than the maximal uncorrected upslope (88% vs 67%; p < 0.001) and the subendocardial perfusion reserve index (88% vs 59%; p < 0.001) (Table 3). Using the cutoff value of 0.84, the relative subendocardial perfusion index had three false-positives and three false-negatives in predicting FFR less than or equal to 0.80. Interestingly, all false-negative cases exhibited the so-called splenic switch-off, which occurs on stress perfusion MRI when the stressor fails to induce significant vasodilatation [15].

Discussion

In the current study, using a cutoff value of 0.84 for the subendocardial relative perfusion index provided an ROC AUC of 0.88 for predicting an FFR less than or equal to 0.80, which is in the range of the previously reported values for adenosine perfusion MRI [16–18]. We nevertheless observed that the relative myocardial perfusion index during maximal hyperemia is the best perfusion MRI predictor for FFR-defined inducible coronary ischemia on a per-lesion basis. Indeed, when compared with the risk-uncorrected hyperemic perfusion and the perfusion reserve index, the relative perfusion index showed a significantly improved correlation with the FFR value. Our observations are in line with those of previous studies evaluating the functional significance of coronary artery stenosis by myocardial blood flow estimates obtained with PET [19, 20]. In those studies, correction of the hyperemic blood flow in risk areas according to that of remote normal ar-

TABLE 1: Patient Demographics and Cardiovascular Risk Factors According to Myocardial Ischemia as Defined by Catheter Fractional Flow Reserve (FFR)

Patient Characteristics	No Ischemia (FFR > 0.80) (*n* = 31)	Ischemia (FFR ≤ 0.80) (*n* = 15)	*p*
Age (y), mean ± SD (range)	61 ± 9 (44–80)	62 ± 9 (48–80)	0.763
Sex, no. of patients			0.867
Male	22	11	
Female	9	4	
Body mass index, mean ± SD (range)[a]	29 ± 5 (21–39)	27 ± 3 (24–35)	0.229
Resting heart rate (beats/min), mean ± SD (range)	68 ± 13 (51–100)	67 ± 8 (54–81)	0.672
Family history of coronary disease	9 (29)	3 (20)	0.513
Personal history of coronary disease	3 (10)	5 (33)	0.047
Diabetes mellitus	10 (32)	2 (13)	0.170
Current tobacco smoker	10 (32)	7 (47)	0.305
Elevated blood lipid profile	23 (74)	13 (87)	0.336
Systemic hypertension	25 (80)	8 (53)	0.053
Agatston coronary calcium score, median (interquartile range)[b]	225 (139–480)	465 (109–578)	0.561

Note—Except where noted otherwise, data are number (percentage) of patients.
[a]Weight in kilograms divided by the square of height in meters.
[b]Four men were not included because of prior coronary stenting.

TABLE 2: Correlations Between Fractional Flow Reserve (FFR) Values and Subendocardial Perfusion Indexes on MRI

Subendocardial Perfusion Index	Mean ± SD	*r*	*p*	Best Cutoff Value for FFR ≤ 0.80	AUC
Stress maximal upslope	0.17 ± 0.04	0.273	0.06	0.16	0.69
Perfusion reserve	1.23 ± 0.53	0.288	0.04	1.25	0.67
Relative perfusion	0.17 ± 0.04	0.587	< 0.001	0.84	0.88

eas also resulted in better correlation with the FFR value, compared with other uncorrected estimates, such as stress-only myocardial blood flow or stress-to-rest ratios.

In contrast to previous reports [7–10], we found a poor correlation between the FFR value and both the uncorrected perfusion and the perfusion reserve index in risk myocardium. Regarding pathophysiology, discordances of 30–40% are observed between FFR and the methods interrogating both epicardial vessel and microvasculature, such as coronary flow reserve and uncorrected perfusion MRI. These discordances are due to several factors, such as the prevalence of microvascular disease or diffuse coronary disease [21]. The proportion of subjects with longstanding symptoms in different study samples theoretically influences the correlations between FFR and stress-perfusion MRI. Coronary microcollateral vessels may develop after long-duration flow reduction, especially when regular physical exercise is performed [22], although this was shown recently to affect the FFR value marginally [23]. A possibly higher proportion of microvascular disease in our study sample as compared with the previous studies should be contemplated as well. In addition, our findings might be due to the narrower FFR range (0.60–0.98) of the lesions in our study compared with previous studies that included lesions with much lower FFR values [7–10, 24]. Independently from the circulatory physiology, the signals as measured by perfusion MRI and the myocardial blood flow are heterogeneous by essence, with a variability of up to 35% of normal myocardial perfusion in highly controlled settings [6]. Finally, a certain number of patients may have no sufficient response from the vasodilator. These technical failures probably explain why, even after correction by using the relative perfusion index, the correlation with the FFR value remains moderate in our study ($r = 0.59$). Indeed, the three false-negative cases in predicting FFR less than or equal to 0.8 all involved patients who did not respond to adenosine. Together, both provide a clue to the low diagnostic value of uncorrected perfusion MRI for FFR-defined myocardial ischemia, as reported in a recent trial [25], and indicate that relative perfusion index is the parameter with the greatest ability to control the confounders and the discrepancies between perfusion MRI and FFR-defined ischemia [17].

Our work also questions the respective prognostic importance of relative and uncorrected perfusion defects, because the use of an FFR less than or equal to 0.80 to determine the need for revascularization and decrease the rate of unnecessary procedures is increasingly debated [26]. It has been shown that uncorrected perfusion MRI defects may provide useful prognostic information regarding event-free survival in patients with ischemic heart disease [27–29], but the contribution of other causes of perfusion defect (e.g., microvascular or spastic diseases) to patient outcomes has not been established yet [21, 28, 30]. Therefore, the FFR less than or equal to 0.80 cutoff remains the most acknowledged determinant of cardiovascular events and death. Accordingly, our findings indicate that the relative perfusion index may be the most relevant prognostic parameter derived from stress perfusion MRI in the current clinical practice [31–33].

Limitations

There are limitations to our study, including the relatively small number of patients examined and its retrospective and observational nature. The use of intracoronary papaverine for invasive FFR measurements was different from the approach of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation studies [1, 14], although similar hyperemia can be obtained compared with IV adenosine administration [34]. Also, because a normal reference myocardial area is required as remote myocardium, our approach may be limited by both the fact that a less than 40% diameter stenosis on the feeding artery does not fully guarantee the control of the FFR confounders on maximal hyperemia, and that the approach is ineffective in patients with multivessel disease in a similar way to other diagnostic techniques [11, 19, 20]. Evaluation of the relative perfusion index also requires knowledge of the coronary artery anatomy. However, patients

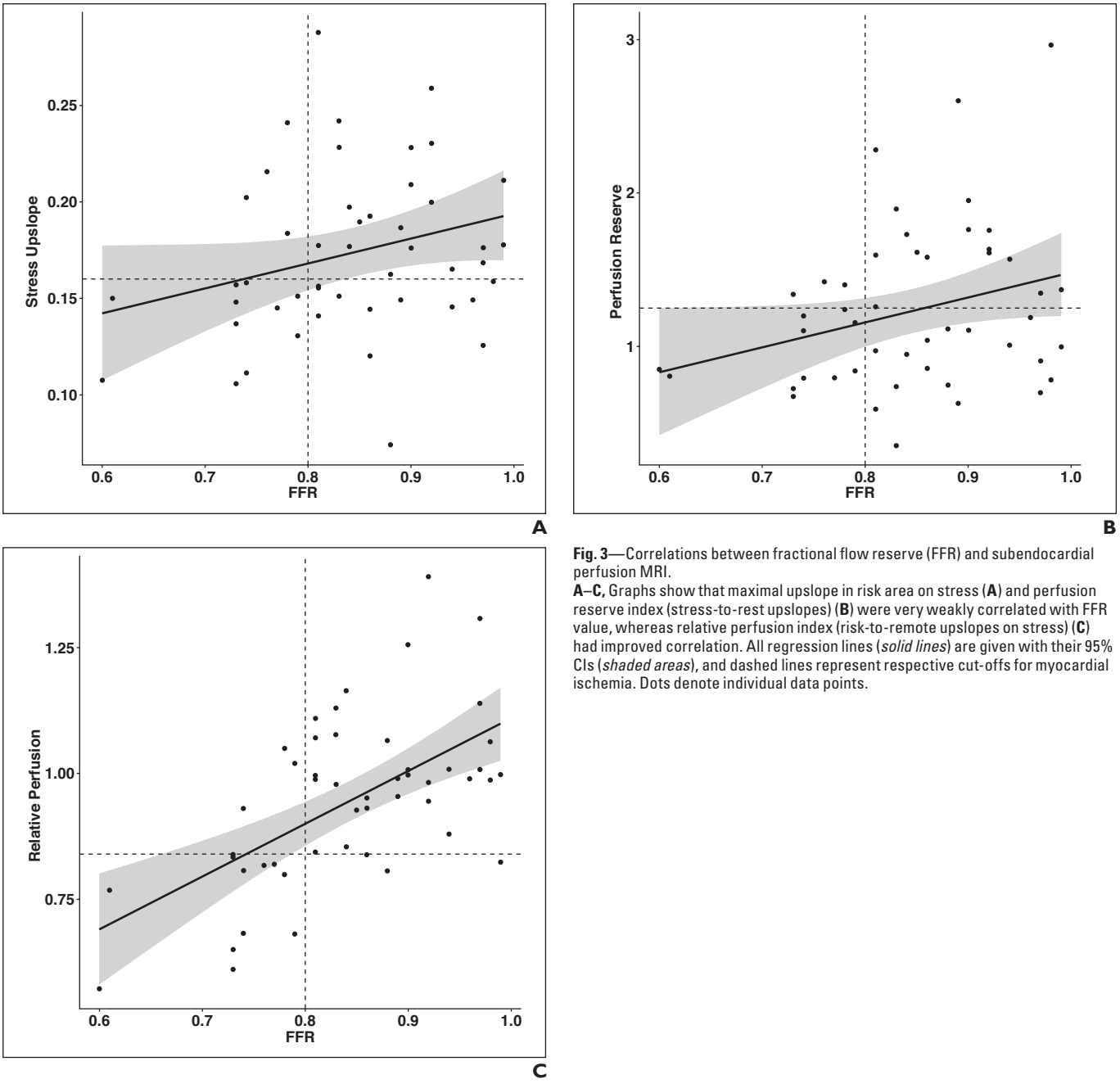


Fig. 3—Correlations between fractional flow reserve (FFR) and subendocardial perfusion MRI.
A–C, Graphs show that maximal upslope in risk area on stress (**A**) and perfusion reserve index (stress-to-rest upslopes) (**B**) were very weakly correlated with FFR value, whereas relative perfusion index (risk-to-remote upslopes on stress) (**C**) had improved correlation. All regression lines (*solid lines*) are given with their 95% CIs (*shaded areas*), and dashed lines represent respective cut-offs for myocardial ischemia. Dots denote individual data points.

TABLE 3: Diagnostic Values of Subendocardial Perfusion Indexes on MRI for Fractional Flow Reserve ≤ 0.80 Coronary Artery Stenosis

Coronary Artery Stenosis (n = 49)	No. of Findings				No. of Findings/Total (%) [95% CI]					Likelihood Ratio (95% CI)	
	TN	TP	FN	FP	Specificity	Sensitivity	NPV	PPV	Accuracy	High	Low
Stress maximal upslope	22	11	4	12	22/34 (65) [63–67]	11/15 (73) [69–77]	22/26 (85) [82–86]	11/23 (48) [45–51]	33/49 (67) [66–69]	2.43 (2.36–2.50)	0.48 (0.47–0.49)
Perfusion reserve	17	12	3	17	17/34 (50) [48–52]	12/15 (80) [75–83]	17/20 (85) [81–87]	12/29 (41) [39–44]	29/49 (59) [58–61]	2.50 (2.42–2.59)	0.62 (0.62–0.63)
Relative perfusion	12	12	3	3	31/34 (91) [89–92]	12/15 (80) [75–83]	31/34 (91) [89–92]	12/15 (80) [73–83]	43/49 (88) [86–89]	4.56 (4.41–4.71)	0.11 (0.11–0.11)

Note—A high likelihood ratio (> 10) is a good indicator for ruling in the ischemia, whereas a low likelihood ratio (< 0.1) is a good indicator for ruling out ischemia. TN = true negative, TP = true positive, FN = false negative, FP = false positive, NPV = negative predictive value, PPV = positive predictive value.

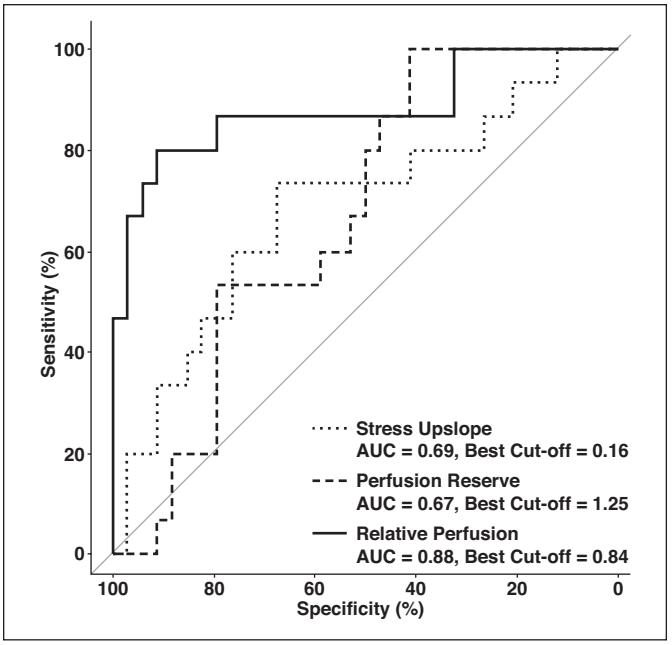


Fig. 4—Graph of ROC analysis of subendocardial perfusion MRI indexes to determine fractional flow reserve less than or equal to 0.80 coronary stenoses.

with obstructive coronary artery disease as diagnosed with coronary CT or invasive coronary angiography are increasingly observed in the daily practice. These patients often require additional functional imaging to assess myocardial ischemia, especially for intermediate-grade coronary stenosis [35].

Conclusion

Using perfusion MRI, assessment of the relative subendocardial perfusion index provides the best prediction for lesion-specific ischemia as defined by FFR. Further studies with larger patient samples and hypothesis verification are needed to confirm these important preliminary findings, emphasizing that this index could be used to noninvasively determine the need for revascularization of coronary stenoses detected on other investigations such as CT or catheter angiographies.

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