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ORIGINAL RESEARCH

Prognostic Impact of Coronary Flow Reserve in Patients With Reduced Left Ventricular Ejection Fraction

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BACKGROUND: Intracoronary physiologic indexes such as coronary flow reserve (CFR) and left ventricular ejection fraction (LVEF) have been regarded as prognostic indicators in patients with coronary artery disease. The current study evaluated the association between intracoronary physiologic indexes and LVEF and their differential prognostic implications in patients with coronary artery disease.

METHODS AND RESULTS: A total of 1889 patients with 2492 vessels with available CFR and LVEF were selected from an international multicenter prospective registry. Baseline physiologic indexes were measured by thermodilution or Doppler methods and LVEF was recorded at the index procedure. The primary outcome was target vessel failure, which was a composite of cardiac death, target vessel myocardial infarction, or clinically driven target vessel revascularization over 5 years of follow-up. Patients with reduced LVEF <50% (162 patients [8.6%], 202 vessels [8.1%]) showed a similar degree of epicardial coronary artery disease but lower CFR values than those with preserved LVEF (2.4±1.2 versus 2.7±1.2, $P<0.001$), mainly driven by the increased resting coronary flow. Conversely, hyperemic coronary flow, fractional flow reserve, and the degree of microvascular dysfunction were similar between the 2 groups. Reduced CFR (≤2.0) was seen in 613 patients (32.5%) with 771 vessels (30.9%). Reduced CFR was an independent predictor for target vessel failure (hazard ratio, 2.081 [95% CI, 1.385–3.126], $P<0.001$), regardless of LVEF.

CONCLUSIONS: CFR was lower in patients with reduced LVEF because of increased resting coronary flow. Patients with reduced CFR showed a significantly higher risk of target vessel failure than did those with preserved CFR, regardless of LVEF.

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Key Words: coronary flow reserve ■ coronary physiology ■ left ventricular ejection fraction ■ prognosis

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CLINICAL PERSPECTIVE

What Is New?

- Compared with patients with preserved left ventricular ejection fraction (LVEF), patients with reduced LVEF had increased resting coronary flow, which led to lower coronary flow reserve values, despite a similar degree of epicardial stenosis.
- Conversely, hyperemic physiologic indexes including fractional flow reserve had no significant correlation with LVEF and were not significantly different between the 2 groups.
- Depressed coronary flow reserve (≤2.0) was independently associated with an increased risk of target vessel failure, regardless of different patterns of resting and hyperemic coronary flow or LVEF.

What Are the Clinical Implications?

- These results suggest that maximally achievable hyperemic flow may not necessarily be affected by the presence of LV dysfunction, and that fractional flow reserve–guided strategy would still be valuable in patients with reduced LVEF, consistent with prior studies showing clinical effectiveness of fractional flow reserve–guided decision making in this patient population.
- Furthermore, the prognostic relevance of depressed coronary flow reserve are consistent despite heterogeneous underlying mechanism such as disturbed autoregulatory processes in coronary circulation, intraindividual variability in resting condition, uncontrolled blood pressure or heart rate, or coronary microcirculatory dysfunction.
- Therefore, measurement of coronary flow reserve in patients with reduced LVEF would provide a significant benefit in risk stratification and enable an individualized approach.

Nonstandard Abbreviations and Acronyms

CFR	coronary flow reserve
FFR	fractional flow reserve
TVF	target vessel failure

Coronary flow reserve (CFR) is a coronary physiologic index defined as a ratio of maximal hyperemic coronary flow to resting coronary flow. Low CFR represents flow limitation of target vessel encompassing the entire coronary circulatory system, from epicardial coronary artery to coronary microvasculature.[1,2] In previous studies, CFR was found to be a prognostic indicator in patients with coronary artery disease (CAD), regardless of the significance of epicardial coronary stenosis or clinical presentation.[3–7]

However, coronary physiologic assessments were mostly confined to patients with preserved left ventricular (LV) systolic function,[3–7] and the clinical implications of coronary physiologic assessment have not been sufficiently validated in patients with reduced LV ejection fraction (LVEF). Theoretically, epicardial coronary stenosis affects LV systolic function by diminished coronary flow and impairment of myocardial perfusion. Conversely, LV systolic function cannot alter the degree of epicardial coronary stenosis or maximal hyperemic flow in an epicardial coronary artery.[8,9] Furthermore, in contrast to hyperemic pressure–derived indexes such as fractional flow reserve (FFR), flow-derived indexes including CFR are known to be affected by various clinical and hemodynamic factors, and there are limited data on the relationship between flow-derived indexes and LVEF and the prognostic role of CFR in patients with reduced LVEF.[10]

Therefore, the current study sought to evaluate (1) the association between intracoronary physiologic indexes and LVEF; and (2) the differential prognostic implications according to LVEF and CFR using 5-year follow-up data from the ILIAS, international multicenter vessel-level pooled registry of intracoronary pressure and flow assessment.

METHODS

Anonymized patient-level data will be made available by the executive and publication committee for reasonable requests. Consent was not obtained for data sharing but the presented data are anonymized and risk of identification is minimal.

Study Design of ILIAS Registry

The ILIAS (Inclusive Invasive Physiological Assessment in Angina Syndromes) registry is an international, multicenter, vessel-level pooled registry of intracoronary pressure and flow assessment. The registry is gathered from 20 institutes located in Korea, the Netherlands, Japan, Spain, Italy, Denmark, and the United States. All data were prospectively recorded according to the protocols of each study. Patients who underwent clinically indicated coronary angiography and comprehensive intracoronary physiologic assessment of at least 1 native coronary artery were included. Patients with hemodynamic instability, significant valvular heart disease, prior coronary artery bypass graft surgery, or culprit vessels of acute coronary syndromes were excluded. Individual patient data were recorded using standardized and anonymized spreadsheets by a fully compliant cloud-based clinical data platform (Castor

EDC, Amsterdam, the Netherlands). Standardized definitions were used for all variables including clinical outcomes. The study protocol was approved by the Institutional Review Board or Ethics Committee at each participating center and written informed consent was obtained from all participants. The study protocol was in accordance with the Declaration of Helsinki. The ILIAS Registry is registered at Clinicaltrials.gov (NCT04485234).

Study Population

A total of 2322 patients with 3046 vessels were enrolled in the ILIAS registry. Among the total population, patients with unavailable baseline LVEF or CFR data and those with no follow-up data were excluded for the current study, leaving 1889 patients with 2492 vessels with clinical outcomes during 5 years of follow-up. According to CFR, the study population was classified into preserved CFR (>2.0) (1276 patients with 1721 vessels) or depressed CFR (≤2.0) (613 patients with 771 vessels) cohorts. The patients were further stratified by LVEF using a cut-off value of 50% into 4 groups: preserved CFR and LVEF group (1185 patients with 1602 vessels); preserved CFR and reduced LVEF group (91 patients with 119 vessels); depressed CFR and preserved LVEF group (542 patients with 688 vessels); and depressed CFR and reduced LVEF group (71 patients with 83 vessels) (Figure 1).

Coronary Angiography and Intracoronary Physiologic Measurements

Coronary angiography and intracoronary physiologic assessment were performed using standard techniques. Angiographic views were obtained following the administration of intracoronary nitrates (100 or 200 μg). After diagnostic coronary angiography, an intracoronary physiological assessment was performed using a pressure–temperature sensor-tipped guide wire (PressureWire; AbbottVascular, St. Paul, MN), a Doppler velocity-equipped coronary guide wire (FloWire; Philips-Volcano, San Diego, CA), or a dual pressure- and Doppler velocity-equipped guide wire (ComboWire; Philips-Volcano, San Diego, CA). Before physiologic assessment, intracoronary nitrates (100 or 200 μg) were administered, and the tip of the guide wire was positioned at the distal segment of the target vessel. Hyperemia was induced by an intravenous infusion of adenosine (140 μg/kg per min) or adenosine triphosphate (150 μg/kg per min) through a peripheral or central vein, an intracoronary bolus injection of adenosine (40–200 μg), or an intracoronary bolus injection of nicorandil (2 mg), according to local standards.[11] For the pressure and flow-derived physiologic measurement, thermodilution or Doppler methods were used in 1569 vessels (63.0%) and 923 vessels (37.0%), respectively. FFR was calculated as the ratio between the mean proximal aortic (Pa) and mean distal coronary pressures (Pd) during maximal hyperemia. For the thermodilution method, resting and hyperemic thermodilution curves were obtained using 3 injections (4 mL each) of room-temperature saline for derivation of resting and hyperemic mean transit times (Tmn). CFR was calculated as the ratio of hyperemic Tmn to resting Tmn. The index of microcirculatory resistance (IMR) was calculated as hyperemic Pd×hyperemic Tmn, and corrected using Yong's formula in case of FFR≤0.80 (corrected IMR=Pa×Tmn×([1.35×Pd/Pa]×0.32)).[12] For the Doppler method, basal and hyperemic average peak flow velocities (APV) were measured, and CFR was calculated as the ratio of hyperemic APV to resting APV. Basal microvascular resistance and hyperemic microvascular resistance were calculated as the ratio of resting Pd to resting APV and hyperemic Pd to hyperemic APV, respectively.[13] After all measurements were completed, the guide wire was pulled back to the guiding catheter. When the pressure drift was larger than >0.03 of an FFR unit, re-equalization and repeated measurements were recommended.

Treatment, Patient Follow-up, and Clinical Outcomes

Percutaneous coronary intervention (PCI) of the target vessel was recommended according to current guidelines at the time of procedure. However, the final decision was at the discretion of the operator. Optimal medical treatments with antiplatelet agents, statins, and antianginal medications were provided based on guidelines.

Follow-up was performed by outpatient visits or telephone contact. The median follow-up duration of the study population was 1140.0 days (interquartile range: 598.0–1826.0 days). The primary outcome was target-vessel failure (TVF), which was defined as a composite of cardiac death, target vessel myocardial infarction (MI), and clinically driven target vessel revascularization. All clinical outcomes were defined according to the Academic Research Consortium report.[14] Periprocedural MI was not coded as a clinical event. All adverse clinical events were verified by assessing hospital records or contacting the primary cardiologist or general practitioner.

Statistical Analysis

Data were analyzed on a per-patient basis for clinical characteristics and a per-vessel basis for comparison of angiographic characteristics, physiologic indexes, and vessel-specific clinical outcomes. For per-vessel analyses, a generalized estimating equation was used to adjust intrasubject variability among vessels from the same patient. Correlation coefficients between LVEF

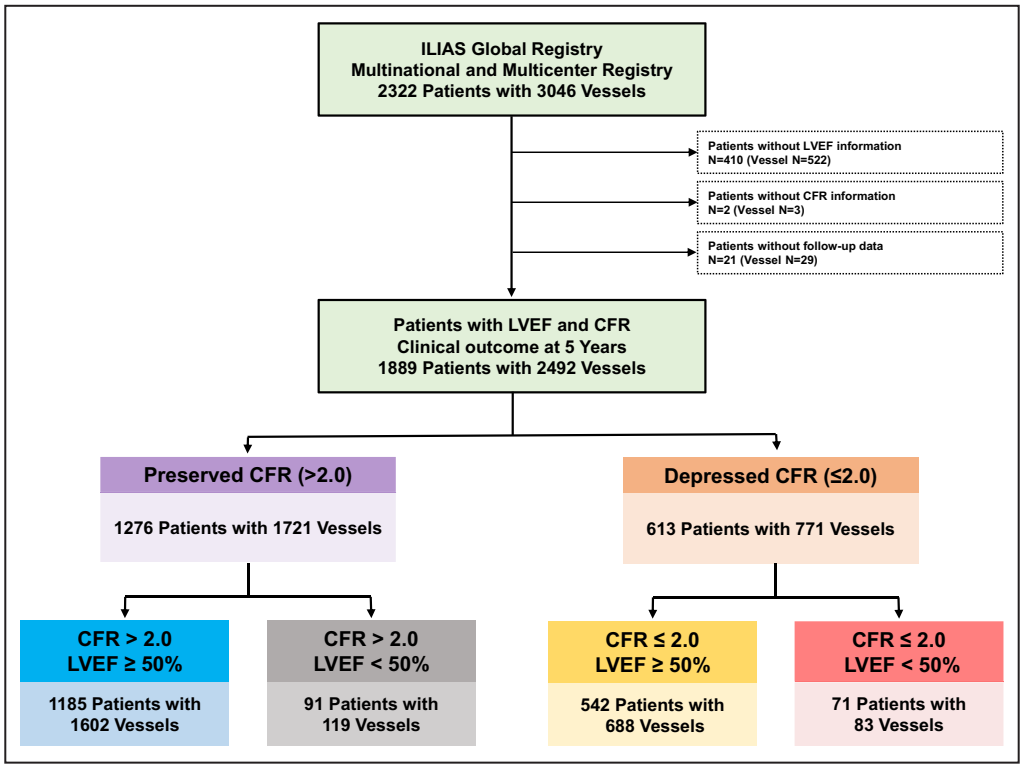

Figure 1. Study flow.
Study flow is presented. Among the total population of the ILIAS registry (2322 patients with 3046 vessels), patients with unavailable baseline LVEF or CFR data and without follow-up data were excluded for the current study, leaving 1889 patients with 2492 vessels with clinical outcomes during 5 years of follow-up. CFR indicates coronary flow reserve; ILIAS (Inclusive Invasive Physiological Assessment in Angina Syndromes) registry; LVEF, left ventricular ejection fraction; and TVF, target vessel failure.

and physiologic indexes were analyzed by Pearson or Spearman methods according to normality. The cumulative incidence of clinical events was presented as Kaplan–Meier estimate and compared using a log-rank test. Multivariable marginal Cox proportional hazard regression was used to calculate adjusted hazard ratio (HR) and 95% CI to compare the risk of clinical events between groups. The restricted cubic spline model was fitted to assess for linearity between continuous variables and risk of clinical events. The assumption of proportionality was assessed by the Schoenfeld residuals and graphically by the log–log plot. The adjusted covariables were age, sex, diabetes, previous MI, clinical presentation, multivessel disease, target vessel intervention, pre-PCI diameter stenosis, pre-PCI FFR≤0.80, and increased microcirculatory resistance (IMR≥25 or hyperemic microvascular resistance≥2.5). The multivariable marginal Cox proportional hazard model was also used to identify independent predictors for TVF. Depressed CFR (≤2.0) and reduced LVEF (<50%) were added to previously listed covariables in this analysis. All probability values were 2-sided, and *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 20.0 for Windows (SPSS-PC, Chicago, IL) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics of Study Population

Figure S1 shows the distribution of LVEF and physiologic indexes of the study population. Table 1 presents baseline patient and vessel characteristics according to LVEF. Among the 1889 patients with 2492 vessels, 162 patients (8.6%) with 202 vessels (8.1%) had LVEF <50% and 1727 patients (91.4%) with 2290 vessels (91.9%) had LVEF ≥50%. Mean LVEF value was 39.4±8.1 in the reduced LVEF group and 63.0±6.2 in the preserved LVEF group. Compared with the preserved LVEF group, the reduced LVEF group showed higher prevalence of men, diabetes, current smoking, previous MI, and previous PCI. There were no significant differences in angiographic lesion severity. In comparison of resting and hyperemic hemodynamics, patients with LV dysfunction showed significantly

higher resting pressure-rate-product but similar hyperemic pressure-rate-product than those with preserved LV function (Table 1).

Table 2 shows baseline patient and vessel characteristics according to pre-PCI CFR using a cut-off value of 2.0. Among the total study population, 613 patients (32.5%) with 771 vessels (30.9%) had depressed CFR ≤2.0 and 1276 patients (67.5%) with 1721 vessels (69.1%) had preserved CFR >2.0. There was no significant difference in clinical characteristics between the 2 groups, except age. Regarding angiographic disease severity, patients with depressed CFR had higher proportions of multivessel disease, left main disease, and higher stenosis severity than those with preserved CFR. In addition, the depressed CFR group had lower pre-PCI resting Pd/Pa and FFR values and a higher degree of microvascular resistance than the preserved CFR group.

Association Between LVEF and Intracoronary Physiologic Indexes

Both CFR and resting Pd/Pa showed a weak correlation with LVEF (R=0.097, P<0.001 and R=0.050, P=0.029, respectively) Conversely, FFR showed no significant correlation with LVEF (R=0.038, P=0.095) (Figure S2). Compared with the preserved LVEF group, the reduced LVEF group had significantly lower CFR values (2.4±1.2 versus 2.7±1.2, P<0.001), which was originated from significantly higher resting coronary flow velocity, represented by lower resting Tmn and higher resting APV values (Table 1 and Figure 2). Conversely, pressure-derived indexes for epicardial coronary stenosis, such as resting Pd/Pa, FFR, and basal and hyperemic stenosis resistance, were not significantly different between the 2 groups (Table 1 and Figure 3).

Clinical Outcomes According to LVEF and CFR

Table 3 and Figure S3 present the cumulative incidence of TVF during 5 years of follow-up. Both LVEF and CFR displayed linear inverse association with 5-year risk of TVF as a continuous variable (Figure S4). Patients with reduced LVEF showed numerically higher risk of TVF than those with preserved LVEF (14.9% versus 9.2%, adjusted HR, 1.386 [95% CI, 0.677–2.840], P=0.372), mainly driven by significantly higher risk of target vessel MI (6.8% versus 1.6%, adjusted HR, 3.257 [95% CI, 1.044–10.167], P=0.042). Conversely, patients with depressed CFR had a significant higher risk of TVF than those with preserved CFR (14.6% versus 7.7%, adjusted HR, 2.080 [95% CI, 1.386–3.122], P<0.001). Patients with depressed CFR also showed a significantly higher risk of cardiac death, target vessel MI, and target vessel revascularization than those with preserved CFR (Table 3).

Prognostic Implications of LVEF and CFR

Table 4 and Figure 4 show clinical outcomes in the 4 groups stratified by CFR and LVEF. These 4 groups showed significantly different risk of TVF during 5 years of follow-up (overall log-rank P<0.001). The cumulative incidence of TVF was highest in the reduced LVEF and depressed CFR group (17.4%) and lowest in the preserved LVEF and CFR group (7.2%). The risk of TVF was similar between the reduced LVEF and preserved CFR group (13.1%) versus the preserved LVEF and depressed CFR group (14.2%). In the multivariable model, the independent predictors for TVF were depressed CFR, pre-PCI FFR (≤0.80) and pre-PCI diameter stenosis, but not LVEF (HR, 1.381 [95% CI, 0.681–2.800], P=0.371). Among them, depressed CFR was the most relevant independent predictor of TVF (HR, 2.081 [95% CI, 1.385–3.126], P<0.001) (Table 5).

Subgroup Analysis According to Different Patterns of Resting and Hyperemic Coronary Flow Among Depressed CFR

Figure S5 presents the tertile distribution of resting or hyperemic surrogate marker of coronary flow (mean transit time, averaged peak velocity) among the depressed CFR cohort. To evaluate the prognostic impact of different patterns of resting and hyperemic flow among the depressed CFR cohort, we classified the depressed CFR cohort into 2 groups: (1) High resting flow and intermediate-to-high hyperemic flow; and (2) Low hyperemic flow and low-to-intermediate resting flow. Figure 5 shows the cumulative incidence of 5-year TVF according to different patterns of depressed CFR. Regardless of different patterns in resting and hyperemic flow, the depressed CFR cohort showed significantly higher risk of TVF than the preserved CFR cohort.

DISCUSSION

The current study evaluated the prognostic implications of coronary physiologic assessment in patients with reduced LVEF (<50%). Key findings are as follows. First, compared with patients with preserved LVEF, patients with reduced LVEF had increased resting coronary flow that led to lower CFR values, despite a similar degree of epicardial stenosis. Second, hyperemic physiologic indexes including FFR had no significant correlation with LVEF and were not significantly different between the 2 groups. Third, depressed CFR (≤2.0) was independently associated with an increased risk of TVF, regardless of LVEF. Fourth, patients with

Table 1. Comparison of Baseline Characteristics According to LVEF

	Total	LVEF ≥50%	LVEF <50%	*P* values
Patient characteristics	1889	1727 (91.4%)	162 (8.6%)	
Demographics				
Age, y	63.5±10.3	63.4±10.3	64.5±10.5	0.197
Male	1407 (74.6%)	1274 (73.9%)	133 (82.1%)	0.028
Body mass index, kg/m^2	25.8±3.9	25.8±3.8	25.5±5.2	0.266
Baseline LVEF (%)	60.9±9.2	63.0±6.2	39.4±8.1	
Cardiovascular risk factors				
Hypertension	1132 (60.1%)	1030 (59.8%)	103 (63.0%)	0.480
Diabetes	540 (28.6%)	475 (27.6%)	65 (40.1%)	0.001
Hyperlipidemia	1194 (63.3%)	1096 (63.5%)	98 (60.5%)	0.495
Current smoker	431 (23.1%)	382 (22.4%)	49 (30.6%)	0.023
Previous myocardial infarction	355 (18.8%)	283 (16.4%)	72 (44.4%)	<0.001
Previous percutaneous coronary intervention	460 (27.2%)	407 (26.1%)	53 (39.6%)	0.001
Family history of coronary artery disease	532 (30.2%)	496 (30.8%)	36 (23.8%)	0.092
Clinical presentation				0.778
Acute coronary syndrome	227 (12.0%)	206 (11.9%)	21 (13.0%)	
Stable ischemic heart disease	1658 (88.0%)	1518 (88.1)	140 (87.0%)	
Discharge medication				
Aspirin	964 (72.7%)	879 (71.9%)	84 (83.2%)	0.020
$P2Y_{12}$ inhibitor	377 (47.5%)	340 (46.2%)	37 (63.8%)	0.014
β-Blocker	519 (39.2%)	441 (36.1%)	78 (77.2%)	<0.001
RAAS blockade	544 (41.1%)	473 (38.7%)	71 (70.3%)	<0.001
Statin	835 (63.1%)	755 (61.7%)	80 (79.2%)	0.001
Vessel characteristics	2492	2290 (91.9%)	202 (8.1%)	
Angiographic evaluation				
Multivessel disease	895 (47.7%)	825 (47.8%)	70 (46.4%)	0.804
LM disease	36 (1.7%)	34 (1.7%)	2 (1.1%)	0.747
Target vessel location				0.349
LAD	1402 (56.8%)	1295 (57.1%)	107 (53.2%)	
LCX	506 (20.5%)	457 (20.2%)	49 (24.4%)	
RCA	560 (22.7%)	515 (22.7%)	45 (22.4%)	
Target vessel intervention	675 (27.1%)	606 (26.5%)	69 (34.2%)	0.023
Quantitative coronary angiography				
Pre-PCI reference vessel size, mm	3.11±0.8	3.12±0.76	3.08±0.67	0.763
Pre-PCI diameter stenosis, %	50.8±18.5	50.8±18.4	51.1±19.2	0.880
Pre-PCI lesion length, mm	15.0±10.6	15.0±10.6	15.3±11.1	0.835
Pre-PCI physiologic indexes				
Measurement methods				0.038
Thermodilution method	1569 (63.0%)	1456 (63.6%)	113 (55.9%)	
Doppler method	923 (37.0%)	834 (36.4%)	89 (44.1%)	
Hemodynamics				
Resting heart rate, bpm	68.5±11.7	68.2±11.6	73.5±13.1	<0.001
Hyperemic heart rate, bpm	75.4±13.2	75.3±13.0	78.0±15.5	0.293
Resting aortic pressure (Pa)	97.2±15.1	97.4±15.1	94.6±15.3	0.017
Resting distal coronary pressure (Pd)	90.5±17.2	90.7±17.1	88.3±17.5	0.063

(*Continued*)

Table 1. Continued

	Total	LVEF ≥50%	LVEF <50%	*P* values
Hyperemic aortic pressure (Pa)	89.3±15.3	89.4±15.2	87.8±16.1	0.251
Hyperemic distal coronary pressure (Pd)	75.0±17.1	75.1±17.0	74.2±18.2	0.570
Resting pressure-rate product, mm Hg·bpm*	6522.0 (5477.9–7722.8)	6486.9 (5458.9–7722.0)	7182.5 (5767.5–7992.0)	0.044
Hyperemic pressure-rate product, mm Hg·bpm†	6706.0 (5595.8–7728.0)	6697.5 (5610.0–7728.0)	6816.0 (5472.0–7980.0)	0.688
Indexes of epicardial coronary stenosis				
Resting Pd/Pa	0.93±0.09	0.93±0.09	0.92±0.09	0.300
FFR	0.83±0.13	0.83±0.13	0.82±0.12	0.266
Basal stenosis resistance	0.26 (0.09–0.53)	0.27 (0.09–0.54)	0.22 (0.10–0.44)	0.279
Hyperemic stenosis resistance	0.32 (0.15–0.63)	0.32 (0.14–0.64)	0.30 (0.18–0.55)	0.739
Flow-derived indexes				
CFR	2.7±1.2	2.7±1.2	2.4±1.2	<0.001
Thermodilution methods (N=1569)				
Resting Tmn	0.68 (0.44–0.99)	0.68 (0.45–1.00)	0.52 (0.36–0.87)	0.013
Hyperemic Tmn	0.24 (0.18–0.36)	0.24 (0.18–0.36)	0.22 (0.16–0.32)	0.357
IMR	20.8±13.1	20.9±13.0	20.3±14.3	0.421
Doppler methods (N=923)				
Resting APV	17.1±7.3	16.9±7.1	18.9±8.9	0.045
Hyperemic APV	38.0±15.1	37.7±15.1	40.4±15.3	0.070
BMR	6.2±2.7	6.2±2.7	5.8±3.0	0.045
HMR	2.3±1.0	2.3±1.0	2.1±0.8	0.055

Data are expressed as number (%), mean±SD, or median (interquartile range). APV indicates averaged peak velocity; BMR, baseline microvascular resistance; CFR, coronary flow reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; IMR, index of microcirculatory resistance; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; LVEF, left ventricular ejection fraction; Pa, aortic pressure; PCI, percutaneous coronary intervention; Pd, distal coronary pressure; RCA, right coronary artery; RAAS, renin-angiotensin-aldosterone system; and Tmn, mean transit time.

*Resting pressure-rate product was calculated as resting heart rates (bpm) × resting aortic pressure (Pa, mm Hg).

†Hyperemic pressure-rate product was calculated as hyperemic heart rates (bpm) × hyperemic aortic pressure (Pa, mm Hg).

depressed CFR had a significantly higher risk of TVF than those with preserved CFR, regardless of different patterns of resting and hyperemic coronary flow.

Coronary Blood Flow and CFR in Reduced LVEF

Clinically, CFR represents the reserve of vasodilatory capacity in the reference vessel.[2] Besides significant epicardial coronary stenosis, CFR values can also be affected by either reduced hyperemic coronary flow because of microvascular dysfunction or increased resting coronary flow in the presence of disturbed coronary autoregulation, or both.[2,15] A few prior studies suggested that reduced hyperemic blood flow because of microvascular dysfunction could be a dominant cause of depressed CFR among patients with reduced LVEF.[16,17] In contrast, the results of the current study suggest that increased resting coronary flow and disturbed coronary autoregulation but not reduced hyperemic blood flow or microvascular dysfunction would be the predominant mechanism for the depressed CFR in patients with reduced LVEF. In the current study, patients with reduced LVEF showed significantly lower resting Tmn and higher resting APV values without difference in hyperemic Tmn or hyperemic APV values than those with preserved LVEF. Furthermore, there was no significant difference in IMR and hyperemic microvascular resistance values, suggesting a similar degree of microvascular dysfunction between the 2 groups. It would be important to notice that the extent, location, quantitative angiographic severity, and physiologic significance of epicardial CAD were similar between the 2 groups, excluding the possible contributions of the difference in epicardial CAD on these findings.

Disturbed coronary autoregulation is well described in patients with CAD. In normal coronary vasculature, coronary blood flow is maintained relatively constant by pressure-flow autoregulation despite changes in coronary perfusion pressure, which is accomplished by adjustment of coronary microvascular resistance via various physiologic, metabolic, endothelial, and neuro-hormonal mechanisms.[18,19] In the setting of decreased coronary perfusion pressure because of significant epicardial stenosis or elevated left ventricular

Table 2. Comparison of Baseline Characteristics According to CFR

	Total	CFR>2.0	CFR ≤2.0	*P* values
Patient characteristics	1889	1276 (67.5%)	613 (32.5%)	
Demographics				
Age, y	63.5±10.3	62.9±10.2	64.9±10.6	<0.001
Male	1407 (74.6%)	946 (74.3%)	461 (75.2%)	0.719
Body mass index, kg/m^2	25.8±3.9	25.8±4.0	25.9±3.8	0.348
Baseline LVEF, %	60.9±9.2	61.4±8.5	60.0±10.6	0.109
Cardiovascular risk factors				
Hypertension	1132 (60.1%)	746 (58.6%)	386 (63.1%)	0.071
Diabetes	540 (28.6%)	348 (27.4%)	192 (31.3%)	0.084
Hyperlipidemia	1194 (63.3%)	802 (63.0%)	392 (63.9%)	0.712
Current smoker	431 (23.1%)	296 (23.5%)	135 (22.2%)	0.557
Previous myocardial infarction	355 (18.8%)	228 (17.9%)	127 (20.7%)	0.162
Previous percutaneous coronary intervention	460 (27.2%)	332 (28.1%)	128 (25.1%)	0.235
Family history of coronary artery disease	532 (30.2%)	357 (29.4%)	175 (31.9%)	0.327
Clinical presentation				0.051
Acute coronary syndrome	227 (12.0%)	140 (11.0%)	87 (14.2%)	
Stable ischemic heart disease	1658 (88.0%)	1134 (89.0%)	524 (85.8%)	
Discharge medication				
Aspirin	964 (72.7%)	659 (70.6%)	304 (77.9%)	0.007
$P2Y_{12}$ inhibitor	377 (47.5%)	233 (44.2%)	144 (53.9%)	0.012
β-Blocker	519 (39.2%)	332 (35.5%)	187 (47.9%)	<0.001
RAAS blockade	544 (41.1%)	370 (39.6%)	174 (44.6%)	0.104
Statin	835 (63.1%)	572 (61.2%)	263 (67.4%)	0.039
Vessel characteristics	2492	1721 (69.1%)	771 (30.9%)	
Angiographic evaluation				
Multivessel disease	895 (47.7%)	579 (44.7%)	316 (54.1%)	<0.001
LM disease	36 (1.7%)	18 (1.2%)	18 (2.7%)	0.022
Target vessel location				0.450
LAD	1402 (56.8%)	968 (56.7%)	434 (57.0%)	
LCX	506 (20.5%)	341 (20.0%)	165 (21.7%)	
RCA	560 (22.7%)	397 (23.3%)	163 (21.4%)	
Target vessel intervention	675 (27.1%)	320 (18.6%)	355 (46.0%)	<0.001
Quantitative coronary angiography				
Pre-PCI reference vessel size, mm	3.11±0.8	3.15±0.73	3.03±0.78	0.006
Pre-PCI diameter stenosis, %	50.8±18.5	48.5±17.9	55.9±18.8	<0.001
Pre-PCI lesion length, mm	15.0±10.6	14.8±10.3	16.0±11.1	0.156
Pre-PCI physiologic indexes				
Flow measurement				0.153
Thermodilution method	1569 (63.0%)	1100 (63.9%)	469 (60.8%)	
Doppler method	923 (37.0%)	621 (36.1%)	302 (39.2%)	
Hemodynamics				
Resting heart rate, bpm	68.5±11.7	67.7±11.4	70.2±12.3	<0.001
Hyperemic heart rate, bpm	75.4±13.2	74.8±12.8	76.9±13.8	0.028
Resting aortic pressure (Pa)	97.2±15.1	97.6±14.9	96.2±15.6	0.112
Resting distal coronary pressure (Pd)	90.5±17.2	92.9±15.6	85.2±19.2	<0.001
Hyperemic aortic pressure (Pa)	89.3±15.3	89.8±15.0	88.2±15.8	0.018
Hyperemic distal coronary pressure (Pd)	75.0±17.1	77.7±15.5	68.9±18.9	<0.001

(*Continued*)

Table 2. Continued

	Total	CFR>2.0	CFR ≤2.0	*P* values
Resting pressure-rate product, mmHg·bpm*	6522.0 (5477.9–7722.8)	6455.9 (5460.5–7700.0)	6714.0 (5570.2–7780.7)	0.176
Hyperemic pressure-rate product, mmHg·bpm†	6706.0 (5595.8–7728.0)	6714.0 (5570.2–7780.7)	6694.0 (5621.8–7588.5)	0.953
Indexes of epicardial coronary stenosis				
Resting Pd/Pa	0.93±0.09	0.95±0.05	0.88±0.13	<0.001
FFR	0.83±0.13	0.86±0.10	0.77±0.16	<0.001
Basal stenotic resistance	0.26 (0.09–0.53)	0.22 (0.08–0.43)	0.40 (0.18–0.93)	<0.001
Hyperemic stenotic resistance	0.32 (0.15–0.63)	0.25 (0.11–0.43)	0.58 (0.31–1.21)	<0.001
Flow-derived indexes				
CFR	2.7±1.2	3.2±1.1	1.5±0.3	
Thermodilution methods (N=1569)				
Resting Tmn	0.68 (0.44–0.99)	0.76 (0.54–1.05)	0.42 (0.28–0.74)	<0.001
Hyperemic Tmn	0.24 (0.18–0.36)	0.23 (0.17–0.31)	0.31 (0.20–0.49)	<0.001
IMR	20.8±13.1	19.0±9.9	24.9±17.7	<0.001
Doppler methods (N=923)				
Basal APV	17.1±7.3	15.7±6.0	20.0±8.8	<0.001
Hyperemic APV	38.0±15.1	41.5±14.4	30.7±14.0	<0.001
BMR	6.2±2.7	6.8±2.7	4.9±2.3	<0.001
HMR	2.3±1.0	2.2±0.8	2.6±1.1	<0.001

Data are expressed as number (%), mean±SD, or median (interquartile range). APV indicates averaged peak velocity; BMR, baseline microvascular resistance; bpm, beats per minute; CFR, coronary flow reserve; FFR, fractional flow reserve, HMR; hyperemic microvascular resistance; IMR, index of microcirculatory resistance; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; LVEF, left ventricular ejection fraction; Pa, aortic pressure; PCI, percutaneous coronary intervention, Pd, distal coronary pressure; RAAS, renin-angiotensin-aldosterone system; RCA, right coronary artery; and Tmn, mean transit time.

*Resting pressure-rate product was calculated as resting heart rates (bpm) × resting aortic pressure (Pa, mmHg).

†Hyperemic pressure-rate product was calculated as hyperemic heart rates (bpm) × hyperemic aortic pressure (Pa, mmHg).

end-diastolic pressure, autoregulatory vasodilation of coronary arterioles occurs to maintain coronary blood flow and myocardial perfusion.[15] Although left ventricular end-diastolic pressure or filling pressures were not available in the current registry, it could be hypothesized that the elevated left ventricular end-diastolic pressure might have caused elevated resting flow and depressed CFR in patients with reduced LVEF. Furthermore, patients with reduced LVEF are likely to have an increased oxygen demand because of elevated resting heart rate and increased LV mass from the remodeling process, which could also lead to increase in the resting blood flow, and thus decrease in the CFR values. Significantly higher resting pressure-rate-product but similar hyperemic pressure-rate-product in the LV dysfunction group compared with the preserved LV function group further support this hypothesis.

Hyperemic Indexes in Reduced LVEF

As opposed to the resting flow indexes, the current study demonstrated that hyperemic indexes including FFR were not significantly different between patients with preserved and reduced LVEF. Although FFR has been used widely to determine the hemodynamic relevance of CAD in various clinical circumstances, some previous studies reported limited reliability of FFR measurement in patients with overt microvascular dysfunction.[2,20,21] This is because maximally achievable hyperemic flow decreases in the presence of overt microvascular dysfunction, which can lead to underestimation of FFR.[22,23] In the same context, accuracy of FFR measurements can be challenging in patients with reduced LVEF given the association between reduced LVEF and microvascular dysfunction. Furthermore, elevated venous pressures in patients with reduced LVEF can theoretically affect FFR measurement.

In the current study, FFR values did not correlate with LVEF and there was no significant difference in other hyperemic indexes such as hyperemic stenosis resistance, hyperemic Tmn, and hyperemic APV between patients with preserved and reduced LVEF. Furthermore, the reduced LVEF group did not show a significantly higher degree of microvascular dysfunction compared with the preserved LVEF group, manifested by similar IMR and hyperemic microvascular resistance values. These results suggest that

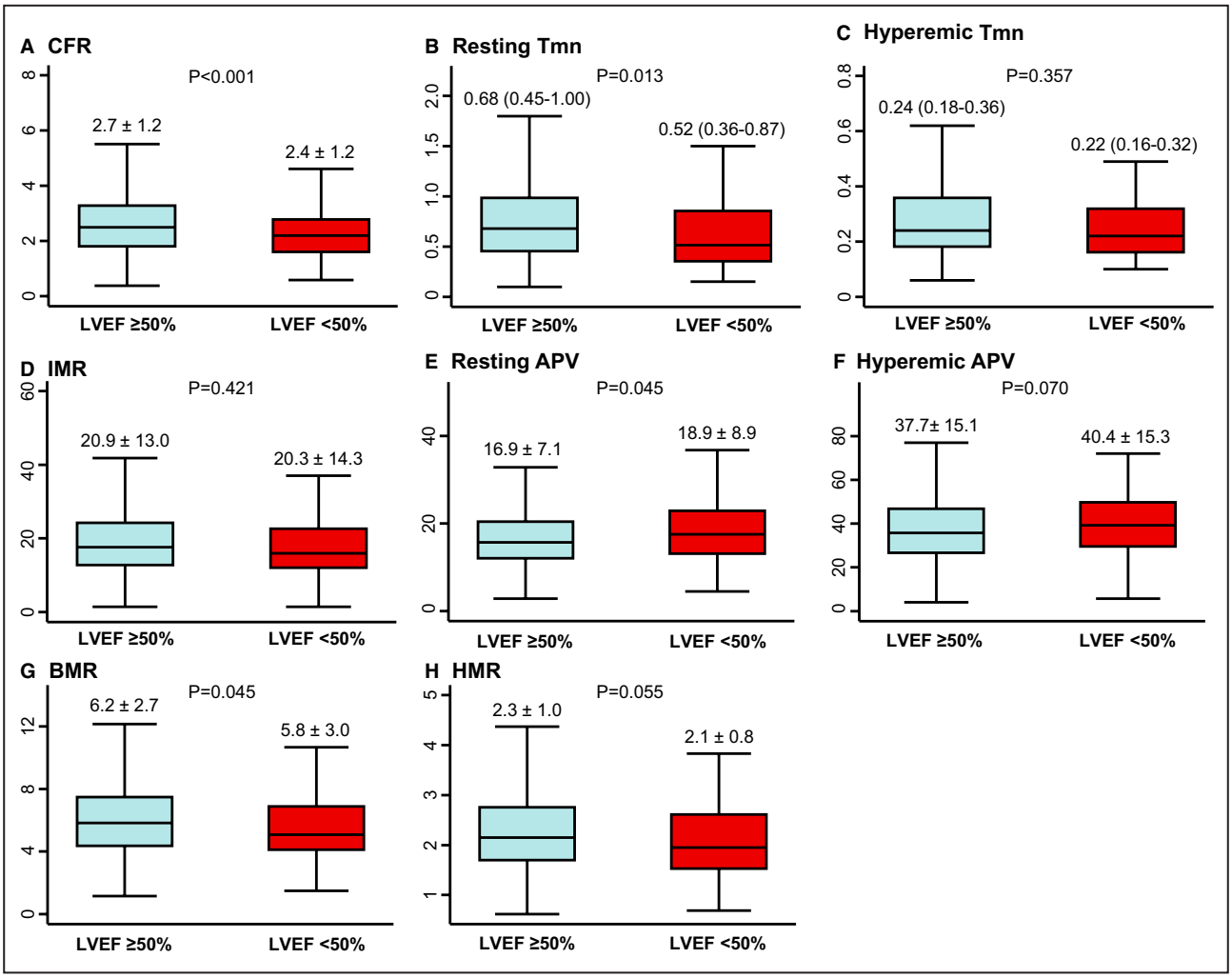

Figure 2. Comparison of flow-derived physiologic indexes according to LVEF.
Comparison of **A**, CFR, **B**, Resting Tmn, **C**, Hyperemic Tmn, **D**, IMR, **E**, Resting APV, **F**, Hyperemic APV, **G**, BMR, **H**, HMR are shown according to LVEF. Data are expressed as mean±SD or median (interquartile range). APV indicates averaged peak velocity; BMR, basal microvascular resistance; CFR, coronary flow reserve; HMR, hyperemic microvascular resistance; IMR, index of microcirculatory resistance; LVEF, left ventricular ejection fraction; and Tmn, mean transit time.

maximally achievable hyperemic flow may not necessarily be affected by the presence of LV dysfunction, and that an FFR-guided strategy would still be valuable in patients with reduced LVEF, consistent with prior studies showing clinical effectiveness of FFR-guided decision making in this patient population.[9,24]

Prognostic Implications of LVEF and CFR

Although both LVEF and CFR have been known to be independent predictors of poor outcomes, to the best of our knowledge, no published studies evaluated the combined prognostic impact of invasively measured CFR and LVEF. In the current study, patients with depressed CFR showed significantly higher cumulative incidence of TVF, its individual components, and all-cause mortality than patients with preserved CFR during 5 years of follow-up. Conversely, although patients with reduced LVEF showed numerically higher cumulative incidence of TVF and all-cause mortality than patients with preserved LVEF, statistical significance disappeared after multivariable adjustment. In multivariable marginal Cox proportional hazard analysis, depressed CFR was the most powerful independent predictor of TVF followed by pre-PCI FFR ≤0.80, but reduced LVEF was not. Although the current study included patients with midrange LVEF (40%–50%) in the reduced LVEF group, which might have mitigated the prognostic impact of LVEF, simply reduced LVEF without significant epicardial CAD or microvascular dysfunction would be less relevant to the risk of future adverse outcomes compared with CFR. Furthermore, it should be noted that patients with depressed CFR showed significantly higher risk of TVF than those

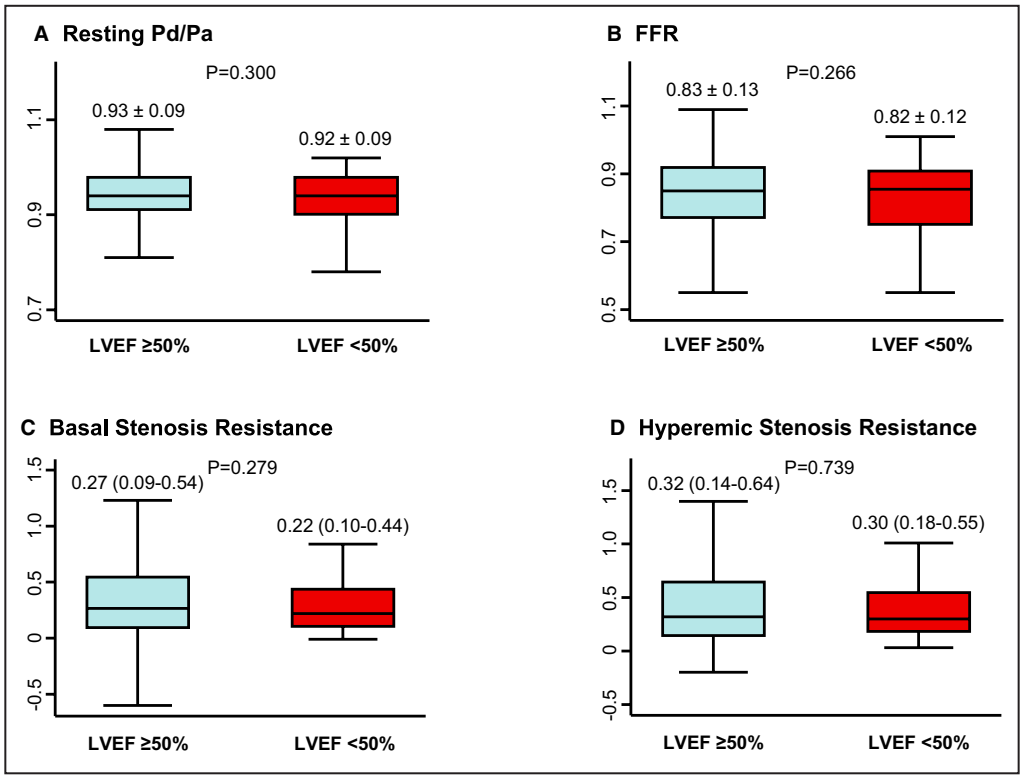

Figure 3. Comparison of physiologic indexes of epicardial coronary stenosis according to LVEF. **A**, Resting Pd/Pa, **B**, FFR, **C**, Basal Stenosis Resistance, **D**, Hyperemic Stenosis Resistance are compared between patients with preserved and reduced LVEF. Data are expressed as mean±SD or median (interquartile range). FFR indicates fractional flow reserve; resting Pd/Pa, resting distal coronary pressure/aortic pressure; and LVEF, left ventricular ejection fraction.

with preserved CFR, irrespective of different patterns in resting and hyperemic coronary flow. These results support the prognostic relevance of depressed CFR despite heterogeneous underlying mechanisms such as disturbed autoregulatory processes in coronary circulation,[15] intraindividual variability in resting condition,[25] uncontrolled blood pressure or heart rate,[26] or coronary microcirculatory dysfunction.[5] Therefore,

Table 3. Clinical Outcomes Over 5 Years of Follow-Up According to LVEF or CFR

Clinical outcomes	LVEF ≥50% (n=2290)	LVEF <50% (n=202)	Univariable HR (95% CI)	Multivariable HR* (95% CI)*	*P* value
Target vessel failure	162 (9.2%)	23 (14.9%)	1.589 (0.961–2.628)	1.386 (0.677–2.840)	0.372
All-cause death	80 (4.7%)	14 (9.8%)	1.960 (1.092–3.519)	1.322 (0.550–3.178)	0.533
Cardiac death	57 (3.4%)	10 (6.9%)	1.953 (0.965–3.952)	1.265 (0.417–3.842)	0.678
Target vessel myocardial infarction	28 (1.6%)	10 (6.8%)	4.037 (1.642–9.928)	3.257 (1.044–10.167)	0.042
Target vessel revascularization	116 (6.5%)	9 (6.3%)	0.875 (0.418–1.832)	0.557 (0.159–1.957)	0.362

Clinical outcomes	CFR >2.0 (n=1721)	CFR ≤2.0 (n=771)	Univariable HR (95% CI)	Multivariable HR* (95% CI)*	*P* value
Target vessel failure	101 (7.7%)	84 (14.6%)	2.071 (1.528–2.806)	2.080 (1.386–3.122)	<0.001
All-cause death	45 (3.7%)	49 (8.6%)	2.738 (1.785–4.200)	2.113 (1.215–3.677)	0.008
Cardiac death	34 (2.7%)	33 (6.3%)	2.444 (1.472–4.057)	1.906 (1.031–3.526)	0.040
Target vessel myocardial infarction	20 (1.6%)	18 (3.3%)	2.237 (1.114–4.491)	3.693 (1.348–10.116)	0.011
Target vessel revascularization	66 (5.0%)	59 (10.2%)	2.213 (1.531–3.198)	2.574 (1.557–4.255)	<0.001

CFR indicates coronary flow reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; HR, hazard ratio; IMR, index of microcirculatory resistance; LVEF, left ventricular ejection fraction; and PCI, percutaneous coronary interventions.

*Adjusted covariables were age, sex, diabetes, previous myocardial infarction, acute coronary syndrome, multivessel disease, target vessel intervention, pre-PCI diameter stenosis, FFR ≤0.80, IMR ≥25, or HMR ≥2.5.

Table 4. Comparison of Clinical Outcomes Among 4 Groups Classified by LVEF and CFR

Clinical outcomes	CFR>2.0		CFR ≤2.0		*P* value*
	LVEF ≥50% (n=1602)	LVEF <50% (n=119)	LVEF ≥50% (n=688)	LVEF <50% (n=83)	
Target vessel failure	89 (7.2%)	12 (13.1%)	73 (14.2%)	11 (17.4%)	<0.001
All-cause death	38 (3.3%)	7 (8.3%)	42 (8.1%)	7 (11.8%)	<0.001
Cardiac death	28 (2.4%)	6 (6.8%)	29 (6.2%)	4 (7.1%)	<0.001
Target vessel myocardial infarction	17 (1.4%)	3 (3.7%)	11 (2.2%)	7 (11.1%)	<0.001
Target vessel revascularization	60 (4.8%)	6 (6.8%)	56 (10.8%)	3 (5.2%)	<0.001

CFR indicates coronary flow reserve; and LVEF, left ventricular ejection fraction.
*Overall Log Rank *P* value.

measurement of CFR in patients with reduced LVEF would provide a significant benefit in risk stratification and enable an individualized approach. Future studies are needed to find effective treatment strategies to improve the prognosis of these patients.

Study Limitations

Some limitations of the study should be acknowledged. First, measured CFR in our study may not represent true value of CFR, especially in patients with reduced LVEF, because of unidentified hemodynamic

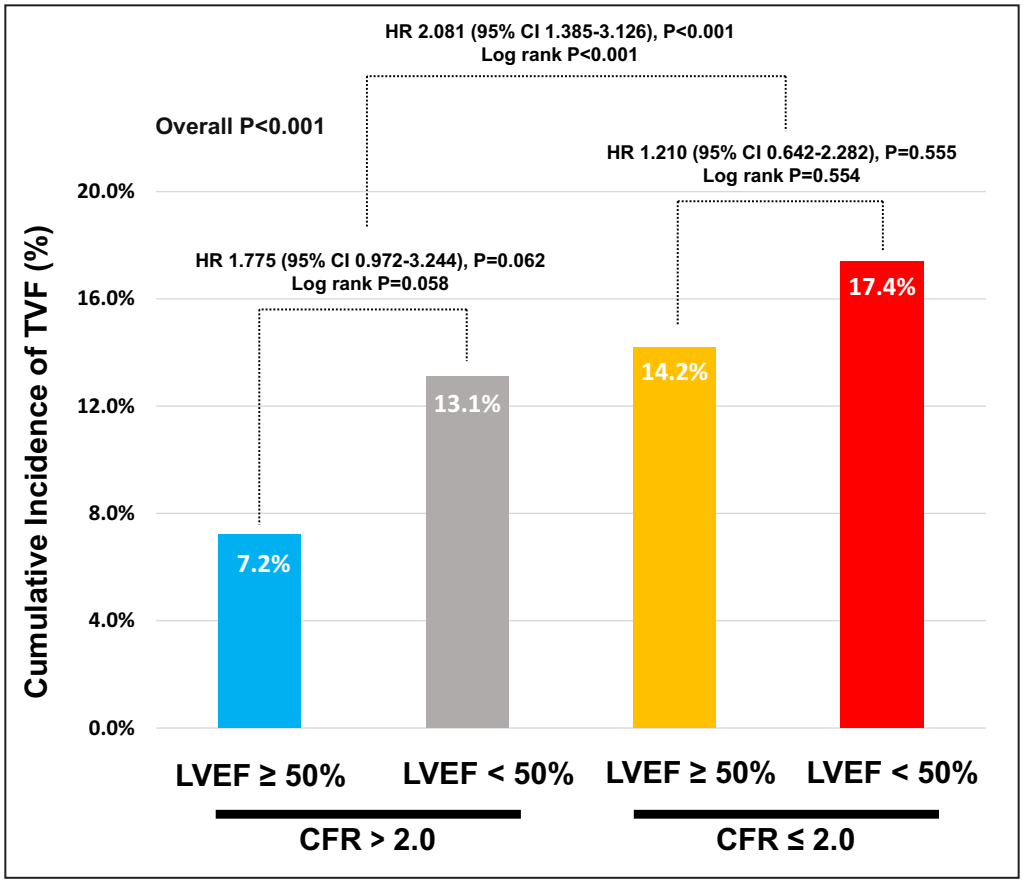

Figure 4. Comparison of TVF According to LVEF and CFR.
Cumulative incidence of TVF at 5 years are compared among 4 groups classified according to LVEF and CFR. Multivariable marginal Cox proportional hazard regression was used to calculate adjusted HR and 95% CI. The adjusted covariables were age, sex, diabetes, previous myocardial infarction, clinical presentation, multivessel disease, target vessel intervention, pre-PCI diameter stenosis, pre-PCI FFR≤0.80, and increased microcirculatory resistance (IMR≥25 or HMR≥2.5). CFR indicates coronary flow reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; HR, hazard ratio; IMR, index of microvascular resistance; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and TVF, target vessel failure.

Table 5. Independent Predictors for Target Vessel Failure

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
CFR ≤2.0	2.070 (1.550–2.766)	<0.001	2.081 (1.385–3.126)	<0.001
LVEF <50%	1.589 (0.961–2.628)	0.040	1.381 (0.681–2.800)	0.371
Age	1.019 (1.001–1.037)	0.035	1.022 (0.998–1.045)	0.069
Male	1.368 (0.901–2.077)	0.142	1.160 (0.681–1.977)	0.586
Diabetes	1.739 (1.247–2.424)	0.001	1.372 (0.871–2.160)	0.172
Previous myocardial infarction	1.721 (1.194–2.481)	0.004	1.446 (0.868–2.408)	0.157
Clinical presentation (ACS)	1.190 (0.709–1.997)	0.510	0.791 (0.399–1.568)	0.502
Multivessel disease	2.049 (1.381–3.039)	<0.001	1.223 (0.741–2.017)	0.431
Target vessel intervention	1.535 (1.126–2.092)	0.007	0.646 (0.392–1.064)	0.086
Pre-PCI diameter stenosis	1.017 (1.008–1.025)	<0.001	1.016 (1.003–1.029)	0.013
Pre-PCI FFR (≤0.80)	2.721 (2.042–3.626)	<0.001	1.987 (1.273–3.101)	0.003
Microvascular dysfunction (IMR ≥25 or HMR ≥2.5)	0.896 (0.631–1.273)	0.541	0.860 (0.554–1.335)	0.502

ACS indicates acute coronary syndrome; CFR, coronary flow reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; HR, hazard ratio; IMR, index of microcirculatory resistance; LVEF, left ventricular ejection fraction; and PCI, percutaneous coronary intervention.

interference and the absence of repeat measurement of CFR. In previous studies, however, reproducibility of CFR measurement was excellent in cases without tachycardia, hypervolemia, and use of inotropic agent.[27,28] Second, the current registry did not collect LV end-diastolic pressure, pulmonary capillary wedge pressure, or central venous pressure. This information represents the overall volume status of the patient, and an abnormal volume status might have affected the results of invasive physiologic assessment. Third, records of follow-up optimal medical management were not available in our registry. Fourth, the exact cause of LV dysfunction was not revealed in our registry, which could affect the clinical outcomes. Finally, since this

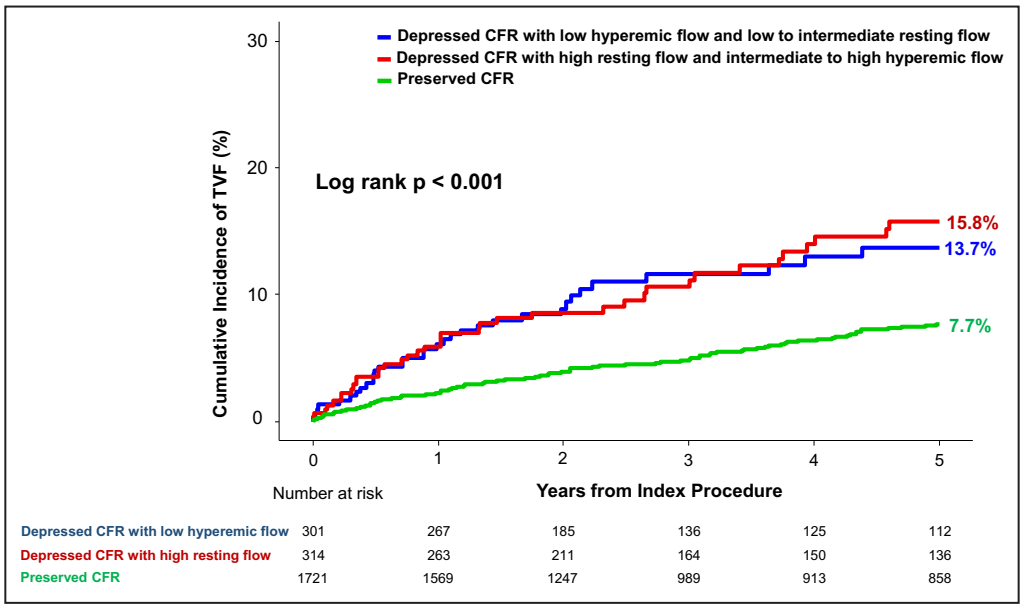

Figure 5. Comparison of target vessel failure according to different patterns of depressed CFR. Cumulative incidence of TVF at 5 years is compared according to different patterns in resting and hyperemic coronary flow among depressed CFR cohort. In this analysis, 305 vessels with missing value in resting and hyperemic Tmn (19.4% of thermodilution technique) were excluded. Regardless of different patterns in resting and hyperemic flow, the depressed CFR cohort showed significantly higher risk of TVF than the preserved CFR cohort. CFR indicates coronary flow reserve; Tmn, mean transit time; and TVF, target vessel failure.

was a registry-based observational study, blinding of neither the patient nor the physician to the results of physiologic evaluation was possible.

CONCLUSIONS

CFR was lower in patients with reduced LVEF because of increased resting coronary flow. Conversely, hyperemic coronary flow and FFR were not changed according to LVEF. Patients with depressed CFR showed significantly higher risk of TVF than did those with preserved CFR, regardless of LVEF. The current study supports the feasibility of the use of intracoronary physiologic indexes in patients with reduced LVEF.

APPENDIX

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ARTICLE INFORMATION

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Supplemental Material

Figures S1-S5

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