Advances in Interventional Cardiology

Invasive Assessment of the Coronary Microvasculature
The Index of Microcirculatory Resistance

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Abstract—Traditionally, invasive coronary physiological assessment has focused on the epicardial coronary artery. More recently, appreciation of the importance of the coronary microvasculature in determining patient outcomes has grown. Several invasive modalities for interrogating microvascular function have been proposed. Angiographic techniques have been limited by their qualitative and subjective nature. Doppler wire-derived coronary flow reserve has been applied in research studies, but its clinical role has been limited by its lack of reproducibility, its lack of a clear normal value, and the fact that it is not specific for the microvasculature but interrogates the entire coronary circulation. The index of microcirculatory resistance—a thermodilution-derived measure of the minimum achievable microvascular resistance—is relatively easy to measure, more reproducible, has a clearer normal value, and is independent of epicardial coronary artery stenosis. The index of microcirculatory resistance has been shown to have prognostic value in patients with ST-segment-elevation myocardial infarction and cardiac allograft vasculopathy after heart transplantation. Emerging data demonstrate its role in evaluating patients with chest pain and nonobstructive coronary artery disease. Increasingly, the index of microcirculatory resistance is used as a reference standard for invasively assessing the microvasculature in clinical trials. (Circ Cardiovasc Interv. 2017;10:e005361. DOI: 10.1161/CIRCINTERVENTIONS.117.005361.)

Key Words: chest pain ■ coronary artery disease ■ humans ■ microcirculation ■ physiology

Since the first percutaneous coronary intervention (PCI) performed in 1977, the primary reason for assessing coronary physiology has been to determine the functional significance of epicardial coronary artery stenosis. This has been driven by the fact that epicardial disease is most commonly responsible for symptoms and adverse outcomes and because it can be readily treated with PCI. Over the years, an appreciation for the role of microvascular dysfunction in patients’ symptoms and adverse events has grown. This expanding interest in the coronary microvasculature and the fact that many patients present to the catheterization laboratory with little if any prior noninvasive evaluation of the coronary circulation has spurred the development of several invasive modalities for assessing microvascular function. The goal of this review is to update the reader on the status of invasive techniques for interrogating coronary microvascular function, with a particular focus on the index of microcirculatory resistance (IMR).

Pathophysiology of Microvascular Dysfunction

The coronary microcirculation is a complex and heterogeneous network of vessels less than ≈500 μm in diameter, which is responsible for regulating blood flow to and the exchange of oxygen, nutrients, and metabolites within the myocardium. Microvascular dysfunction is a generic term with multiple possible pathogeneses, including smooth muscle cell dysfunction, microvascular remodeling, vascular rarefaction, luminal obstruction, inflammation, and endothelial dysfunction. Some of these can occur acutely, for example, in the setting of myocardial infarction, whereas others are related to chronic changes. With our current invasive techniques, it is challenging to distinguish between these various causes of microvascular dysfunction. A full review of the pathophysiology of microvascular dysfunction is beyond the scope of this article but is available elsewhere.

Why Assess Microvascular Function?

Before reviewing the methods for invasive coronary microvascular assessment, it is important to understand when and why one might consider investigating microvascular function (Table 1). The most common clinical scenario for considering microvascular dysfunction is the patient who presents to the catheterization laboratory with an abnormal stress imaging study or symptoms consistent with angina but is found to have no significant epicardial coronary disease. This type of patient may constitute ≤20% of patients evaluated in the cardiac catheterization laboratory. Another common scenario is the patient who has undergone successful PCI, yet continues to have angina, despite no residual epicardial coronary disease. Series have shown that this may occur in as many as 30% of patients undergoing PCI. The rationale for identifying microvascular dysfunction in either of these settings is to provide a definitive diagnosis for the patient and to hopefully
Avoid further unnecessary expensive and potentially risky testing. Additionally, by identifying microvascular dysfunction, one can focus medical therapy on the microvasculature with statins, angiotensin-converting enzyme inhibitors, β-blockers, statins, and nitrates, although the most effective regimen remains unclear.

Another common presentation in which microvascular dysfunction occurs is the acute coronary syndrome and, in particular, ST-segment–elevation myocardial infarction (STEMI). Significant damage to the microcirculation at the time of STEMI portends a poor prognosis; methods for reversing the damage and improving prognosis are still evolving but seem to be most beneficial when delivered early, further emphasizing the need for an accurate invasive technique for diagnosing acute myocardial damage.

In the stable setting, assessing microvascular function before and after elective PCI allows identification of patients at higher risk for periprocedural myocardial infarction. Final reasons to assess the microvasculature occur in particular disease entities, such as after cardiac transplantation, where microvascular dysfunction has been linked with decreased long-term survival, and in the research setting to evaluate new therapies.

**Angiographic Methods for Assessing Microvascular Function**

Noninvasive imaging and, in particular, positron emission tomography remains the reference standard for diagnosing microvascular dysfunction. Postitron emission tomography allows quantification of absolute myocardial blood flow and has been shown to predict mortality in patients without obstructive coronary artery disease but with abnormal positron emission tomography–derived coronary flow reserve (CFR). Unfortunately, most patients who present to the cardiac catheterization laboratory for invasive coronary angiography have not had any noninvasive evaluation of their microvasculature. Moreover, in patients with acute coronary syndromes, it is often logistically challenging to perform noninvasive imaging of the microvasculature. For these reasons, there is a need for an invasive technique to rapidly, reliably, and relatively easily assess for microvascular dysfunction.

Direct visualization of the coronary microvasculature with traditional invasive coronary angiography is not possible because of the lack of resolution of the angiogram and the small size of the microvessels. However, 2 methods for assessing the passage of contrast media through the microcirculation have been proposed as techniques for evaluating microvascular function. The myocardial blush grading system, described by van’t Hof et al, focused on qualitatively assessing the brightness or density of contrast media blush in the microvasculature with grade 0 representing no myocardial blush; grade 1, minimal blush; grade 2, moderate blush; and grade 3, normal blush. These investigators found the myocardial blush grade to be an independent predictor of long-term mortality in patients undergoing primary PCI for STEMI.

The thrombolysis in myocardial infarction (TIMI) myocardial perfusion grading system, described by Gibson et al, focused on the duration of contrast media blush in the microvasculature with grade 0 representing no blush; grade 1, slow entering of contrast with failure to exit; grade 2, delayed entering and exiting of contrast; and grade 3, normal entering and exiting of contrast. These investigators found the TIMI myocardial perfusion grading system to be predictive of mortality in patients with STEMI and treated with fibrinolysis. The advantage of these 2 techniques is that they are readily available and do not require manipulation of the coronary artery with a pressure or Doppler sensor-tipped guidewire. However, both of these techniques are limited by their qualitative nature and lack of reproducibility, as well as their use being primarily in the setting of STEMI. For these reasons, neither is applied regularly in clinical practice.

**Coronary Flow Reserve**

CFR is defined as hyperemic coronary flow divided by resting flow and can be measured invasively in the catheterization laboratory using a Doppler velocity wire (Philips/Volcano, Inc). With the Doppler wire, one can estimate coronary flow at rest and hyperemia by multiplying the velocity by the cross-sectional area of the vessel; however, more commonly, the coronary flow velocity reserve is calculated by simply comparing the average peak velocity at rest to the average peak velocity during hyperemia. More recently, a thermodilution-derived method for estimating coronary flow has allowed measurement of CFR simultaneously with fractional flow reserve (FFR) using a coronary pressure wire (Abbott Vascular).

CFR was developed first as an invasive method to interrogate intermediate epicardial coronary lesions. Because it interrogates the entire coronary circulation, both the epicardial...
vessel and the microvasculature, CFR has been applied more recently as a technique for diagnosing microvascular dysfunction in patients without obstructive epicardial coronary disease. Several studies have demonstrated the role of CFR for investigating microvascular function. However, for several reasons, the clinical application of CFR has been limited. Because CFR incorporates resting flow in its definition, it has more variability and less reproducibility compared with newer measures of microvascular resistance made during hyperemia. The lack of a clearly normal value in any given patient can make CFR difficult to interpret, as can the effect of epicardial disease, even in patients with angiographically normal epicardial vessels. Finally, newer methods for measuring microvascular resistance independent of the epicardial vessel have been shown to be more predictive of outcomes, for example, in patients with microvascular dysfunction at the time of STEMI (Figure 1).15,16

## Index of Microcirculatory Resistance

### Derivation and Validation of IMR

IMR, first described in 2003,17 leverages the ability of the sensor of the PressureWire (Abbott Vascular) to act as a thermistor and also measure temperature. With commercially available software, the pressure sensor of the wire acts as a distal thermistor, whereas the shaft of the wire serves as a proximal thermistor. In this manner, the mean transit time (Tmn) of room-temperature saline injected into a coronary artery can be determined from a thermodilution curve. De Bruyne et al12 and Pijls et al18 applied the thermodilution technique in an experimental model and found a strong correlation between the inverse of Tmn (1/Tmn) and absolute coronary flow.

\[
\text{Absolute coronary flow} = \frac{1}{T\text{mn}}
\]

They also showed that the thermodilution-derived CFR (CFRThermo), defined as the resting Tmn (TmnRest) divided by the hyperemic Tmn (TmnHyp), correlated well with standard CFR, both in their experimental model and in humans.

\[
\text{CFR} = \frac{\text{Coronary flow at hyperemia}}{\text{Coronary flow at rest}} = \frac{1}{T\text{mnHyp}} = \frac{T\text{mnRest}}{T\text{mnHyp}}
\]

CFRThermo was further validated in an open-chest porcine model.19 CFRThermo showed better correlation with the absolute coronary flow–derived CFR than did Doppler velocity–derived CFVR.19

The derivation of IMR is based on Ohm law (the potential difference across an ideal conductor is proportional to the current through the conductor) applied to the coronary microcirculation.

\[
\text{Ohm law} : V = I \times R \rightarrow R = \frac{V}{I}
\]

(R = R = resistance, V = voltage, I = current)

In the coronary circulation, voltage is analogous to the difference in pressure across the microvasculature (the mean distal coronary pressure [Pd] minus venous pressure [Pv]) and the current is myocardial flow (1/Tmn). The minimal achievable resistance is calculated by making the measurement during maximal hyperemia. Therefore, IMR is defined as

\[
\text{IMR} = \frac{\text{Pd} - \text{Pv}}{\text{Tmn}} \text{ at maximal hyperemia}
\]

Because Pd is generally negligible relative to Pd, it is eliminated from the formula.

\[
\text{IMR} = \frac{\text{Pd}}{\text{TmnHyp}}
\]

IMR is calculated as a following formula in its simplest form.

\[
\text{IMR} = \frac{\text{Pd} \times \text{TmnHyp}}{1}
\]

Using the same porcine model mentioned above, the true microvascular resistance was compared with IMR at baseline and after disruption of microcirculation and with and without an epicardial stenosis. IMR and true microvascular resistance correlated significantly, as did the percent change from baseline to after disruption of the microcirculation, validating this new technique for measuring microvascular resistance.17

### Standard Measurement Technique of IMR

Systemic administration of heparin (50–100 IU/kg; or an alternative antithrombotic agent) and intracoronary nitroglycerin (100–200 μg) is necessary before measuring IMR. Currently, the RadiAnalyzer console (Abbott Vascular) must be used. A coronary pressure–temperature sensor guidewire (PressureWire; Abbott Vascular) is calibrated, equalized to the guide catheter pressure with the pressure sensor positioned at the tip of the catheter, and advanced to the distal two thirds of the target vessel. For an accurate thermodilution measurement, the sensor needs to be at least 6 centimeters into the

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**Figure 1.** Cartoon of the coronary circulation demonstrating which segments of the coronary system are interrogated by the various indices. cFFR indicates contrast fractional flow reserve; CFR, coronary flow reserve; CFRThermo, thermodilution-derived CFR; CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; hMR, hyperemic microvascular resistance; iFR, instantaneous wave free ratio; IMR, index of microcirculatory resistance; Pdmean proximal coronary pressure; and Pdmean distal coronary pressure.
coronary artery. The typical position of the sensor for IMR measurement should be in the distal two thirds of the left anterior descending, in the distal right coronary artery, just before the takeoff the posterior descending branch, and ≈8 to 10 centimeters down the circumflex, resting in the main obtuse marginal branch, or in the true circumflex, if it is a dominant vessel. A 3-way stopcock and 3-mL syringe are connected to the back of the manifold (see Movie I in the Data Supplement for set-up and measurement of IMR). The guide catheter is flushed with saline, clearing all contrast, and the operator should pause for a minute to allow coronary flow to return to baseline. If the operator intends to calculate CFR also, then 3 mL of room-temperature saline is briskly injected through the guide catheter under resting conditions, and the console automatically calculates the $T_{mn}$ at rest. If the operator is not interested in CFR, or after making the resting measurement, hyperemia is induced by either infusing intravenous adenosine (140 μg·kg$^{-1}$·min$^{-1}$) or by injecting intracoronary papaverine (10–20 mg). During maximal hyperemia, 3 mL of room-temperature saline is briskly injected through the guide catheter, and $T_{mn}$ Hyp is measured again as described above. The system allows the operator to examine the $T_{mn}$ curve and calculated time; if the operator is not happy, the value can be replaced with another injection. In some cases, variability in the $T_{mn}$ values can occur, particularly if the guide catheter is moving out of the ostium of the coronary during injection of saline. If all 3 $T_{mn}$ values are <0.25, then the variability can be ignored because in most cases, IMR will be in the normal range. If $T_{mn}$ is >0.25% and ([the maximum individual $T_{mn}$ value minus the minimum $T_{mn}$ value]/the maximum $T_{mn}$ value×100%) >30%, then the $T_{mn}$ value that is furthest from the mean $T_{mn}$ should be replaced. $P_{d}$ is measured simultaneously with the same PressureWire during maximal hyperemia, and IMR is calculated as $P_{d}$ multiplied by $T_{mn}$ Hyp (Figure 2).20 As shown, FFR is measured and recorded automatically as well, allowing the operator to independently interrogate both the epicardial vessel and the microvasculature.

**Normal Range of IMR**

The normal range of IMR is <25, based on 3 studies reporting the IMR value in healthy populations. Melikian et al$^{21}$ found a mean IMR of 19±5 in 15 patients without coronary disease or risk factors for coronary disease referred to the cardiac catheterization laboratory for a noncoronary reason. Luo et al$^{23}$ performed a similar study and found a similar mean IMR of 19±6.5 in 18 patients without coronary disease or risk factors. Finally, Solberg et al$^{23}$ found a mean IMR of 14.0±4.7 in 20 otherwise healthy patients who were referred for electrophysiological evaluation. In a much larger study of coronary disease patients, Lee et al recently measured IMR in 1096 patients and 1452 coronary arteries as part of an international registry. When the 75th percentile of IMR was used as a normal threshold, the cutoff values in each of the major coronary arteries were 22.0 in the left anterior descending coronary artery, 24.0 in the left circumflex coronary artery, and 28.0 in the right coronary artery, respectively.$^{24}$ The higher values reported in this study may be related to the inclusion of patients with acute coronary syndrome and those with typical cardiac risk factors, such as hypertension, dyslipidemia, and diabetes mellitus, which have been associated with microvascular dysfunction. In addition, the higher IMR in the right coronary artery may be related to the longer length of the vessel leading to a slightly longer $T_{mn}$ or to the smaller amount of myocardial mass, which can influence resistance.$^{25}$

**Reproducibility of IMR**

The effect of changes in heart rate, blood pressure, and contractility on the reproducibility of IMR was tested in a study of 15 patients in whom IMR was measured at baseline, then while pacing the right ventricle at 110 beats per minute, then during nitroprusside infusion, then during dobutamine infusion, and finally at baseline again.$^{26}$ IMR was shown to have a low coefficient of variation (6.9±6.5%) between the 2 baseline measurements and a high correlation between baseline and each hemodynamic perturbation ($r$=0.90±0.05). IMR had superior reproducibility and less hemodynamic dependence compared with CFR and similar to FFR. In another study of 22 patients, IMR was measured at baseline and again 7 weeks later.$^{28}$ There was no significant difference between the mean IMR values at the 2 time points (13.5 versus 13.8; $P=0.31$), and the inclusion or exclusion of $P_{d}$ did not have a significant impact on the calculation of IMR. In addition, the variation in the 3 hyperemic T measurements at baseline was 7.6±3.2%, and at 7 weeks, it was 6.6±4.8%. Another study examined the interobserver variability of IMR measurements between 4 different operators measuring IMR in the same 12 STEMI patients and found a high correlation ($r$=0.99; $P<0.001$), with a mean difference between IMR measurements of 0.01 (mean standard error, 1.59; 95% confidence interval, −3.52 to 3.54; $P=0.48$). These studies demonstrate that although IMR requires manual injection of saline into the guiding catheter, the measurements are remarkably reproducible both between operators and by the same operator, even at different time points.

**Pitfalls of IMR Measurement**

IMR in its simplest form is independent of epicardial coronary stenosis unless a significant epicardial narrowing is present, in which case IMR can be falsely elevated. This is because IMR is defined as change in pressure across the microvasculature divided by myocardial flow, with myocardial flow consisting of both coronary flow and collateral flow. However, $T_{mn}$ is an estimate of coronary flow alone. In the absence of significant epicardial stenosis, most of myocardial flow is accounted for by coronary flow. In the presence of a severe epicardial stenosis (FFR<0.75), collateral flow contributes to a greater degree, and if one does not account for it, the denominator in the calculation of resistance will be underestimated and resistance will be overestimated. By measuring the coronary wedge pressure ($P_{w}$) during balloon inflation, an estimate of collateral flow, and by incorporating it into a more complex formula for IMR, IMR remains stable in the presence of increasing epicardial stenosis severity both in an experimental model$^{23}$ but also in humans.$^{29,31}$

$$IMR = \frac{Pa \times T_{mn} Hyp \times (P_d - P_w)}{Pa - P_w}$$

Recently, Yong et al$^{32}$ described a method to estimate IMR without needing the coronary wedge pressure measurement.
in the presence of significant epicardial stenosis, which showed excellent correlation and agreement with true IMR (IMR with the coronary wedge pressure incorporated).

\[
\text{Calculated IMR} = \text{Pa} \times \text{TmnHyp} \times \left(1.35 \times \frac{\text{Pd}}{\text{Pa}} - 0.32\right)
\]

Fortunately, in most cases in which IMR is being measured, significant epicardial disease is not present, and the simple formula for IMR can be applied.

There are some other potential pitfalls of IMR measurement, which should be considered. First, achieving maximal hyperemia is necessary to accurately measure the minimum achievable resistance. Second, to obtain accurate coronary pressures and Tmn, wedging of the guide catheter or using a guide catheter with side holes should be avoided. A 6F guide catheter is recommended because the accuracy of IMR using a smaller guide catheter has not been fully investigated. Third, Tmn can be influenced by the distance of the thermistor from the ostium of the coronary artery; in general, 1 or 2 centimeters has little effect, but movement of the sensor >2 centimeters may affect the Tmn measurement. Finally, some operators can become frustrated with the apparent variability in transit times produced with each injection of room-temperature saline. The greatest variability occurs with resting measurements, which are not necessary for IMR calculation. The hyperemic measurements have less variability, and with consistent technique, reproducible IMR values can be achieved.

**Clinical Applications of IMR**

**STEMI**

IMR was initially validated in the setting of acute coronary syndrome. In a small study involving 29 patients undergoing primary PCI for STEMI, IMR was measured immediately after successful PCI. IMR correlated significantly with the peak creatine kinase (\(R=0.61; P=0.0005\)) and with 3-month echocardiographic wall motion score (\(R=0.59; P=0.002\)), whereas the TIMI myocardial perfusion grade, corrected TIMI frame count, CFR, and ST-segment resolution on the ECG did not. Furthermore, on multivariate analysis, IMR was the strongest predictor of peak CK and 3-month wall motion score on the echocardiogram.\(^{33}\) Patients with a low IMR (below the median value of 32) had significant improvement in their wall motion score from baseline to 3-month echocardiogram, whereas patients with elevated IMR (indicative of significant microvascular damage) did not have improvement in their wall motion score, despite similar medical treatment. Subsequent studies by other groups have confirmed the ability of IMR to predict recovery of left ventricular function after...
primary PCI for STEMI and correlate with other noninvasive measures of left ventricular function, such as fludeoxyglucose positron emission tomography (CMR),16,27,35–40 while showing remarkably similar mean and median values of IMR in this setting.15,34,41 Studies correlating IMR and noninvasive imaging are summarized in Table 2.

IMR has also been shown to predict clinical outcome after STEMI. A large, international multicenter registry including 253 patients in whom IMR was measured immediately after primary PCI for STEMI found that patients with an IMR up to the mean value of 40 had significantly lower rates of death or rehospitalization for congestive heart failure (P=0.030) and death alone (P=0.018) at a median follow-up of 2.8 years (Figure 3). On multivariable analysis, IMR was an independent predictor of the composite of survival or rehospitalization for congestive heart failure, as well as survival alone. Other conventional invasive methods for assessing the microvasculature (CFR, TIMI myocardial perfusion grade, and corrected TIMI frame count) were not significant predictors.15 Carrick et al16 extended these findings in a cohort of 283 patients with STEMI who had IMR measured immediately after primary PCI, followed by CMR at day 2 and at 6 months. IMR was a significant independent predictor of myocardial hemorrhage

Table 2. Relationship of IMR/Thermodilution-Derived CFR Immediately After ST-Segment–Elevation Myocardial Infarction and Noninvasive Imaging

<table>
<thead>
<tr>
<th>Modality</th>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Finding</th>
<th>IMR</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography</td>
<td>Fearon et al15</td>
<td>J Am Coll Cardiol</td>
<td>2008</td>
<td>Correlation with WMS at 3 mo</td>
<td>r=−0.59, P=0.002</td>
<td>r=−0.35, P=NS</td>
</tr>
<tr>
<td></td>
<td>Lim et al14</td>
<td>Eur Heart J</td>
<td>2009</td>
<td>AUC to predict wall motion recovery at 6 mo</td>
<td>AUC=0.89, P&lt;0.05*</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Yoo et al12</td>
<td>J Korean Med Sci</td>
<td>2012</td>
<td>Predictor of WMS index improvement at 6 mo</td>
<td>Multivariate predictor</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Fearon et al15</td>
<td>Circulation</td>
<td>2013</td>
<td>Correlation with ejection fraction during the initial hospitalization</td>
<td>r=−0.31, P&lt;0.001</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Park et al13</td>
<td>Coron Artery Dis</td>
<td>2016</td>
<td>Predictor of WMS index improvement at 3 mo</td>
<td>Univariate predictor</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Palmer et al41</td>
<td>J Interv Cardiol</td>
<td>2016</td>
<td>Correlation with WMS score at 3 mo</td>
<td>r=0.65, P=0.005</td>
<td>r=−0.16, P=NS</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Lim et al14</td>
<td>Eur Heart J</td>
<td>2009</td>
<td>Correlation with regional myocardial FDG uptake at 8 d</td>
<td>r=−0.74, P&lt;0.001</td>
<td>Not reported</td>
</tr>
<tr>
<td>CMR</td>
<td>McGeoch et al43</td>
<td>JACC Cardiovasc Interv</td>
<td>2010</td>
<td>Predictor of infarct volume at 2 d and ejection fraction at 3 mo</td>
<td>Multivariate predictor</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Yoo et al42</td>
<td>J Korean Med Sci</td>
<td>2012</td>
<td>Correlation with the extent of MVO at 4–7 d</td>
<td>r=−0.75, P&lt;0.001</td>
<td>r=−0.37, P=0.03</td>
</tr>
<tr>
<td></td>
<td>Payne et al27</td>
<td>J Am Heart Assoc</td>
<td>2012</td>
<td>Predictor of early (2 d) and late (3 mo) myocardial salvage</td>
<td>Multivariate predictor</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Cuculi et al36</td>
<td>J Am Coll Cardiol</td>
<td>2014</td>
<td>Value between patients with vs without MVO at 1 d</td>
<td>42.9 vs 31.3, P=0.07</td>
<td>1.6 vs 2.3, P=0.02</td>
</tr>
<tr>
<td></td>
<td>Fukunaga et al37</td>
<td>Circ Cardiovasc Interv</td>
<td>2014</td>
<td>Value between patients with vs without MVO at 7 d</td>
<td>58.2 vs 28.8, P=0.002</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Ahn et al44</td>
<td>Yonsei Med J</td>
<td>2014</td>
<td>Value between patients with vs without MVO at 5 d</td>
<td>53.4 vs 21.5, P=0.02</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Patel et al38</td>
<td>JACC Cardiovasc Interv</td>
<td>2015</td>
<td>AUC to predict ejection fraction ≥50% at 6 mo</td>
<td>r=0.71, P=0.14</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Hoole et al39</td>
<td>Open Heart</td>
<td>2015</td>
<td>Value between patients with vs without MVO at 2 d</td>
<td>50.2 vs 24.6, P=0.01</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Ahn et al45</td>
<td>JACC Cardiovasc Interv</td>
<td>2016</td>
<td>AUC to predict MVO at 7 d</td>
<td>AUC=0.87, P=0.001</td>
<td>AUC=0.71, P=0.03</td>
</tr>
<tr>
<td></td>
<td>Carrick et al39</td>
<td>Circulation</td>
<td>2016</td>
<td>Predictor of myocardial hemorrhage, changes in LVEF, and LVEDV</td>
<td>Multivariate predictor</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Carrick et al40</td>
<td>JCI Insight</td>
<td>2016</td>
<td>Predictor of change in LVEDV</td>
<td>Multivariate predictor</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; CFR, coronary flow reserve; CMR, cardiac magnetic resonance imaging; FDG, fluorodeoxyglucose; IMR, index of microcirculatory resistance; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; NS, nonsignificant; PET, positron emission tomography; and WMS, wall motion score. Reprinted from JACC Cardiovasc Interv, Vol 9/Edition number 8, Fearon WF, Kobayashi Y, Invasive assessment of the coronary microcirculation, 802–804, 2016, with permission from American College of Cardiology.46 *P value was not reported in the article; however, 95% confidence interval 0.888–0.894 suggests AUC is significant.
Fearon and Kobayashi  Coronary Microvascular Assessment

IMR also predicted left ventricular ejection fraction at 6 months on CMR, independent of infarct size. IMR was a highly significant independent predictor of death or heart failure during a median follow-up of 845 days. The addition of CFR data did not provide incremental prognostic value to the IMR data alone.

Based on these findings, IMR may be a useful method for identifying patients who have not achieved successful reperfusion of the microvasculature after primary PCI for STEMI and are, therefore, at high risk for adverse outcome. It has the advantage of being immediately measurable, before biomarkers or noninvasive imaging data are available. This could allow for earlier administration of adjunctive therapy. For example, the effect of intracoronary streptokinase, intracoronary nicorandil, nitroprusside, and ticagrelor on IMR have all been investigated.47–50 Prospective, randomized controlled trials are ongoing to assess the impact of fibrinolytic and antiplatelet therapy on IMR and outcome in patients presenting with STEMI (T-TIME, NCT02257294 and REDUCE-MVI, NCT02422888).51

**Angina and Nonobstructive Coronary Artery Disease**

The scenario in which IMR may have its greatest clinical application is the patient presenting with angina or an abnormal stress test but nonobstructive coronary artery disease on invasive coronary angiography. Approximately 20% of these patients are found to have an elevated IMR, suggesting microvascular dysfunction as the source of angina in a significant minority of these patients (Figure 4).4 Another publication compared microvascular function in 18 patients with cardiac syndrome X with age- and sex-matched control subjects. Significantly more patients with syndrome X had an abnormal IMR or CFRThermo compared with control (IMR: 33.1±7.9 versus 18.8±5.6 and CFRThermo: 2.37±0.81 versus 3.68±0.72; \( P < 0.001 \) for both); however, IMR correlated more closely with disease severity as assessed by the Duke treadmill (IMR: \( r = -0.742, P < 0.001 \) and CFRThermo: \( r = 0.539, P = 0.021 \)).22 Lee et al, in a study of 313 patients with nonobstructive coronary artery disease based on a nonischemic FFR value, found that patients with microvascular dysfunction based on both an elevated IMR and reduced CFRThermo had worse outcome compared with those with preserved...
microvascular function. Of note, IMR alone was not predictive of outcomes in this study.52

Elective PCI
IMR has also been measured to assess the effect of a variety of adjunctive interventions at the time of elective PCI. For example, Mangiacapra et al demonstrated an intracoronary bolus injection of the angiotensin-converting enzyme inhibitor, enalaprilat before PCI significantly reduces post-PCI IMR compared with patients randomized to placebo, and results in significantly smaller increases in high-sensitivity troponin. The change in high-sensitivity troponin levels correlated significantly with IMR levels post-PCI.53 In a similar study, Fujii et al54 randomized 80 patients to pretreatment with pravastatin or with placebo and found that the pravastatin-treated patients had significantly lower IMR values and tended to have lower troponin levels post-PCI. Cuisset et al55 randomized 50 stable patients undergoing elective PCI to a direct stenting strategy or to a conventional strategy with balloon predilatation before stenting and found that direct stenting resulted in lower IMR and troponin values post-PCI. Those patients who had troponin elevation, regardless of stenting strategy had significantly higher post-PCI IMR values. Finally, Ng et al reported that a pre-PCI IMR of ≥27 was associated with a 23-fold risk of developing periprocedural myocardial infarction during elective PCI, suggesting that preexisting microvascular dysfunction results in less microvascular reserve and less ability to tolerate distal embolization of debris at the time of PCI. By measuring IMR before PCI, one might be able to identify patients at higher risk for periprocedural adverse events, and one might select alternative pharmacological or technical strategies.7

Heart Transplantation and Other Cardiomyopathies
Cardiac allograft vasculopathy is a leading cause of late mortality after heart transplantation. Cardiac allograft vasculopathy affects both the epicardial coronary arteries and the coronary microvasculature. For many years, the diagnosis of cardiac allograft vasculopathy has relied on assessing intimal thickening of the epicardial artery with intravascular ultrasound. More recently, invasive coronary physiology and, in particular, IMR have been used to assess the microvasculature after cardiac transplantation.56–59 IMR served as the reference standard for microvascular dysfunction because of cardiac allograft vasculopathy in 1 study testing the diagnostic accuracy of CMR in transplant recipients.60 Yang et al61 found in 74 cardiac transplant recipients followed for an average of 4.5 years that IMR measured at 1 year after heart transplantation was an independent predictor of long-term mortality or the need for retransplantation, whereas intravascular ultrasound parameters were not (Figure 5). IMR has also been found to be useful for testing adjunctive pharmacology in this population. For example, a recent study randomized 96 transplant patients to ramipril or placebo and found that IMR improved from baseline to 1 year in the ramipril arm (21.4±14.7 versus 14.4±6.3; P<0.001) but did not change in the placebo arm (17.4±8.4 versus 21.5±20.0; P=0.72), suggesting that ramipril might have long-term clinical benefit in this population.62 Finally, IMR has been used to assess the success of cell therapy for cardiomyopathies63 and clarify the pathophysiology in Takotsubo cardiomyopathy64,65 and hypertrophic cardiomyopathy.66

Other Invasive Methods for Assessing Microvascular Resistance
The hyperemic microvascular resistance is another method for assessing the minimal achievable microvascular resistance using a dual sensor Doppler flow and pressure wire (Philips/Volcano) and should be as equally applicable but has
not been as well studied as IMR. It has been evaluated in a similar manner to IMR after primary PCI for STEMI and found to correlate with noninvasive measures of microvascular dysfunction. The main limitation of this technique has been the technical challenges related to the Doppler velocity measurements.

Conclusions
Our ability to relatively easily and reliably assess invasively the coronary microvasculature in the catheterization laboratory has improved significantly. FFR and IMR can be measured simultaneously in <5 minutes, allowing the operator to determine whether or not inducible ischemia is present and to independently interrogate the epicardial coronary conduit (FFR) and the microvasculature (IMR) to decide whether epicardial artery revascularization will be beneficial. A recent survey among European centers of excellence found that IMR is measured routinely in 50% of these centers for daily clinical decision making. More data regarding the beneficial effects of therapy aimed specifically at the microvasculature are necessary to further broaden the adoption of this strategy.

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