의학석사 학위논문

Clinical Implications of Coronary Flow Reserve and Index of Microcirculatory Resistance in Patients with Intermediate Coronary Stenosis and High Fractional Flow Reserve

높은 분획혈류 예비력을 가진 환자에서 **coronary flow reserve**와 **microcirculatory resistance**의 임상적인 의미

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Abstract

Background: The clinical manifestations and prognostic impact of microvascular status in patients with high fractional flow reserve (FFR) have not yet been clearly defined.

Objectives: We sought to investigate the clinical implications of coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) in patients who underwent fractional flow reserve (FFR) measurement.

Methods: Anatomical lesion severity was evaluated by Gensini and SYNTAX scores. Patients with high FFR (>0.80) were divided into 4 groups according to CFR (≤2) and IMR (≥23U) levels: high CFR and low IMR (61.3%), high CFR and high IMR (18.3%), low CFR and low IMR (13.5%), and low CFR and high IMR (7.0%). Clinical outcome was assessed by the patient-oriented composite outcome (POCO, a composite of any death, any myocardial infarction, and any revascularization). The median follow-up duration was 658.0 (IQR 503.8–1139.3) days.

Results: The physiologic characteristics of 313 patients (663 vessels) were assessed with FFR, CFR, and IMR. Mean FFR and CFR values were 0.85±0.09 and 2.81±1.02, respectively. The mean angiographic percent diameter stenosis was 41.0±17.2%. The median IMR was 16.0U. Among patients with high FFR, those with low CFR had a higher POCO than did those with high CFR (HR, 4.189; 95% confidence interval [CI], 1.117–15.715; *P*=0.034). There were no significant differences in clinical and

angiographic characteristics and FFR values among the 4 groups. Patients with high IMR and low CFR (overt microvascular disease) showed the highest POCO of all groups (*P*=0.002). Overt microvascular disease (HR, 4.845; 95% CI, 1.509–15.557; *P*=0.008), multivessel disease (HR, 3.254; 95% CI, 1.082–9.787; *P*=0.033), and diabetes mellitus (HR, 2.828; 95% CI, 1.088–7.349; *P*=0.033) were independent predictors of POCO in patients with high FFR.

Conclusion: CFR and IMR can provide additional information on coronary circulation and improve risk stratification of patients with high FFR. Overt microvascular disease (low CFR and high IMR) was associated with poor prognosis.

Keywords: coronary artery disease; fractional flow reserve; index of microcirculatory resistance; microvascular function.

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Contents

Lists of tables and figures

Lists of abbreviations

CFR : coronary flow reserve

FFR : fractional flow reserve

IMR : index of microcirculatory resistance

IMR_{corr} : corrected index of microcirculatory resistance by Yong's formula

MI : myocardial infarction

PCI : percutaneous coronary intervention

POCO : patient-oriented composite outcomes

Introduction

The coronary artery system has 3 components with different functions: conductive epicardial coronary arteries, arterioles, and capillaries(1). When any one of these systems fails, myocardial ischemia can occur(1). Therefore, the presence of epicardial coronary artery stenosis is not necessarily a prerequisite for ischemic heart disease (IHD). Although it has not been established that microvascular disease is independent of macrovascular disease(1-3), clinical studies have consistently shown that the presence of microvascular disease is an independent predictor of poor clinical outcomes, especially in patients with acute myocardial infarction (MI)(4,5).

The pressure-derived fractional flow reserve (FFR) index has become a standard invasive method to evaluate the functional significance of epicardial coronary artery stenosis, and clinical outcomes of FFR-guided percutaneous coronary intervention (PCI) have proven to be better than those of angiography-guided PCI or medical treatment(6-8). However, clinical events occur even in patients with high FFR(6). Therefore, microvascular assessment using coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) can provide additional diagnostic and prognostic insights for IHD patients, especially in those with high FFR. Nevertheless, the clinical implications of CFR and IMR measurements in patients who have undergone FFR measurement in daily routine practice remain unknown and have not been clearly defined in a large number of

patients.

We sought to investigate the clinical, angiographic, and hemodynamic characteristics of high-FFR patients according to their CFR and IMR values and to evaluate the prognostic implications of abnormal CFR and IMR in these patients.

Methods

Patient Population

Between April 2009 and September 2013, consecutive patients who underwent clinically-indicated invasive coronary angiography and who received FFR, CFR, and IMR measurements for ≥1 coronary artery with intermediate stenosis (40%–70% by visual assessment) were enrolled from 4 university hospitals in Korea (Seoul National University Hospital, Inje University Ilsan Paik Hospital, Keimyung University Dongsan Medical centre, and Ulsan University Hospital). Patients with hemodynamic instability, left ventricular dysfunction, elevation of cardiac enzymes, evidence of acute MI, or a culprit vessel of acute coronary syndrome were excluded. All patients gave informed consent, and Institutional Review Board approval was obtained per current regulations. The study protocol was in accordance with the Declaration of Helsinki (clinicaltrials.gov identifier, NCT02186093).

Angiographic Analysis and Quantitative Coronary Angiography

Coronary angiography was performed by standard techniques. Angiographic views were obtained following the administration of intracoronary nitrate (100 or 200 μg). All angiograms were analysed at a core laboratory in a blinded fashion. Quantitative coronary angiography was performed in optimal projections with validated software (CAAS II, Pie Medical System,

Maastricht, the Netherlands). Percent diameter stenosis, minimum lumen diameter, reference vessel size, and lesion length were measured. To quantify patients' macrovascular disease burden, Gensini and SYNTAX scores were measured(9).

Coronary Physiologic Measurements

All coronary physiologic measurements were obtained after diagnostic angiography(10). When PCI was performed with FFR guidance, pre-interventional physiologic indices were used for the analysis. Measurement protocols for FFR, CFR, and IMR were standardized among the 4 participating centres before the beginning of this study. In each patient, a 5–7F guide catheter without side holes was used to engage the coronary artery, and a pressure-temperature sensor-tipped guide wire (St. Jude Medical, St. Paul, MN, USA) was introduced. The pressure sensor was positioned at the distal segment of a target vessel, and intracoronary nitrate (100 or 200 μg) was administered before each physiologic measurement. To derive resting mean transit time (Tmn), a thermodilution curve was obtained by using 3 injections of 4 mL of room-temperature saline. Hyperaemia was induced by intravenous infusion of adenosine (140 μg/kg/min) through a peripheral or central vein. Hyperaemic proximal aortic pressure (Pa), distal arterial pressure (Pd), and hyperaemic Tmn were measured during sustained hyperaemia. After measurements were complete, the guide wire was pulled back to the guide catheter, and the presence of pressure drift was checked. FFR was calculated by mean Pd/Pa during hyperaemia, and CFR was calculated by resting

Tmn/hyperaemic Tmn. The uncorrected IMR was calculated by Pd × Tmn during hyperaemia. All IMR values were corrected by Yong's formula (corrected IMR [IMR_{corr}]=Pa×Tmn×([1.35×Pd/Pa]−0.32)(10).

Reproducibility testing for IMR measurements was performed at the beginning of the registry after standardization of the procedure. IMR measurement was repeated after a 5-minute interval in each of 60 patients (15 consecutive patients from each centre). Both measurements showed significant correlation (r = 0.957, P < 0.001), and the intraclass correlation coefficient was 0.991 (95% confidence interval [CI], 0.984–0.994), suggesting excellent reproducibility for the IMR measurement in the study cohort.

Cut-off Values for Physiological Indices and Classification of Patients

Cut-off values were set at FFR ≤ 0.80 (low FFR) and CFR ≤ 2 (low CFR), as previously described(3,6). The cut-off for high IMR was defined as values ≥75^{th} percentile of IMR_{corr} in the overall study population. Because the 75^{th} percentile value of IMR_{corr} was 22.8U, IMR_{corr}≥23U was defined as high IMR in our study. Patients with high FFR (>0.80) were classified according to CFR and IMR values as follows: (1) Group A (high CFR and low IMR); (2) Group B (high CFR and high IMR); (3) Group C (low CFR and low IMR); and (4) Group D (low CFR and high IMR).

Follow-up of the Patients and Adjudication of Clinical Events

Clinical data were obtained at outpatient clinic visits or by telephone and/or medical questionnaires as needed. All relevant medical records were reviewed for clinical events and adjudicated by an external clinical event committee. The vital status of all patients was crosschecked by using the Korean Health System's unique identification numbers. In this way, occurrence of mortality was confirmed even in patients who were lost to follow-up. The primary outcome was patient-oriented composite outcomes (POCO), including all-cause mortality, any MI, and any revascularization. The major secondary outcome was target vessel failure, defined as a composite of cardiac death, MI, or clinically indicated target vessel revascularization by percutaneous or surgical methods. The individual components of the composite outcome were also evaluated. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of MI. All deaths were considered cardiac unless an undisputable noncardiac cause was present. Fourteen patients (4.2%) were lost to follow-up; however, the vital status of these patients was assessed as previously described. The median follow-up duration was 658.0 (interquartile range [IQR] 503.8–1139.3) days.

Statistical Analysis

Categorical variables were presented as numbers and relative frequencies (percentages); continuous variables were presented either as means and

standard deviations or medians with interquartile ranges (IQR) according to their distributions, which were checked by the Kolmogorov-Smirov and Levene tests. Data were analysed on a per-patient basis for clinical characteristics and clinical outcomes and on a per-vessel basis for other factors. Of the 424 patients, 111 (26.2%) showed discordant classification in 4 quadrant models according either to FFR and CFR or to CFR and IMR. Patients with >1 interrogated vessel and different quadrant model classifications were excluded from the per-patient analysis, including the comparison of clinical outcomes. Kaplan-Meier analysis was used to calculate the cumulative incidence of primary and secondary clinical outcomes, and the log-rank test or the Breslow test was used to compare between-group differences.

For per-vessel analyses, a generalized estimating equation (GEE) was used to adjust intrasubject variability among vessels from the same patient. Estimated means and 95% confidence intervals were presented as summary statistics. A GEE procedure with pairwise comparison was used to compare per-vessel variables in the 4-quadrant classification. No post-hoc adjustment was performed. Linear regression analysis was used to estimate the correlation coefficient (Pearson or Spearman, according to the normality of the variables) between quantitative variables. For the reproducibility testing of IMR measurements, the difference between 2 IMR values was analysed with the Wilcoxon signed-rank test and the Spearman correlation coefficient. In addition, the intraclass correlation coefficient, which reflects relative intraobserver variability, was used to assess the degree of agreement between

the 2 IMR values. A Cox proportional hazard regression model was used to identify independent predictors of POCO among patients with high FFR. The improvement in discriminant function of the model with or without incorporation of physiologic index was compared by the category-free net reclassification index (NRI) and integrated discrimination improvement (IDI). The covariates used in multivariate analysis were selected with the criterion of $P < 0.1$. The statistical package SPSS, version 18.0 (SPSS Inc., Chicago, IL, USA) and R programming language, version 3.1.3 (R Foundation for Statistical Computing) were used for statistical analyses.

Results

General Characteristics of Patients and Target Vessels

Table 1 shows clinical, angiographic, and physiologic characteristics of the patients. 84.2% of patients presented in stable condition. The distribution of risk factors was similar between patients in high- and low-FFR groups except for a higher proportion of men and hypercholesterolemia among patients with low FFR.

The anatomical severity of epicardial coronary stenosis was mostly intermediate, with a mean stenosis diameter of 41.0 ± 17.2%. The mean FFR was 0.85 ± 0.09; FFR was ≤0.8 in 147 vessels (22.2%). The mean CFR was 2.81 ± 1.02; CFR was ≤2 in 190 vessels (28.7%). The median unadjusted IMR was 16.0 U (IQR 12.5–22.4 U); the median IMR_{corr}, 15.7U (IQR12.0–21.6U). Compared with patients in the high-FFR group, those in the low-FFR group had more severe stenosis, higher SYNTAX and Gensini scores, and lower CFR. However, IMR_{corr} was not different between the high- and low-FFR groups.

Table 1. General Characteristics of Study Population and Target Vessels

	Total	High-FFR	Low-FFR	P value	High-FFR		
					High-CFR	Low-CFR	P value
Per-patient analysis (n=313)	**313**	**230/313**	**83/313 (26.5%)**		**183/230**	**47/230 (20.4%)**	
General characteristics							
Age, years	61.2 ± 9.7	61.8 ± 9.9	63.3 ± 9.0	0.216	61.0 ± 9.8	64.6 ± 9.7	0.030
Male	206 (65.8%)	140 (60.9%)	66 (79.5%)	0.002	112 (61.2%)	28 (59.6%)	0.838
BMI, kg/m^2	24.7 ± 3.0	24.6 ± 2.9	24.9 ± 3.3	0.383	24.6 ± 3.0	24.8 ± 2.7	0.627
Clinical Presentation				*0.025*			*0.743*
Stable angina	152 (48.6%)	103 (44.8%)	49 (59.0%)		83 (45.4%)	20 (42.6%)	
Unstable angina	49 (15.7%)	37 (16.1%)	12 (14.5%)		31 (16.9%)	6 (12.8%)	
Atypical chest pain	69 (22.0%)	60 (26.1%)	9 (10.8%)		45 (24.6%)	15 (31.9%)	
Silent ischemia	43 (13.7%)	30 (13.0%)	13 (15.7%)		24 (13.1%)	6 (12.8%)	
Cardiovascular Risk Factors							
Hypertension	189 (60.4%)	133 (57.8%)	56 (67.5%)	0.124	105 (57.4%)	28 (59.6%)	0.786

Diabetes mellitus	90 (28.8%)	67 (29.1%)	23 (27.7%)	0.807	54 (29.5%)	13 (27.7%)	0.804
Hypercholesterolemia	195 (62.3%)	135 (58.7%)	60 (72.3%)	0.028	111 (60.7%)	24 (51.1%)	0.234
Current smoker	50 (16.0%)	36 (15.7%)	14 (16.9%)	0.796	31 (16.9%)	5 (10.6%)	0.289
Obesity (BMI>25 kg/m^2)	135 (43.1%)	98 (42.6%)	37 (44.6%)	0.756	80 (43.7%)	18 (38.3%)	0.503
Family history	50 (16.0%)	34 (14.8%)	16 (19.3%)	0.338	30 (16.4%)	4 (8.5%)	0.174
Previous MI	12 (3.8%)	8 (3.5%)	4 (4.8%)	0.585	8 (4.4%)	0 (0.0%)	0.145
Previous PCI	86 (27.5%)	58 (25.2%)	28 (33.7%)	0.136	47 (25.7%)	11 (23.4%)	0.748
Multivessel disease	141 (45.0%)	86 (37.4%)	55 (66.3%)	<0.001	69 (37.7%)	17 (36.2%)	0.846
SYNTAX score	7.0 (0.0-14.5)	5.0 (0.0-11.0)	14.0 (9.0-20.0)	<0.001	5.0 (0.0-11.0)	6.0 (0.0-12.0)	0.905
Gensini score	17.0 (8.5-33.0)	12.3 (6.5-25.5)	36.0 (19.0-52.0)	<0.001	12.0 (6.5-24.5)	16.5 (8.0-28.5)	0.341
Per-vessel analysis (n=663)	**663**	**516/663**	**147/663**		**382/516**	**134/516**	
Measured vessel location				*<0.001*			*0.142*
Left anterior descending artery	378 (57.0%)	255 (49.4%)	123 (83.7%)		187 (49.0%)	68 (50.7%)	
Left circumflex artery	137 (20.7%)	127 (24.6%)	10 (6.8%)		88 (23.0%)	39 (29.1%)	

Right coronary artery	148 (22.3%)	134 (26.0%)	14 (9.5%)		107 (28.0%)	27 (20.1%)	
Quantitative coronary angiography							
Reference diameter, mm	2.99 ± 0.61	3.04 (3.00-3.10)	2.81 (2.72-2.90)	<0.001	3.06 (3.00-3.13)	3.00 (2.89-3.07)	0.106
Diameter stenosis, %	41.0 ± 17.2	36.8 (32.4-38.2)	55.6 (53.0-58.1)	<0.001	36.7 (35.1-38.3)	37.1 (34.5-39.6)	0.790
Lesion length, mm	11.8 ± 7.9	10.9 (10.2-11.5)	15.2 (13.5-16.8)	<0.001	10.9 (10.2-11.6)	10.8 (9.6-11.9)	0.849
Coronary physiological parameters							
FFR	0.85 ± 0.93	0.91 (0.90-0.91)	0.73 (0.72-0.74)	<0.001	0.91 (0.90-0.91)	0.91 (0.90-0.92)	0.656
CFR	2.81 ± 1.02	2.88 (2.78-2.97)	2.48 (2.32-2.64)	<0.001	3.34 (3.25-3.42)	1.57 (1.52-1.61)	<0.001
IMR, U	16.0(12.5-22.4)	20.2 (19.3-21.1)	18.9 (17.2-20.6)	0.200	19.9 (19.0-20.9)	21.0 (19.0-23.0)	0.347
IMR_{corr},U	15.7 (12.0-21.6)	20.5 (19.5-21.5)	17.2 (15.7-18.8)	<0.001	20.3 (19.1-21.4)	21.1 (19.1-23.1)	0.452

Values are mean ± SD, median (interquartile ranges, 25^{th}-75^{th}), estimated mean (95% confidence interval) (per-vessel analysis), or n (%).

Generalized estimating equation model or maximum likelihood χ^2 tests were used for overall and between groups comparison in per-vessel analysis.

Abbreviations: BMI, body-mass index; CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; IMR_{corr}, corrected IMR with Yong′s formula (IMR_{corr}=PaxTmnx([1.35xPd/Pa]-0.32); MI, myocardialinfarction; PCI, percutaneous coronary intervention

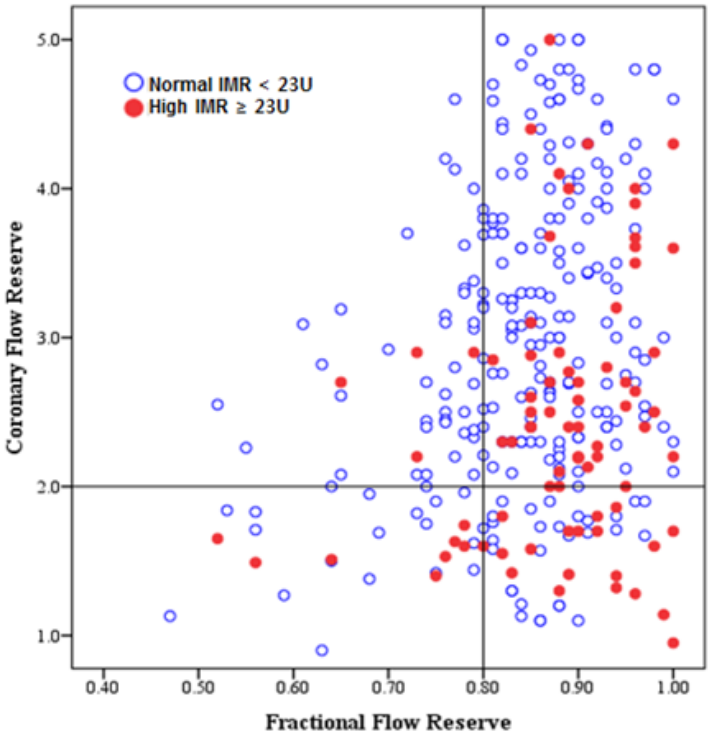

Figure 1. Distribution of patients according to fractional flow reserve and coronary flow reserve.

Figure 1 shows the population distribution according to FFR and CFR cut-off values. There was a modest correlation between FFR and CFR (r = 0.201, P < 0.001). Categorical agreement of FFR and CFR was low (kappa value = 0.178, P < 0.001), and 98 patients (31.3%) showed discordant results. The distributions of IMR_{corr} values were different across each quadrant classification, and IMR_{corr} was highest in patients with high FFR and low CFR (mean, 21.1; 95%CI, 19.2–23.2U; P for overall comparison <0.001).

Comparison of High- and Low-CFR Groups in Patients with High FFR

In patients with high FFR, there was no difference in clinical characteristics between those in the high- and low-CFR groups other than age. Angiographic lesion severity was not different between the 2 groups (mean percent diameter stenosis, 36.7% vs 37.1% for high and low CFR, respectively, P = 0.790; mean lesion length, 10.9 mm vs 10.8 mm, P = 0.849; median Gensini score, 12.0 vs 16.5, P = 0.341; and median SYNTAX score, 5.0 vs 6.0, P = 0.938). In addition, FFR values were similar between patients in the high- and low-CFR groups (0.91 [IQR 0.90–0.92] vs 0.91 [IQR 0.90–0.91], P = 0.656) (Table 1). Among the patients with high FFR, those with high IMR had a higher body mass index, a lower proportion of multivessel disease, and lower SYNTAX and Gensini scores than did those with low IMR. Other cardiovascular risk factors and epicardial lesion severity were mostly similar between the 2 groups.

Figure 2 shows the clinical outcomes among patients with high or low FFR according to the CFR level. In patients with low FFR, the POCO rate was not different between high- and low-CFR groups (hazard ratio [HR], 1.012; 95% CI, 0.242–4.236; P = 0.988; log-rank P = 0.987). Conversely, in patients with high FFR, those in the low-CFR group had a significantly higher POCO rate than did those in the high-CFR group (HR, 4.189; 95% CI, 1.117–15.715; P = 0.034; log-rank P = 0.021). The difference in the POCO rate was driven mainly by a revascularization rate in the low-CFR group.

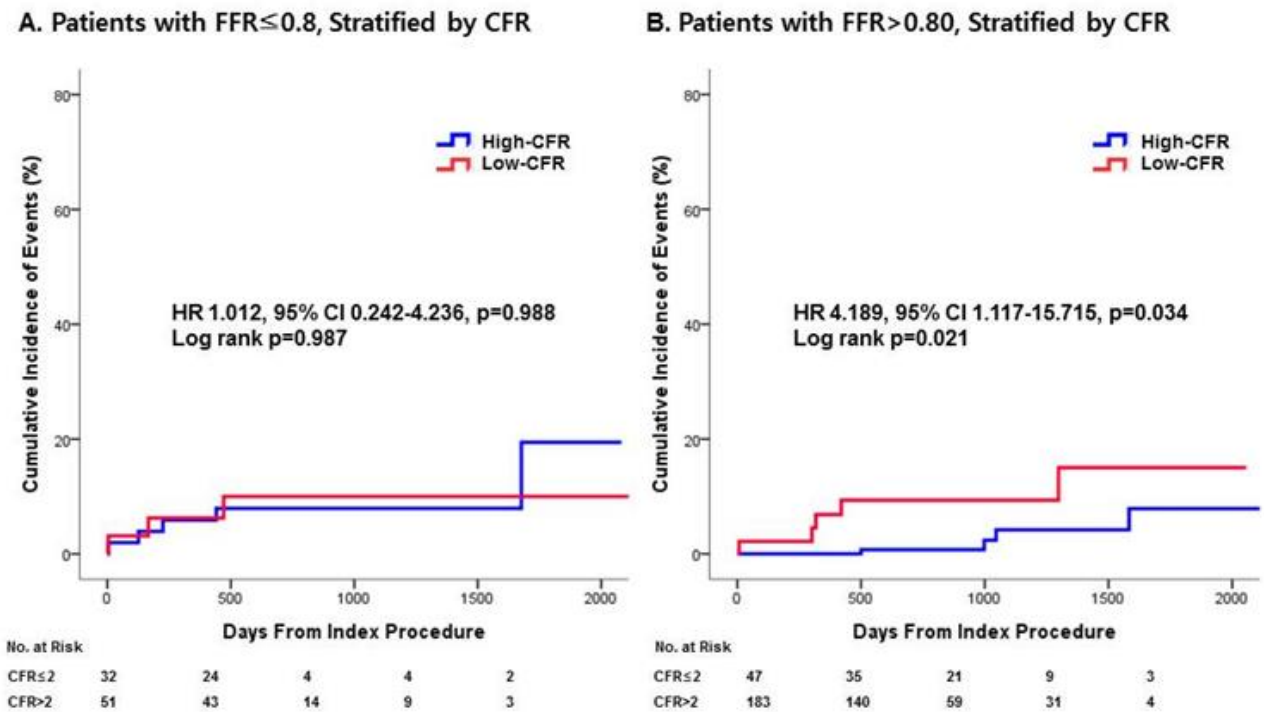

Figure 2. The impact of coronary flow reserve on cumulative incidence of patient-oriented composite outcome.

Clinical Outcomes in Four Groups Divided by CFR and IMR

In order to distinguish among heterogeneous populations in patients with high FFR, patients were divided into 4 groups according to CFR and IMR_{corr} values (Figure3 and Table2). Of the patients with high FFR, 61.3% had normal CFR and IMR_{corr} (Group A), 18.3% had high CFR despite high IMR_{corr} (Group B), 13.5% had low CFR despite low IMR_{corr} (Group C), and 7.0% had low CFR and high IMR (Group D). The distribution of cardiovascular risk factors and angiographic lesion severity was mostly similar among the 4groups (Table2). There was also no difference in FFR values. IMR_{corr} was the highest in Group D, and CFR was the lowest in Group C. In Group B, CFR was preserved despite high IMR_{corr} because the resting Tmn was higher than that of the other groups (1.20 [95% CI, 1.10–1.31] vs 0.60 [95% CI, 0.57–0.63], $P < 0.001$). In Group C, low CFR was mainly due to a lower resting Tmn than that of the other groups (0.31 [95% CI, 0.29–0.34] vs 0.80 [95% CI 0.76–0.85], $P < 0.001$).

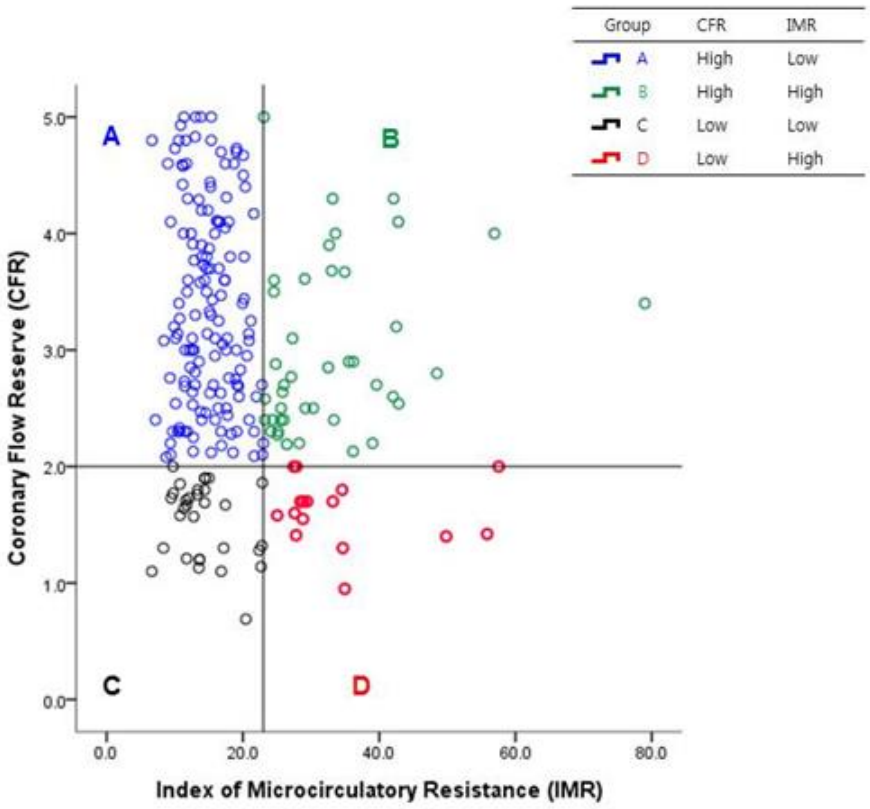

Figure 3. The 4 patterns of microvascular status according to coronary flow reserve and index of microcirculatory resistance among patients with high fractional flow reserve.

Table 2. Angiographic Characteristics and Physiological Differences in Patients with High-FFR, According to Microvascular Function

	Group A (CFR>2 and IMR<23U)	Group B (CFR>2 and IMR≥23U)	Group C (CFR≤2 and IMR<23U)	Group D (CFR≤2 and IMR≥23U)	p value
Per-patient analysis (n=230)	**141 (61.3%)**	**42 (18.3%)**	**31 (13.5%)**	**16 (7.0%)**	
Age, years	60.2 ± 9.9	63.9 ± 7.1	65.6 ± 9.7	62.6 ± 9.9	0.017
Male	90 (63.8%)	22 (52.4%)	18 (58.1%)	10 (62.5%)	0.591
BMI, kg/m^2	24.3 ± 2.9	25.4 ± 3.1	24.6 ± 2.5	25.2 ± 3.3	0.161
Hypertension	78 (55.3%)	27 (64.3%)	18 (58.1%)	10 (62.5%)	0.747
Diabetes mellitus	44 (31.2%)	10 (23.8%)	8 (25.8%)	5 (31.3%)	0.784
Hypercholesterolemia	88 (62.4%)	23 (54.8%)	17 (54.8%)	7 (43.8%)	0.434
Current smoker	25 (17.7%)	6 (14.3%)	3 (9.7%)	2 (12.5%)	0.687

Obesity (BMI>25 kg/m^2)	57 (40.4%)	23 (54.8%)	11 (35.5%)	7 (43.8%)	0.326
Family history	23 (16.3%)	7 (16.7%)	3 (9.7%)	1 (6.3%)	0.548
Previous MI	6 (4.3%)	2 (4.8%)	0 (0.0%)	0 (0.0%)	0.541
Previous PCI	40 (28.4%)	7 (16.7%)	9 (29.0%)	2 (12.5%)	0.263
Multivessel disease	57 (40.4%)	12 (28.6%)	14 (45.2%)	3 (18.8%)	0.163
SYNTAX score	6.0 (0.0-13.0)[‡]	2.0 (0.0-7.0)[†]	8.0 (0.0-16.0)	0.0 (0.0-7.8)	0.014
Gensini score	12.0 (6.5-25.5)	11.3 (5.0-18.8)	20.5 (9.0-37.0)	9.3 (4.8-19.5)	0.114
Per-vessel analysis (n=516)	**283 (54.8%)**	**99 (19.2%)**	**94 (18.2%)**	**40 (7.8%)**	
Angiographic characteristics					
Reference diameter	3.02 (2.95-3.09)	3.18 (3.03-3.34)[§]	2.91 (2.80-3.01)[‡]	3.12 (2.92-3.32)	0.017
Diameter stenosis, %	36.8 (34.9-38.6)	36.4 (33.4-39.4)	38.7 (35.6-41.9)	33.2 (28.3-38.1)	0.343

Lesion length, mm	10.9 (10.1-11.8)	10.7 (9.4-12.4)	10.9 (9.4-12.4)	10.4 (8.6-12.2)	0.961
Coronary Physiological parameters					
FFR	0.91 (0.90-0.91)	0.92 (0.91-0.93)	0.90 (0.89-0.91)	0.92 (0.90-0.94)	0.150
CFR	3.38 (3.28-3.48)$^{\S\#}$	3.21 (3.06-3.36)$^{\S\#}$	1.56 (1.50-1.62)†‡	1.59 (1.50-1.67)†‡	<0.001
Resting Tmn, sec	0.68 (0.65-0.72)‡§	1.20 (1.10-1.31)$^{\dagger\S\#}$	0.31 (0.29-0.34)$^{\dagger\ddagger\#}$	0.67 (0.61-0.74)$^{\S\#}$	<0.001
Hyperemic Tmn, sec	0.20 (0.20-0.21)$^{\ddagger\#}$	0.39 (0.37-0.42)†§	0.20 (0.19-0.22)$^{\ddagger\#}$	0.42 (0.37-0.47)†§	<0.001
IMR_{corr},U	15.5 (15.1-16.0)$^{\ddagger\#}$	33.5 (31.2-35.9)†§	15.5 (14.7-16.3)$^{\ddagger\#}$	34.0 (30.5-37.6)†§	<0.001

Values are mean ± SD (per-patients analysis), estimated mean (95% confidence interval) (per-vessel analysis), or n (%).

Generalized estimating equation model or maximum likelihood χ^2 tests were used for overall and between groups comparison in per-vessel analysis.

$^{\dagger}p<0.05$ compared with group A;‡ $p<0.05$ compared with group B;$^{\S}p<0.05$ compared with group C; $^{\#}p<0.05$ compared with group D

Abbreviations: MI, myocardial infarction; Pa, aortic pressure; Pd, distal pressure; Tmn, mean transit time; FFR, fractional flow reserve; CFR, coronary flow reserve; IMR, index of microcirculatory resistance; IMR_{corr}, corrected IMR.

The cumulative incidence of POCO was 9.5%, 0.0%, 7.0%, and 27.9% for Groups A, B, C, and D, respectively (Breslow *P* value for overall comparison = 0.002). Group D had a significantly higher risk of POCO than did Group A (HR, 5.623; 95% CI, 1.234–25.620; *P* = 0.026) (Figure 4). A multivariate model without a physiologic index found that multivessel disease (HR 3.254; 95% CI, 1.082–9.787; *P* = 0.033) and diabetes mellitus (HR 2.828; 95% CI, 1.088–7.349; *P* = 0.33) were independent predictors of POCO (Table 3). When low CFR and high IMR were added into the model, the presence of low CFR in conjunction with high IMR_{corr} was the most powerful independent predictor for POCO in patients with high FFR (HR 4.914; 95% CI, 1.541–15.663; *P* = 0.007) (Table 3). A model using a physiologic index showed significantly improved discriminant function (relative IDI, 0.467, *P* = 0.037; category-free NRI, 0.648, *P* = 0.007). Sensitivity analysis excluding 5 patients who underwent PCI despite a high FFR altered none of the above results.

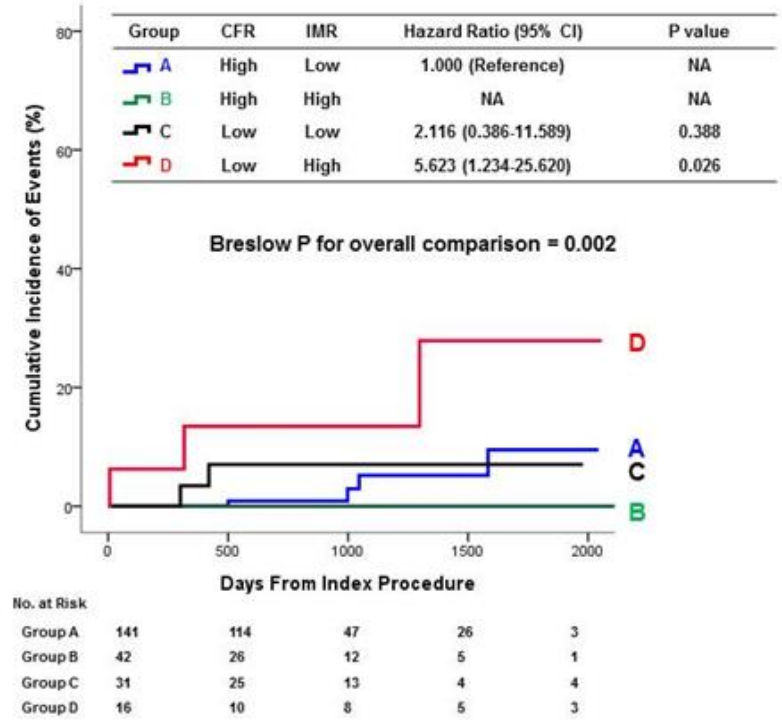

Figure 4. Clinical outcomes according to the patterns of microvascular status defined by coronary flow reserve and index of microcirculatory resistance among patients with high fractional flow reserve.

Table 3. Independent Predictors of Patient-Oriented Composite Outcomes† Among Patients with High-FFR

	Hazard Ratio	95% Confidence Interval	P value
Model 1			
Multivessel disease	3.254	1.082-9.787	0.033
Diabetes mellitus	2.828	1.088-7.349	0.033
Current smoking	0.773	0.218-2.739	0.690
Hypercholesterolemia	0.893	0.325-2.450	0.826
Acute coronary syndrome	0.237	0.031-1.833	0.168
Model 2 (Model 1 + low-CFR and high-IMR)			
Low-CFR and high-IMR	4.914	1.541-15.663	0.007
Multivessel disease	3.639	1.238-10.699	0.019
Diabetes mellitus	2.714	1.050-7.016	0.039
Current smoking	0.928	0.257-3.354	0.910
Hypercholesterolemia	0.859	0.304-2.424	0.774
Acute coronary syndrome	0.162	0.019-1.359	0.094

† Patient-oriented composite outcomes included all-cause mortality, any myocardial infarction, and any revascularization.

C-index of models were 0.755 and 0.789 for model 1 and 2, respectively (p for difference=0.314). The relative integrated discrimination improvement of model 2 was 0.467 (p=0.037) and category-free net reclassification index was 0.648 (p=0.007).

Discussion

This study focused on the clinical relevance of CFR and IMR measurements in patients with high FFR. Those with low CFR had poorer clinical outcomes than did those with high CFR, despite an absence of significant differences in clinical or angiographic characteristics. Measurement of CFR and IMR in patients with high FFR provided information on the status of the microvascular system which was not evident by clinical or angiographic characteristics. Patients with low CFR and high IMR_{corr} had poorer clinical outcomes than did patients in other groups. The independent prognostic factors in patients with high FFR were the presence of low CFR and high IMR_{corr}, diabetes mellitus, and multivessel disease. These findings suggest that the integration of CFR and IMR with FFR can provide additional information on coronary circulation and improve risk stratification for patients with high FFR.

Clinical Implication of CFR in Patients With High FFR

Although FFR-guided PCI has been reported to improve patient outcomes(6,7,11,12) and FFR is now regarded as the gold-standard invasive method to assess the functional significance of coronary artery stenosis(13), there is still room for further improvement in the diagnosis and treatment of patients with high FFR. In the FAME II study, 14.6% of the registry arm (FFR > 0.80 and deferral of PCI) experienced persistent angina, and 9.0% of these patients had clinical events during a 2-year follow-up period(6).

Previous studies have suggested that the measurement of CFR could be helpful in risk stratification for patients with high FFR. Meuwissen et al. reported that among patients with FFR ≥ 0.75, those with abnormal Doppler-derived coronary flow velocity reserve (CFVR) had a higher 1-year event rate than those with normal CFVR(14). Our study also

demonstrated that CFR had prognostic implications in patients with high FFR. Among patients with high FFR, the low-CFR group had poorer clinical outcomes than did the high-CFR group. Because the 2 groups had no differences in angiographic characteristics or FFR, the difference in CFR appears to be due to the difference in microvascular status. However, as presented in Figure 1, patients with high IMR_{corr} were widely distributed between the high- and low-CFR groups, and there was no difference in IMR_{corr} between the 2groups. These results suggest the presence of heterogeneous populations and that classification by CFR levels alone cannot characterize the differences between these patients.

Discordance between CFR and IMR

CFR and IMR are physiologic indices commonly used to assess microvascular status in patients without significant epicardial coronary artery disease. However, because CFR represents the flow ratio between hyperaemic and resting conditions and IMR represents microvascular resistance in a hyperaemic condition, some patients may have discordant results. Although several studies have focused on the relationship between FFR and CFR, the clinical relevance of IMR and CFR in patients with high FFR has not been thoroughly investigated. In our study, 45.0% of the total population had no abnormality in either FFR, CFR, or IMR, and 61.3% of the patients with high FFR had no abnormality in either CFR or IMR. When 230 patients with high FFR were stratified according to CFR and IMR, 73 (31.7%) had discordant classifications using CFR or IMR. It is interesting to note that clinical and angiographic characteristics other than age did not differ between concordant and discordant patients and were mostly similar among the 4 groups when divided by IMR and CFR (Table 2).

Of the discordant patients, those with high CFR and high IMR (Group B, 18.3% of the patients with high FFR) were considered to have high microvascular resistance with preserved flow reserve. The resting Tmn was higher in Group B than in the other groups

(1.20 [95% CI, 1.10–1.31] vs 0.60 [95% CI, 0.57–0.63], $P < 0.001$), suggesting relatively lower resting coronary flow in this group of patients. The clinical outcomes of this group were not different from those of the concordant normal group (Group A, high CFR and low IMR). These results align with those of a previous report by Johnson and Gould in which low resting and hyperaemic flow along with preserved CFR were not associated with myocardial ischemia(15).

Patients with low CFR and low IMR (Group C) had a high resting flow with normal microvascular resistance. In our study, CFR was lowest in patients in Group C, mainly because their resting Tmn was lower than that of patients in the other groups (0.31 [95% CI, 0.29–0.34] vs 0.80 [95% CI, 0.76–0.85], $P < 0.001$). Previously, van de Hoef et al. reported the long-term outcomes of 157 patients with intermediate stenosis who were evaluated with FFR and CFVR(16). They showed that patients with high FFR and low CFVR (n = 10) had a higher 10-year major adverse cardiovascular event rate than did patients with high FFR and high CFVR (n = 78; relative risk, 2.8; 95% CI, 1.8–4.6; $P < 0.001$)(16). Another study from van de Hoef et al. also showed that a low reference vessel CFVR (≤2.7) was associated with higher all-cause mortality than was a normal reference vessel CFVR (>2.7) in stable patients (n = 178) during a 12-year follow-up period(17). In both studies, low CFVR was due to high resting flow velocity or low resting resistance, not from low hyperaemic flow velocity.

In our study, Group C had a numerically higher POCO rate than did Group A, but the difference was not statistically significant. This could be attributed to the difference in patient characteristics among the studies or to the heterogeneous mechanisms of low CFR. Because high resting coronary flow can reflect various conditions, including disturbed autoregulatory processes in coronary circulation(17), intraindividual variability in resting condition(18), or uncontrolled blood pressure or heart rate(15), clinical outcomes could be dependent on the different mechanisms of low CFR in these patients.

Overt Microvascular Disease and Its Prognostic Implication

In our study, 7.0% of patients with high FFR had high IMR and low CFR (Group D) and were regarded as having overt microvascular disease. These patients seemed to have both high microvascular resistance and impaired flow reserve. Among the 4 groups, IMR_{corr} was highest in this group. Although the proportion of patients with high FFR who had overt microvascular disease was small, Group D had the poorest clinical outcomes during follow-up. The presence of overt microvascular disease was an independent prognostic factor in patients with high FFR. In addition, the presence of overt microvascular disease had additive prognostic value aside from clinical risk factors, with significantly improved discriminant function of the prediction model (relative IDI, 0.467, P = 0.037; category-free NRI, 0.648, P = 0.007). These results suggest that the invasive physiologic assessment for microvascular disease combined with CFR and IMR can help identify patients at high risk for future cardiovascular events among those with high FFR.

Previous studies have shown that the presence of microvascular disease is associated with a higher risk of cardiovascular events such as cardiac death, MI, or revascularization in patients without flow-limiting epicardial stenosis(19-22). Several mechanisms have been proposed for the association of microvascular disease and poor clinical outcomes. In addition to myocardial ischemia, microvascular disease is reportedly associated with endothelial dysfunction and inflammatory activity that precedes intimal thickening, lipid deposition in the macrovascular system, and coronary vasomotor dysfunction(20,23-26). In a study by Dhawan et al., coronary microvascular dysfunction in patients with nonobstructive coronary artery disease was associated with higher serum high-sensitivity C-reactive protein and a higher frequency of thin-cap fibroatheroma(19).

Clinical Implications

In clinical practice, if a target lesion's FFR is low, the macrovascular disease should be treated by the appropriate revascularization method, according to the guideline(13). Our study showed that comprehensive physiologic assessment using both CFR and IMR to stratify high-FFR patients could differentiate distinct patterns of microvascular status among these patients with functionally insignificant macrovascular disease. Although the medication of choice for overt microvascular disease is still unclear, the treatment goal for patients with normal resistance and relatively high resting flow or overt microvascular disease differs because the mechanism of limited coronary flow reserve is inherently different. Thus, patients with overt microvascular disease should be closely followed with the best available medical treatment for IHD.

Limitations

Some limitations of this study should be noted. First, our study included patients without evidence of acute MI; therefore, our findings cannot be applied to patients with acute MI(1,4). Second, an intravascular imaging assessment, such as intravascular ultrasound, that could differentiate between diffuse atherosclerotic narrowing and pure microvascular disease, especially in patients with high FFR and low CFR, was not available. However, because there was no difference in any of the angiographic parameters among high-FFR patients, the proportion of patients with diffuse atherosclerotic narrowing could have been minimal in our study population. Third, coronary wedge pressure was not integrated to adjust IMR values. However, IMR values corrected by Yong's formula were used to minimize the influence of collateral flow because it was not practical to measure wedge pressure in patients with intermediate stenosis. Although we used IMR_{corr} values with Yong's formula, it should be noted that the difference between IMR and IMR_{corr} was almost negligible, and using IMR did not alter any of the original results. Fourth, we used the 75^{th} percentile of the IMR as the cut off to define high IMR, since a well-validated cut off value for IMR is not yet established.

Further study is warranted to determine the IMR cutoff value that has independent prognostic impact. Fifth, of the original population of 424 enrolled patients, 111 (26.2%) were excluded from the analysis because they showed discordant classification according either to FFR and CFR or to CFR and IMR across the different interrogated vessels. The clinical significance of these discordant results within individual patients requires further investigation. Last, although the overall follow-up period was approximately 3 years, the median follow-up duration (658.0 days; IQR 503.8–1139.3 days) was too short to explore the long-term clinical impact of overt microvascular disease.

Conclusion

Integration of microvascular assessment using CFR and IMR with FFR can provide additional information on coronary circulation and improve risk stratification of patients with high FFR. The presence of overt microvascular disease (low CFR and high IMR) was an independent prognostic factor in patients with high FFR.

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국문 초록

서론: 현재까지 분획혈류 예비력 (Fractional flow reserve)이 높은 사람들에서 미세혈관 질환에 따른 임상적인 의의와 예후는 아직까지 알려진 바가 없다. 따라서, 본 연구는 심혈관 조영술을 시행한 환자 중, 분획혈류 예비력, Coronary flow reserve (CFR), Index of microcirculatory resistance (IMR)을 모두 측정한 환자들을 대상으로 CFR, IMR에 따른 예후를 분석해 보고자 하였다.

방법: 분획혈류 예비력이 높은 (>0.80) 환자를 CFR (≤2)과 IMR (≥23U) 을 기준으로 4개의 그룹으로 분류하였다. CFR이 높으며 IMR이 낮은 그룹은 전체의 61.3%, CFR과 IMR이 모두 높은 그룹은 18.3%, CFR과 IMR이 모두 낮은 그룹은 13.5%였으며, CFR이 낮으며 IMR이 높은 그룹은 7.0%가 관찰되었다. 일차 평가 항목 (primary endpoint)은 환자관련 사건 (Patient-oriented composite outcome)으로 평가하였으며, 이는 모든 원인에 의한 사망, 심근 경색, 모든 재관류 치료의 합으로 정의하였다. 추적 관찰 기간의 중앙값은 658.0 (사분위 범위 503.8–1139.3)일이었다. 또한, 객관적으로 관상동맥 질환의 해부학적 중증도를 평가하기 위해 Gensini score와 SYNTAX score을 구하였다.

결과: 총 313명의 환자의 663개의 혈관을 분석하였다. 분획혈류 예비력과 CFR의 중앙값은 각각 0.85±0.09, 2.81±1.02이었다. 혈관 조영술상 직경 협착율은 41.0±17.2%이었으며, IMR의 중앙값은 16.0U이었다. FFR이 높은 환자들만으로 분석을 해보았을 때, 낮은 CFR을 가지는 환자군에서 높은 CFR을 가진 환자군보다 환자관련 사건이 높게 나타났으며 (위험비, 4.189; 95% 신뢰구간, 1.117–15.715; *P*=0.034) 높은 분획혈류 예비력을 가지는 환자군에서는 CFR에 따른 사건 발생율의 차이는 관찰되지 않았다. 또, 분획혈류 예비력이 높은 환자들을 IMR, CFR에

따라 4그룹으로 나누어 분석한 경우, 임상적인 위험 인자와 혈관 조영술상의 특징들은 유의한 차이가 관찰되지 않았다. 다만, CFR이 낮고 IMR이 높은, 즉 미세혈관 병변이 있는 환자에서 환자 관련 사건이 다른 그룹에 비해 높게 발생하였다(*P*=0.002). 분획혈류 예비력이 높은 환자에서, 환자관련 사건을 결정하는 독립적인 요인들은 미세혈관 병변 (위험비, 4.845; 95% 신뢰구간, 1.509–15.557; *P*=0.008), 다혈관 질환 (위험비, 3.254; 95% 신뢰구간, 1.082–9.787; *P*=0.033), 당뇨 (위험비, 2.828; 95% 신뢰구간 , 1.088–7.349; *P*=0.033)임을 확인하였다.

결론: 분획혈류 예비력이 높은 환자에서 CFR과 IMR을 추가로 측정하는 것은 관상동맥 순환과 예후를 예측, 위험인자를 조절하는데 있어 도움이 되겠다. CFR이 낮고 IMR이 높은 명백한 미세혈관 질환의 경우 예후가 좋지 않다.

주요어: 관상동맥 질환; 분획혈류 예비력; Coronary flow reserve; Index of microcirculatory resistance

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