## **Coronary Physiologic Assessment and Imaging**

## Integrated Physiologic Assessment of Ischemic Heart Disease in Real-World Practice Using Index of Microcirculatory Resistance and Fractional Flow Reserve Insights From the International Index of Microcirculatory Resistance Registry

Joo Myung Lee, MD, MPH; Jamie Layland, MBCHB; Ji-Hyun Jung, MD; Hyun-Jung Lee, MD; Mauro Echavarria-Pinto, MD; Stuart Watkins, MBChB, MD; Andy S. Yong, MBBS, PhD; Joon-Hyung Doh, MD, PhD; Chang-Wook Nam, MD, PhD; Eun-Seok Shin, MD, PhD; Bon-Kwon Koo, MD, PhD; Martin K. Ng, MBBS, PhD; Javier Escaned, MD, PhD; William F. Fearon, MD; Keith G. Oldroyd, MBChB

*Background*—The index of microcirculatory resistance (IMR) is a quantitative and specific index for coronary microcirculation. However, the distribution and determinants of IMR have not been fully investigated in patients with ischemic heart disease (IHD).

- *Methods and Results*—Consecutive patients who underwent elective measurement of both fractional flow reserve (FFR) and IMR were enrolled from 8 centers in 5 countries. Patients with acute myocardial infarction were excluded. To adjust for the influence of collateral flow, IMR values were corrected with Yong's formula (IMR<sub>corr</sub>). High IMR was defined as greater than the 75th percentile in each of the major coronary arteries. FFR≤0.80 was defined as an ischemic value. 1096 patients with 1452 coronary arteries were analyzed (mean age 61.1, male 71.2%). Mean FFR was 0.84 and median IMR<sub>corr</sub> was 16.6 U (Q1, Q3 12.4 U, 23.0 U). There was no correlation between IMR<sub>corr</sub> and FFR values (*r*=0.01, *P*=0.62), and the categorical agreement of FFR and IMR<sub>corr</sub> was low (kappa value=−0.04, *P*=0.10). There was no correlation between IMR<sub>corr</sub> and angiographic % diameter stenosis (*r*=−0.03, *P*=0.25). Determinants of high IMR were previous myocardial infarction (odds ratio [OR] 2.16, 95% confidence interval [CI] 1.24–3.74, *P*=0.01), right coronary artery (OR 2.09, 95% CI 1.54–2.84, *P*<0.01), female (OR 1.67, 95% CI 1.18–2.38, *P*<0.01), and obesity (OR 1.80, 95% CI 1.31–2.49, *P*<0.01). Determinants of FFR ≤0.80 were left anterior descending coronary artery (OR 4.31, 95% CI 2.92–6.36, *P*<0.01), angiographic diameter stenosis ≥50% (OR 5.16, 95% CI 3.66–7.28, *P*<0.01), male (OR 2.15, 95% CI 1.38–3.35, *P*<0.01), and age (per 10 years, OR 1.21, 95% CI 1.01–1.46, *P*=0.04).
- *Conclusions*—IMR showed no correlation with FFR and angiographic lesion severity, and the predictors of high IMR value were different from those for ischemic FFR value. Therefore, integration of IMR into FFR measurement may provide additional insights regarding the relative contribution of macro- and microvascular disease in patients with ischemic heart disease.

*Clinical Trial Registration*—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02186093. (*Circ Cardiovasc Interv.* 2015;8:e002857. DOI: 10.1161/CIRCINTERVENTIONS.115.002857.)

Key Words: coronary artery disease ■ fractional flow reserve ■ ischemic heart disease ■ microcirculation ■ physiology

Received March 3, 2015; accepted September 30, 2015.

From the Department of Medicine, Seoul National University Hospital, Seoul, South Korea (J.M.L., J.-H.J., H.-J.L., B.-K.K.); Department of Cardiology, West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, United Kingdom (J.L., S.W., K.G.O.); BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom (J.L., S.W., K.G.O.); Servicio de Cardiología, Hospital Clinico San Carlos, Faculty of Medicine Complutense University of Madrid, Madrid, Spain (M.E.-P., J.E.); Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain (M.E.-P., J.E.); Department of Cardiovasculare Medicine, Stanford University Medical Center, Stanford, CA (A.S.Y., W.F.F.); Department of Medicine, Inje University IIsan Paik Hospital, Goyang, South Korea (J.-H.D.); Department of Medicine, Keimyung University Dongsan Medical Center, Daegu, South Korea (C.-W.N.); Department of Cardiology, Ulsan University. Hospital, University of Ulsan College of Medicine, Ulsan, South Korea (E.-S.S.); Institute on Aging, Seoul National University, Seoul, South Korea (B.-K.K.); and Departments of Cardiology, Royal Prince Alfred and Concord Hospitals and University of Sydney, Sydney, Australia (M.K.N.).

The Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.115.002857/-/DC1.

Correspondence to Bon-Kwon Koo, MD, PhD, Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 101 Daehang-ro, Chongno-gu, Seoul, 110–744, Korea. E-mail bkkoo@snu.ac.kr

<sup>© 2015</sup> American Heart Association, Inc.

Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org

The coronary microcirculation is one of the major com-L ponents of the coronary vascular system and an important contributor to the development of ischemic heart disease (IHD). However, limitations in the methods available to visualize or evaluate the microcirculatory system have been an obstacle to the diagnosis and treatment of microvascular disease. The index of microcirculatory resistance (IMR) is a pressure-temperature-derived parameter for quantifying microcirculatory resistance.1 Because distal coronary pressure is used in the calculation of IMR, this index can be used to interrogate selectively the microcirculation of vessels with a coronary stenosis, in contrast to coronary flow reserve, which is a combined assessment of the macro- and microcirculation. Previous studies have shown that IMR is independent of the severity of epicardial coronary stenosis as determined by angiographic or functional (fractional flow reserve [FFR]) criteria so long as the influence of collateral flow is taken into account.2.3 IMR is also relatively independent of hemodynamic conditions, such as blood pressure and heart rate.<sup>4</sup>

Recent clinical studies have shown that IMR is useful for the risk stratification in patients with acute myocardial infarction (MI).<sup>5-7</sup> However, in the setting of IHD other than MI, the distribution and determinants of abnormal IMR remain to be clearly identified. Therefore, we sought to investigate the clinical relevance of microvascular assessment using IMR and the relative contribution of macro- and microvascular disease in non-MI patients enrolled from an international multicenter IMR registry.

### WHAT IS KNOWN

- Fractional flow reserve-guided decision-making for patients with epicardial coronary stenosis is a wellvalidated approach.
- The index of microcirculatory resistance (IMR) is a quantitative and specific index for microcirculation. However, the distribution and determinants of IMR have not been fully investigated in patients with stable coronary artery disease.

### WHAT THE STUDY ADDS

- In 1096 patients with 1452 vessels who underwent invasive coronary physiological assessment, fractional flow reserve and IMR showed no categorical agreement, and the presence of microvascular disease was suspected to be a contributor for the myocardial ischemia in a significant portion of patients (17% of the population studied).
- The predictors of high IMR (previous myocardial infarction, right coronary artery, female, and obesity) and low fractional flow reserve (angiographic percent diameter stenosis, left anterior descending artery, male, and age) were substantially different.
- The integration of IMR into fractional flow reserve measurement can provide additional insights regarding the relative contribution of macro- and microvascular disease in patients with ischemic heart disease.

### Methods

### **Patient Population**

From April 2009 to September 2013, patients underwent FFR and IMR measurements and, with available clinical and angiographic information, were registered from 8 hospitals from 5 countries (South Korea, United Kingdom, Spain, USA, and Australia). The investigators were asked to provide the data of eligible patients, and those enrolled in other study protocols or those who underwent FFR and IMR measurements were both included in this study. The operators involved in this study used FFR and IMR in their daily clinical practice. Patients with acute MI with cardiac enzyme elevation were excluded. All patients underwent preinterventional measurement of FFR and IMR, and the postinterventional data were excluded from the analysis. Institutional Review Board approval was obtained with regard to current regulations, and the study protocol was in accordance with the Declaration of Helsinki (clinicaltrials.gov identifier, NCT02186093).

## Coronary Angiography and Coronary Physiological Measurements

Coronary angiography was performed by standard techniques. Angiographic views were obtained after the administration of intracoronary nitrate (100 or 200  $\mu$ g). Quantitative coronary angiography was performed at each participating center using a contour-detection quantitative coronary angiography system and the guiding catheter tip as a scaling device. Percent diameter stenosis, minimum lumen diameter, reference vessel size, and lesion length were measured.

All coronary physiological measurements were obtained as previously described.7-9 In brief, a 5-7F guiding catheter without side holes was used to engage the coronary artery, and a pressure-temperature sensor guidewire (St Jude Medical, St Paul, MN) was used for FFR and IMR measurement. The pressure sensor was positioned at the distal segment of the target vessel, and intracoronary nitrate (100 or 200 µg) was administered before each physiological measurement. To derive resting mean transit time  $(T_{\rm mn})$ , a thermodilution curve was obtained by 3 injections of 3-4 mL of room temperature saline. Hyperemia was induced by intravenous infusion of adenosine (140 µg/kg/min) through a central or peripheral vein. Hyperemic proximal aortic pressure  $(P_a)$ , distal arterial pressure  $(P_d)$ , and hyperemic  $T_{\rm mn}$  were obtained during sustained hyperemia. FFR was calculated as mean  $P_d/P_a$  during hyperemia and apparent IMR (IMR<sub>app</sub>) as  $P_d \times T_{mn}$  during hyperemia. All IMR values were also corrected by Yong's formula (IMR<sub>cor</sub>= $P_a \times T_{mn} \times ([1.35 \times P_d/P_a]-0.32))$  to adjust for the influence of collateral flow.<sup>6</sup> At the end of the study, the guidewire was pulled back to the guiding catheter, and the presence of pressure drift was assessed.

### **Cut-Off Values for Physiological Indices**

Because the distribution of  $IMR_{corr}$  was significantly different among the 3 epicardial coronary arteries, 75th percentile values in each of epicardial coronary arteries were used to define an elevated  $IMR_{corr}$ . Patients with at least 1 elevated  $IMR_{corr}$  were categorized as having high microvascular resistance. Ischemic FFR value was defined as FFR  $\leq 0.80$ . All patients were classified according to the cut-off values of FFR and  $IMR_{corr}$  to explore the relative contributions of macrovascular and microvascular disease.

### **Statistical Analysis**

Categorical variables are presented as numbers and relative frequencies (percentages), and continuous variables as means and standard deviations or median with interquartile range (first, third quartiles) according to their distribution and homogeneity in their variances, which was checked by the Kolmogorov–Smirov test. Data were analyzed on a per-patient basis for clinical characteristics and classification according to FFR and IMR<sub>corr</sub> and on a per-vessel basis for the rest of analysis.

For per-vessel analysis, including comparison of  $IMR_{app}$  or  $IMR_{corr}$  values according to the target vessels or comparison of FFR,

IMR<sub>ann</sub>, or IMR<sub>corr</sub> values according to the clinical diagnosis, the generalized estimating equation with exchangeable correlation structure was used to adjust for intrasubject variability among vessels from the same patients. Estimated mean and 95% confidence interval (CI) were presented as summary statistics. No post hoc adjustment was performed. A model to determine the predictors of abnormal FFR or IMR<sub>corr</sub> was constructed. The included covariates were variables having clinical importance or those with a single variable P value <0.1, as follows: sex, hypertension, diabetes mellitus, hypercholesterolemia, family history of coronary artery disease (CAD), obesity defined as body mass index  $\geq 25 \text{ kg/m}^2$  for the Asian population or ≥30 kg/m<sup>2</sup> for the Western population, current smoking, acute coronary syndrome, history of MI or percutaneous coronary intervention, target vessel, diameter stenosis  $\geq$  50%, lesion length, reference vessel diameter, and age. The discriminant functions of each model were presented with c-index and 95% CI. The statistical package SPSS, version 18.0 (SPSS Inc., Chicago, IL), and R programming language, version 3.1.3 (R Foundation for Statistical Computing), were used for statistical analyses.

### Results

### **Baseline Characteristics**

The enrolled population was 1096 patients with 1452 vessels. Table 1 and Table 2 show their baseline clinical characteristics and the details of the coronary stenoses studied. Six hundred and thirty-five patients (58%) and 364 patients (42%) were from Asian and Western populations, respectively. 51% of patients presented as stable angina and 10% as asymptomatic CAD with evidence of myocardial ischemia in noninvasive tests. More than half of the vessels studied were left anterior descending artery (LAD), and most stenoses had an intermediate degree of severity (mean diameter stenosis,

### Table 1. General Characteristics of Study Population (n=1096)

Demographics	
Age, y	61.1±9.7
Male	780 (71%)
BMI, kg/m <sup>2</sup>	25.4±3.7
Asian population	635 (58%)
Western population	364 (42%)
Clinical presentations	
Stable angina	562 (51%)
Unstable angina	284 (26%)
Atypical chest pain	137 (13%)
Silent ischemia	113 (10%)
Cardiovascular risk factors	
Hypertension	683 (62%)
Diabetes mellitus	281 (26%)
Hypercholesterolemia	709 (65%)
Current smoker	357 (33%)
Obesity*	326 (30%)
Family history	120 (11%)
Previous MI	93 (9%)
Previous PCI	237 (22%)

Values are mean±SD, median (interquartile ranges, 25th–75th), or n (%). BMI indicates body mass index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

\*Obesity was defined as body mass index  $\geq$ 25 kg/m<sup>2</sup> in Korean patients and  $\geq$ 30 kg/m<sup>2</sup> in Western patients.

40.5 $\pm$ 17.3%). The reference diameter of right coronary artery (RCA) was larger than LAD or left circumflex artery (LCX; 3.32 $\pm$ 0.59 mm in RCA, 2.90 $\pm$ 0.55 mm in LAD, or 2.89 $\pm$ 0.61 mm in LCX, *P*<0.001).

#### **Distribution of Physiological Indices**

Figure 1 shows the distribution of measured FFR and IMR values. The mean FFR was  $0.84\pm0.14$ , and median IMR<sub>app</sub> and IMR<sub>corr</sub> were 17.0 U (13.0 U, 23.5 U) and 16.6 U (12.4 U, 23.0 U), respectively (Table 2). Compared with patients with stable CAD, patients with unstable angina had lower FFR values (0.81, 95% CI 0.78–0.83 versus 0.85, 95% CI 0.84–0.86, P<0.01) and higher IMR<sub>corr</sub> values (20.7 U [19.4 U, 22.0 U] versus 18.9 U [18.3 U, 19.6 U], P=0.02).

There was no correlation between IMR<sub>app</sub> and FFR values (r=0.01, P=0.62). Angiographic percent diameter stenosis correlated modestly with FFR (r=-0.56, P<0.01), but not with IMR<sub>app</sub> (r=0.01, P=0.86) or IMR<sub>corr</sub> (r=-0.03, P=0.25) (Figure 2).

Regardless of  $IMR_{app}$  or  $IMR_{corr}$ , the RCA showed significantly higher IMR values than either the LAD or LCX. There was no difference in IMR between LAD and LCX. The 75th percentile values of  $IMR_{corr}$  were 21.3 U, 23.0 U, 27.1 U for LAD, LCX, and RCA, respectively (Figure I in the Data Supplement). Therefore, the cut-off values for an abnormal  $IMR_{corr}$  were defined as greater than 22 U, 24 U, and 28 U for LAD, LCX, and RCA, respectively.

# Populations Distribution According to the FFR and IMR Values

The categorical agreement of FFR and IMR<sub>corr</sub> was low (kappa value=-0.04, P=0.10; Figure 3A). 55% of patients showed discordant results. Figure 3B shows the categorization of patients according to the cut-off values of FFR and IMR<sub>corr</sub>. Overall, 17% of patients had stenoses with nonischemic FFR values but abnormally high microvascular resistance, whereas 8% of patients had both stenoses with ischemic FFR values and abnormally high microvascular resistance.

### Table 2. General Characteristics of Target Vessels and Physiological Parameters (n=1452)

Measured vessel location	·
Left anterior descending artery	784 (54%)
Left circumflex artery	295 (20%)
Right coronary artery	373 (26%)
Quantitative coronary angiography	1202
Reference diameter, mm	3.01±0.60
Minimum lumen diameter, mm	1.81±0.69
Diameter stenosis, %	40.5±17.3
Lesion length, mm	11.59±7.67
Coronary physiological indices	
FFR	0.84±0.14
IMR, U	17.0 (13.0, 23.5
IMR U	16.6 (12.4, 23.0

Values are mean±SD, n (%), or median (Q1, Q3). CFR indicates coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; IMR<sub>ourr</sub>, calculated IMR with Yong's formula (IMR<sub>ourr</sub>= $P_a \times T_{max} \times ([1.35 \times P_d/P_a] - 0.32)$ ).



**Figure 1.** Distribution of fractional flow reserve (FFR) and index of microcirculatory resistance (IMR). The per-vessel distribution of prepercutaneous coronary intervention values of FFR (**A**) and IMR (**B**) were presented. The apparent IMR and corrected IMR by Yong's formula (IMR<sub>corr</sub>= $P_a \times T_{mn} \times ([1.35 \times P_d/P_a] - 0.32)$ ) were presented in **B**. IMR<sub>app</sub> indicates apparent IMR; IMR<sub>corr</sub>, corrected IMR; and IQR, interquartile range.

### **Predictors of IMR and FFR**

The multivariate generalized estimating equation model identified different predictors of IMR and FFR. Previous MI (odds ratio [OR] 2.16, 95% CI 1.24–3.74, P=0.01), RCA (OR 2.09, 95% CI 1.54–2.84, P<0.01), female sex (OR 1.67, 95% CI 1.18–2.38, P<0.01), and obesity (OR 1.80, 95% CI 1.31–2.49, P<0.01) were predictors of high IMR<sub>corr</sub> (Table 3). The dichotomous data of IMR<sub>corr</sub> in these cohorts are presented in Table I in the Data Supplement. LAD (OR 4.31, 95% CI

2.92–6.36, P<0.01), angiographic diameter stenosis  $\geq$ 50% (OR 5.16, 95% CI 3.66–7.28, P<0.01), male sex (OR 2.15, 95% CI 1.38–3.35, P<0.01), and age (per 10 years, OR 1.21, 95% CI 1.01–1.46, P=0.04) were predictors of a low FFR (Table 3).

### Discussion

This study provides new insights into the overall characteristics of IMR in patients with coronary atherosclerosis without MI.



**Figure 2.** The association between angiographic % diameter stenosis and physiological indices. The association between percent diameter stenosis and FFR/IMR<sub>app</sub>/IMR<sub>corr</sub> was plotted. Angiographic diameter stenosis correlated modestly with FFR (r=–0.56, P<0.01), but not with IMR<sub>app</sub> (r=0.01, P=0.86) or IMR<sub>corr</sub> (r=–0.03, P=0.25). The correlations and P values in the figure did not account for intrapatient repeated measurements. FFR indicates fractional flow reserve; IMR, index of microcirculatory resistance; IMR<sub>app</sub>, apparent IMR; and IMR<sub>corr</sub>, corrected IMR.

### A Fractional Flow Reserve





**Figure 3.** Classification of patients according to the FFR and IMR values. **A**, The patients' distribution according to the cut-off values of FFR ( $\leq 0.80$ ) and IMR<sub>corr</sub> (cut-off: 75th percentile value according to the target vessels). **B**, The conceptual distribution of the patients. The proportions among the total population were presented in each section of the classification. FFR indicates fractional flow reserve; IMR, index of microcirculatory resistance; and IMR<sub>corr</sub>, corrected IMR.

The distinct value of these observations is that they are derived from a large, multiethnic patient population. The main findings of the study are (1) FFR and  $IMR_{corr}$  showed no categorical agreement, and the presence of microvascular disease was suspected to be a contributor for the myocardial ischemia in a significant portion of patients (17% of the population studied); (2) more than one quarter (26%) of vessels with functionally non-significant stenoses (FFR >0.80) had abnormally high  $IMR_{corr}$ 

Table 3.	Predictors for High I	MR or L	.ow FFR in	Target
Vessels*				

Variables	OR	95% CI	<i>P</i> Value
High IMR (≥75th perc	centile)		
Previous MI	2.16	1.24-3.74	0.01
RCA	2.09	1.54-2.84	<0.01
Female	1.67	1.18-2.38	<0.01
Obesity†	1.80	1.31-2.49	<0.01
Low-FFR (≤0.80)			
LAD	4.31	2.92-6.36	<0.01
%DS≥50%	5.16	3.66-7.28	<0.01
Male	2.15	1.38–3.35	< 0.01
Age (10 y)	1.21	1.01-1.46	0.04

Cl indicates confidence interval; FFR, fractional flow reserve; IMR, index of microvascular resistance; LAD, left anterior descending artery; %DS, percent diameter stenosis; and RCA, right coronary artery.

\*Generalized estimating equation model or maximum likelihood  $\chi^2$  tests were used to evaluate the predictors. C-indexes were 0.67 (95% Cl 0.63–0.70) and 0.81 (95% Cl 0.78–0.85) in predicted model for high IMR and low FFR, respectively.

 $\pm 0$  besity was defined as body mass index  $\geq 25$  kg/m<sup>2</sup> in Korean patients and  $\geq 30$  kg/m<sup>2</sup> in Western patients.

values; and (3) the predictors of high IMR<sub>corr</sub> or ischemic FFR were substantially different. These findings suggest the need to integrate IMR with FFR when evaluating patients with CAD.

# Relative Contribution of Macro- and Microvascular Disease to IHD

Currently, FFR-guided decision-making for epicardial coronary stenosis has been a well-validated approach to avoid unnecessary stent implantation and to enhance patient clinical outcomes.10-12 However, epicardial coronary stenosis is one of the components in the coronary circulatory system; therefore, the presence of epicardial stenosis is not a sole cause of IHD. Furthermore, lesions with the same degree of stenosis may have different FFR values, according to the microvascular status. In our study, among patients with nonischemic FFR values (>0.80), 26% had high IMR<sub>corr</sub>. These patients could potentially experience myocardial ischemia secondary to microvascular disease.13 A similar percentage of microvascular dysfunction based on IMR measurement was seen in a recent study evaluating patients with chest pain and nonobstructive coronary disease.<sup>14</sup> This could at least partly explain why some patients with nonischemic FFR values continue to report symptoms consistent with angina. In the FAME II registry population, (FFR >0.80 and deferral of percutaneous coronary intervention), ≈15% of patients had persistent Canadian Cardiovascular Society (CCS) class II-IV angina at 2-years follow-up. Additional evidence supporting the potential prognostic relevance of documenting coexisting coronary circulatory abnormalities in patients with nonsignificant FFR values comes from recently published research on the long-term follow-up of patients interrogated with FFR and concomitant

Doppler-derived flow measurements.<sup>15</sup> In this report, van de Hoef et al compared 10-year MACE rates according to the FFR and coronary flow velocity reserve (CFVR) levels of target vessel from 157 patients with intermediate stenosis. Compared with concordant normal FFR (>0.80) and CFVR ( $\geq$ 2.0) group, a normal FFR and abnormal CFVR (<2.0) group showed excess risk of 10-year MACE rates, regardless of FFR cut-off values (0.75 or 0.80). Although difference in MACE rates was mainly driven by excess risk of target vessel revascularization in a normal FFR and abnormal CFVR group, this report emphasized the importance of microvascular disease on future adverse events.<sup>15</sup>

It has been reported that ischemic FFR values are less likely to occur in a vessel with high IMR values.<sup>16</sup> In our population, 7.5% of cases had both ischemic FFR values and high IMR<sub>corr</sub> values. However, the mean FFR value in our study population was higher (0.84 $\pm$ 0.14) and IMR<sub>corr</sub> were lower (median 16.6 U, [12.4 U, 23.0 U]) than in the study from Echavarria-Pinto et al (mean FFR 0.81 $\pm$ 0.12 and median IMR 18.1 U [12.1 U, 29.1 U]). IMR cut-off values in these studies are based on frequency distributions, and the FFR values will also influence IMR<sub>corr</sub> values (through Yong's correction). Accordingly, the observed differences between these 2 studies may have been influenced in part by their different study populations.

#### **Determinants of High IMR**

In the current study, multivariate generalized estimating equation model showed that previous MI, RCA, female sex, and obesity were significantly associated with high IMR<sub>corr</sub>. The pathophysiologic mechanisms of primary microvascular disease have not been well defined. Nonetheless, recent studies report sex differences in the presentation, diagnosis, management, and pathophysiological mechanisms of CAD.17 So-called cardiac Syndrome X, which is the presence of myocardial ischemia without significant epicardial coronary stenosis, is more common in females,18 and recent reports suggest that microvascular dysfunction might be the main pathophysiological mechanism in this condition.18-20 Luo et al presented that the patients with cardiac syndrome X (female 72% of the patients) had significantly higher IMR compared with ageand sex-matched control patients (33.1±7.9 versus 18.8±5.6, P < 0.01).<sup>19</sup> Further reports suggest that estrogen deficiency, which is commonly observed in menopausal females, might be related to coronary microvascular disease.<sup>18,21</sup> Our finding that female sex is a predictor of high IMR<sub>corr</sub> is consistent with the previous studies which reported a higher prevalence of cardiac syndrome X in female patients, especially with postmenopausal status, and suggest microvascular disease as a potential mechanism of IHD in these patients.

Interestingly, obesity was also a determinant for high  $IMR_{corr}$ . There is evidence that obesity is a contributor to coronary microvascular disease.<sup>22</sup> Expansion of adipose tissue leads to tissue hypoxia and results in an increased production of various cytokines (leptin, resistin, tumor necrosis factor, and interleukin-6). These secreted adipokines and proinflammatory cytokines can induce oxidative stress, which leads to reduced availability of nitric oxide and limits vasodilatory capacity. However, Echavarria-Pinto et al reported a relationship between obesity (defined as body mass index  $\geq$ 30 kg/

m<sup>2</sup>), lower IMR<sub>corr</sub> values, and more frequent hypotensive responses to intravenous adenosine infusion in 79 patients with intermediate stenosis.<sup>23</sup> Likewise, there have been controversies whether common cardiovascular risk factors which have been known to cause macrovascular disease are also risk factors for primary microvascular disease.<sup>24</sup> In our results, conventional risk factors of macrovascular disease, as well as stenosis severity of epicardial coronary stenosis, were not associated with high IMR.

These results, along with the lack of correlation and categorical agreement between FFR and IMR, suggest the hypothesis that macro- and microvascular disease are different disease processes with different predisposing factors.<sup>1,24,25</sup> In addition, these results reinforce the clinical relevance of IMR measurement in current FFR-guided strategy to enhance patient stratification and to clarify the relative contribution of macro- and microvascular disease as a cause of IHD.

### Assessment for Microvascular Disease With IMR

The major obstacle to integrate the concept of IMR into the clinical fields has been a lack of well-validated normal ranges, especially for IHD patients without MI. Most of the previous studies evaluated IMR in patients with acute MI.<sup>5-7</sup> Recently, Fearon et al reported that in patients who underwent primary percutaneous coronary intervention for acute MI and had immediate post–percutaneous coronary intervention measurement of IMR and those with IMR >40 U had significantly higher 1-year rates of death or hospitalization with heart failure than patients with an IMR <40 U.<sup>5</sup>

Previous studies suggested that the upper normal value of IMR is between 25 and 29 U. Melikian et al found that IMR values in a small normal control group without evidence of atherosclerosis were lower than 25 U.26 In patients with intermediate coronary stenoses, Echavarria-Pinto et al derived an IMR<sub>corr</sub> cut-off value of 29 U based on the 75th percentile of observed IMR<sub>corr</sub> values.<sup>16</sup> In their study, 91 arteries in 78 patients were interrogated and 31% of patients were presented as post-MI. However, there have been no large studies exploring the real-world distribution of IMR among IHD patients without MI. In the current study, we evaluated 1096 patients with 1452 vessels who underwent invasive coronary physiological assessment. From the results, the IMR<sub>corr</sub> showed median of 16.6 U (12.4 U, 23.0 U), and >75th percentile cut-off in all lesions was 23 U. It is reassuring that the upper limit of the normal value for IMR is within the same range as previous studies of patients with stable IHD. Nonetheless, it should be noticed that most patients enrolled to this registry had undergone FFR and IMR measurement with clinical indications of invasive coronary angiography and FFR measurement. Therefore, the distribution of IMR values in a healthy population, without any symptoms and clinical indications of invasive coronary angiography, might be different.

In addition, the distribution of IMR<sub>corr</sub> was different among the 3 major coronary arteries, even though the observed differences were relatively small. As the IMR is the product of myocardial flow  $(1/T_{mn})$  and distal arterial pressure  $(P_d)$ , it can be influenced by blood flow pattern, flow rate, vessel geometry, and the myocardial mass that is supplied by the specific target vessel.<sup>27,28</sup> This influence is supported by the work of Murai et al, in which RCA location was a predictor of high IMR.<sup>29</sup> The relative longer length and larger reference diameter of the RCA may also contribute to a longer mean transit time and higher IMR in this vessel.

Although we used  $IMR_{corr}$  values with Yong's formula, it should be noted that the difference between  $IMR_{app}$  and  $IMR_{corr}$  was almost negligible, and using  $IMR_{app}$  did not alter any of the original results. Even though  $IMR_{corr}$  is scientifically more accurate,  $IMR_{app}$  seems a more practical way to assess microvascular function in daily routine practice, unless the epicardial stenosis is severe.

In summary, with consideration of our results along with the previous evidences, <sup>1,15,16,30</sup> FFR alone may not be sufficient for the evaluation of IHD. Although not all patients with high-FFR need IMR measurement, IMR can be a useful diagnostic tool for those with clinical evidence of IHD.

#### Limitations

First, because we excluded patients with elevated cardiac enzyme, our findings cannot be applied to patients with acute MI. However, the main purpose of this study was to explore the practical value of IMR in assessing CAD patients without MI. Second, we did not use the wedge pressure to adjust the IMR values because it was not practical to measure wedge pressure in patients with intermediate stenosis. However, corrected IMR values by Yong's formula9 were used to minimize the influence of collateral flow, and the differences between the uncorrected (IMR  $_{app}$ ) and corrected IMR (IMR  $_{corr}$ ) values were small. Third, the results of noninvasive test were not available in our study. Although patients with high FFR and high IMR might have myocardial ischemia because of microvascular disease, this relationship was not confirmed by noninvasive tests. Fourth, a comparative analysis regarding clinical outcomes according to the different IMR level was not performed. The prognostic impact of high IMR<sub>corr</sub> in stable IHD population and the optimal cut-off value to discriminate patients at higher risk of future events need further investigation. Fifth, although only experienced operators participated in our study, the reproducibility and variability of IMR measurements among the operators were not tested. Sixth, although multivariate model for predictor of high IMR showed clinically relevant results, the c-index of the model was within borderline range. Seventh, the roles of endothelial dysfunction or coronary vasospasm were not assessed in our study. Finally, the data regarding quantitative measures of angina symptom status, for example, Seattle Angina Questionnaire, were not available in this study.

### Conclusions

IMR showed no correlation with FFR and angiographic lesion severity, and the predictors of high IMR value were different from those for ischemic FFR value. Therefore, integration of IMR into FFR measurement may provide additional insights regarding the relative contribution of macro- and microvascular disease in patients with IHD.

### Sources of Funding

This study was supported by the unrestricted research grant from St Jude Medical.

### **Disclosures**

Dr Koo has received institutional research grant from St Jude Medical. Dr Oldroyd has received honoraria from St Jude Medical. Dr Escaned reports consultancies for St Jude Medical and Volcano Corporation. Dr Echavarria-Pinto's work was funded with a clinical scholarship from the Fundación Interhospitalaria Investigacion Cardiovascular, Madrid, Spain. Dr Fearon receives institutional research funding from St Jude Medical. Dr Ng has received honoraria from St Jude Medical. The other authors report no conflicts.

#### References

- Yong AS, Ho M, Shah MG, Ng MK, Fearon WF. Coronary microcirculatory resistance is independent of epicardial stenosis. *Circ Cardiovasc Interv.* 2012;5:103–108, S1. doi: 10.1161/CIRCINTERVENTIONS.111.966556.
- Aarnoudse W, Fearon WF, Manoharan G, Geven M, van de Vosse F, Rutten M, De Bruyne B, Pijls NH. Epicardial stenosis severity does not affect minimal microcirculatory resistance. *Circulation*. 2004;110:2137– 2142. doi: 10.1161/01.CIR.0000143893.18451.0E.
- Fearon WF, Aarnoudse W, Pijls NH, De Bruyne B, Balsam LB, Cooke DT, Robbins RC, Fitzgerald PJ, Yeung AC, Yock PG. Microvascular resistance is not influenced by epicardial coronary artery stenosis severity: experimental validation. *Circulation*. 2004;109:2269–2272. doi: 10.1161/01. CIR.0000128669.99355.CB.
- Kobayashi Y, Fearon WF. Invasive coronary microcirculation assessment-current status of index of microcirculatory resistance. *Circ J*. 2014;78:1021–1028.
- Fearon WF, Low AF, Yong AS, McGeoch R, Berry C, Shah MG, Ho MY, Kim HS, Loh JP, Oldroyd KG. Prognostic value of the index of microcirculatory resistance measured after primary percutaneous coronary intervention. *Circulation*. 2013;127:2436–2441. doi: 10.1161/ CIRCULATIONAHA.112.000298.
- McGeoch R, Watkins S, Berry C, Steedman T, Davie A, Byrne J, Hillis S, Lindsay M, Robb S, Dargie H, Oldroyd K. The index of microcirculatory resistance measured acutely predicts the extent and severity of myocardial infarction in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv.* 2010;3:715–722. doi: 10.1016/j. jcin.2010.04.009.
- Fearon WF, Shah M, Ng M, Brinton T, Wilson A, Tremmel JA, Schnittger I, Lee DP, Vagelos RH, Fitzgerald PJ, Yock PG, Yeung AC. Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2008;51:560–565. doi: 10.1016/j.jacc.2007.08.062.
- Ng MK, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve. *Circulation*. 2006;113:2054–2061. doi: 10.1161/ CIRCULATIONAHA.105.603522.
- Yong AS, Layland J, Fearon WF, Ho M, Shah MG, Daniels D, Whitbourn R, Macisaac A, Kritharides L, Wilson A, Ng MK. Calculation of the index of microcirculatory resistance without coronary wedge pressure measurement in the presence of epicardial stenosis. *JACC Cardiovasc Interv*. 2013;6:53–58. doi: 10.1016/j.jcin.2012.08.019.
- De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med.* 2014;371:1208–1217. doi: 10.1056/NEJMoa1408758.
- 11. Park SJ, Ahn JM, Park GM, Cho YR, Lee JY, Kim WJ, Han S, Kang SJ, Park DW, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW. Trends in the outcomes of percutaneous coronary intervention with the routine incorporation of fractional flow reserve in real practice. *Eur Heart J*. 2013;34:3353–3361. doi: 10.1093/eurheartj/eht404.
- 12. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol. 2010;56:177–184. doi: 10.1016/j.jacc.2010.04.012.
- Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med. 2007;356:830–840. doi: 10.1056/NEJMra061889.

- Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, Lee DP, Yeung AC, Tremmel JA. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation*. 2015;131:1054–1060. doi: 10.1161/CIRCULATIONAHA.114.012636.
- 15. van de Hoef TP, van Lavieren MA, Damman P, Delewi R, Piek MA, Chamuleau SA, Voskuil M, Henriques JP, Koch KT, de Winter RJ, Spaan JA, Siebes M, Tijssen JG, Meuwissen M, Piek JJ. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ Cardiovasc Interv.* 2014;7:301–311.
- 16. Echavarria-Pinto M, Escaned J, Macías E, Medina M, Gonzalo N, Petraco R, Sen S, Jimenez-Quevedo P, Hernandez R, Mila R, Ibañez B, Nuñez-Gil IJ, Fernández C, Alfonso F, Bañuelos C, García E, Davies J, Fernández-Ortiz A, Macaya C. Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve: a combined analysis of epicardial and microcirculatory involvement in ischemic heart disease. *Circulation*. 2013;128:2557–2566. doi: 10.1161/ CIRCULATIONAHA.112.001345.
- Nugent L, Mehta PK, Bairey Merz CN. Gender and microvascular angina. J Thromb Thrombolysis. 2011;31:37–46. doi: 10.1007/s11239-010-0477-1.
- Kaski JC. Cardiac syndrome x in women: the role of oestrogen deficiency. *Heart*. 2006;92(suppl 3):iii5–iii9.
- Luo C, Long M, Hu X, Huang Z, Hu C, Gao X, Du Z. Thermodilutionderived coronary microvascular resistance and flow reserve in patients with cardiac syndrome X. *Circ Cardiovasc Interv.* 2014;7:43–48. doi: 10.1161/CIRCINTERVENTIONS.113.000953.
- Recio-Mayoral A, Rimoldi OE, Camici PG, Kaski JC. Inflammation and microvascular dysfunction in cardiac syndrome X patients without conventional risk factors for coronary artery disease. *JACC Cardiovasc Imaging*. 2013;6:660–667. doi: 10.1016/j.jcmg.2012.12.011.
- Roqué M, Heras M, Roig E, Masotti M, Rigol M, Betriu A, Balasch J, Sanz G. Short-term effects of transdermal estrogen replacement therapy on coronary vascular reactivity in postmenopausal women with angina pectoris and normal results on coronary angiograms. *J Am Coll Cardiol.* 1998;31:139–143.
- Bagi Z, Broskova Z, Feher A. Obesity and coronary microvascular disease - implications for adipose tissue-mediated remote inflammatory response. *Curr Vasc Pharmacol.* 2014;12:453–461.

- 23. Echavarría-Pinto M, Gonzalo N, Ibañez B, Petraco R, Jimenez-Quevedo P, Sen S, Nijjer S, Tarkin J, Alfonso F, Núñez-Gil IJ, Bañuelos C, Quirós A, Fernández-Ortiz A, Macaya C, Koo BK, Davies J, Escaned J. Low coronary microcirculatory resistance associated with profound hypotension during intravenous adenosine infusion: implications for the functional assessment of coronary stenoses. *Circ Cardiovasc Interv.* 2014;7:35–42. doi: 10.1161/CIRCINTERVENTIONS.113.000659.
- Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. *Circulation*. 2010;121:2317–2325. doi: 10.1161/CIRCULATIONAHA.109.900191.
- 25. Wessel TR, Arant CB, McGorray SP, Sharaf BL, Reis SE, Kerensky RA, von Mering GO, Smith KM, Pauly DF, Handberg EM, Mankad S, Olson MB, Johnson BD, Merz CN, Sopko G, Pepine CJ; NHLBI Women's Ischemia Syndrome Evaluation (WISE). Coronary microvascular reactivity is only partially predicted by atherosclerosis risk factors or coronary artery disease in women evaluated for suspected ischemia: results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE). *Clin Cardiol.* 2007;30:69–74. doi: 10.1002/clc.19.
- Melikian N, Vercauteren S, Fearon WF, Cuisset T, MacCarthy PA, Davidavicius G, Aarnoudse W, Bartunek J, Vanderheyden M, Wyffels E, Wijns W, Heyndrickx GR, Pijls NH, de Bruyne B. Quantitative assessment of coronary microvascular function in patients with and without epicardial atherosclerosis. *EuroIntervention*. 2010;5:939–945. doi: 10.4244/.
- Akasaka T, Yoshikawa J, Yoshida K, Hozumi T, Takagi T, Okura H. Comparison of relation of systolic flow of the right coronary artery to pulmonary artery pressure in patients with and without pulmonary hypertension. *Am J Cardiol.* 1996;78:240–244.
- Heller LI, Silver KH, Villegas BJ, Balcom SJ, Weiner BH. Blood flow velocity in the right coronary artery: assessment before and after angioplasty. *J Am Coll Cardiol*. 1994;24:1012–1017.
- Murai T, Lee T, Yonetsu T, Iwai T, Takagi T, Hishikari K, Masuda R, Iesaka Y, Isobe M, Kakuta T. Variability of microcirculatory resistance index and its relationship with fractional flow reserve in patients with intermediate coronary artery lesions. *Circ J*. 2013;77:1769–1776.
- Dhawan SS, Corban MT, Nanjundappa RA, Eshtehardi P, McDaniel MC, Kwarteng CA, Samady H. Coronary microvascular dysfunction is associated with higher frequency of thin-cap fibroatheroma. *Atherosclerosis*. 2012;223:384–388. doi: 10.1016/j.atherosclerosis.2012.05.034.





### Integrated Physiologic Assessment of Ischemic Heart Disease in Real-World Practice Using Index of Microcirculatory Resistance and Fractional Flow Reserve: Insights From the International Index of Microcirculatory Resistance Registry Joo Myung Lee, Jamie Layland, Ji-Hyun Jung, Hyun-Jung Lee, Mauro Echavarria-Pinto, Stuart Watkins, Andy S. Yong, Joon-Hyung Doh, Chang-Wook Nam, Eun-Seok Shin, Bon-Kwon Koo, Martin K. Ng, Javier Escaned, William F. Fearon and Keith G. Oldroyd

Circ Cardiovasc Interv. 2015;8: doi: 10.1161/CIRCINTERVENTIONS.115.002857 Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2015 American Heart Association, Inc. All rights reserved. Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circinterventions.ahajournals.org/content/8/11/e002857

Data Supplement (unedited) at:

http://circinterventions.ahajournals.org/content/suppl/2015/10/21/CIRCINTERVENTIONS.115.002857.DC1

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Interventions* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at: http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Circulation: Cardiovascular Interventions* is online at: http://circinterventions.ahajournals.org//subscriptions/

## **Supplementary Material**

# Integrated Physiologic Assessment of Ischemic Heart Disease in Real World Practice using Index of Microcirculatory Resistance and Fractional Flow Reserve: Insights from the International IMR registry

Joo Myung Lee, MD, MPH<sup>1</sup>, Jamie Layland, MBC<sub>H</sub>B<sup>2,3</sup>, Ji-Hyun Jung, MD<sup>1</sup>, Hyun-Jung
Lee, MD<sup>1</sup>, Mauro Echavarria-Pinto, MD<sup>4,5</sup>, Stuart Watkins MBChB, MD<sup>2,3</sup>, Andy S. Yong,
MBBS, PhD<sup>6</sup>, Joon-Hyung Doh, MD, PhD<sup>7</sup>, Chang-Wook Nam, MD, PhD<sup>8</sup>, Eun-Seok Shin,
MD, PhD<sup>9</sup>, Bon-Kwon Koo, MD, PhD<sup>1,10</sup>, Martin K. Ng, MBBS, PhD<sup>11</sup>, Javier Escaned,
MD, PhD<sup>4,5</sup>, William F. Fearon, MD<sup>6</sup>, Keith G. Oldroyd, MBChB, MD(Hons)<sup>2,3</sup>

### **Supplementary Tables**

### **Supplementary Figure Legends**

## **Supplementary Tables**

Supplementary Table 1. Comparison of IMR<sub>corr</sub> values and proportion of high-IMR among the cohorts of predictors of high-IMR

	High-IMR <sub>corr</sub> (%)	P value	
Previous MI	34.9%	0.012	
No previous MI	24.7%	0.015	
RCA	39.1%	<0.001	
Other vessels	23.9%	<0.001	
Female	31.5%	0.041	
Male	26.0%	0.041	
Obesity	30.8%	0.081	
No obesity	26.4%	0.001	

### **Supplementary Figure Legends**

### Supplementary Figure 1. Comparison of IMR values among 3 coronary arteries

The per-vessel distribution of (A) apparent IMR ( $IMR_{app}$ ) and (B) corrected IMR ( $IMR_{corr}$ ) among the 3 coronary arteries.

Abbreviations: IMR, index of microcirculatory resistance; IMR<sub>app</sub>, apparent IMR; IMR<sub>corr</sub>, corrected IMR; IQR, interquartile range; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

Supplementary Figure 1. Comparison of IMR values among 3 coronary arteries

A. IMR<sub>app</sub>



B. IMR<sub>corr</sub>

