Improved Regional Myocardial Blood Flow and Flow Reserve After Coronary Revascularization as Assessed by Serial ^{15}O-water PET/CT

Short title: Improved Regional MBF and MFR After Revascularization

Tadao Aikawa,[1,2] Masanao Naya,[1] Kazuhiro Koyanagawa,[1] Osamu Manabe,[3] Masahiko Obara,[1] Keiichi Magota,[4] Noriko Oyama-Manabe,[5] Nagara Tamaki,[6] and Toshihisa Anzai[1]

This work was performed in Hokkaido University Hospital, Japan.

[1]Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan; [2]Minimally Invasive Advanced Heart Failure Therapeutics, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan; [3]Department of Nuclear Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan; [4]Division of Medical Imaging and Technology, Hokkaido University Hospital, Kita-14, Nishi-5, Kita-ku, Sapporo 060-8648, Japan; [5]Department of Diagnostic and Interventional Radiology, Hokkaido University Hospital, Kita-14, Nishi-5, Kita-ku, Sapporo 060-8648, Japan; [6]Department of Radiology, Kyoto Prefectural University of Medicine, Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

Address for Correspondence:
Dr. Masanao Naya
Department of Cardiovascular Medicine
Hokkaido University Hospital
Kita-14, Nishi-5, Kita-ku, Sapporo 060-8648, Japan
Tel.: +81-11-706-6973, Fax: +81-11-706-7874,
E-mail: naya@med.hokudai.ac.jp

Introduction

Myocardial perfusion imaging without and with quantitative myocardial blood flow (MBF) and myocardial flow reserve (MFR) by positron emission tomography (PET) plays an important role in the diagnosis[1] and risk stratification[2] of patients with stable coronary artery disease (CAD). However, there is a paucity of data linking the pre-revascularization regional quantitative MBF to post-revascularization improvement in perfusion metrics, and whether or not persistent improvement in the regional MBF occurs could provide mechanistic insight into the failure of randomized controlled trials to reduce mortality in patients with stable CAD.[3,4]

Recently, Gould et al. provided the first observational evidence that early revascularization yields improved outcomes based on pre-revascularization perfusion metrics.[5] Such results require that revascularization have a persistent effect on perfusion metrics. Other recent studies have shown that the short-term effects of coronary revascularization improve the regional stress MBF and MFR by 40%-60%.[6,7] In addition, given that the probability of improvement in regional wall motion abnormalities after coronary revascularization is related to the transmural extent of myocardial infarction,[8] the effects of coronary revascularization on quantitative perfusion metrics may differ by the presence of subendocardial infarction.

We therefore investigated the intermediate-term effects of coronary revascularization on the regional stress MBF and MFR and examined whether or not the presence of pre-revascularization subendocardial infarction modifies these effects.

Methods

Study population

The study population consisted of a subset of patients with obstructive CAD from a prospective, multicenter study prospectively examining the effects of coronary revascularization on the global MFR assessed by serial ^{15}O-water PET at enrollment and after 6 months of follow-up.[9] Patients diagnosed with obstructive CAD (defined as stenosis of ≥50% diameter in coronary arteries with an estimated diameter of ≥1.5 mm visualized on invasive coronary angiography) were identified and recruited at 4 centers in Japan from July 2015 to August 2017. Exclusion criteria included acute coronary syndrome, second- or third-degree atrioventricular block, bronchial asthma, and known or suspected pregnancy.

For the present analysis, only patients who underwent clinically indicated cardiovascular magnetic resonance (CMR) imaging within 14 days of the first PET scan were considered. Among the 82 patients who underwent the first PET scan, 35 were excluded because they did not undergo CMR within 14 days of the first PET scan (n=30), developed atrioventricular block during adenosine triphosphate infusion at the first PET scan (n=1), or failed to complete the second PET scan (n=4). Thus, the remaining 47 patients were included in the analysis (**Figure 1**). The median interval between the first PET scan and CMR was 3 days (interquartile range, 1-4; range, 0-14); 10 patients underwent both on the same day, and no adverse events occurred between the examinations in any cases.

This study was approved by the ethics committee at each participating site and registered with the University Hospital Medical Information Network clinical trials registry (UMIN000018160; http://www.umin.ac.jp/ctr/index.htm). All patients provided their written

informed consent.

A detailed treatment protocol was published previously.[9] In brief, all patients were treated with guideline-directed optimal medical therapy (OMT) for patients with obstructive CAD.[10] Stress myocardial perfusion imaging or invasive fractional flow reserve (FFR) was performed to assess hemodynamically significant CAD at the discretion of the treating clinicians. The cardiovascular team at each institution was blinded to the PET results and considered percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for patients with coronary artery lesions with stenoses of ≥50% diameter and myocardial ischemia; therefore, quantitative PET perfusion metrics had no influence on revascularization decision-making.

PET imaging

^{15}O-water PET stress scanning was performed at Hokkaido University Hospital before and after treatment, as previously reported,[9] and the details are shown in the **Supplementary material**. The MBF (mL/g/min) was calculated for the three main coronary arteries based on the American Heart Association 17-segment model[11] using an in-house developed software program.[9] The MFR was calculated as the ratio of the stress MBF to the rest MBF.

CMR imaging

CMR imaging was performed at Hokkaido University Hospital, as previously reported,[12] and the details are shown in the **Supplementary material**. CMR images were analyzed using a dedicated software program (Ziostation2; Ziosoft Inc., Tokyo, Japan). The left ventricular ejection fraction, volume, and mass were measured semiautomatically using short-axis cine images.[12]

Hyperenhanced myocardium was defined as having a signal intensity ≥5 standard deviations above the mean of remote myocardium.[12] The software program automatically divided the left ventricular myocardium into the 16 segments, excluding the apex, of the American Heart Association 17-segment model using the short-axis images with 5-mm slice thickness. The 16 segments were assigned to the three coronary artery territories based on recommendations,[11] and the extent of LGE in each vessel territory was quantified.

The anatomical assessment of coronary artery stenosis

On a vessel territory basis, the stenosis diameter was obtained by a visual estimation in a blinded fashion. The anatomical severity and extent of CAD were quantified from baseline and follow-up coronary angiography findings using the Leaman score.[13] Each coronary lesion was assigned to the American Heart Association 15-segment classification and scored according to the dominance of the coronary artery distribution and the fraction of blood flow perfusing the left ventricle. The Leaman score was expressed as the sum of respective segmental scores multiplied by the weighting factor based on the percent diameter stenosis (70%-89%, ×1; 90%-99%, ×3; 100%, ×5). Coronary lesions supplied by bypass grafts were considered normal for calculating post-revascularization Leaman scores. A jailed, side-branch ostium with a reference diameter of ≥1.5 mm after PCI was also considered normal in the post-revascularization Leaman score. If follow-up coronary angiography was not performed, Leaman scores were estimated using coronary angiography performed during PCI or based on surgical reports in conjunction with coronary angiography findings from before CABG. In addition, the Leaman score was divided into the three coronary artery territories.

A value of unprotected left main disease was assigned to the left anterior descending and circumflex arteries with different weighting factors based on the type of coronary dominance.[13] The pre-procedural SYNTAX score[14] in patients without CABG or the CABG SYNTAX score[15] in post-CABG patients was also calculated.

Statistical analyses

All statistical analyses were performed using JMP Pro 14.2.0 software program (SAS Institute Inc., Cary, NC, USA). A two-sided P value <0.05 was considered statistically significant. Continuous variables were expressed as the median and interquartile range. Categorical variables were expressed as absolute numbers with percentages. Comparisons between groups were performed using Wilcoxon's rank-sum test, followed by the Steel-Dwass test for continuous data and the Fisher exact test for categorical data. Comparisons between paired data were performed using Wilcoxon's signed-rank test or the McNemar test, as appropriate. A two-way analysis of variance with repeated measures was used to detect interaction effects between groups and time. Correlations between continuous variables were defined by Pearson's Spearman rank correlation coefficients (rρ). A receiver-operating characteristic (ROC) curve analysis and the Youden index were used to define the optimal cut-off values of pre-revascularization perfusion metrics for predicting >20% improvement in the regional stress MBF after coronary revascularization, which is greater than the expected day-to-day variability.[16] A comparisons between ROC curve was performed using the chi-square test.

To test the effects of revascularization on changes in the regional stress MBF or MFR, multivariable analyses (Model 1 and 2) were performed using multilevel mixed-effects models

with an unstructured covariance matrix to account for the clustering of data within patients or the correlation between vessel territories. Model 1 was adjusted for the pretest likelihood of obstructive CAD, left ventricular ejection fraction, and history of PCI or CABG selected based on clinical relevance[9,17] and the presence of subendocardial infarction (LGE extent ≥1% of vessel territory). The pretest likelihood of CAD was estimated using the Duke clinical risk score.[18] To adjust for baseline differences between vessel territories undergoing CABG or not (Model 2), vessel territories undergoing CABG were added to Model 1. The degree of angiographic improvement after coronary revascularization, assessed by the per-vessel Leaman score reduction, was corrected for skewness using log transformation in the multivariable analysis. The assumption of linearity for continuous covariates was evaluated by plotting residual values against fitted values. Trends across strata were also assessed using multilevel mixed-effects models with an unstructured covariance matrix and dummy coding for the number of strata. To test the effects of medications at follow-up on changes in the regional stress MBF or MFR, a mixed-effects model analysis was also performed.

Sensitivity analyses were conducted using a stepwise variable selection procedure; patient factors (age, sex, body mass index, hypertension, diabetes, hyperlipidemia, and current smoker at follow-up) and medications at follow-up (angiotensin inhibitors, beta-blockers, calcium-channel blockers, statins, and nitrates) were selected on the basis of the corrected Akaike's information criterion score, and regional factors were forced into the multivariable model.

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the 47 patients. The median age was 69 (62-75) years old, 39 participants (83%) were men, 34 (72%) had multivessel disease, and the median SYNTAX and Leaman scores were 15 (8-25) and 6.5 (2.5-13.5), respectively. All patients received OMT; 18 (38%) underwent PCI, and 13 (28%) underwent CABG. The median interval between the first PET scan and coronary revascularization was 13 (6-26) days. Representative images are shown in **Figure 2**. Of the 16 patients who did not undergo coronary revascularization, 13 had significant comorbidities (e.g. advanced cancer or severely atheromatous aorta) or a coronary anatomy unsuitable for revascularization, 1 preferred medical therapy, and 2 had fixed perfusion defects in the target area on myocardial perfusion imaging.

Table 2 summarizes angiographic characteristics and the extent of myocardial scarring in all vessel territories. Of the total of 141 vessels, 98 (70%) had stenosis of ≥50% diameter, 37 of which had stenosis diameters of 70%-89%, and 49 of which had stenosis diameters of ≥90%. On a per-vessel basis, 24 (17%) underwent PCI, 34 (24%) underwent CABG, and the remaining 83 (59%) did not undergo revascularization. The Leaman scores at baseline were significantly higher in vessel territories undergoing PCI or CABG than in those without revascularization ($P<0.001$ for both). The extent of LGE at baseline was significantly larger in vessel territories undergoing CABG than in those undergoing PCI or without revascularization ($P<0.001$ and $P=0.002$, respectively), whereas almost all vessel territories had no segments with a transmural LGE extent >50%.

The regional stress MBF and MFR at baseline were inversely correlated with the percent

diameter stenosis, per-vessel Leaman score, and extent of LGE (P<0.05 for all; **Figure 2**), whereas the regional rest MBF was not significantly correlated with the percent diameter stenosis or per-vessel Leaman score (**Figure 2**).

Changes in the regional myocardial perfusion and angiographic CAD burden

Scheduled follow-up angiography was performed in 12 of 18 patients undergoing PCI at a median of 238 (163-272) days after PCI and in 12 of 13 patients undergoing CABG at a median of 9 (8-12) days after CABG. Per-vessel Leaman scores were significantly decreased in vessel territories that underwent PCI or CABG (P<0.001 for both; **Table 2**). No adverse cardiac events occurred during the two PET studies. Medications at baseline and follow-up for the different groups are shown in **Table S1**.

During a median follow-up duration of 6.1 (5.8-6.8) months, PCI and CABG significantly increased regional MFR from baseline to follow-up (1.84 [1.28-2.17] vs. 2.12 [1.69-2.63], P<0.001) caused by increasing regional stress MBF (1.33 [0.97-1.67] mL/g/min vs. 1.64 [1.38-2.17] mL/g/min, P<0.001) in all vessel territories. There were no significant changes in the regional stress MBF and MFR in vessel territories without revascularization (P=0.66 and P=0.07, respectively).

Changes in the quantitative myocardial perfusion on a per-vessel basis between the different categories are compared in **Table 3**. The regional MFR was significantly increased only in vessel territories undergoing CABG (P<0.001, P=0.002 for interaction), resulting in similar regional MFRs at follow-up among the three subgroups. When vessel territories were classified according to the per-vessel Leaman score reduction after coronary revascularization, the regional

MFR was significantly increased only in vessels achieving a Leaman score reduction >3 (P<0.001, P<0.001 for interaction). When vessel territories with chronic total occlusion (n=22) were analyzed, those undergoing revascularization (n=12) showed a significant increase in the regional stress MBF (0.90 [0.57-1.49] vs. 1.42 [1.28-2.19] mL/g/min, P=0.001) and MFR (1.24 [1.09-2.04] vs. 2.09 [1.54-3.15], P=0.009), while those without revascularization (n=10) did not show a significant change in the regional stress MBF (1.94 [1.12-2.35] vs. 2.01 [1.22-2.33] mL/g/min, P=0.16) and MFR (1.84 [1.61-2.47] vs. 2.26 [1.69-2.72], P=0.19). When the 83 vessel territories without revascularization were classified according to the percent diameter stenosis at baseline (<50%, 50-69%, ≥70%), there were no significant differences in the changes in quantitative perfusion metrics among the groups (**Table S2**). **Table S3** summarizes the hemodynamic characteristics of all patients during each PET scan.

Figure 3 shows the relationship between changes in quantitative myocardial perfusion and the degree of angiographic improvement after coronary revascularization. The percent changes in regional stress MBF and MFR were significantly correlated with the per-vessel Leaman score reduction after coronary revascularization (P<0.001 for both).

The ROC analysis for predicting >20% improvement in the regional stress MBF after coronary revascularization showed that area under the curve values for the regional stress MBF, MFR, and a combination of stress MBF and MFR were 0.80 (95% confidence interval [CI], 0.71-0.86), 0.76 (95% CI, 0.67-0.83), and 0.80 (95% CI, 0.71-0.86), respectively, which were not significantly different from each other (P=0.32). The optimal cut-off values of regional stress MBF and MFR for predicting >20% improvement in the regional stress MBF were 1.66 mL/g/min (sensitivity, 0.78; specificity, 0.69; positive predictive value, 0.65; negative predictive

value, 0.81) and 1.75 (sensitivity, 0.55; specificity, 0.89; positive predictive value, 0.79; negative predictive value, 0.73), respectively.

Predictors of regional stress MBF or MFR improvement after coronary revascularization

Predictors of regional MFR improvement after coronary revascularization are shown in **Table 4**. The per-vessel Leaman score reduction after coronary revascularization was significantly associated with changes in the regional MFR ($P<0.05$ for all). Vessel territories that underwent CABG were associated with percent changes in the regional MFR ($P=0.040$) but not absolute changes ($P=0.31$), reflecting the fact that vessel territories referred for CABG had low MFRs at baseline. When analyzing predictors of regional stress MBF improvement after coronary revascularization (**Table 5**), a per-vessel Leaman score reduction was also significantly associated with only percent changes in the regional stress MBF in Model 1.

Table S4 shows the mixed-effects models including medications at follow-up for predicting changes in the regional stress MBF or MFR. Statin use was significantly associated with only absolute changes in the MFR ($P=0.028$).

Table S5 shows the results of sensitivity analyses using a stepwise variable selection procedure to predict changes in the regional stress MBF and MFR after coronary revascularization on a per-vessel basis. A per-vessel Leaman score reduction after revascularization was significantly associated with changes in the regional stress MBF or MFR ($P<0.05$ for all), which was consistent with the original analyses. Furthermore, beta-blocker use at follow-up was significantly associated with an increase in changes in the regional MFR and absolute changes in the regional stress MBF ($P<0.05$ for all).

Discussion

This study showed that coronary revascularization improved the regional stress MBF and MFR in patients with CAD. Importantly, the magnitude of these changes was associated with the extent of revascularization, independent of the presence of subendocardial infarction, suggesting that complete revascularization is beneficial when the underlying myocardium is viable. We also found that the regional stress MBF and MFR at baseline were inversely correlated with the extent and anatomical severity of CAD as well as the extent of LGE.

Our findings of improvement of the regional stress MBF and MFR after coronary revascularization are in agreement with the results of previous studies.[6,7,19,20] Driessen et al. reported that the magnitude of these changes was correlated with changes in the FFR despite the exclusion of patients with prior myocardial infarction.[6] We previously reported that the improvement of the global MFR after coronary revascularization was associated with the degree of reduction in the epicardial CAD burden;[9] however, the myocardial viability was not assessed. A previous CMR perfusion study showed that the regional stress MBF significantly decreased with the extent of LGE both at baseline and after coronary revascularization,[19] suggesting that the presence of subendocardial infarction might diminish the effect of coronary revascularization on these perfusion metrics. ^{15}O-water tracer measures MBF defined as the blood flow (mL) per gram of ^{15}O-water perfusable (viable) tissue (i.e. the water-perfusable tissue fraction).[21] Since necrotic tissue does not exchange water, note that the non-perfusable region in the subendocardial infarcted myocardium is excluded from this parameter. Nevertheless, a previous study showed that the extent of hyperenhancement, as assessed by CMR, was accompanied by a gradual decrease in regional perfusable tissue fraction and regional rest MBF assessed by ^{15}O-water

PET.[22] The use of PET and CMR imaging enables the elucidation of the detailed mechanisms underlying improvements in these perfusion metrics. The current results support and extend these findings by showing that the magnitude of improvement was associated with the degree of angiographic improvement after coronary revascularization, regardless of the presence of myocardial infarction when the underlying myocardium was substantially viable. Subendocardial infarction may not have influenced the improvement of the regional stress MBF and MFR because many of the territories did not have segments with transmural infarction (**Table 2**). In addition, we performed follow-up PET at six months after baseline PET because a previous ^{15}O-water PET study reported that patients with three-vessel disease achieved a higher stress MBF and MFR six months after CABG than before CABG and at one month after CABG,[23] suggesting that impaired perfusion metrics with severe CAD were slowly increased after CABG. This may help explain why Driessen et al. showed a greater effect of PCI on these perfusion metrics than that of CABG within three months after coronary revascularization.[6]

We focused on the regional stress MBF and MFR because a significant reduction in both, termed the coronary flow capacity, has been identified as a significant predictor of adverse cardiovascular events in clinical practice, similar to global stress MBF and MFR.[5] Furthermore, coronary revascularization within 90 days after PET was associated with a reduced rate of adverse events in patients with a drastic reduction in the regional stress MBF and MFR.[5] Although a significant improvement in the regional stress MBF and MFR after coronary revascularization is to be expected, data supporting this phenomenon are lacking. To our knowledge, this is the first study showing a quantitative association between changes in the regional stress MBF, MFR, pre-existing myocardial infarction, and the degree of coronary

revascularization.

Our findings provide mechanistic insights into the difference between the effects of PCI and CABG on improving the regional stress MBF and MFR, especially in patients with complex coronary lesions. PCI is targeted at the culprit lesion, whereas CABG is targeted at the distal end of the artery, enabling more complete revascularization without side-branch occlusion. Although the angiographic CAD burden at baseline was more severe in the vessel territories referred for CABG than those for PCI, due to the observational nature of the study, the rate of achieving complete revascularization was higher in those undergoing CABG than in those receiving PCI. This may explain the superiority of CABG over PCI for intermediate-term outcomes.[24]

The median follow-up MBF and MFR values for CABG still being lower than those at baseline for PCI and 'no revascularization' cases may be due to the difference in the extent of LGE at baseline, which was negatively correlated with these perfusion metrics (**Figure 3**). Vessel territories undergoing CABG had a larger extent of LGE than those without revascularization and those undergoing PCI (**Table 2**), resulting in a persistent reduction in these perfusion metrics after coronary revascularization.

Study limitations

The present study has several limitations. First, this study was not designed for routine FFR measurements at baseline and follow-up, which may affect the change in the regional stress MBF and MFR after treatment. The FFR can be measured in jailed side-branch lesions;[25] however, in contrast to the Leaman score, the FFR is difficult to apply to chronic total occlusions or vessels with bypass grafts. Second, co-registration of PET and invasive coronary angiography was not

performed. Individual variations in the coronary anatomy may results in the inaccurate assignment of coronary artery territories. However, a previous study reported that regional MBFs in the three main coronary artery territories individualized by co-registration of PET and coronary CT angiography did not significantly differ from those of the standard 17-segment model.[26] Third, the results of subgroup analyses should be interpreted with caution due to the small sample size. Fourth, our results are subject to selection bias and confounding factors due to the non-randomized nature of the study. There are some variations in follow-up procedures after coronary revascularization between hospitals because follow-up angiography was not performed for the purpose of this study. The significance of the coronary hemodynamic findings after revascularization needs to be confirmed with a predefined procedure of follow-up angiography. Finally, the regional stress MBF and MFR after coronary revascularization may be useful for risk stratification or monitoring, although we were unable to test these hypotheses in the current study. Long-term follow-up studies are needed in order to assess the long-term benefits of an increase in the regional stress MBF and MFR in patients with stable CAD.

Conclusion

Coronary revascularization improved the regional stress MBF and MFR in patients with stable CAD. The magnitude of these changes was associated with the extent of revascularization independent of the presence of subendocardial infarction. These results suggest that complete revascularization has greater potential to improve the stress MBF and MFR in patients with high-risk CAD when the underlying myocardium is viable.

Supplementary material

Supplementary material is available at online.

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Conflict of Interest

Dr. Aikawa has been affiliated with the endowed department by Medtronic Japan Co., Ltd. and Win International Co., Ltd. since 2019. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Figure Legends

Figure 1. Study population. CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; PET, positron emission tomography.

Figure 2. Representative images in a 70-year-old man receiving PCI to the LAD and RCA. Invasive coronary angiography showed severe stenoses of the mid LAD (90% and 80% stenoses, *white arrows*), the first diagonal branch (*red arrow*), and the RCA (70% stenosis, *yellow arrow*) and total occlusion of the LCX (*blue arrow*). LGE cardiovascular magnetic resonance imaging showed subendocardial infarction in the anterolateral wall with myocardium ≥5 standard deviations above the mean for signal intensity (*yellow areas*), indicating poor myocardial viability in the LCX territory. Perfusion polar maps at baseline showed a decrease in the LAD territory and a marked decrease in the LCX territory. ^{99m}Tc-tetrofosmin SPECT showed myocardial ischemia in all three vessel territories (**Figure S1**). After the drug-eluting stent implantations in the LAD and RCA, the stress MBF was increased in the LAD territory from 1.21 to 1.66 mL/g/min (by +37%) but decreased in the RCA territory from 1.55 to 1.21 mL/g/min (by −22%). The MFR increased in both; however, this was due to a reduction in the rest MBF in the RCA territory from 0.84 to 0.53 mL/g/min and no marked change in the rest MBF in the LAD territory from 0.79 to 0.72 mL/g/min. The lack of change in the regional stress MBF in the LCX territory without revascularization confirms that the PET analysis is precise. This patient's global stress MBF was slightly increased from 1.12 to 1.27 mL/g/min, and the increase in the MFR is a result of the increased stress MBF in the LAD territory and decreased rest MBF in the other territories. There were no signs of angina or cardiac events during follow-up. LCX, left

circumflex artery; LAD, left anterior descending artery; LGE, late gadolinium enhancement; MBF, myocardial blood flow; MFR, myocardial flow reserve; PCI, percutaneous coronary intervention; RCA, right coronary artery; SPECT, single-photon emission computed tomography.

Figure 3. Baseline relationships between quantitative myocardial perfusion and percent diameter stenosis (**A–C**), per-vessel Leaman score (**D–F**), or the extent of LGE (**G–I**) on a per-vessel basis. Vertical bars represent the median with the interquartile range.

Figure 4. Relationship between changes in regional stress MBF (**A, B**) or regional MFR (**C, D**) and per-vessel Leaman score reduction after coronary revascularization on a per-vessel basis.

Table 1. Baseline characteristics of the study patients (n=47)

Age (years)	69 (62-75)
Male	39 (83)
Body mass index (kg/m^2)	23.3 (21.0-25.9)
Pretest likelihood of obstructive CAD (%)	93 (76-98)
Anginal Symptoms	
Typical angina	24 (51)
Atypical angina	5 (11)
Nonanginal chest pain	2 (4)
Hypertension	35 (74)
Diabetes	23 (49)
Hyperlipidemia	35 (74)
Family history of CAD	4 (9)
Current smoker	8 (17)
Prior myocardial infarction	17 (36)
Prior PCI	11 (23)
Prior CABG	3 (6)
Vessels involved	
1-vessel disease	13 (28)
2-vessel disease	15 (32)
3-vessel disease	15 (32)
Left main disease	4 (9)
SYNTAX score	15 (8-25)
0-22	33 (70)
23-32	9 (19)
≥33	5 (11)
Leaman score	6.5 (2.5-13.5)
Coronary artery calcium score (n=34)	594 (155-1516)
0	0 (0)
1-400	15 (44)
>400	19 (56)
Global rest MBF (mL/g/min)	0.80 (0.61-0.96)
Global stress MBF (mL/g/min)	1.72 (1.28-2.15)
Global MFR	1.96 (1.71-2.79)
CMR findings	
LV end-diastolic volume index (mL/m^2)	57.4 (43.2-72.9)
LV end-systolic volume (mL/m^2)	25.0 (14.3-33.8)
LV ejection fraction (%)	55.2 (45.4-67.4)
LV mass index (g/m^2)	56.1 (48.4-67.9)
LGE extent (% of total left ventricular mass)	4.7 (0.7-10.8)
Medications	
Antiplatelet agents	43 (91)
Angiotensin inhibitors	28 (60)
Beta-blockers	30 (64)
Calcium-channel blockers	20 (43)
Statins	42 (89)
Nitrates	19 (40)
Diuretics	12 (26)
Insulin	5 (11)
Warfarin	4 (9)
Direct oral anticoagulants	9 (19)

Data are presented as the median (interquartile range) or n (%).

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricular; MBF, myocardial blood

flow; MFR, myocardial flow reserve; PCI, percutaneous coronary intervention.

Table 2. Angiographic characteristics and the extent of myocardial infarction on a per-vessel basis (n=141)

Characteristics	No revascularization (n=83)	PCI (n=24)	CABG (n=34)	P
Diameter stenosis				<0.001
<50%	43 (52)	0 (0)	0 (0)	
50% to 69%	7 (8)	2 (8)	3 (9)	
70% to 89%	13 (16)	13 (54)	11 (32)	
90% to 99%	10 (12)	9 (38)	8 (24)	
Total occlusion	10 (12)	0 (0)	12 (35)	
Bifurcation lesion	14 (17)	8 (33)	14 (41)	0.013
Trifurcation lesion	1 (1)	1 (4)	0 (0)	0.37
Aorto-ostial lesion	0 (0)	0 (0)	1 (3)	0.41
Severe tortuosity	1 (1)	0 (0)	0 (0)	1.00
Long lesion (>20 mm)	11 (13)	9 (38)	17 (50)	<0.001
Heavily calcified lesion	4 (5)	1 (4)	7 (21)	0.022
Thrombotic lesion	1 (1)	0 (0)	0 (0)	1.00
Diffuse disease/small vessel	0 (0)	0 (0)	1 (3)	0.41
Baseline Leaman score	0 (0-1.5)	2 (1-4.3)*	4.5 (1.5-7.6)*	<0.001
Number of segments with transmural LGE extent >50%	0 (0-0)	0 (0-0)	0 (0-0)	0.35
LGE extent (% of territory)	2.1 (0.3-9.3)	1.5 (0.5-3.4)	8.8 (3.0-18.8)*†	<0.001
Follow-up Leaman score	–	0 (0-1)	0 (0-0)†	0.014
Final Leaman score=0	51 (61)	17 (71)	32 (94)*†	<0.001
Leaman score reduction after revascularization	0 (0-0)	2 (1-3.4)*	4 (1.5-7.1)*	<0.001

Data are presented as the median (interquartile range) or n (%).

*P<0.05 vs. the no revascularization territory.

†P<0.05 vs. the PCI territory.

Table 3. Comparisons of changes in quantitative myocardial perfusion on a per-vessel basis

(a) Subgroups based on treatment

	No revascularization (n=83)	PCI (n=24)	CABG (n=34)	P	P for interaction (group×time)
Rest MBF					
Baseline	0.82 (0.81 [0.61-1.02])	0.80 (0.78 [0.59-1.02])	0.73 (0.78 [0.60-0.87])	0.28	0.50
Follow-up	0.90 (0.84 [0.69-0.99))	0.86 (0.76 [0.62-1.10])	0.75 (0.69 [0.62-0.88])	0.09	
P	0.051	0.47	0.63		
Stress MBF					
Baseline	1.95 (1.85 [1.49-2.32])	1.72 (1.54 [1.23-2.13])	1.21 (1.16 [0.79-1.51])	<0.001	0.016
Follow-up	2.08 (1.99 [1.54-2.47])	1.95 (2.03 [1.57-2.28])	1.61 (1.45 [1.27-1.88])	0.001	
P	0.07	0.04	<0.001		
MFR					
Baseline	2.46 (2.41 [1.86-2.98])	2.24 (2.00 [1.74-2.66])	1.68 (1.44 [1.09-1.94])	<0.001	0.002
Follow-up	2.46 (2.33 [1.80-2.91])	2.44 (2.26 [1.85-2.72])	2.22 (1.93 [1.64-2.56])	0.12	
P	0.66	0.20	<0.001		

Data are presented as the mean (median [interquartile range]).

(b) Subgroups based on the degree of angiographic improvement after revascularization

	Leaman score reduction=0 (n=89)	Leaman score reduction 1-3 (n=27)	Leaman score reduction >3 (n=25)	P	P for interaction (group×time)
Rest MBF					
Baseline	0.81 (0.81 [0.61-1.01])	0.76 (0.74 [0.60-0.91])	0.78 (0.78 [0.61-0.92])	0.55	0.21
Follow-up	0.89 (0.83 [0.68-0.99])	0.82 (0.81 [0.62-0.99])	0.76 (0.72 [0.62-0.86])	0.16	
P	0.020	0.27	0.47		
Stress MBF					
Baseline	1.94 (1.84 [1.48-2.31])	1.62 (1.51 [1.24-1.86))	1.19 (1.01 [0.77-1.53])	<0.001	0.003
Follow-up	2.05 (1.96 [1.52-2.45])	1.84 (1.89 [1.51-2.20])	1.68 (1.46 [1.26-1.99])	0.029	
P	0.07	0.026	<0.001		
MFR					
Baseline	2.44 (2.41 [1.84-2.98])	2.19 (2.02 [1.83-2.64])	1.56 (1.29 [1.08-1.80])	<0.001	<0.001
Follow-up	2.44 (2.27 [1.77-2.89])	2.40 (2.19 [1.77-2.73])	2.25 (2.11 [1.66-2.63])	0.47	
P	0.61	0.14	<0.001		

Data are presented as the mean (median [interquartile range]).

Table 4. A multilevel mixed-effects model analysis for predicting absolute and percent changes in the regional MFR after coronary revascularization on a per-vessel basis

	Model 1			Model 2		
	β	**95% CI**	**P**	**β**	**95% CI**	**P**
Dependent variable: absolute change in regional MFR						
Intercept	−0.76	−1.97-0.44	0.21	−0.89	−2.11-0.33	0.15
Patient factors						
Pretest likelihood of obstructive CAD (per 10%)	0.08	−0.03-0.18	0.16	0.08	−0.03-0.19	0.14
Left ventricular ejection fraction (per 10%)	0.02	−0.09-0.14	0.66	0.04	−0.08-0.15	0.52
Prior PCI or CABG	−0.20	−0.62-0.23	0.35	−0.15	−0.58-0.28	0.49
Regional factors						
LGE extent ≥1% of territory	−0.04	−0.26-0.19	0.75	−0.03	−0.26-0.20	0.79
Log (1+Leaman score reduction) (per 1)	0.18	0.06-0.29	0.003	0.14	0.007-0.28	0.040
Vessel territory undergoing CABG	–	–	–	0.19	−0.18-0.57	0.31
Dependent variable: percent change in regional MFR						
Intercept	−32.8	−95.1-29.4	0.29	−44.3	−104.8-16.2	0.15
Patient factors						
Pretest likelihood of obstructive CAD (per 10%)	4.2	−1.3-9.8	0.13	4.4	−0.9-9.6	0.10
Left ventricular ejection fraction (per 10%)	0.8	−4.9-6.5	0.78	2.0	−3.5-7.5	0.47
Prior PCI or CABG	−15.6	−37.5-6.2	0.16	−11.0	−32.3-10.2	0.30
Regional factors						
LGE extent ≥1% of territory	0.8	−10.2-11.9	0.88	2.0	−9.3-13.2	0.73
Log (1+Leaman score reduction) (per 1)	11.3	5.6-17.1	<0.001	8.0	1.2-14.8	0.022
Vessel territory undergoing CABG	–	–	–	20.2	0.9-39.5	0.040

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; LGE, late gadolinium enhancement; PCI, percutaneous coronary intervention.

Table 5. A multilevel mixed-effects model analysis for predicting absolute and percent changes in the regional stress MBF after coronary revascularization on a per-vessel basis

	Model 1			Model 2		
	β	**95% CI**	**P**	**β**	**95% CI**	**P**
Dependent variable: absolute change in regional stress MBF						
Intercept	−0.36	−1.16-0.45	0.38	−0.39	−1.22-0.45	0.36
Patient factors						
Pretest likelihood of obstructive CAD (per 10%)	0.01	−0.06-0.09	0.75	0.06	−0.02-0.13	0.13
Left ventricular ejection fraction (per 10%)	−0.18	−0.46-0.11	0.22	0.02	−0.06-0.09	0.69
Prior PCI or CABG	−0.02	−0.18-0.14	0.80	−0.17	−0.46-0.13	0.26
Regional factors						
LGE extent ≥1% of vessel territory	−0.36	−1.16-0.45	0.38	−0.02	−0.18-0.14	0.81
Log (1+Leaman score reduction) (per 1)	0.05	−0.02-0.13	0.13	0.09	−0.009-0.18	0.07
Vessel territory undergoing CABG	–	–	–	0.05	−0.21-0.31	0.72
Dependent variable: percent change in regional stress MBF						
Intercept	14.6	−54.1-83.3	0.67	5.3	−61.1-71.8	0.87
Patient factors						
Pretest likelihood of obstructive CAD (per 10%)	2.8	−3.3-8.9	0.36	2.9	−3.0-8.6	0.34
Left ventricular ejection fraction (per 10%)	−4.0	−10.3-2.4	0.21	−3.0	−9.1-3.0	0.32
Prior PCI or CABG	−21.3	−45.3-2.8	0.08	−17.0	−40.4-6.3	0.15
Regional factors						
LGE extent ≥1% of vessel territory	0.4	−11.9-12.6	0.95	1.2	−11.3-13.8	0.85
Log (1+Leaman score reduction) (per 1)	9.8	3.4-16.2	0.003	5.8	−1.8-13.4	0.13
Vessel territory undergoing CABG	–	–	–	20.5	−1.1-42.0	0.06

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; LGE, late gadolinium enhancement; PCI, percutaneous coronary intervention.

Figure 1

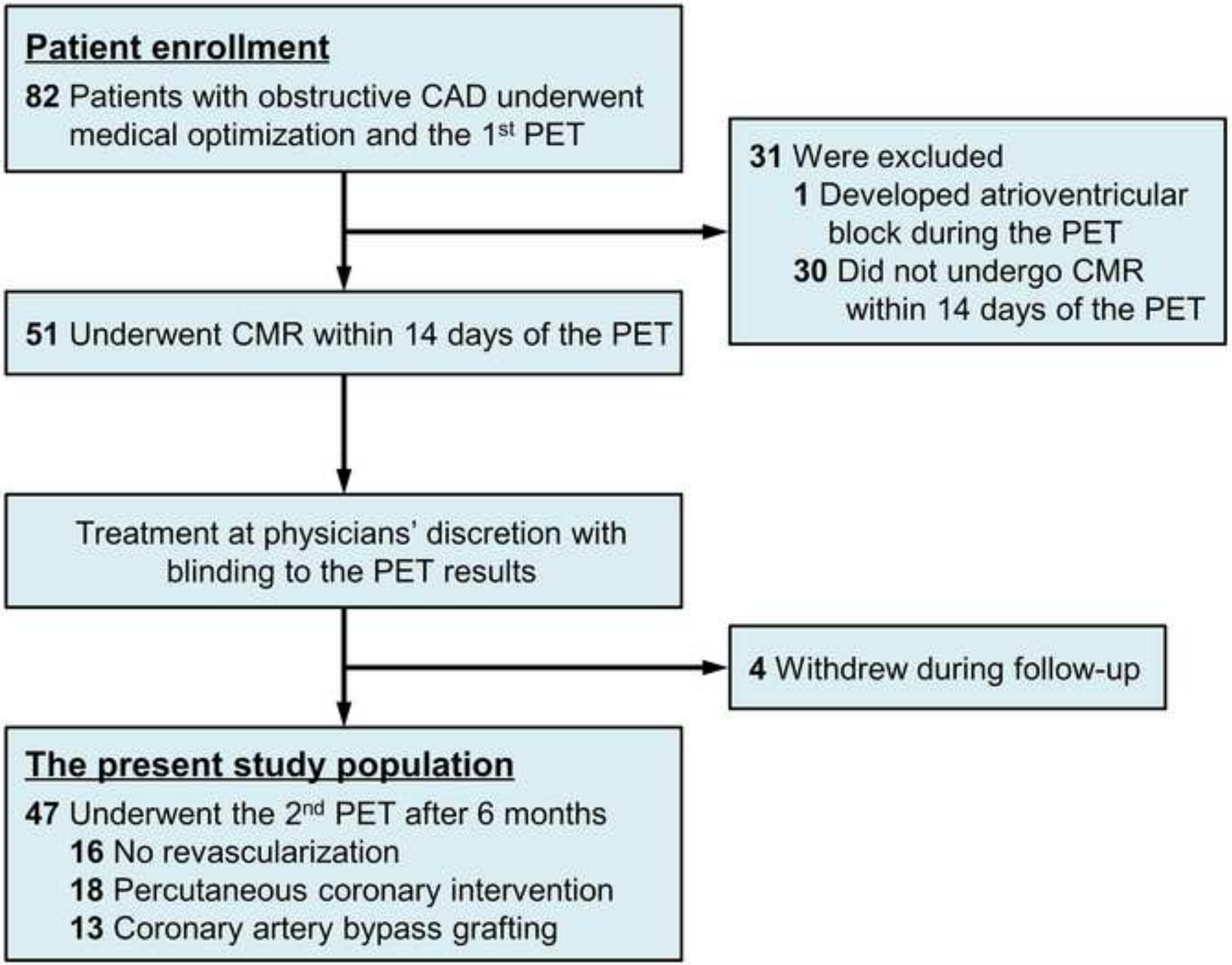

Figure 2

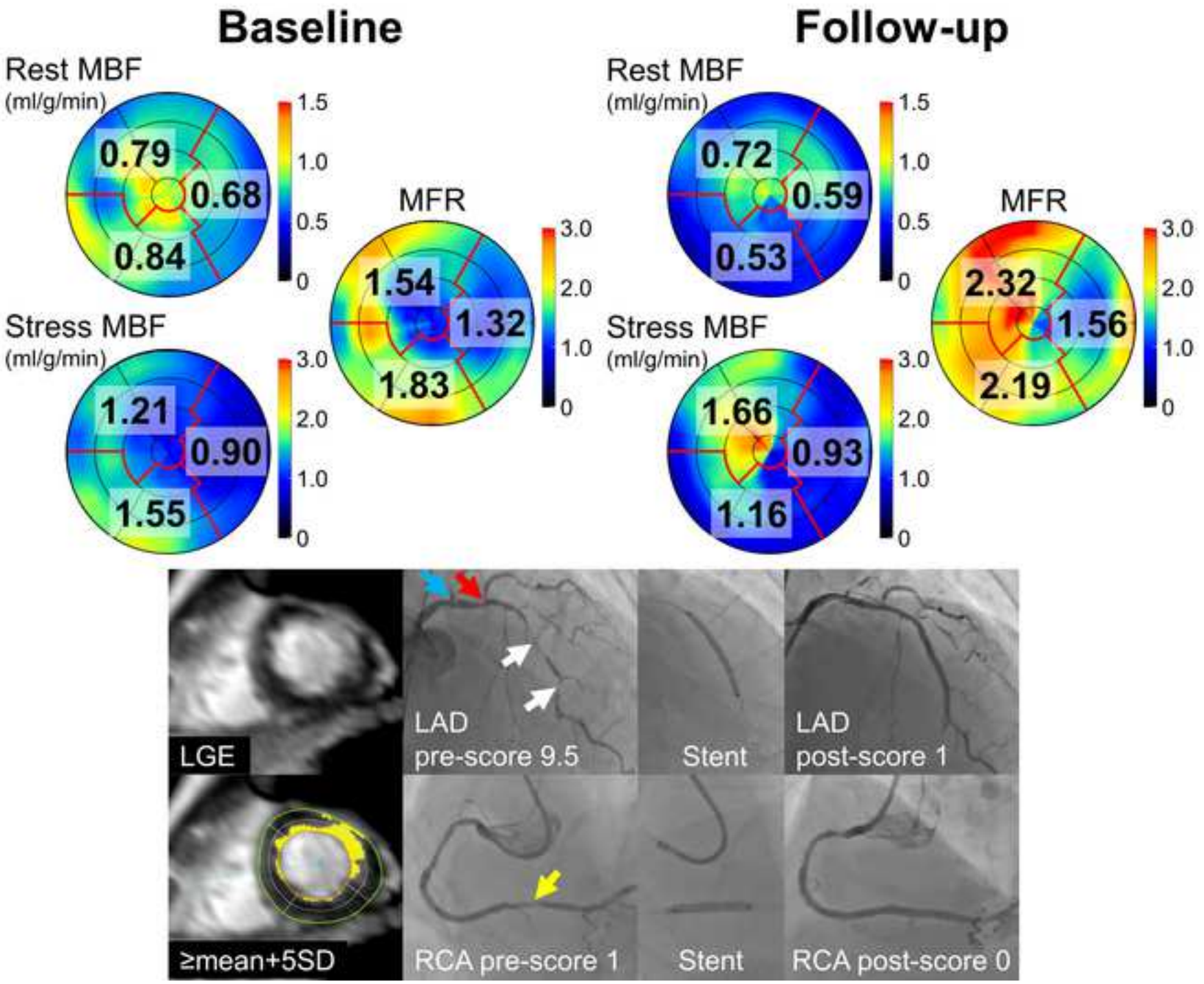

Figure 3

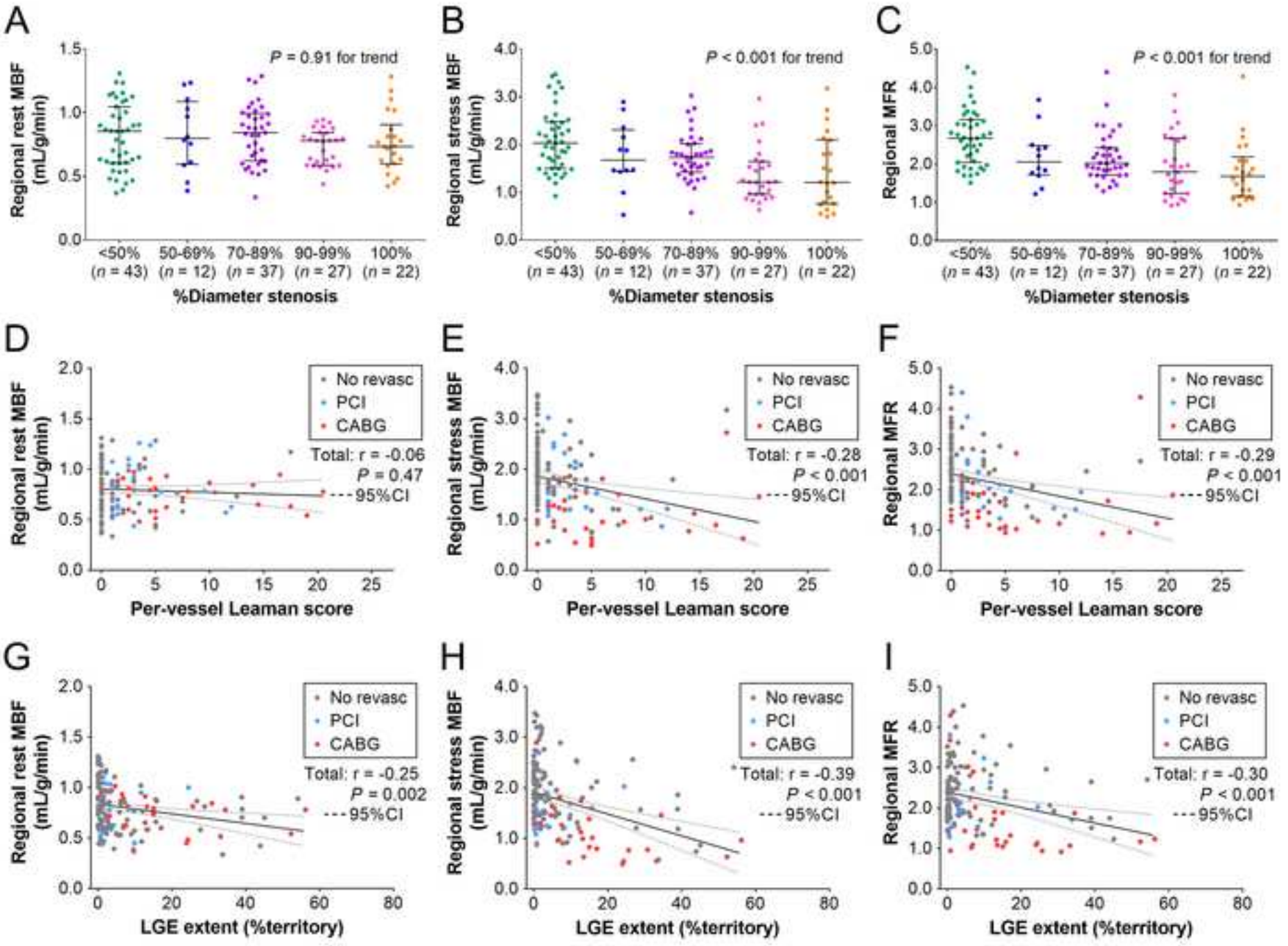

Figure 4