JACC: CARDIOVASCULAR INTERVENTIONS VOL. 11, NO. 18, 2018

PUBLISHED BY ELSEVIER

Fractional Flow Reserve and Instantaneous Wave-Free Ratio for Nonculprit Stenosis in Patients With Acute Myocardial Infarction

Ki Hong Choi, MD,[a] Joo Myung Lee, MD, MPH, PhD,[a] Hyun Kuk Kim, MD, PhD,[b] Jihoon Kim, MD,[a] Jonghanne Park, MD,[c] Doyeon Hwang, MD,[c] Tae-Min Rhee, MD,[c] Taek Kyu Park, MD, PhD,[a] Jeong Hoon Yang, MD,[a,d] Young Bin Song, MD, PhD,[a] Eun-Seok Shin, MD, PhD,[e,f] Chang-Wook Nam, MD, PhD,[g] Joon-Hyung Doh, MD, PhD,[h] Joo-Yong Hahn, MD, PhD,[a] Jin-Ho Choi, MD, PhD,[a] Seung-Hyuk Choi, MD, PhD,[a] Bon-Kwon Koo, MD, PhD,[c,i] Hyeon-Cheol Gwon, MD, PhD[a]

ABSTRACT

OBJECTIVES The aim of this study was to compare the changes of fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) with severity of epicardial coronary stenosis between nonculprit vessel of acute myocardial infarction (AMI) and stable ischemic heart disease (SIHD).

BACKGROUND There has been debate regarding the reliability of FFR or iFR for nonculprit stenosis in the acute stage of AMI.

METHODS A total of 100 AMI patients underwent comprehensive physiologic assessment including FFR, iFR, coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) for nonculprit vessel stenosis after primary percutaneous coronary intervention (PCI) for culprit vessel. The changes in FFR and iFR for diameter stenosis (%DS) of nonculprit vessel stenosis were compared with FFR and iFR measured in 203 patients with SIHD.

RESULTS From 40% to 80% stenosis, FFR and iFR measured in nonculprit vessel of AMI patient showed significant decrease with worsening stenosis severity (all p values < 0.001). Nonculprit vessels of AMI patients showed lower CFR than SIHD; however, IMR was not different between the nonculprit vessel of AMI and SIHD patients. FFR and iFR were not significantly different between the nonculprit vessel of AMI and SIHD patients in all %DS groups from 40% to 80% (all p values > 0.05). In addition, percent difference of FFR and iFR according to the increase in %DS was also not significantly different between nonculprit vessel of AMI or SIHD. There was no significant interaction between clinical presentation and the changes of FFR and iFR for worsening %DS (interaction p value $= 0.698$ and 0.257, respectively).

CONCLUSIONS Changes in FFR and iFR for the nonculprit stenosis of AMI patients were not significantly different from those in SIHD patients. These data support the use of invasive physiological parameters to guide treatment of nonculprit stenoses in the acute stage of successfully revascularized AMI. (J Am Coll Cardiol Intv 2018;11:1848–58)

From the [a]Department of Internal Medicine and Cardiovascular Center, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [b]Department of Internal Medicine and Cardiovascular Center, Chosun University Hospital, University of Chosun College of Medicine, Gwangju, Korea; [c]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea; [d]Department of Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [e]Division of Cardiology, Dietrich Bonhoeffer Hospital, Academic Teaching Hospital of University of Greifswald, Greifswald, Germany; [f]Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea; [g]Department of Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea; [h]Department of Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea; and the [i]Institute on Aging, Seoul National University, Seoul, Korea. Dr. Lee has received research grant support from St. Jude Medical (Abbott Vascular) and Philips Volcano. Dr. Koo has received institutional research grant support from St. Jude Medical (Abbott Vascular) and Philips Volcano. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 23, 2018; revised manuscript received June 26, 2018, accepted June 27, 2018.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2018.06.045

Among acute myocardial infarction (AMI) patients, about 50% present with an accompanying nonculprit vessel stenosis and have been shown to experience worse clinical outcomes than do those AMI patients who present without. Previous consensus based on nonrandomized observational studies was to revascularize only the culprit lesion in patients with AMI (1). However, recent randomized trials showed better clinical outcomes when both culprit and nonculprit vessels underwent revascularization in contrast to culprit vessel only (2–5). Based on these results, the recent update of the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for acute ST-segment elevation MI (STEMI) changed the recommendations regarding nonculprit revascularization in AMI patients from Class III to IIb, yet debate remains regarding the optimal treatment strategy for nonculprit stenosis in AMI patients, especially for optimal criteria and modality to decide nonculprit vessel revascularization (6).

SEE PAGE 1859

Two invasive pressure-derived physiologic indices, fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR), have become standard methods to evaluate the functional significance of epicardial coronary artery stenosis in patients with stable ischemic heart disease (SIHD) (7–10). However, both pressure-derived indices can be influenced by alterations in coronary flow velocity and microvascular resistance as in cases of AMI, especially for culprit vessels. Previous studies evaluating changes of coronary blood flow in the culprit vessel and nonculprit vessel territories showed globalized depression of hyperemic coronary blood flow in both territories (11–14). Other studies also showed clinical applicability of FFR and iFR measured in nonculprit vessels at index procedure and follow-up in patients with AMI (15,16). The greatest concern in measuring FFR or iFR for nonculprit stenosis in an acute stage of AMI is the possibility of underestimation or overestimation of stenosis severity due to various changes in coronary circulatory indices in AMI patients.

Therefore, clarification as to whether invasive physiologic indices would show similar changes according to worsening stenosis between the nonculprit vessel of AMI patients compared with vessels in SIHD patients is indicated. In this regard, the current study compared changes in FFR or iFR with the severity of epicardial coronary stenosis and other invasive physiologic indices between the nonculprit vessel of AMI patients and vessels of SIHD patients.

METHODS

STUDY POPULATION. Between April 2016 and November 2017, consecutive AMI patients who underwent physiologic assessment for nonculprit stenosis and prospectively enrolled to the Institutional Registry of Samsung Medical Center were included for the current analysis. AMI was defined as third universal definition of MI (17). Briefly, AMI including non-ST-segment elevation MI (NSTEMI) was defined as a combination of criteria with mandated elevation of a cardiac biomarker, preferably high-sensitive cardiac troponin, and at least 1 of the following: symptoms of ischemia, significant ST-T-wave changes, pathological Q waves, imaging evidence of new regional wall motion abnormality, or intracoronary thrombus. Acute STEMI was defined as elevation of ST-segment more than 0.1 mV in 2 or more contiguous electrocardiography leads or new left bundle branch block with elevated cardiac biomarker.

In AMI patients, nonculprit stenoses ranging from 40% to 80% visual stenosis underwent invasive physiologic assessment. The SIHD population was derived from a prospective registry which enrolled consecutive patients who underwent clinically indicated invasive coronary angiography and measurements of FFR, coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) for at least 1 coronary artery from 5 university hospitals in Korea (Seoul National University Hospital, Samsung Medical Center, Inje University Ilsan Paik Hospital, Keimyung University Dongsan Medical Center, and Ulsan University Hospital) (NCT02186093). A part of this registry population was included in another published study (18). The study protocol was approved by the Institutional Review Board or Ethics Committee at each participating center and all patients provided written informed consent. The study protocol was in accordance with the Declaration of Helsinki.

ANGIOGRAPHIC ANALYSIS AND QUANTITATIVE CORONARY ANGIOGRAPHY. Coronary angiography was performed using standard techniques. Angiographic views were obtained following the administration of intracoronary nitrate (100 or 200 μg). All angiograms 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 (%DS),

ABBREVIATIONS AND ACRONYMS

%DS = percent diameter stenosis

AMI = acute myocardial infarction

CFR = coronary flow reserve

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

IMR = index of microcirculatory resistance

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

Pd/Pa = distal coronary pressure to aortic pressure

SIHD = stable ischemic heart disease

STEMI = ST-segment elevation myocardial infarction

Tmn = mean transit time

minimum lumen diameter, reference vessel size, and lesion length were measured. The atherosclerotic burden in epicardial coronary arteries was assessed by SYNTAX score.

CORONARY PHYSIOLOGIC MEASUREMENTS. All coronary physiologic measurements were performed as previously described (18). A guide catheter (5-F to 7-F) without side holes was used to engage the coronary artery, and a pressure-temperature sensor guidewire (St. Jude Medical [Abbott Vascular], St. Paul, Minnesota) was used. Measurement protocols for resting distal coronary pressure to aortic pressure (Pd/Pa), FFR, CFR, and IMR were standardized among the participating centers before the beginning of this study, and all coronary physiologic data were collected and validated at a core laboratory in a blinded fashion.

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 (4 ml each) of room-temperature saline. Hyperemia was induced by intravenous infusion of adenosine (140 μg/kg/min) through a peripheral or central vein or intracoronary bolus injection of nicorandil (2 mg) to avoid hypotension. Hyperemic Pa, Pd, and hyperemic Tmn were measured during sustained hyperemia. After measurements were complete, the guidewire was pulled back to the guide catheter, and the presence of pressure drift was checked.

Resting Pd/Pa was calculated as the ratio of mean Pa to mean Pd. iFR was calculated as the mean pressure distal to the stenosis divided by the mean aortic pressure during the diastolic wave-free period. The resting tracing data were extracted and the iFR was calculated using automated algorithms acting over the wave-free period over a minimum of 5 beats as previously described (19). CFR was calculated as resting Tmn/hyperemic Tmn. FFR was calculated as the lowest average of 3 consecutive beats during hyperemia. IMR was calculated by Pd × Tmn during hyperemia. For lesions with significant FFR (≤0.80), IMR values were corrected by Yong's formula (corrected IMR = Pa × Tmn × ([1.35 × Pd/Pa] − 0.32).

In SIHD patients and nonculprit vessel of AMI patients, all coronary physiologic measurements were performed after diagnostic angiography or after PCI for the culprit vessel, respectively. For the culprit vessel of AMI patients, PCI was performed according to current guidelines and invasive physiologic data were obtained after PCI for the culprit lesion.

STATISTICAL ANALYSIS. Categorical variables were expressed as number and relative frequency (percentage) and continuous variables as mean ± SD or median (interquartile range), according to their distribution, which was checked by Kolmogorov-Smirnov test. Data were analyzed on a per-patient basis for clinical characteristics and on a per-vessel basis for comparison of lesion characteristics and physiologic indices. For per-vessel analyses, a generalized estimating equation was used to adjust intrasubject variability among vessels from the same patient. Estimated mean ± SD are presented as summary statistics. The comparisons of pre-PCI invasive physiologic indices between SIHD and AMI nonculprit vessels were adjusted by %DS and lesion length. No post hoc adjustment was performed. In addition, as a sensitivity analysis, multivariable generalized estimating equation models, including clinical presentation (NSTEMI or STEMI), were constructed to explore independent predictors of FFR or iFR. All probability values were 2 sided and p values <0.05 were considered statistically significant.

RESULTS

PATIENT AND LESION CHARACTERISTICS. Table 1 shows the characteristics of the study population. Among 100 patients with AMI, 66.0% presented with NSTEMI and 34.0% presented with STEMI. There were no significant differences in clinical characteristics between SIHD and AMI patients except age. Although systolic or diastolic blood pressure were not different between SIHD and AMI patients, AMI patients showed slightly lower left ventricular ejection fraction. All AMI patients underwent culprit vessel PCI and were discharged on a dual antiplatelet regimen. Among the AMI population, patients with STEMI showed significantly higher cardiac enzyme release and lower left ventricular ejection fraction (Online Table 1). In AMI patients, the nonculprit vessel showed higher %DS and longer lesion length than in SIHD patients. There was no significant difference in resting Pd/Pa, iFR, or FFR between SIHD and nonculprit vessel of AMI after adjustment of %DS and lesion length (Table 2). All culprit vessels of AMI patients were successfully revascularized with no significant residual stenosis in the target vessel (Table 2).

COMPARISON OF CFR AND IMR AMONG SIHD AND THE NONCULPRIT AND CULPRIT VESSELS OF AMI PATIENTS. Figure 1 demonstrates the distribution of invasive physiologic indices among total patients and

Online Figure 1 presents the distribution of invasive physiologic indices, according to clinical presentation. The culprit vessel of AMI patients showed significantly lower CFR and higher IMR compared with SIHD or nonculprit vessel. Compared with CFR in SIHD, depressed CFR in the culprit vessel originated from statistically insignificant 11.5% increase of resting Tmn than SIHD ($p = 0.301$), and significant 73.3% increase of hyperemic Tmn than SIHD ($p < 0.001$). Although CFR in the nonculprit vessel was slightly lower than that of SIHD, the difference was not significant (2.88 ± 1.38 vs. 3.16 ± 1.31; $p = 0.208$). In addition, there were no significant differences in resting and hyperemic Tmn and IMR between nonculprit vessel and SIHD (**Figure 2 and Table 2**).

CHANGES IN FFR AND iFR FOR NONCULPRIT VESSEL IN AMI PATIENTS. **Figure 3 and Table 3** present changes in FFR and iFR according to worsening stenosis severity in nonculprit vessel of AMI or SIHD patients. In both nonculprit vessel of AMI and SIHD patients, FFR and iFR showed significant decrease along with worsening stenosis severity from <40% to >80% of %DS (all p values < 0.001). In every stratum of %DS, FFR and iFR were not significantly different between nonculprit vessel of AMI and SIHD patients (all p values > 0.05) (**Table 3**). In addition, percent difference of FFR and iFR according to the increase in %DS was not significantly different between nonculprit vessel of AMI and SIHD patients (**Figure 3**). Furthermore, there was no significant interaction between clinical presentation and the changes of FFR and iFR for worsening %DS (interaction p value = 0.698 and 0.257 for FFR and iFR, respectively) (**Figure 3**).

TABLE 1 Baseline Clinical Characteristics

	Total (N = 303)	SIHD (n = 203)	AMI (n = 100)	p Value
Demographics				
Age, yrs	60.8 ± 13.2	59.6 ± 13.7	63.3 ± 11.8	0.020
Male	230 (75.9)	150 (73.9)	80 (80.0)	0.305
Body mass index, kg/m^2	24.2 ± 3.3	24.0 ± 3.6	24.7 ± 2.6	0.078
Cardiovascular risk factors				
Hypertension	160 (52.8)	100 (49.3)	60 (60.0)	0.101
Diabetes mellitus	109 (36.0)	74 (36.5)	35 (35.0)	0.904
Hyperlipidemia	175 (57.8)	129 (63.5)	46 (46.0)	0.005
Chronic kidney disease*	47 (15.5)	36 (17.7)	11 (11.0)	0.176
Current smoker	59 (19.5)	34 (16.7)	25 (25.0)	0.121
Previous myocardial infarction	20 (6.6)	14 (6.9)	6 (6.0)	0.960
Previous percutaneous coronary intervention	48 (15.8)	37 (18.2)	11 (11.0)	0.146
Complexity of CAD				
Clinical presentation				<0.001
SIHD	203 (67.0)	203 (100.0)	0 (0.0)	
NSTEMI	66 (21.8)	0 (0.0)	66 (66.0)	
STEMI	34 (11.2)	0 (0.0)	34 (34.0)	
SYNTAX score	11.2 ± 8.6	8.8 ± 8.0	16.2 ± 7.7	<0.001
Hemodynamic parameters				
Systolic blood pressure, mm Hg	123.3 ± 17.0	123.0 ± 16.2	124.0 ± 18.5	0.641
Diastolic blood pressure, mm Hg	73.1 ± 11.6	73.0 ± 11.3	73.3 ± 12.1	0.838
Left ventricular ejection fraction, %	61.3 ± 9.5	62.9 ± 8.5	58.2 ± 10.4	<0.001
Laboratory profiles				
Peak troponin I, ng/ml	NA	NA	26.1 ± 48.8	NA
Peak CK-MB, ng/ml	NA	NA	55.1 ± 106.6	NA
White blood count, /mm^3	7,628.9 ± 2,824.5	7,056.6 ± 2,592.3	8,767.9 ± 2,933.3	<0.001
Creatinine, mg/dl	1.1 ± 1.3	1.2 ± 1.4	1.1 ± 0.8	0.561
Low-density lipoprotein, mg/dl	101.7 ± 40.8	94.6 ± 39.5	115.2 ± 40.1	<0.001
Glucose, mg/dl	133.5 ± 56.8	121.9 ± 42.6	156.5 ± 72.9	<0.001
High sensitivity CRP, mg/dl	0.51 ± 1.76	0.41 ± 1.55	0.69 ± 2.10	0.255

Values are mean ± SD or n (%). *Chronic kidney disease was defined as estimated glomerular filtration rate <60ml/min/m^2 or serum creatinine >1.4 mg/dl.

AMI = acute myocardial infarction; CAD = coronary artery disease; CK-MB = creatine kinase-myocardial band; CRP = C-reactive protein; NA = not applicable; NSTEMI = non-ST-segment elevation myocardial infarction; SIHD = stable ischemic heart disease; STEMI = ST-segment elevation myocardial infarction.

INVASIVE PHYSIOLOGIC INDICES IN THE NONCULPRIT VESSEL OF STEMI PATIENTS. In STEMI patients, the culprit vessel showed the lowest CFR and the highest IMR compared with SIHD and the nonculprit vessel. Although the resting Tmn was not significantly different among SIHD and the nonculprit and culprit vessels of STEMI patients, the culprit vessel showed a significant increase in hyperemic Tmn compared with the other groups. For nonculprit vessel of STEMI patients, IMR and hyperemic Tmn were similar with SIHD; however, CFR was significantly lower than SIHD (Online Figure 2).

Nevertheless, FFR and iFR in the nonculprit vessel of STEMI patients also showed significant changes according to worsening stenosis severity, and neither FFR nor iFR were significantly different in all strata of %DS compared with SIHD or NSTEMI patients (Online Table 2). Similarly, changes in FFR and iFR for worsening %DS did not show significant interaction according to SIHD, NSTEMI, and STEMI patients (interaction p value = 0.625 and 0.257 for FFR and iFR, respectively) (Online Figure 3). Likewise, changes in FFR and iFR did not show any difference in accordance with nonculprit vessel location (Online Table 2). In addition, although %DS, lesion length, hyperemic Tmn, and IMR were independently associated with FFR or iFR, neither STEMI or NSTEMI were independently associated with FFR or iFR in multivariable models (Online Table 3).

DISCUSSION

The current study compared the changes in FFR and iFR for worsening nonculprit vessel stenosis in AMI patients with those in SIHD patients. The main findings were as follows. First, the culprit vessel of AMI

TABLE 2 Baseline Lesion Characteristics Among SIHD and AMI Nonculprit and Culprit Lesions

	SIHD (n = 329)	AMI Nonculprit (n = 128)	AMI Culprit (n = 110)	p Value	
				SIHD vs. AMI Nonculprit	SIHD vs. AMI Culprit
Lesion location					
LAD	203 (61.7)	56 (43.8)	43 (39.1)	0.001	<0.001
LCX	65 (19.5)	40 (31.2)	21 (19.1)	0.012	0.989
RCA	61 (18.5)	32 (25.0)	46 (41.8)	0.158	<0.001
Quantitative coronary angiography, pre-PCI					
Reference diameter, mm	3.11 ± 0.66	3.10 ± 0.69	3.22 ± 0.65	0.821	0.173
Minimal lumen diameter, mm	1.51 ± 0.76	1.35 ± 0.76	0.56 ± 0.65	0.044	<0.001
Diameter stenosis, %	51.57 ± 20.62	61.61 ± 15.44	85.29 ± 13.76	<0.001	<0.001
Lesion length, mm	14.22 ± 9.60	16.46 ± 9.25	19.93 ± 10.83	0.027	<0.001
Quantitative coronary angiography, post-PCI					
Diameter stenosis, %	NA	NA	16.8 ± 15.4	NA	NA
Invasive physiologic indices*					
Resting Pd/Pa	0.93 ± 0.08	0.91 ± 0.10	0.94 ± 0.06†	0.801	NA
Instantaneous wave-free ratio	0.89 ± 0.11	0.86 ± 0.13	0.93 ± 0.08†	0.375	NA
Fractional flow reserve	0.82 ± 0.11	0.80 ± 0.11	0.89 ± 0.08†	0.406	NA
Resting mean transit time	0.87 ± 0.42	0.80 ± 0.41	0.97 ± 0.59†	0.218	0.301
Hyperemic mean transit time	0.30 ± 0.16	0.30 ± 0.16	0.52 ± 0.33†	0.971	<0.001
Coronary flow reserve	3.16 ± 1.31	2.88 ± 1.38	2.04 ± 1.05†	0.208	<0.001
Index of microcirculatory resistance	18.5 ± 11.4	17.9 ± 10.5	33.0 ± 21.0†	0.693	<0.001

Values are n (%) or mean ± SD. *The comparisons of pre-PCI invasive physiologic indices between SIHD and acute coronary syndrome nonculprit were adjusted by diameter stenosis and lesion length. †Invasive physiologic indices in the culprit vessel were measured after percutaneous coronary intervention (PCI) for the culprit lesion.

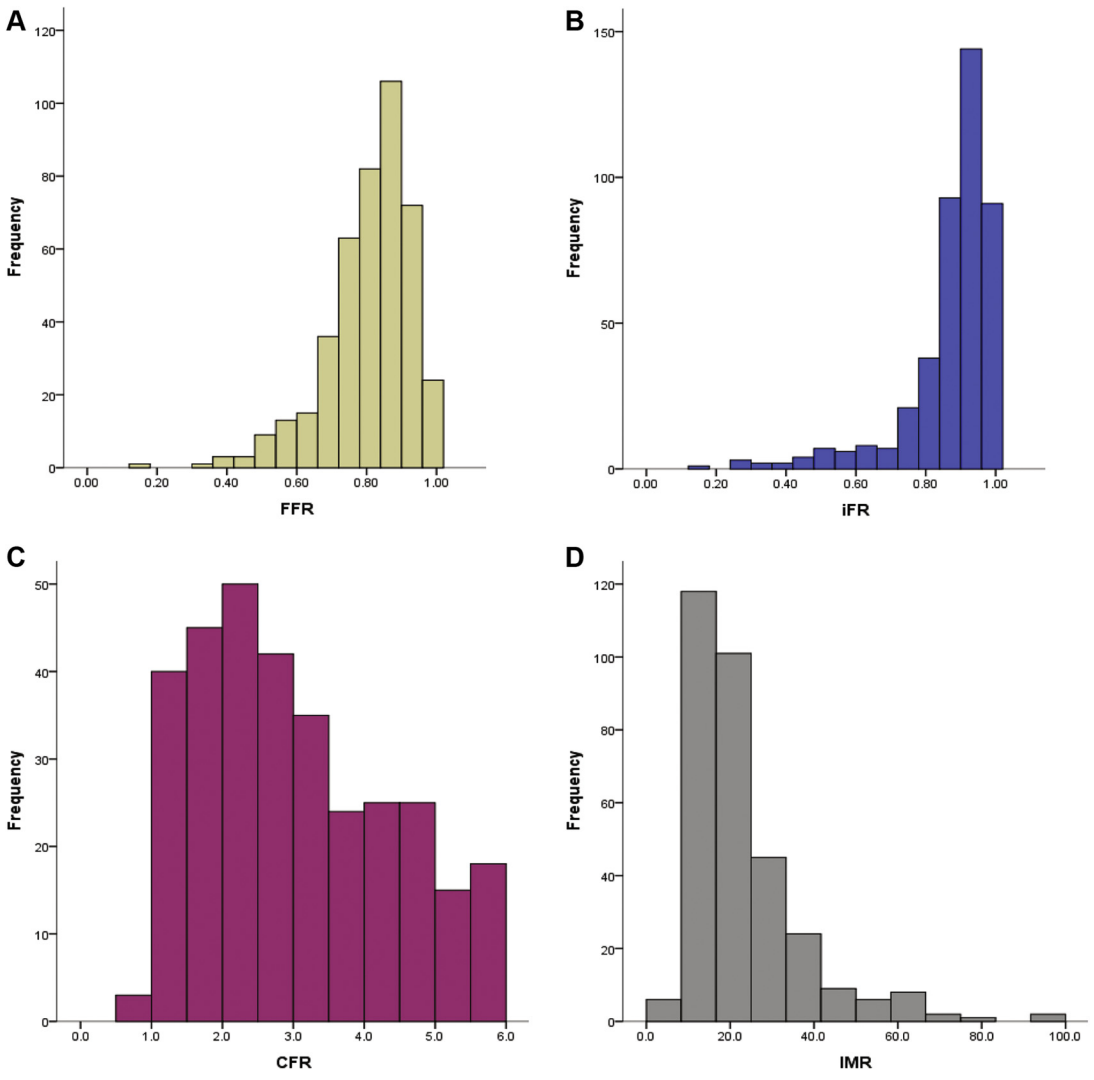
LAD = left anterior descending artery; LCX = left circumflex artery; Pd/Pa = distal coronary to aortic pressure; RCA = right coronary artery; other abbreviations as in Table 1.

patients showed significantly depressed CFR and significantly increased IMR compared with SIHD or nonculprit vessel of AMI patients. Second, although the nonculprit vessel showed slightly lower CFR than SIHD patients, IMR and hyperemic Tmn were similar with SIHD patients. Third, FFR and iFR measured in nonculprit vessel during acute stage of AMI showed significant changes according to increased stenosis severity and those changes were not significantly different compared with SIHD. In addition, in every stratum of %DS, FFR and iFR values were similar between the nonculprit vessel of AMI patients and SIHD patients. Fourth, although the nonculprit vessel in STEMI patients showed depressed CFR, IMR and hyperemic Tmn were similar with SIHD and changes of FFR and iFR for nonculprit stenosis did not differ with those in SIHD patients.

CHANGES OF CORONARY FLOW AND CFR IN AMI PATIENTS. Previous studies demonstrated the relationship between absolute coronary flow assessed by positron emission tomography or surrogate index of absolute coronary flow, coronary flow velocity measured by Doppler wire, and pressure gradient across epicardial coronary stenosis (20,21). As absolute coronary flow or coronary flow velocity is also regulated by microvascular resistance (20), the presence of local myocardial damage in the culprit vessel territory of AMI patients could influence pressure-derived physiologic indices such as FFR and iFR (22). In this regard, significant microvascular dysfunction or damage can increase FFR values given the same stenosis, especially for the culprit vessel, and was demonstrated by patient data (23) as well as porcine microvascular injury model testing (22). As with the previous studies, the current study demonstrated significantly lower CFR, mainly driven by significantly increased hyperemic Tmn and higher IMR value in the culprit vessel compared with SIHD and the nonculprit vessel of AMI patients. Although the derangement in coronary circulation and microvascular resistance can be transient and recover over time in some patients, these results imply the limited role of FFR and iFR in evaluating the functional significance of culprit vessel stenosis, especially at the acute stage of AMI.

Conversely, in the nonculprit vessel in AMI patients, there was no significant difference in CFR or IMR compared with that of SIHD. Although CFR in the nonculprit vessel was slightly lower than that of SIHD, the difference was not significant and was mainly due to decreased resting Tmn rather than increased hyperemic Tmn. It should be noted that

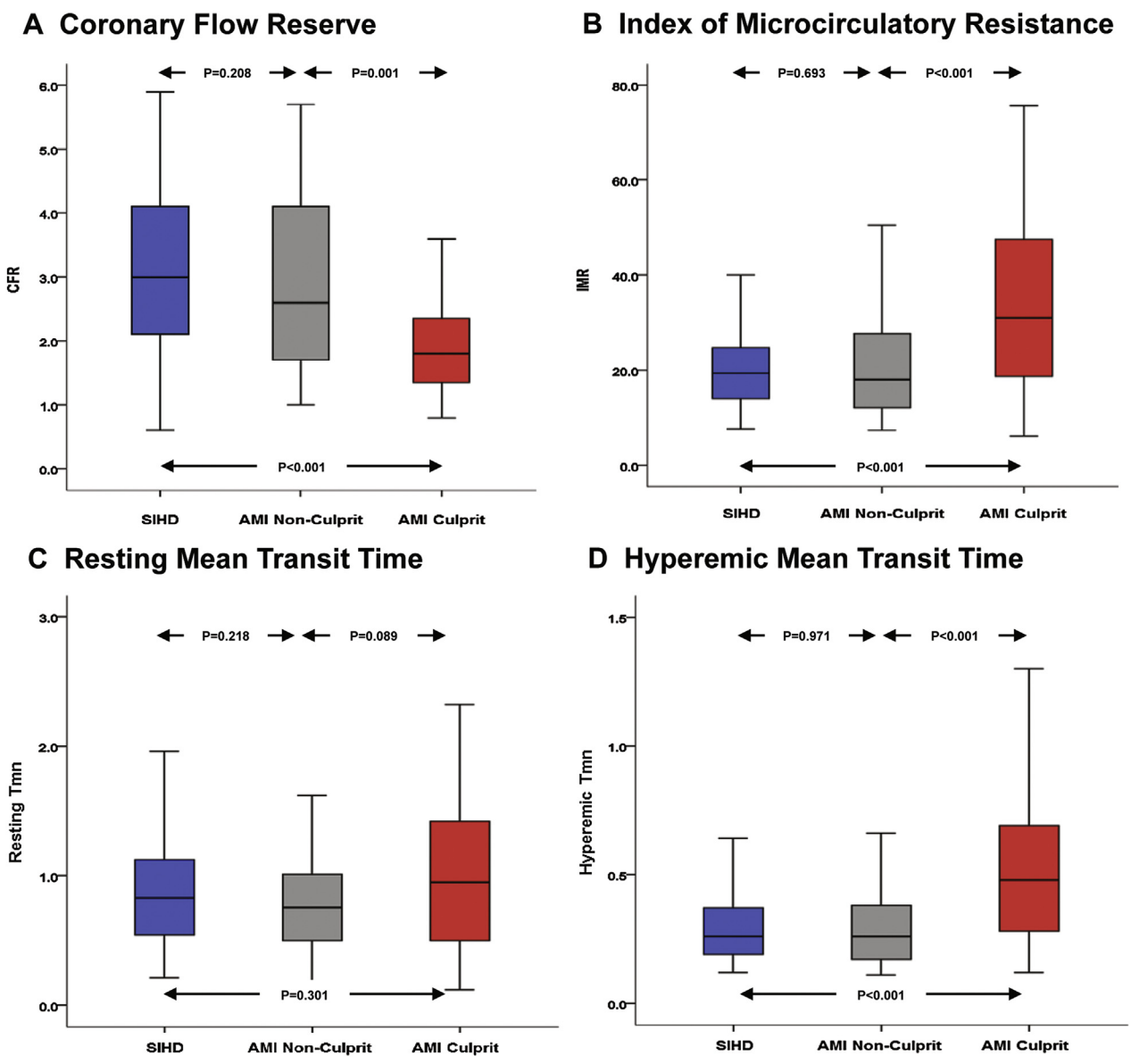
FIGURE 1 Distribution of Invasive Physiologic Indices



Distributions of invasive physiologic indices: **(A)** fractional flow reserve (FFR), **(B)** instantaneous wave-free ratio (iFR), **(C)** coronary flow reserve (CFR), and **(D)** index of microcirculatory resistance (IMR) are shown among the study population.

STEMI patients showed more prominent changes in resting and hyperemic Tmn and CFR in both culprit and nonculprit vessels. In STEMI patients, the nonculprit vessel also showed depressed CFR originated from a 18.4% decrease of resting Tmn and a 23.3% increase of hyperemic Tmn compared with SIHD patients. Nevertheless, IMR in the nonculprit vessel was not different than that in SIHD patients, even among STEMI population. These results are in line with the recent animal experiment using a porcine microvascular injury model (22). In that study, Lee et al. (22) selectively injected microspheres into the left anterior descending artery and serially evaluated the physiologic parameters of a remote vessel, the left circumflex artery. With selective injection of microspheres into the left anterior descending artery, both IMR and FFR were significantly increased in the left anterior descending artery. However, the left circumflex artery did not show any change in FFR or IMR values, despite significant microvascular damage

FIGURE 2 Comparison of Thermodilution-Derived Physiologic Indices Among AMI Culprit and Nonculprit Vessels and SIHD



Thermodilution-derived physiologic indices were compared among culprit and nonculprit vessels of both acute myocardial infarction (AMI) and stable ischemic heart disease (SIHD) patients: **(A)** CFR, **(B)** IMR, **(C)** resting mean transit time (Tmn), and **(D)** hyperemic Tmn. The **boxplot** shows numerical data through the 25th quartile, median, and 75th quartile, and the **whiskers** represent the minimum and maximum observations. Abbreviations as in Figure 1.

in the left anterior descending artery (22). These results suggest that microvascular damage may be predominantly localized in the culprit vessel territory, even in STEMI patients.

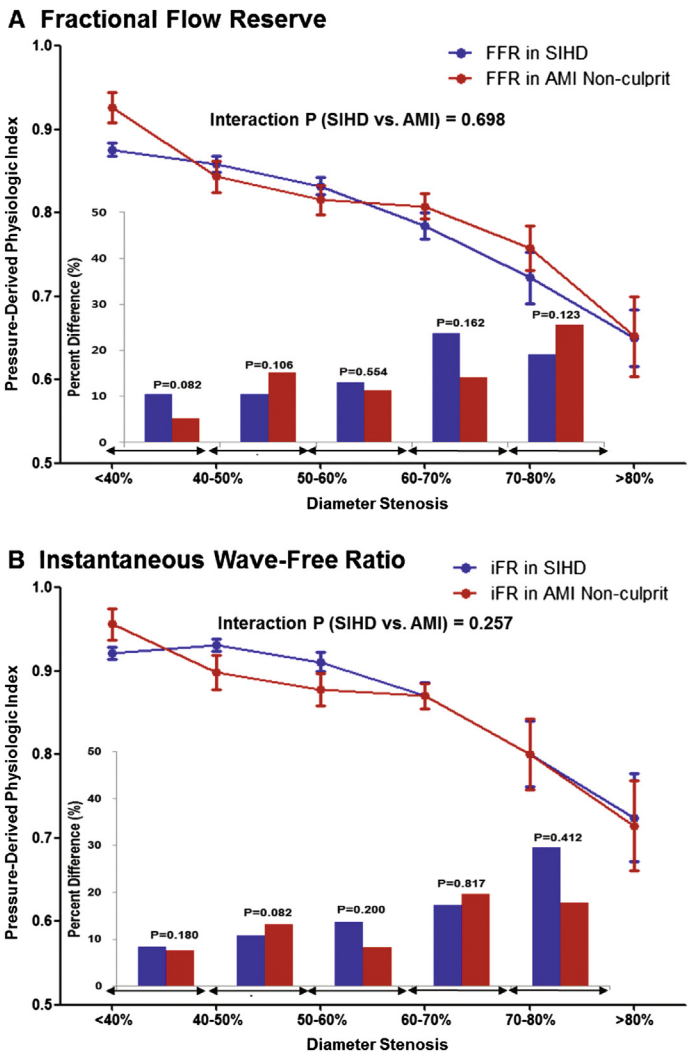
RELEVANCE OF MEASURING PRESSURE-DERIVED INDICES FOR NONCULPRIT VESSEL STENOSIS. Regarding the relevance of pressure-derived indices for evaluation of nonculprit vessel stenosis, conflicting results, especially during the acute stage of AMI, have been reported. Uren et al. (12) evaluated 13 AMI patients with single-vessel culprit lesions using $^{15}[H_2O]$ positron emission tomography and showed that coronary vasodilator response (ratio of hyperemic to resting myocardial blood flow, conceptually equivalent to CFR) was depressed in both the infarct

and remote regions supplied by the normal artery at 1 week and 6 months after AMI (12). The depression of nonculprit vessel CFR in AMI patients was similarly reported in previous studies. Teunissen et al. (13) evaluated 44 patients with AMI using $^{15}[H_2O]$ positron emission tomography. In their study, CFR were 1.81 ± 0.66, 2.51 ± 0.81, and 4.16 ± 1.45 for culprit, nonculprit, and age- and sex-matched control groups, respectively (13). Bax et al. (14) evaluated 73 anterior wall AMI patients using Doppler wire and similarly reported that both culprit and nonculprit vessels showed significant increase of CFR after 6 months from acute stage, suggesting depressed CFR due to disturbed autoregulation, even in the nonculprit vessel territory, during the acute stage of MI. A more recent study by de Waard et al. (11) reported that CFR was lower in both culprit and nonculprit vessels in STEMI patients compared with control vessels in propensity score-matched stable patients. In their results, the depressed CFR was derived from both a 12% increase in resting average peak velocity and a 16% decrease in hyperemic average peak velocity.

Based on these results, the possibility of underestimation of lesion severity by FFR measured in nonculprit vessels has been raised due to decreased hyperemic coronary flow or flow velocity in the acute stage of AMI, due to limited coronary flow and decreased pressure gradient across the same degree of stenosis. However, when Ntalianis et al. (15) measured FFR in the nonculprit vessels of 101 AMI patients in the acute phase and at 1-month follow-up, there was no change in FFR during follow-up. Furthermore, 79% of IMR values measured in nonculprit vessels were within normal range (<30 U).

The current study also presented the changes of resting and hyperemic Tmn as surrogate marker of resting and hyperemic coronary flow velocity in nonculprit vessels of AMI patients. CFR in the nonculprit vessel of AMI patients was lower than SIHD patients, numerically in the total AMI population and significantly in the STEMI population. Although lower CFR in the nonculprit vessel originated from numerically lower resting Tmn and higher hyperemic Tmn, those numerical differences were not significant, even in the STEMI population. Conversely, IMR was similar between the nonculprit vessel and SIHD patients, even in the STEMI patients. Furthermore, FFR showed similar changes according to worsening %DS in the nonculprit vessel compared with SIHD patients. These results indirectly suggest the larger influence of CFR value from hemodynamic status (24) and also suggest that a small reduction in hyperemic coronary blood flow in the nonculprit vessel might not translate to significant overestimation of distal coronary pressure and increased FFR value in the nonculprit vessel, unless microvascular resistance in the nonculprit vessel is significantly elevated (22). In this regard, the current results support the clinical benefit of an FFR-guided strategy for nonculprit vessel stenosis, even in the acute phase, as supported by 2 recent randomized controlled trials (3,5).

FIGURE 3 Changes in FFR and iFR in the Nonculprit Vessel of AMI Patients Compared With SIHD Patients



The changes in **(A)** FFR and **(B)** iFR measured in the nonculprit vessel of AMI patients **(red lines)** and SIHD patients **(blue lines)** according to diameter stenosis are shown. The **circle** represents estimated mean by generalized estimating equation, and the **vertical line** represents 95% SE. There was no significant interaction between clinical presentation and the changes in FFR and iFR for worsening diameter stenosis. The **bar graph** represents the percent differences of FFR or iFR, measured in the nonculprit vessel of AMI patients **(red bars)** and SIHD patients **(blue bars)** between the 2 successive subgroups **(arrow)**. The p value represents the significance in comparison of percent differences between AMI and SIHD. Abbreviations as in Figures 1 and 2.

TABLE 3 Changes of Pressure-Derived Physiologic Indices According to Angiographic Stenosis Severity Stratified by Clinical Presentation

	Angiographic Diameter Stenosis						
	<40%	40%–50%	50%–60%	60%–70%	70%–80%	>80%	p Value*
Fractional flow reserve							
SIHD	0.88 ± 0.08	0.86 ± 0.07	0.83 ± 0.09	0.78 ± 0.12	0.72 ± 0.14	0.65 ± 0.13	<0.001
AMI nonculprit	0.92 ± 0.05	0.84 ± 0.09	0.82 ± 0.11	0.81 ± 0.09	0.76 ± 0.11	0.65 ± 0.15	<0.001
p value†	0.140	0.471	0.417	0.285	0.393	0.970	
Instantaneous wave-free ratio							
SIHD	0.92 ± 0.07	0.93 ± 0.05	0.91 ± 0.09	0.87 ± 0.12	0.80 ± 0.18	0.72 ± 0.20	<0.001
AMI nonculprit	0.96 ± 0.05	0.90 ± 0.09	0.88 ± 0.12	0.87 ± 0.08	0.80 ± 0.17	0.71 ± 0.17	<0.001
p value†	0.080	0.140	0.150	0.990	0.993	0.896	

Values are mean ± SD. *For overall difference of instantaneous wave-free ratio or fractional flow reserve values among strata of diameter stenosis. †For comparison between SIHD and AMI nonculprit values in each stratum of diameter stenosis.

Abbreviations as in Table 1.

Considering limited evidence for resting pressure-derived indices, previous observations of increased resting coronary blood flow or resting average peak velocity in the nonculprit vessel raised concern about overestimation of lesion severity by iFR due to increased resting coronary pressure gradient across the stenosis. The recent study compared nonculprit vessel iFR measured at the time of primary PCI and at follow-up (median follow-up time 16 days) (16). In this study, the absolute difference between acute iFR and follow-up iFR was 0.01 (interquartile range: -0.01 to 0.06; paired test p value < 0.001). Although the difference was statistically significant, classification agreement between initial and follow-up iFR value was 78% and negative predictive value of acute iFR was 89%. As with previous studies, the current study also demonstrated decreased resting Tmn, suggesting increased resting coronary flow, in the nonculprit vessel compared with SIHD patients (8.0% and 18.4% decrease of resting Tmn than SIHD in all AMI patients and STEMI patients, respectively); however, those numerical differences were not statistically significant. In addition, iFR in the nonculprit vessel showed similar changes for worsening %DS with those in SIHD patients. These results suggest that iFR could be another option for guiding clinical decision making for nonculprit vessel stenosis, especially for the insignificant range of iFR (>0.90). Nevertheless, iFR-guided nonculprit vessel treatment during the acute stage of AMI patient needs to be validated by future trials.

CLINICAL IMPLICATIONS. The current study evaluated the changes of invasive physiologic indices among culprit, nonculprit vessel of AMI patients, and SIHD patients and focused on the changes of pressure-derived indices according to worsening stenosis severity in the nonculprit vessel of AMI patients compared with those in SIHD patients. When comparing resting and hyperemic Tmn, CFR, and IMR among the culprit and nonculprit vessels and SIHD, only the culprit vessel showed significant changes. Although STEMI patients showed more prominent changes of CFR in both culprit and nonculprit vessels, there was no significant difference in resting and hyperemic Tmn of nonculprit vessel and IMR was also preserved in the nonculprit vessel. More importantly, the responses of FFR and iFR for the nonculprit stenosis of AMI patients did not differ with those in SIHD patients. These results support the clinical applicability of FFR and iFR to evaluate the functional significance of nonculprit stenosis, even in the acute stage of AMI.

Considering the knowledge gap regarding FFR or iFR-guided complete revascularization in AMI multivessel disease patients, 2 studies currently underway should offer further clarification: 1) FRAME-AMI (FRactional Flow Reserve versus Angiography-Guided Strategy for Management of Non-Infarction RElated Artery Stenosis in Patients with Acute Myocardial Infarction) trial (NCT02715518), comparing 2-year clinical outcomes between acute FFR-guided complete revascularization versus angiography-only guided complete revascularization in AMI multivessel disease patients; and 2) iMODERN (iFR Guided Multi-vessel Revascularization During Percutaneous Coronary Intervention for Acute Myocardial Infarction) trial (NCT03298659), comparing 1-year clinical outcomes between acute iFR-guided complete revascularization versus staged stress perfusion cardiac magnetic resonance-guided revascularization within 6 weeks in STEMI multivessel disease patients.

STUDY LIMITATIONS. First, we evaluated the invasive physiologic indices measured during the acute stage of AMI patients and lacked data from follow-up physiologic assessment. Second, although the current study comprehensively explored both thermodilution-derived and pressure-derived physiologic indices, the relatively small number of the STEMI population warrants future study with a larger number of STEMI patients. Third, although the association between infarct size and degree of microvascular damage measured by culprit vessel IMR or other measures are well validated by previous studies (25), the current results might not represent patients with larger infarctions, as most AMI patients showed preserved left ventricular ejection fraction and modest elevation of cardiac enzymes. Considering the possible association between left ventricular end-diastolic pressure and fractional flow reserve (26), huge anterior wall infarction with extremely elevated LV end-diastolic pressure might influence nonculprit vessel FFR or iFR. Fourth, in the current study, resting and hyperemic Tmn derived by thermodilution methods were used as surrogate markers for resting and hyperemic coronary flow velocity, respectively. Fifth, coronary wedge pressure was not systematically collected. Sixth, iFR was calculated off-line using the resting pressure tracing data.

CONCLUSIONS

Changes in FFR and iFR for the nonculprit stenosis of AMI patients were not significantly different from those in SIHD patients. These data support the use of invasive physiological parameters to guide treatment of nonculprit stenoses in the acute stage of successfully revascularized AMI.

ADDRESS FOR CORRESPONDENCE: Dr. Joo Myung Lee, Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea. E-mail: drone80@hanmail.net.

PERSPECTIVES

WHAT IS KNOWN? There have been concerns in measuring FFR or iFR for nonculprit stenosis in patients in the acute stage of AMI. Clarification is needed as to whether invasive physiologic indices would show similar changes according to worsening stenosis between the nonculprit vessel of AMI patients and vessels in SIHD patients.

WHAT IS NEW? The current study compared the changes in FFR or iFR to the severity of epicardial coronary stenosis with other invasive physiologic indices between nonculprit vessels of AMI patients and vessels of SIHD patients. Although the nonculprit vessel of AMI patients showed lower CFR than SIHD, IMR was not different between the nonculprit vessel of AMI and SIHD patients. More importantly, in every stratum of %DS, FFR and iFR were not significantly different between nonculprit vessel of AMI and SIHD patients, and there was no significant interaction between clinical presentation and the changes in FFR and iFR for worsening %DS, supporting the clinical applicability of FFR and iFR to evaluate the functional significance of nonculprit stenosis, even in the acute stage of AMI.

WHAT IS NEXT? The prognostic implications of FFR- or iFR-guided complete revascularization in AMI multivessel disease patients needs further validation in future randomized controlled trials.

REFERENCES

1. American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, O'Gara PT, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.

2. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med 2013;369:1115–23.

3. Engstrom T, Kelbaek H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. Lancet 2015;386:665–71.

4. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2015;65:963–72.

5. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. N Engl J Med 2017;376:1234–44.

6. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. J Am Coll Cardiol 2016;67:1235–50.

7. van Nunen LX, Zimmermann FM, Tonino PA, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet 2015;386:1853–60.

8. Fearon WF, Nishi T, De Bruyne B, et al. Clinical outcomes and cost-effectiveness of fractional flow reserve-guided percutaneous coronary intervention in patients with stable coronary artery disease: three-year follow-up of the FAME 2 trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). Circulation 2018;137:480–7.

9. Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. N Engl J Med 2017;376:1824–34.

10. Gotberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. N Engl J Med 2017;376:1813–23.

11. de Waard GA, Hollander MR, Teunissen PF, et al. Changes in coronary blood flow after acute myocardial infarction: insights from a patient study and an experimental porcine model. J Am Coll Cardiol Intv 2016;9:602–13.

12. Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. N Engl J Med 1994;331:222–7.

13. Teunissen PF, Timmer SA, Danad I, et al. Coronary vasomotor function in infarcted and remote myocardium after primary percutaneous coronary intervention. Heart 2015;101:1577–83.

14. Bax M, de Winter RJ, Koch KT, Schotborgh CE, Tijssen JG, Piek JJ. Time course of microvascular resistance of the infarct and noninfarct coronary artery following an anterior wall acute myocardial infarction. Am J Cardiol 2006;97:1131–6.

15. Ntalianis A, Sels JW, Davidavicius G, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. J Am Coll Cardiol Intv 2010;3:1274–81.

16. Thim T, Gotberg M, Frobert O, et al. Nonculprit stenosis evaluation using instantaneous wave-free ratio in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol Intv 2017;10:2528–35.

17. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.

18. Lee JM, Jung JH, Hwang D, et al. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. J Am Coll Cardiol 2016;67:1158–69.

19. Lee JM, Park J, Hwang D, et al. Similarity and difference of resting distal to aortic coronary pressure and instantaneous wave-free ratio. J Am Coll Cardiol 2017;70:2114–23.

20. Lee JM, Hwang D, Park J, et al. Exploring coronary circulatory response to stenosis and its association with invasive physiologic indexes using absolute myocardial blood flow and coronary pressure. Circulation 2017;136:1798–808.

21. Nijjer SS, de Waard GA, Sen S, et al. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. Eur Heart J 2016;37:2069–80.

22. Lee JM, Kim HK, Lim KS, et al. Influence of local myocardial damage on index of microcirculatory resistance and fractional flow reserve in target and nontarget vascular territories in a porcine microvascular injury model. J Am Coll Cardiol Intv 2018;11:717–24.

23. van de Hoef TP, Nolte F, Echavarría-Pinto M, et al. Impact of hyperaemic microvascular resistance on fractional flow reserve measurements in patients with stable coronary artery disease: insights from combined stenosis and microvascular resistance assessment. Heart 2014;100:951–9.

24. de Bruyne B, Bartunek J, Sys SU, Pijls NH, Heyndrickx GR, Wijns W. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. Circulation 1996;94:1842–9.

25. McGeoch R, Watkins S, Berry C, et al. The index of microcirculatory resistance measured acutely predicts the extent and severity of myocardial infarction in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol Intv 2010;3:715–22.

26. Leonardi RA, Townsend JC, Patel CA, et al. Left ventricular end-diastolic pressure affects measurement of fractional flow reserve. Cardiovasc Revasc Med 2013;14:218–22.

KEY WORDS acute myocardial infarction, coronary flow reserve, fractional flow reserve, index of microcirculatory resistance, instantaneous wave-free ratio

APPENDIX For supplemental tables and figures, please see the online version of this paper.