Invasive Coronary Microcirculation Assessment
– Current Status of Index of Microcirculatory Resistance –

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Assessment of the coronary microvasculature in the clinical setting is a key issue, given that microvascular dysfunction itself has a predictive value for cardiovascular events. The index of microcirculatory resistance (IMR) is an invasive method of interrogating the microvasculature and provides further insight into the physiology of cardiovascular diseases. It is simple and readily applicable in the cardiac catheterization laboratory where many patients first present for evaluation of their coronary circulation. In contrast to other invasive and non-invasive tests, this method is known to be stable and reproducible under various hemodynamics and even in the presence of epicardial coronary artery stenosis. IMR has been shown to have prognostic value in patients with ST-segment elevation myocardial infarction; therefore it can be a surrogate marker of cardiovascular events. At the same time, it has the potential to be a therapeutic as well as an investigational tool in the physiology of cardiovascular diseases. This review summarizes the development of IMR, tips and tricks for its measurement, and its usefulness in various clinical settings. (Circ J 2014; 78: 1021–1028)

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Recent studies have demonstrated the importance of the coronary microvasculature in various clinical settings and in the development of non-invasive tests for assessing it, including Doppler echocardiography, contrast echocardiography, cardiovascular magnetic resonance, and positron emission tomography. However, conventional invasive parameters for assessing the microvasculature such as coronary flow reserve (CFR), Thrombolysis In Myocardial Infarction (TIMI) flow grade, corrected TIMI frame count, and TIMI myocardial perfusion grades have important limitations, including their dependence on resting hemodynamics, semiquantitative nature, and lack of independence of the epicardial vessel. For these reasons, it became important to develop an invasive method for independently, quantitatively and reproducibly assessing the microvasculature, which is predictive of outcomes in various settings.

Against this background and with the development of a thermodilution technique for estimating coronary flow while simultaneously measuring coronary pressure, the index of microcirculatory resistance (IMR) was first described just over 10 years ago. This method enables investigation of the coronary microvasculature directly with high reproducibility and reliability in the cardiac catheterization laboratory where many patients in the USA first present for evaluation of their coronary circulation. This review discusses the development of IMR, tips and tricks for its measurement, and its usefulness in various clinical settings.

Development of IMR Theory

The technological advance of the coronary pressure wire enabled simultaneous measurement of coronary artery pressure and coronary artery flow. With commercially available software, the pressure sensor of the wire acts as a distal thermistor, while 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 (Figure 1).

De Bruyne and Pijls et al applied the thermodilution technique in an experimental model and found a strong correlation between the inverse of Tmn and absolute coronary flow. They also showed that the thermodilution-derived coronary flow reserve (CFRthermo), defined as the resting mean transit time (TmnRest) divided by the hyperemic mean transit time (TmnHyp), correlated well with the standard CFR, both in their experimental model and in humans.

Fearon et al further elucidated the usefulness of CFRthermo in open-chest porcine models. Using an ultrasonic flow probe placed around the proximal left anterior descending coronary artery (LAD) and a vascular occluder placed distal to the flow probe, the resting and hyperemic absolute coronary flow could be measured at baseline and after creation of an epicardial stenosis. CFRthermo showed better correlation with the absolute coronary flow-derived CFR than the Doppler velocity-derived CFR, which further validated the thermodilution technique as a method of estimating coronary flow.
The derivation of IMR is based on Ohm’s law (the potential difference across an ideal conductor is proportional to the current through the conductor) applied to the coronary microcirculation. IMR is defined as the mean distal coronary pressure (Pd) minus venous pressure divided by flow. Because venous pressure is generally negligible relative to distal coronary pressure, it is ignored. Because flow is inversely proportional to the mean transit time, IMR is therefore defined as Pd divided by the inverse of the mean transit time or as Pd multiplied by Tmn\text{Hyp} (Figure 2). Because the IMR incorporates only hyperemic parameters, it eliminates the variability of resting vascular tone and hemodynamics and estimates the minimum achievable microvascular resistance.

Using the same porcine model, the true microvascular resistance (defined as Pd divided by the absolute coronary flow measured with a flow probe around the LAD [mmHg · ml⁻¹ · min⁻¹] at hyperemia) was compared with IMR (defined as Pd×Tmn\text{Hyp} [mmHg · s or units]) at baseline and after disruption of microcirculation. The IMR and true microvascular resistance correlated significantly, as did the percent change from baseline to after disruption of the microcirculation.⁶

**Advantage of IMR Compared With CFR**

**Hemodynamic Stability**

As previously described,¹²,¹³ CFR is affected by hemodynamic changes because of the resting parameter included in its formula. IMR has shown superior reproducibility and less hemodynamic dependence in humans under several hemodynamic perturbations including rapid ventricular pacing, intravenous nitroprusside infusion, and intravenous dobutamine infusion.¹⁴

**Effect of Epicardial Stenosis**

CFR interrogates the entire coronary circulation and is therefore affected by both epicardial stenosis and microvascular dysfunction.¹³ IMR, calculated in its simplest form, is falsely elevated in the presence of significant epicardial stenosis, because Tmn is a measurement of coronary flow alone. In the presence of a severe epicardial stenosis, both coronary flow and collateral flow contribute to overall myocardial flow, and if one does not account for collateral flow, the denominator in the calculation of resistance will be underestimated and resistance will be overestimated. However, when collateral flow is taken into account by incorporating the coronary wedge pressure into a more complex formula (Figure 2B), IMR remains stable in the presence of increasing epicardial stenosis severity both in an experimental model¹⁵ and humans.¹⁶–¹⁸ Recently, Yong et al described a method of estimating IMR without coronary wedge pressure measurement (calculated IMR: IMR\text{calc}) in the presence of significant epicardial stenosis, and showed excellent correlation and agreement with true IMR (IMR\text{true}).¹⁹ Details of IMR measurement in the presence of epicardial stenosis will be discussed later.

**Standard Measurement Technique of IMR**

In this section, specific measurement methods and pitfalls of IMR are discussed.

As in conventional interventional therapy, systemic administration of heparin (50–100IU/kg) and intracoronary nitroglycerin (100–200μg) is necessary before the procedure. A coronary pressure-temperature sensor guide wire (Certus Pressure Wire, St. Jude Medical, St. Paul, MN, USA) is calibrated, equalized to the guide catheter pressure with the pressure wire sensor positioned at the tip of the catheter, and advanced to the distal two-thirds of the target vessel. Next, 3ml of room-temperature saline are briskly injected through the guide catheter. With commercially available software (Radi Analyzer, St. Jude Medical), the transit time of the room-temperature saline injected into a coronary artery can be automatically determined with a ther-
Assessment of Microcirculation Using IMR

Figure 2.  (A) Understanding the index of microcirculatory resistance (IMR) based on Ohm’s law (the potential difference across an ideal conductor is proportional to the current through it). In this image, the potential difference is \( P_d - P_v \), the conductor is microcirculatory resistance, and the current is myocardial flow. \( P_d \gg P_v \) Coronary flow strongly correlates the inverse of mean transit time. \[ \text{Index of Microcirculatory Resistance (IMR)} = P_d \times \text{hyperemic mean transit time} \]

(B) IMR formula in the presence of a severe epicardial stenosis. Collateral flow is taken into account by incorporating the coronary wedge pressure \( P_w \) into a more complex formula. \( P_a \), mean proximal coronary pressure; \( P_d \), mean distal coronary pressure; \( P_v \), mean central venous pressure; \( P_w \), coronary wedge pressure; RA, right atrium.

\[ \text{Coronary wedge pressure (P}_w\text{)} \text{ should be measured to take collateral flow into account.} \]

\[ \text{IMR} = P_a \times \text{hyperemic mean transit time} \times \left( \frac{P_d - P_w}{P_a - P_w} \right) \]
Figure 3. Schematic of physiological assessment using a single coronary pressure wire. CFR_{thermo}, thermodilution-derived coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; P_a, mean proximal coronary pressure; P_d, mean distal coronary pressure; T_{mn,Hyp}, hyperemic mean transit time; T_{mn,Rest}, resting mean transit time.

- FFR = P_d / P_a at maximal hyperemia
- CFR_{thermo} = T_{mn,Hyp} / T_{mn,Rest}
- IMR = P_d \times T_{mn,Hyp}

Figure 4. Example of physiologic assessment using a pressure wire. CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; P_a, mean proximal coronary pressure; P_d, mean distal coronary pressure; T_{mn,Hyp}, hyperemic mean transit time; T_{mn,Rest}, resting mean transit time.

IMR = P_d \times T_{mn,Hyp} = 76 \times 0.26 = 19.8
Assessment of Microcirculation Using IMR

follows:

\[ \text{IMR} = P_d \times T_{\text{mn Hyp}} = 76 \times 0.26 = 19.8. \]

The normal range of IMR is generally thought to be <25, based on a study by Melikian et al demonstrating a mean IMR value of 19±5 (range 8–28) in a small, healthy control group. Luo et al reported a similar mean IMR value of 18.9±5.6 in a small control group referred for coronary angiography but with completely normal angiographic findings.

**IMR Measurement in the Presence of Epicardial Stenosis**

As previously discussed, the simple formula for IMR can overestimate microvascular resistance in the presence of a significant epicardial stenosis because collateral flow is not taken into account. In such cases, coronary wedge pressure (Pw) during modulation technique (Figure 1). After repeating the injection of saline 3 times, the resting mean transit time (T_{\text{mn Rest}}) can be calculated from the average transit time of the 3 injections. Maximal hyperemia is then induced by infusing intravenous adenosine (140 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\)) or by injecting intracoronary papaverine (10–20 mg). During maximal hyperemia, T_{\text{mn Hyp}} is measured again as has been described. Together with the T_{\text{mn Hyp}} measurement, P_d measured simultaneously with the same pressure wire and P_a measured with the guide catheter are automatically recorded during maximal hyperemia.

Fractional flow reserve (FFR) is defined as P_d divided by P_a during maximal hyperemia, CFR_{\text{thermo}} is defined as T_{\text{mn Hyp}} divided by T_{\text{mn Rest}}, and IMR is defined as P_d multiplied by T_{\text{mn Hyp}} (Figure 3). Figure 4 shows an example of physiologic assessment. In this particular case, IMR is calculated as

**Figure 5.** (A) Kaplan-Meier curves displaying the relationship between IMR and survival free of death or rehospitalization for heart failure after primary PCI for STEMI. (B) Kaplan-Meier curves displaying the relationship between IMR and survival free of death after primary PCI for STEMI. IMR, index of microcirculatory resistance; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
balloon inflation should be measured. Then, IMRtrue can be obtained using the following more complex formula:

\[ IMR_{true} = P_a \times T_{true} \times H_{Hyp} \times \left( \frac{P_d - P_w}{P_a - P_w} \right) \]

A recent study described a simple method of calculating IMR without measuring coronary wedge pressure in the presence of significant epicardial stenosis. IMRcalc is obtained using the following formula:

\[ IMR_{calc} = P_a \times T_{true} \times H_{Hyp} \times \left( 1.35 \times P_d / P_a - 0.32 \right) \]

**Pitfalls of IMR Measurement and Interpretation**

There are several pitfalls of IMR measurement. First, a characteristic of the IMR is its independence of resting hemodynamic parameters. To maximize this characteristic, care must be taken to ensure maximal hyperemia (drug type, dose, infusion route, contraindication for drug etc.).

Second, to obtain accurate coronary pressures and \( T_{true} \), wedging of the guide catheter and using a guide catheter with side holes should be avoided. A 6Fr guide catheter is generally recommended, because the accuracy of the IMR using a smaller guide catheter has not been fully evaluated.

Third, the pressure wire should be advanced to the distal two-thirds of the target coronary artery and kept in the same position during repeated measurement, because \( T_{true} \) can be influenced by the distance of the thermistor from the ostium of the coronary artery.

**IMR Measurement in STEMI or Stable Patients Undergoing PCI, and in Patients With Angina and Normal-Appearing Coronary Arteries**

In this section, IMR measurement in ST-segment elevation myocardial infarction (STEMI) or stable patients undergoing percutaneous coronary intervention (PCI), and in patients with angina and normal-appearing coronaries will be discussed separately.

**STEMI**

The IMR can be readily and safely measured after primary PCI in patients with STEMI. In the first study examining IMR in this setting, patients with an IMR below the median value of 32 had significantly lower peak creatine kinase (CK) concentrations and improved echocardiography-derived wall motion scores at 3 months. A second study performed in South Korea found similar results with an optimal cutoff value of 33 for predicting LV wall motion recovery based on PET and echo imaging. Another study from Scotland reported that the IMR was significantly higher in patients with microvascular obstruction detected by contrast-enhanced cardiac magnetic resonance than in patients without microvascular obstruction (27 [interquartile range (IQR) 18–36] without microvascular obstruction vs. 38 [IQR 29–55] with microvascular obstruction). Recently, a large multicenter registry including 253 patients in whom the IMR was measured immediately after primary PCI for STEMI found that patients with an IMR ≤ the mean value of 40 had significantly lower rates of death or rehospitalization for congestive heart failure and death alone (Figure 5). It was also shown in multivariate analysis that the IMR was an independent predictor of both survival alone and survival or rehospitalization for congestive heart failure, whereas other common invasive methods for assessing microvasculature (CFR, TIMI myocardial perfusion grade and TIMI frame count) were not. Beneficial effects of adjunctive therapy to improve microvascular dysfunction assessed by the IMR were described by Ito et al (intracoronary nicorandil [2 mg]) and Camici et al (intracoronary streptokinase [250 kIU]). Another study showed the effectiveness of using a distal protection device (Filtrap, Nipro, Japan) to minimize microvascular damage during primary PCI at the time of STEMI.

An important aspect of IMR measurement in this setting is that STEMI patients can be stratified immediately after primary PCI. Therefore, operators do not have to postpone a decision regarding adjunctive therapy until other clinical markers (eg, peak CK) can be obtained.

**Stable Patients Undergoing PCI**

Beneficial effects of adjunctive therapy to improve the IMR were also shown in stable patients undergoing PCI. Mangiacapra et al demonstrated that an intracoronary bolus injection of angiotensin-converting enzyme inhibitor (enalaprilat [50 μg]) before PCI could result in a significant reduction in the post-procedural IMR. Another study described that pretreatment with HMG-CoA reductase inhibitors (pravastatin [20 mg/day]) was associated with reduced microvascular dysfunction induced by PCI regardless of side branch occlusions. Regarding the detection of high-risk plaque causing microvascular dysfunction, Yamada et al found that target lesion thin-cap fibroatheroma detected by virtual histology intravascular ultrasound may be related to a high IMR after PCI. Cuisset et al showed, even in stable angina patients, that a direct stenting strategy led to a lower post-PCI IMR value compared with conventional stenting with predilation. In addition to those findings, Ng et al reported that a pre-PCI IMR ≥27 was associated with a 23-fold risk of developing periprocedural MI during elective PCI; therefore, the pre-PCI IMR can predict the subsequent risk of periprocedural myocardial necrosis by determining susceptibility and may guide adjunctive prevention strategies.

**Patients With Angina and Normal-Appearing Coronary Arteries**

Diagnosis of the source of angina in patients with normal coronary arteries is challenging. Lee et al recently reported their results of a thorough invasive assessment including assessment of endothelial function and performance of intravascular ultrasound, FFR, CFR\_thermo and IMR measurements in 139 patients with angina without angiographic epicardial disease. Microvascular dysfunction (IMR ≥25) was present in 29 patients (20.9%), suggesting that microvascular dysfunction is the source of angina in a significant minority of these patients. There is another publication in which the microvascular function of cardiac syndrome X patients was compared with that of age- and sex-matched control subjects. Although the IMR and CFR\_thermo revealed significantly worse microvasculature than in the controls (IMR 33.1±7.9 vs. 18.8±5.6, and CFR\_thermo 2.37±0.81 vs. 3.68±0.72, \( P<0.001 \) for both), the correlation with disease severity assessed by Duke treadmill score was better with the IMR than with CFR\_thermo (IMR \( r=0.742, P<0.001; \) CFR\_thermo \( r=0.539, P=0.021 \)).

**Application of IMR in Other Clinical Settings**

The contribution of abnormal microvasculature to various cardiovascular diseases can be clarified by measuring the IMR.

**Transplant Arteriopathy**

The IMR can be measured to interrogate the microvasculature in orthotopic heart transplant recipients. Hirohata et al dem-
onstrated progression of epicardial cardiac allograft vasculopathy on early follow-up, with subsequent spread to the microcirculation on later follow-up, after heart transplantation (IMR 24.1±14.3 for early group vs. 29.4±18.8 for later group, P=0.05). The IMR was also measured to demonstrate the beneficial effect of the immunosuppressant, rapamycin, in this patient population.

**Takotsubo Cardiomyopathy (Ampulla Cardiomyopathy)**

The IMR has been measured to assess acute hemodynamics in takotsubo cardiomyopathy. They reported a substantial decrement of the IMR from 44.9±24.4 to 21.2±14.1 (P=0.001) during 6-month follow-up and also found improvement in coronary collateral vessel formation, resulting from myocardial regeneration.

We have summarized what is currently known about the IMR. It is important to note that IMR studies have been mainly performed in the LAD, otherwise focused on serial changes with intervention in the respective arteries. Therefore, care must be taken when extrapolating the results of these studies to daily clinical practice and clinical decision-making.

**Conclusions**

The IMR is a simple and readily applicable method of assessing microvascular function during cardiac catheterization. It is useful for stratifying STEMI patients, as well as for assessing the effect of adjunctive therapy. Furthermore, it can predict periprocedural MI and assess the effect of therapeutic interventions in stable patients undergoing PCI. Finally, it has been shown to help diagnose the etiology of chest pain in patients with normal-appearing coronary arteries. Future studies will be needed to determine whether a high IMR should trigger a particular therapeutic intervention to improve outcome.

**Conflict of Interest Disclosures**

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**References**


