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# Coronary Flow Reserve and Microcirculatory Resistance in Patients With Intermediate Coronary Stenosis

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## ABSTRACT

**BACKGROUND** The prognostic impact of microvascular status in patients with high fractional flow reserve (FFR) is not clear.

**OBJECTIVES** The goal of this study was to investigate the implications of coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) in patients who underwent FFR measurement.

**METHODS** Patients with high FFR (>0.80) were grouped according to CFR (≤2) and IMR (≥23 U) levels: group A, high CFR with low IMR; group B, high CFR with high IMR; group C, low CFR with low IMR; and group D, low CFR with high IMR. Patient-oriented composite outcome (POCO) of any death, myocardial infarction, and revascularization was assessed. The median follow-up was 658 days (interquartile range: 503.8 to 1,139.3 days).

**RESULTS** A total of 313 patients (663 vessels) were assessed with FFR, CFR, and IMR. Correlation ($r = 0.201$; $p < 0.001$) and categorical agreement (kappa value = 0.178; $p < 0.001$) between FFR and CFR were modest. Low CFR was associated with higher POCO than high CFR ($p = 0.034$). There were no significant differences in clinical and angiographic characteristics among groups. Patients with high IMR with low CFR had the highest POCO ($p = 0.002$). Overt microvascular disease ($p = 0.008$), multivessel disease ($p = 0.033$), and diabetes mellitus ($p = 0.033$) were independent predictors of POCO. Inclusion of a physiological index significantly improved the discriminant function of a predictive model (relative integrated discrimination improvement 0.467 [$p = 0.037$]; category-free net reclassification index 0.648 [$p = 0.007$]).

**CONCLUSIONS** CFR and IMR improved the risk stratification of patients with high FFR. Low CFR with high IMR was associated with poor prognosis. (Clinical, Physiological and Prognostic Implication of Microvascular Status; NCT02186093) (J Am Coll Cardiol 2016;67:1158–69) © 2016 by the American College of Cardiology Foundation.

Epicardial coronary artery stenosis is not a prerequisite for ischemic heart disease. Although it has not been established that microvascular coronary disease is independent of macrovascular disease (1–3), clinical studies show that microvascular disease is an independent predictor of poor clinical outcomes in patients with acute myocardial infarction (MI) (4,5).

The pressure-derived fractional flow reserve (FFR) index is a standard method for evaluating the functional significance of epicardial coronary artery stenosis, and clinical outcomes of FFR-guided

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percutaneous coronary intervention (PCI) are better than those of angiography-guided PCI or medical treatment (6–8). However, clinical events occur even in patients with high FFR (6). Coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) may provide additional diagnostic and prognostic insights for patients with ischemic heart disease, but the clinical implications of CFR and IMR measurements in patients who have undergone FFR measurement remain unclear.

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We investigated clinical, angiographic, and hemodynamic characteristics of patients with high FFR and 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 had FFR, CFR, and IMR measurements for ≥1 coronary artery with intermediate stenosis (40% to 70% by visual assessment) were enrolled from 4 Korean university hospitals (Seoul National University Hospital, Inje University Ilsan Paik Hospital, Keimyung University Dongsan Medical Centre, and Ulsan University Hospital). FFR was measured to identify functionally significant stenosis in accordance with current guidelines (9,10). CFR and IMR were measured as part of routine clinical practice or for research purposes. Patients with hemodynamic instability, left ventricular dysfunction, elevated cardiac enzyme levels, or evidence of acute MI 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.

**CORONARY ANGIOGRAPHY AND QUANTITATIVE ANALYSIS.** Coronary angiography was performed by using standard techniques. Angiographic views were obtained after administration of intracoronary nitrate (100 or 200 μg). All angiograms and coronary physiological data were analyzed at a core laboratory in a blinded fashion. Quantitative coronary angiography was performed in optimal projections with validated software (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). Percent diameter stenosis, minimum lumen diameter, reference vessel size, and lesion length were measured. Gensini and SYNTAX scores were measured to quantify patients' macrovascular disease burden (11).

**CORONARY PHYSIOLOGICAL MEASUREMENTS.** All measurements were obtained after diagnostic angiography (12). When PCI was performed with FFR guidance, pre-interventional physiological indices were used for analysis. Measurement protocols for FFR, CFR, and IMR were standardized among the 4 participating centers. A 5- to 7-F guide catheter without side holes was used to engage the coronary artery, and a pressure temperature sensor-tipped guidewire (St. Jude Medical, St. Paul, Minnesota) 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 measurement. To derive resting mean transit time ($T_{mn}$), a thermodilution curve was obtained by using 3 injections of 4 ml of room temperature saline. Hyperemia was induced by intravenous infusion of adenosine (140 μg/kg/min) via a peripheral or central vein. Hyperemic proximal aortic pressure (Pa), distal arterial pressure (Pd), and hyperemic $T_{mn}$ were measured during sustained hyperemia. The guidewire was then pulled back to the guide catheter, and the presence of pressure drift was checked. FFR was calculated as the lowest average of 3 consecutive beats during stable hyperemia. CFR was calculated by resting $T_{mn}$/hyperemic $T_{mn}$. The uncorrected IMR was calculated by Pd × $T_{mn}$ during hyperemia. All IMR values were corrected by using Yong's formula (corrected IMR [$IMR_{corr}$] = Pa × $T_{mn}$ × ([1.35 × Pd/Pa] − 0.32) (12).

Reproducibility testing for IMR measurements was performed at the beginning of the registry after standardization of the procedure. IMR measurements were repeated after a 5-min interval in each of 60 patients (15 consecutive patients from each center). 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 to 0.994), suggesting excellent reproducibility for the IMR measurement in the study cohort (Online Figure 1).

**CUTOFF VALUES AND CLASSIFICATION OF PATIENTS.** Cutoff values were FFR ≤0.80 (low FFR) and CFR ≤2 (low CFR), as previously described (3,6). High IMR was defined as values ≥75th percentile of $IMR_{corr}$ in the study population. For our study, high IMR was defined as $IMR_{corr}$ ≥23 U. Patients with high FFR (>0.80) were grouped according to CFR and IMR values as follows: high CFR with low IMR (group A), high CFR with high IMR (group B), low CFR

**ABBREVIATIONS AND ACRONYMS**

**CFR** = coronary flow reserve
**FFR** = fractional flow reserve
**HR** = hazard ratio
**IMR** = index of microcirculatory resistance
**$IMR_{corr}$** = index of microcirculatory resistance corrected according to Yong's formula
**IQR** = interquartile range
**MI** = myocardial infarction
**Pa** = proximal aortic pressure
**PCI** = percutaneous coronary intervention
**Pd** = distal arterial pressure
**POCO** = patient-oriented composite outcome
**$T_{mn}$** = mean transit time

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