Clinical Trial Registration

Conclusions

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_{corr}). High IMR was defined as greater than the 75th percentile in each of the major coronary arteries. FFR \leq 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_{corr} was 16.6 U (Q1, Q3 12.4, 23.0 U). There was no correlation between IMR_{corr} and FFR values (r=0.01, P=0.62), and the categorical agreement of FFR and IMR_{corr} was low (kappa value=−0.04, P=0.10). There was no correlation between IMR_{corr} 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 \leq 0.80 were left anterior descending coronary artery (OR 4.31, 95% CI 3.66–7.28, P<0.01), left main coronary artery (OR 2.09, 95% CI 1.54–2.84, P<0.01), age (per 10 years, OR 1.21, 95% CI 1.01–1.46, P=0.04), and smoking (OR 1.44, 95% CI 1.11–1.88, P=0.004).

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.

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Key Words: coronary artery disease ■ fractional flow reserve ■ ischemic heart disease ■ microcirculation ■ physiology
The coronary microcirculation is one of the major components 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. 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. IMR is also relatively independent of hemodynamic conditions, such as blood pressure and heart rate.

Recent clinical studies have shown that IMR is useful for the risk stratification in patients with acute myocardial infarction (MI). 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 well-validated 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 μg). 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. 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 ($T_{mn}$), 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 arterial pressure ($P_{ra}$), distal arterial pressure ($P_{rd}$), and hyperemic $T_{mn}$ were obtained during sustained hyperemia. FFR was calculated as $P_{ra}/P_{rd}$ during hyperemia and apparent IMR ($IMR_{app}$) as $P_{ra}×T_{mn}$ during hyperemia. All IMR values were also corrected by Yong’s formula ($IMR_{corr}=P_{ra}×T_{mn}×(1.35×P_{rd}/P_{ra}–0.32)$) to adjust for the influence of collateral flow. 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 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. Patients with at least 1 elevated IMR were categorized as having high microvascular resistance. Ischemic FFR value was defined as FFR ≤0.80. All patients were classified according to the cut-off values of FFR and IMR 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–Smirnov test. Data were analyzed on a per-patient basis for clinical characteristics and classification according to FFR and IMR, and on a per-vessel basis for the rest of analysis.

For per-vessel analysis, including comparison of IMR or IMR values according to the target vessels or comparison of FFR,
IMR_{app} or IMR_{corr} values according to the clinical diagnosis, the generalized estimating equation with exchangeable correlation structure was used to adjust for intra-subject 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_{app} 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 ≥25 kg/m² for the Asian population or ≥30 kg/m² for the Western population, current smoking, acute coronary syndrome, history of MI or percutaneous coronary intervention, target vessel, diameter stenosis ≥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 silent ischemia. 55% of patients showed discordant results. Figure 3B shows the categorization of patients according to the cut-off values of FFR and IMR_{corr}. 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 1. General Characteristics of Study Population (n=1096)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Value</th>
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<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>61.1±9.7</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>780 (71%)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>25.4±3.7</td>
</tr>
<tr>
<td><strong>Asian population</strong></td>
<td>635 (58%)</td>
</tr>
<tr>
<td><strong>Western population</strong></td>
<td>364 (42%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical presentations</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stable angina</strong></td>
<td>562 (51%)</td>
</tr>
<tr>
<td><strong>Unstable angina</strong></td>
<td>284 (26%)</td>
</tr>
<tr>
<td><strong>Atypical chest pain</strong></td>
<td>137 (13%)</td>
</tr>
<tr>
<td><strong>Silent ischemia</strong></td>
<td>113 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular risk factors</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td>683 (62%)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>281 (26%)</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>709 (65%)</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>357 (33%)</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>326 (30%)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>120 (11%)</td>
</tr>
<tr>
<td><strong>Previous MI</strong></td>
<td>93 (9%)</td>
</tr>
<tr>
<td><strong>Previous PCI</strong></td>
<td>237 (22%)</td>
</tr>
</tbody>
</table>

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.

Distribution of Physiological Indices

Figure 1 shows the distribution of measured FFR and IMR values. The mean FFR was 0.84±0.14, and median IMR_{app} and IMR_{corr} 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 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_{app} 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_{app} (r=−0.01, P=0.86) or IMR_{corr} (r=−0.03, P=0.25) (Figure 2).

Regardles 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_{corr} 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_{corr}. 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)

<table>
<thead>
<tr>
<th>Measured vessel location</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left anterior descending artery</strong></td>
<td>784 (54%)</td>
</tr>
<tr>
<td><strong>Left circumflex artery</strong></td>
<td>295 (20%)</td>
</tr>
<tr>
<td><strong>Right coronary artery</strong></td>
<td>373 (26%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantitative coronary angiography</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference diameter, mm</strong></td>
<td>3.01±0.60</td>
</tr>
<tr>
<td><strong>Minimum lumen diameter, mm</strong></td>
<td>1.81±0.69</td>
</tr>
<tr>
<td><strong>Diameter stenosis, %</strong></td>
<td>40.5±17.3</td>
</tr>
<tr>
<td><strong>Lesion length, mm</strong></td>
<td>11.59±7.67</td>
</tr>
</tbody>
</table>

Coronary physiological indices

| FFR | 0.84±0.14 |
| IMR, U | 17.0 (13.0, 23.5) |
| IMR_{corr}, 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_{corr}, calculated IMR with Yong’s formula (IMR_{corr}=P_{max}/T_{max}×[1.35×P/P_{0}]=0.32).
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 IMRcorr (Table 3). The dichotomous data of IMRcorr 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 ≥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 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 (IMRcorr=Pa×Tmn×[(1.35×Pd/Pa)−0.32]) were presented in B. IMRapp indicates apparent IMR; IMRcorr corrected IMR; and IQR, interquartile range.

Figure 2. The association between angiographic % diameter stenosis and physiological indices. The association between percent diameter stenosis and FFR/IMRapp/IMRcorr was plotted. Angiographic diameter stenosis correlated modestly with FFR (r=−0.56, P<0.01), but not with IMRapp (r=0.01, P=0.86) or IMRcorr (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; IMRapp, apparent IMR; and IMRcorr, 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 IMRcorr 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 IMRcorr values; and (3) the predictors of high IMRcorr 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. 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 IMRcorr. These patients could potentially experience myocardial ischemia secondary to microvascular disease. 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. This could at least partly explain why some patients with nonischemic FFR values continue to report symptoms consistent with angina.

Table 3. Predictors for High IMR or Low FFR in Target Vessels

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

CI 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 χ² tests were used to evaluate the predictors. C-indexes were 0.67 (95% CI 0.63–0.70) and 0.81 (95% CI 0.78–0.85) in predicted model for high IMR and low FFR, respectively.
†Obesity was defined as body mass index ≥25 kg/m² in Korean patients and ≥30 kg/m² in Western patients.
Doppler-derived flow measurements. In this report, van de Hoef et al compared 10-year MACE rates according to the FFR and coronary flow reserve (CFVR) levels of the target vessel from 157 patients with intermediate stenosis. Compared with concordant normal FFR (>0.80) and CFVR (≥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.

It has been reported that ischemic FFR values are less likely to occur in a vessel with high IMR values. In our population, 7.5% of cases had both ischemic FFR values and high IMRcorr values. However, the mean FFR value in our study population was higher (0.84±0.14) and IMRcorr 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±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 IMRcorr 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 IMRcorr. 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. The so-called cardiac Syndrome X, which is the presence of myocardial ischemia without significant epicardial coronary stenosis, is more common in females, and recent reports suggest that microvascular dysfunction might be the main pathophysiological mechanism in this condition. The pathophysiologic mechanisms of primary microvascular disease as a cause of IHD. 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. 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.

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. In patients with intermediate coronary stenoses, Echavarria-Pinto et al derived an IMRcorr cut-off value of 29 U based on the 75th percentile of observed IMRcorr values. 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 IMRcorr 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.

**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. 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.

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In addition, the distribution of IMRcorr 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/Tmn) and distal arterial pressure (Pd), it can be influenced by blood flow pattern, flow rate, vessel geometry, and the myocardial mass that is supplied by the specific target vessel. This influence is supported by the work of Murai.
et al, in which RCA location was a predictor of high IMR.\textsuperscript{29} 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\textsubscript{corr} values with Yong’s formula, it should be noted that the difference between IMR\textsubscript{app} and IMR\textsubscript{corr} was almost negligible, and using IMR\textsubscript{app} did not alter any of the original results. Even though IMR\textsubscript{corr} is scientifically more accurate, IMR\textsubscript{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,\textsuperscript{1,15,16,30} 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 formula\textsuperscript{9} were used to minimize the influence of collateral flow, and the differences between the uncorrected (IMR\textsubscript{app}) and corrected IMR (IMR\textsubscript{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\textsubscript{corr} 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.

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**Disclosures**

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**References**


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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

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Supplementary Tables

Supplementary Figure Legends
## Supplementary Tables

### Supplementary Table 1. Comparison of IMR$_{corr}$ values and proportion of high-IMR among the cohorts of predictors of high-IMR

<table>
<thead>
<tr>
<th></th>
<th>High-IMR$_{corr}$ (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>34.9%</td>
<td>0.013</td>
</tr>
<tr>
<td>No previous MI</td>
<td>24.7%</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>39.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other vessels</td>
<td>23.9%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31.5%</td>
<td>0.041</td>
</tr>
<tr>
<td>Male</td>
<td>26.0%</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>30.8%</td>
<td>0.081</td>
</tr>
<tr>
<td>No obesity</td>
<td>26.4%</td>
<td></td>
</tr>
</tbody>
</table>
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_{app}, apparent IMR; IMR_{corr}, 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_{app}

- LAD: 16.2 U (12.5, 22.2)
- LCX: 17.0 U (12.5, 22.1)
- RCA: 19.0 U (14.0, 26.5)

B. IMR_{corr}

- LAD: 15.7 U (11.9, 21.3)
- LCX: 16.9 U (12.5, 23.0)
- RCA: 19.1 U (13.5, 27.1)