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Calculation of the Index of Microcirculatory Resistance Without Coronary Wedge Pressure Measurement in the Presence of Epicardial Stenosis

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Objectives This study sought to investigate a novel method to calculate the index of microcirculatory resistance (IMR) in the presence of significant epicardial stenosis without the need for balloon dilation to measure the coronary wedge pressure (P_w).

Background The IMR provides a quantitative measure of coronary microvasculature status. However, in the presence of significant epicardial stenosis, IMR calculation requires incorporation of the coronary fractional flow reserve (FFR_{cor}), which requires balloon dilation within the coronary artery for P_w measurement.

Methods A method to calculate IMR by estimating FFR_{cor} from myocardial FFR (FFR_{myo}), which does not require P_w measurement, was developed from a derivation cohort of 50 patients from a single institution. This method to calculate IMR was then validated in a cohort of 72 patients from 2 other different institutions. Physiology measurements were obtained with a pressure-temperature sensor wire before coronary intervention in both cohorts.

Results From the derivation cohort, a strong linear relationship was found between FFR_{cor} and FFR_{myo} ($FFR_{cor} = 1.34 \times FFR_{myo} - 0.32$, $r^2 = 0.87$, $p < 0.001$) by regression analysis. With this equation to estimate FFR_{cor} in the validation cohort, there was no significant difference between IMR calculated from estimated FFR_{cor} and measured FFR_{cor} (21.2 ± 12.9 U vs. 20.4 ± 13.6 U, $p = 0.161$). There was good correlation ($r = 0.93$, $p < 0.001$) and agreement by Bland-Altman analysis between calculated and measured IMR.

Conclusions The FFR_{cor}, and, by extension, microcirculatory resistance can be derived without the need for P_w. This method enables assessment of coronary microcirculatory status before or without balloon inflation, in the presence of epicardial stenosis. (J Am Coll Cardiol Intv 2013;6:53–8) © 2013 by the American College of Cardiology Foundation

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Recent studies have highlighted the importance of assessing the coronary microcirculation in various settings (1–6). However, most of the currently available methods to assess the coronary microcirculation are dependent on exclusion of concurrent coronary epicardial disease (1–4).

The index of microcirculatory resistance (IMR) is a pressure-temperature sensor guidewire-based measurement, performed during cardiac catheterization, of the minimum microcirculatory resistance in a target coronary artery territory (7). It provides a specific quantitative method to assess the coronary microvasculature in the clinical setting (8–11).

In the absence of significant coronary epicardial disease, the IMR can be derived by a simplified formula for the apparent IMR (IMR_{app}), which is equivalent to the distal coronary pressure divided by coronary flow. This formula assumes that coronary flow is equivalent to myocardial flow and that collateral flow is negligible (7). In the presence of significant epicardial stenosis, collateral flow contributes substantially to myocardial flow, while coronary flow decreases. Distal coronary pressure will decrease to a lesser degree, given that it will be augmented by the collateral flow. Therefore, the IMR_{app} will overestimate microcirculatory resistance in the presence of significant epicardial stenosis (12–15).

Abbreviations and Acronyms

- FFR_{cor} = coronary fractional flow reserve
- FFR_{myo} = myocardial fractional flow reserve
- IMR = index of microcirculatory resistance
- IMR_{app} = apparent index of microcirculatory resistance
- IMR_{calc} = calculated index of microcirculatory resistance
- P_a = proximal arterial pressure
- PCI = percutaneous coronary intervention
- P_d = distal arterial pressure
- P_w = coronary wedge pressure
- T_{mn} = transit time during hyperemia

Calculation of the IMR in the presence of significant epicardial stenosis is possible but requires additional measurement of the coronary wedge pressure (P_w) during balloon inflation to account for collateral flow in an expanded formula for the true IMR (12–15). This means that IMR measurement in this setting requires balloon inflation within the coronary arteries. Therefore, IMR measurement in patients with epicardial stenosis has generally been restricted to only those who are undergoing percutaneous coronary intervention (PCI). In this current study, we aimed to develop a method to calculate the IMR without the need for wedge pressure measurement, because this could enable specific interrogation of the microcirculation in the presence of significant epicardial disease in the cardiac catheterization before or without performing PCI.

Methods

Formula derivation. True IMR, in the presence of epicardial stenosis, can be calculated by the formula $IMR = P_a \times T_{mn} \times ([P_d - P_w]/[P_a - P_w])$, where P_a = mean proximal coronary pressure, T_{mn} = mean hyperemic transit time, and P_d = mean distal coronary pressure (16). The terminal part of the formula ($[P_d - P_w]/[P_a - P_w]$) is also known as the coronary fractional flow reserve (FFR_{cor}), which refers to the ratio of maximal blood flow in the target coronary artery to the hypothetical maximal blood flow in the same territory if there was no stenosis (17). This is distinct from the FFR commonly used in clinical practice, the myocardial FFR ($FFR_{myo} = P_d/P_a$), which represents the ratio of maximal blood flow in the target myocardium to the hypothetical maximal blood flow in the same territory as if there was no stenosis (18,19). We hypothesized that FFR_{cor} is associated with FFR_{myo} in a mathematically predictable relationship. We sought to determine the mathematical relationship between FFR_{cor} and FFR_{myo} in a derivation cohort. With this relationship to calculate the FFR_{cor} without P_w measurement in a separate validation cohort, the accuracy of calculated IMR (IMR_{calc}) without P_w measurement was examined.

Study population. The relationship between FFR_{myo} and FFR_{cor} was investigated in 50 consecutively recruited patients from a tertiary referral hospital, who formed the derivation cohort. The validation cohort comprised 72 patients who underwent PCI from 2 separate tertiary institutions. Patients undergoing elective PCI for stable angina or unstable angina were included in the study for both derivation and validation cohorts. Patients with recent myocardial infarction or previous infarction in the territory of interest were excluded from this study. The study was approved by the human research ethics review boards of the respective institutions. Written informed consent was obtained from all participants.

Coronary physiology measurements. For both the derivation and validation cohorts, coronary physiology measurements were performed before PCI as we have previously described (8,13,20). In brief, a 6-F angioplasty guiding catheter without side-holes was first used to engage the left main coronary artery. A pressure-temperature sensor guidewire (Certus Pressure Wire, St. Jude, St. Paul, Minnesota) was used for physiology measurements and PCI. Pressure measurement from the wire was first equalized with that of the guiding catheter. The lesion was crossed, and the pressure sensor was positioned two-thirds of the way down the artery, at least 3 cm beyond the lesion. Intracoronary nitroglycerin was administered (100 to 200 μg). Hyperemia was induced with adenosine infusion (140 μg/kg/min) via the femoral vein. The P_a, P_d, and T_{mn} were recorded. Patients then underwent PCI, and P_w was recorded during the first balloon inflation.

Statistical analysis. Results are expressed as mean ± SD unless otherwise stated. Linear and nonlinear regression analyses were used to determine the relationship between 2 variables. To obtain the regression formula of best fit, curves of increasing complexity starting from a straight line were tested against one another with the F test. Independent *t* tests were used to compare variables between patient cohorts, and Fisher exact test was used to compare categorical variables. Paired *t* tests were used to compare the different

methods to calculate IMR. Pearson's correlation analyses were used to evaluate associations between variables, and Bland-Altman analyses were used to test for agreement. All formal statistical analyses were performed with SPSS (version 15, SPSS, Chicago, Illinois). Figures and graphs were generated with Prism (version 5.01, Graphpad, La Jolla, California). A 2-tailed p value of <0.05 is considered significant.

Results

Population characteristics. A comparison of the clinical characteristics between the derivation and validation cohorts is shown in Table 1. Compared with the derivation cohort, the validation cohort had higher estimated glomerular filtration rate, higher FFR_{myo}, and fewer number of anterior descending artery lesions. The differences between the patient groups in the 2 institutions of the validation cohort are shown in Online Table 1.

Derivation of method to calculate IMR without the wedge pressure. There was a strong linear relationship between FFR_{cor} and FFR_{myo} in the derivation cohort, and FFR_{cor} could be predicted by the Equation $1.34 \times FFR_{myo} - 0.32$ ($r^2 = 0.87$, $p < 0.001$) (Fig. 1). The equation for a straight line was a better fit compared with more complex nonlinear equations, including exponential and second order polynomial equations.

Table 1. Baseline Clinical Characteristics in the Derivation and Validation Cohorts

Variable	Derivation Cohort (n = 50)	Validation Cohort (n = 72)	p Value
Age, mean yrs	62.0 ± 10.2	61.9 ± 11.2	0.945
Male	37 (74)	59 (82)	0.493
Body mass index	28.6 ± 5.4	28.7 ± 4.5	0.915
Comorbidities			
Diabetes	10 (20)	20 (28)	0.519
Hypertension	31 (62)	52 (72)	0.423
Dyslipidemia	32 (64)	53 (74)	0.421
Family history	15 (30)	22 (31)	1.000
History of smoking	23 (46)	35 (49)	0.848
eGFR, ml/min/1.73 m^2	83.5 ± 18.6	100.5 ± 37.8	0.001
Coronary physiology measurements			
Myocardial fractional flow reserve	0.57 ± 0.16	0.67 ± 0.18	0.002
IMR, U	23.2 ± 13.8	20.4 ± 13.6	0.282
Coronary wedge pressure, mm Hg	17.7 ± 9.3	17.8 ± 8.6	0.920
Target territory			
Left anterior descending	41 (82)	41 (57)	
Left circumflex	4 (8)	20 (28)	0.011
Right coronary artery	5 (10)	11 (15)	
Indication			
Stable angina	35 (70)	68 (94)	0.001
Unstable angina	15 (25)	4 (6)	

Values are mean ± SD or n (%).
eGFR = estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula; IMR = index of microcirculatory resistance.

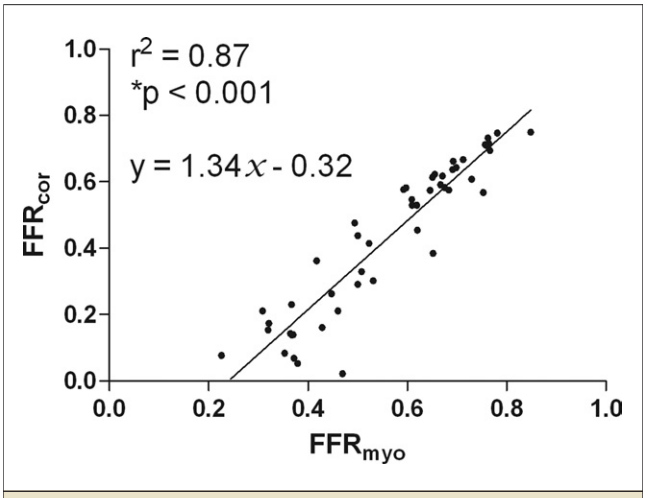

Figure 1. Linear Regression of FFR_{cor} Versus FFR_{myo} in the Derivation Cohort

Solid line and formula shown were derived from the linear regression. The r^2 represents the fit of the regression model, and p value reflects significance of the fit. FFRcor = coronary fractional flow reserve; FFRmyo = myocardial fractional flow reserve.

Validation of method to calculate IMR without the wedge pressure. In the validation cohort, there was no significant difference between measured and calculated FFR_{cor} (0.56 ± 0.25 vs. 0.57 ± 0.24, p = 0.090). There was also good correlation (r = 0.96, p < 0.001) and agreement between the 2 variables (Fig. 2).

The IMR_{calc} was derived with the calculated FFR_{cor} in the validation cohort. There was no significant difference between true IMR and IMR_{calc} (20.4 ± 13.6 U vs. 21.2 ± 12.9 U, p = 0.161) (Fig. 3A). There was good correlation (r = 0.93 p < 0.001) and agreement between true IMR and IMR_{calc} (Figs. 3B and 3C). Figure 3C also demonstrates that IMR_{calc} deviated from true IMR when FFR_{myo} was <0.45. The FFR_{myo} was ≥0.45 in 76.2% of the whole cohort, 72.0% of the derivation cohort, and 80.6% of the validation cohort, respectively.

In contrast to IMR_{calc}, IMR_{app} was significantly higher compared with the true IMR (Fig. 3D). The correlation and agreement between IMR_{app} and true IMR were also less strong compared with between IMR_{calc} and true IMR (Figs. 3E and 3F).

Subgroup analysis according to coronary artery distribution. There were no significant differences between true IMR and IMR_{calc} in both patients with left anterior descending artery lesions as well as patients with non-left anterior descending artery lesions (Online Fig. 1).

Discussion

A method to calculate the IMR in the presence of significant epicardial stenosis without the need for P_w measure-

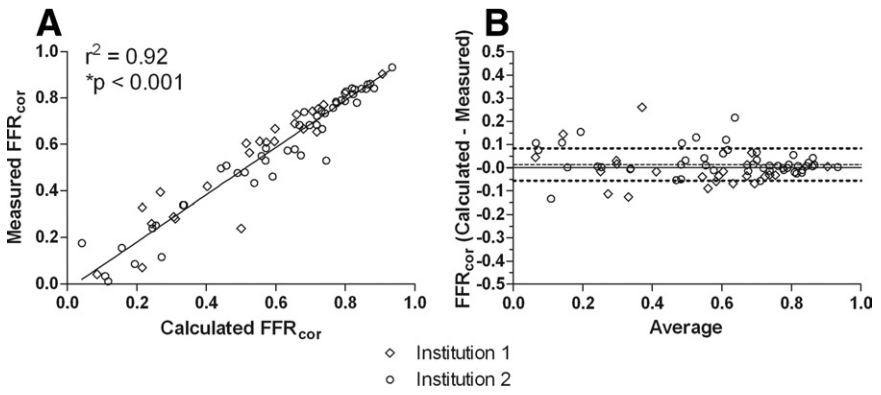

Figure 2. Validation of Method to Calculate FFR_{cor}

(A) Linear regression of measured coronary fractional flow reserve (FFR_{co}) versus calculated FFR_{cor}. The r^2 represents the fit of the regression models, and p values reflect significance of the fit. **(B)** Corresponding Bland-Altman plot. **Dashed line** denotes the bias of the agreement and **dotted lines** represent SDs of the bias.

ment is demonstrated. The IMR_{calc} correlated and had good agreement with the measured true IMR.

Measuring microcirculatory resistance. Recent studies suggest that coronary microcirculatory impairment is an independent predictor of poor prognosis in patients with mild or no significant epicardial coronary disease (1–4). However, there is a paucity of studies assessing coronary microcirculatory status in the presence of concurrent epicardial disease, and the relative prognostic significance of coronary microcirculatory impairment in this setting is unknown. This is

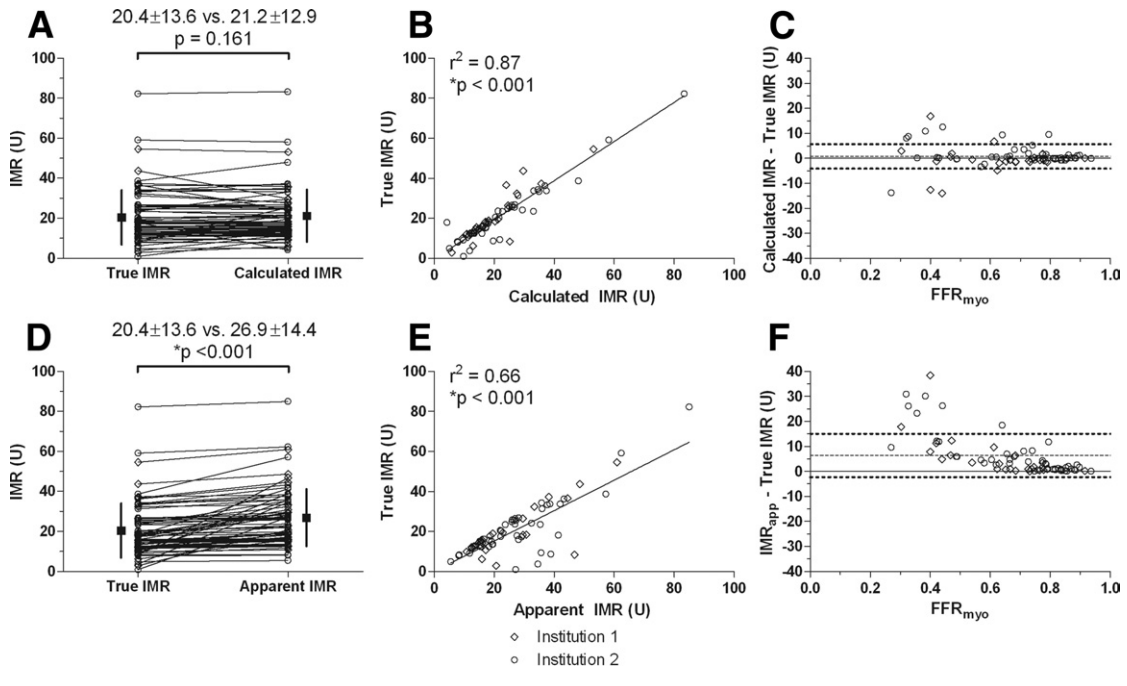

Figure 3. Validation of Method to Calculate IMR

(A) Comparison between true index of microcirculatory resistance (IMR) and calculated index of microcirculatory resistance (IMR_{calc}). **Solid square boxes** and **error bars** represent mean ± SD. **(B)** Linear regression of true versus IMR_{calc}. The r^2 represents the fit of the regression models, and p values reflect significance of the fit. **(C)** Modified Bland-Altman plot showing the effect of myocardial fractional flow reserve (FFR_{myo}) on the difference between IMR_{calc} and true IMR. **Dashed line** denotes the bias of the agreement, and **dotted lines** represent SDs of the bias. **(D to F)** Corresponding comparison between true IMR and apparent index of microcirculatory resistance (IMR_{app}).

likely because research in this area has been hampered by the lack of a technique that independently interrogates the microcirculation.

Techniques to evaluate the coronary microcirculation, such as positron-emission tomography, nuclear perfusion imaging, magnetic resonance imaging, echocardiographic Doppler imaging, and invasive coronary flow reserve measurements, by Doppler or thermodilution, are all based on assessing absolute or relative microcirculatory blood flow (2–4). Microcirculatory blood flow will be affected by epicardial flow in the presence of significant epicardial disease. Therefore, in the presence of significant epicardial disease, all these techniques are unable to distinguish between epicardial and microcirculatory impairment.

Invasive measurements of absolute or relative microcirculatory resistance with Doppler or thermodilution-based techniques, including the IMR, are able to exclusively evaluate the coronary microcirculation (7,21,22). However, in the presence of significant epicardial stenosis, balloon dilation is required for P_w measurement to account for collateral flow in the calculation of microcirculatory resistance (12–15). This has previously limited the measurement of microcirculatory resistance in patients with significant epicardial stenosis to those who are undergoing PCI (5,14,15).

The development of FFR as a simple method to assess the functional severity of epicardial stenosis severity has led to its widespread use to aid revascularization strategy in the cardiac catheterization laboratory (17,23). The method presented in this study to measure microcirculatory resistance in the presence of obstructive coronary disease, without having to perform PCI, could potentially aid in the clinical management of coronary microvascular issues, such as post-infarction necrosis, myocardial recoverability, and primary microvascular dysfunction.

Utility of the IMR_{app} in the presence of significant epicardial stenosis. The IMR is a quantitative measurement of minimum microcirculatory resistance (7) and is stable in response to varying systemic hemodynamic conditions (20). Previous studies that have measured IMR in the absence of significant epicardial stenosis have shown that the IMR can predict infarct size after ST-segment elevation myocardial infarction (8,10,24), that the IMR after elective PCI can be used to quantify size of periprocedural microcirculatory disruption (9), and that the IMR can be used to determine coronary microvascular status in heart transplant patients (11). In addition, a previous study using Doppler-derived microcirculatory resistance measured during balloon occlusion in patients undergoing PCI showed that microcirculatory resistance was associated with periprocedural myocardial necrosis (5).

In the absence of significant epicardial stenosis, as in these studies, contribution of collateral flow to the target microcirculation is insignificant. Therefore, the IMR was calculated with the simplified formula for IMR_{app} in these previous studies (8–11). The results of the current study are consistent with previous published data in showing that it is reasonable to calculate IMR with the formula for IMR_{app} when FFR >0.80 and that the true IMR will be overestimated by the IMR_{app} formula when FFR ≤ 0.80 (Fig. 3F) (12,13).

Calculation of the IMR without P_w measurement. The current study presents a novel, fairly simple mathematical method to calculate the IMR without P_w. The IMR_{calc}, derived by the formula: $P_a \times T_{mn} \times ([1.35 \times P_d/P_a] - 0.32)$, demonstrated good correlation and agreement with the true IMR in the validation cohort.

The IMR_{calc} is less accurate when $FFR_{myo} < 0.45$. A possible explanation is that P_d decreases as FFR_{myo} decreases. This causes an increase in the contribution of P_w toward the equation to calculate FFR_{cor} ($[P_d - P_w]/[P_a - P_w]$) and results in greater discrepancy between estimated FFR_{cor} and measured FFR_{cor}. From the regression line in Figure 2, it is evident that this formula is also not valid when FFR_{myo} is <0.24 when FFR_{cor} becomes <0. Regardless of these issues, the IMR_{calc} was valid in most unselected patients undergoing PCI where FFR ≥ 0.45.

Cohort heterogeneity. The significant variations in renal function, lesion stenosis severity, and target vessel between the derivation and validation cohorts likely reflect the differences in geography and practice among the different institutions. That there was good agreement between IMR_{calc} and true IMR despite these differences supports the validity of the proposed method to calculate the IMR.

There were also several significant differences between the institutions of the validation cohort. However, there were no perceptible differences between the patients from these 2 institutions in validation of the IMR_{calc} (Figs. 3A to 3C).

There were also no significant differences between true IMR and IMR_{calc} in both patients with left anterior descending artery lesions and patients with non-left anterior descending artery lesions (Online Fig. 1). Microcirculatory resistance might be affected by size of the distal microvasculature and therefore could be dependent on lesion site. However, FFR_{cor} and FFR_{myo} are both indexes that are independent of distal territory size. Therefore, the current proposed algorithm to calculate IMR on the basis of estimation of FFR_{cor} from FFR_{myo} should be independent of lesion site, and the results shown are consistent with this fact.

Study limitations. First, IMR was only measured in 1 of the major epicardial coronary arteries. Therefore, the results of this study currently cannot be extrapolated to the left main coronary artery or smaller branch vessels. Second, the current method was only tested with the IMR. Although the general principles described here should apply to other methods, further studies will be required to validate the application of the current algorithm to methods, such as the

absolute measurement of microcirculatory resistance with thermodilution (21) or Doppler ultrasound (22). Last, this study excluded patients with previous infarction in the target territory, and caution has to be exercised when extrapolating the results of this study to these patients. There was, however, no observable difference between stable and unstable angina patients in terms of the difference between the IMR_{calc} and true IMR in the derivation cohort (Online Fig. 2).

Conclusions

This study presents a method to assess the coronary microvasculature in the presence of significant epicardial stenosis without the need for balloon dilation for wedge pressure measurement. Given the increasing awareness of the importance of the coronary microvasculature and the likely increasing application of coronary physiological measurements, we hope that the present method will facilitate future studies involving assessment of the coronary microcirculation in the cardiac catheterization laboratory.

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Key Words: coronary intervention ■ coronary microvascular function ■ index of microcirculatory resistance ■ microcirculation.

APPENDIX

For supplementary figures and tables, please see the online version of this article.