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The Relationship between Microcirculatory Resistance and Fractional Flow Reserve in Patients with Acute Myocardial Infarction

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Background and Objectives: It was demonstrated that the fractional flow reserve (FFR) with partial balloon obstruction may have implications for assessing viable myocardium. In a different way, the index of microcirculatory resistance (IMR) was introduced as a useful indicator for assessing microvascular function. We evaluated the relationship between the $FFR_{0.8}$ and the IMR.

Subjects and Methods: We studied 48 consecutive patients who had undergone coronary intervention for acute myocardial infarction (AMI). After revascularization using stent(s), an undersized short balloon was positioned inside the stent and inflated to create a specific normalized pressure drop of FFR (distal coronary/aortic pressure=0.80) at rest. The $FFR_{0.8}$ was obtained during hyperemia with the fixed state balloon-induced partial obstruction. IMR was measured by three injections of saline. The association between the $FFR_{0.8}$ and the IMR was investigated.

Results: The mean age of the patients was 60±12 years and 36 (75%) overall presented with ST-segment elevation myocardial infarction. The mean $FFR_{0.8}$ was 0.68±0.06. A statistically significant correlation between the $FFR_{0.8}$ and the log-transformed IMR_{true} ($LnIMR_{true}$) was found through a multivariable linear regression analysis (β=0.056, p<0.001). Both the $FFR_{0.8}$ and the $LnIMR_{true}$ had a positive correlation with the log-transformed peak troponin I (TnI) with statistical significance (r^2=0.119, p=0.017; r^2=0.225, p=0.006, respectively).

Conclusion: There was a positive correlation between the $LnIMR_{true}$ and the $FFR_{0.8}$. Both of the values were associated with peak TnI. Those values may be used as appropriate surrogate measures of microvascular function after AMI. **(Korean Circ J 2013;43:534-540)**

KEY WORDS: Myocardial infarction; Fractional flow reserve, myocardial; Microcirculation; Percutaneous coronary intervention.

Introduction

Percutaneous coronary intervention (PCI) has been a pivotal treatment for acute myocardial infarction (AMI). Despite the successful restoration of epicardial coronary artery flow, a substantial amount of microvascular damage remains and affects patient prognosis.[1)2)] The index of microcirculatory resistance (IMR) is a well-validated measure of microvasculature function in the human heart.[3-6)] A recent study has demonstrated that a simple invasive pressure-only test measuring the change of fractional flow reserve (FFR) value (designated as $\Delta FFR_{0.8}$) from a specifically designated value of 0.8 had a significant relationship with the extent of non-viable myocardium.[7)] However, the relationship between this modified FFR value and the IMR has not been investigated prospectively. The aim of this study was to evaluate the association between the $FFR_{0.8}$ and the IMR immediately after PCI for AMI.

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Subjects and Methods

Study population

Forty-eight patients who underwent PCI for AMI were recruited prospectively during the period April 1, 2012 through December 31, 2012. AMI was diagnosed by typical ischemic chest pain and elevated cardiac troponin I (TnI) with a rise and fall pattern, according to

the third universal definition of myocardial infarction.[8] Patients were eligible if they had a target lesion in the proximal to mid segments of one of the major epicardial coronary arteries and successful stent(s) treatment. We excluded patients with left main disease, cardiogenic shock requiring inotropic support, the presence of an additional lesion (>50% in diameter stenosis) distal to the target site, a severely tortuous vessel unsuitable for wire placement, and who had undergone previous coronary artery bypass surgery. This study was approved by the local ethics committees and all patients provided informed consent.

Study protocol

All patients were pretreated with 300 mg aspirin, 600 mg clopidogrel followed by maintenance doses of 100 mg/day of aspirin and 75 mg/day of clopidogrel. Patients received an initial bolus of 5000 units of unfractionated heparin intravenously and additional heparin to maintain an activated clotting time of 250-300 seconds during the procedure. Right atrial pressure (Pv) was measured with a 5 Fr right Judkins diagnostic catheter via the femoral vein. PCI was performed using a 7 Fr guiding catheter. When a large thrombus was present on an initial coronary angiography, manual aspiration thrombectomy using a 7 Fr Thrombuster II® catheter (Kaneka Corporation, Osaka, Japan) was performed with or without abciximab administration at the operator's discretion. All culprit lesions were treated with stent(s). Cardiac enzymes were measured at 8 hours after PCI and followed up for at least two days.

Intracoronary hemodynamic measurement

After PCI, 200 μg intracoronary nitroglycerin was administered to avoid coronary spasm. A 0.014-inch PressureWire® (St. Jude Medical, MN, USA) was introduced and equalized with the aorta pressure. The tip pressure sensor was advanced across the stented segment, and at least beyond the mid-to-distal portion of the culprit vessel. An undersized short balloon, which was smaller by 0.5 mm in diameter and 8-15 mm in length, was placed within the deployed stent and inflated to achieve a specifically designated FFR value of 0.8 in the resting state. After securing a steady-state FFR value of 0.8, hyperemia was induced with 140 μg/kg/min of adenosine infusion through the femoral vein. Aortic pressure (Pa) and distal intracoronary pressure (Pd) were obtained at maximal hyperemia. The $FFR_{0.8}$ was defined as the value of FFR in the hyperemic state with the calibrated in-stent balloon obstruction to create the FFR value of 0.80 in the resting state. An adjunctive or stent balloon was used to form a total occlusion of the culprit artery and obtain coronary

Table 1. Baseline demographics and clinical characteristics

	Overall (n=48)	$FFR_{0.8}$ ≥0.70 (n=21)	$FFR_{0.8}$ <0.70 (n=27)	p
Age, mean (years)	60±12	62±12	59±11	0.415
Male sex (%)	41 (85.4)	16 (76.2)	25 (92.6)	0.215
Hypertension (%)	17 (35.4)	6 (28.6)	11 (40.7)	0.286
Diabetes mellitus (%)	12 (25.0)	8 (38.1)	4 (14.8)	0.066
Hypercholesterolemia (%)	27 (56.3)	12 (57.1)	15 (55.6)	0.573
Current smoker (%)	27 (56.3)	11 (22.9)	16 (33.3)	0.427
Clinical presentation (%)				0.319
STEMI	36 (75)	14 (66.7)	22 (81.5)	
NSTEMI	12 (25)	7 (33.3)	5 (18.5)	
At presentation				
SBP (mm Hg)	127±21	120±21	133±21	0.038
DBP (mm Hg)	79±14	77±13	81±14	0.308
HR (beats/min)	82±18	83±19	82±18	0.832
Prior medications (%)				
Aspirin	3 (6.3)	1 (4.8)	2 (7.4)	1.000
Clopidogrel	1 (2.1)	0 (0)	1 (3.7)	1.000
ACEi/ARB	4 (8.3)	2 (9.5)	2 (7.4)	1.000
Beta blockers	2 (4.2)	1 (4.8)	1 (3.7)	1.000
CCBs	7 (14.6)	2 (9.5)	5 (18.5)	1.000
Statins	2 (4.2)	1 (4.8)	1 (3.7)	1.000

Values are shown as mean±SD or n (%). FFR: fractional flow reserve, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker

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wedge pressure (Pw). A conventional FFR value (the ratio of Pd/Pa without in-stent balloon obstruction) was obtained after balloon extraction. The mean transit time (Tmn) was determined by three injections of 3 mL of room temperature saline while the guiding catheter was engaged. IMR was calculated as Tmn×Pd. IMR_{true} was calculated using (Pa-Pv)×Tmn (Pd-Pw)/(Pa-Pw) to account for collateral flow and Pv.[4] All the measurements were obtained during the state of hyperemia.

Statistical analysis

All continuous variables are expressed as mean±standard deviation or median (interquartile range) for non-parametric data. A Student t-test or Mann-Whitney U test was used for comparison. Categorical variables were presented as numbers with proportions and compared using a chi-squared or Fisher's exact test. Linear regression analyses were performed to evaluate the associations between the variables. Skewed variables underwent log transformation for analysis. An optimal IMR cut-off value for predicting the $FFR_{0.8}$ <0.70 was determined by receiver operating characteristics (ROC) analysis. A 2-tailed value of p<0.05 was considered significant. Statistical analysis was performed using Stata for Windows (version 12.0, StataCorp, College Station, TX, USA).

Results

A total of 48 patients with AMI were subject to analyses. Patients were divided into two groups based on the $FFR_{0.8}$ value of 0.70. Baseline clinical characteristics are listed in Table 1. Overall, the mean age was 60±12 years and 36 (75%) patients presented with ST-segment elevation myocardial infarction (STEMI). The most common culprit arteries in both groups were the left anterior descending coronary artery in both groups (Table 2). There was no difference in regard to the number of diseased vessels, symptom onset to balloon time, baseline Thrombolysis in Myocardial Infarction (TIMI) flow grade, reference lumen diameter, and number of stents used between the two groups. Patients who had a lower $FFR_{0.8}$ (<0.70) had a trend toward a higher post-procedural TIMI flow grade and more receiving collateral flow. Coronary physiological data are outlined in Table 3. Among 8 patients (1 in the higher $FFR_{0.8}$ group and 7 in the lower $FFR_{0.8}$ group), Pw was not available. Pv was measured in 33 patients (16 in the higher $FFR_{0.8}$ group, 17 in the lower $FFR_{0.8}$ group) and did not differ between the two groups with a mean value of 14±6 (15±6 vs. 13±5, p=0.148). IMR_{true} could be calculated in 32 patients because 16 patients did not have either a Pv or Pw value. The FFR, Pw, distance between the sensor and catheter tip, Q-wave after PCI, peak creatine kinase-myocardial band (CK-MB), and left

Table 2. Angiographic and procedural characteristics

	Overall (n=48)	$FFR_{0.8}$ ≥0.70 (n=21)	$FFR_{0.8}$ <0.70 (n=27)	p
Infarct-related artery (%)				0.303
LAD	27 (56.3)	14 (66.7)	13 (48.1)	
LCX	5 (10.4)	2 (9.5)	3 (11.1)	
RCA	15 (31.3)	4 (19.0)	11 (40.7)	
Number of diseased vessels (%)				0.285
1 vessel disease	24 (50.0)	13 (61.9)	11 (40.7)	
2 vessel disease	16 (33.3)	6 (28.6)	10 (37.0)	
3 vessel disease	8 (16.7)	2 (9.5)	6 (22.2)	
Time interval (minutes)				
STB time	351 (131-1410)	323 (134-1291)	370 (120-3905)	0.963
Baseline TIMI flow grade 0 or 1 (%)	27 (56.3)	11 (52.4)	16 (59.3)	0.771
Post-procedural TIMI flow grade (%)				0.077
TIMI flow grade 0 or 1	0 (0)	0 (0)	0 (0)	
TIMI flow grade 2	3 (6.3)	3 (14.3)	0 (0)	
TIMI flow grade 3	45 (93.8)	18 (85.7)	27 (100)	
Reference lumen diameter (mm)	3.27±0.37	3.29±0.42	3.25±0.33	0.733
Number of stents	1.17±0.38	1.19±0.40	1.15±0.36	0.704
Total length of implanted stents (mm)	28.0±11.9	28.5±14.8	27.6±9.3	0.801
Side branch embolization (%)	4 (8.3)	2 (9.5)	2 (7.4)	1.000
Receiving collateral flow (%)	14 (29.2)	3 (14.3)	11 (40.7)	0.060

Values are shown as mean±SD or median (interquartile range) or n (%). FFR: fractional flow reserve, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, STB: symptom onset to balloon, TIMI: Thrombolysis in Myocardial Infarction

ventricular ejection fraction (LVEF) did not differ between the two groups. The lower $FFR_{0.8}$ group had a higher Pd, and a lower Tmn, IMR, IMR_{true}, and peak TnI concentration.

In the univariate analysis, the $FFR_{0.8}$ had a marginal positive correlation with the log-transformed IMR (LnIMR) (r^2=0.073, p=0.063), and a statistically significant positive correlation with the log-transformed IMR_{true} ($LnIMR_{true}$) (r^2=0.276, p=0.002) (Fig. 1). There were statistically significant correlations between the $FFR_{0.8}$ and the log-transformed peak TnI (LnpTnI) (r^2=0.119, p=0.017), and the $LnIMR_{true}$ and the LnpTnI (r^2=0.225, p=0.006) (Fig. 2). Both the LnIMR and the $LnIMR_{true}$ remained in a significant correlation with the $FFR_{0.8}$ after adjustment for age, the male gender, tip sensor position down the vessel, and culprit vessel (Table 4). ROC analysis discovered an optimal cut-off value of 35 for IMR {sensitivity 74%, specificity 71%, area under the curve (AUC)=0.713, p=0.012} and 23 for IMR_{true} (sensitivity 88%, specificity 75%, AUC=0.785, p=0.006) in predicting $FFR_{0.8}$ ≥0.70 (Fig. 3).

Table 3. Coronary physiological data and other measurements of infarct size

	Overall (n=48)	$FFR_{0.8}$ ≥0.70 (n=21)	$FFR_{0.8}$ <0.70 (n=27)	p
Intracoronary measurements				
Pa (mm Hg)				
Baseline	100±15	95±15	104±15	0.067
Hyperemia	92±15	89±15	95±14	0.198
Pd (mm Hg)				
Baseline	96±15	89±15	100±14	0.008
Hyperemia	84±14	81±15	86±14	0.225
FFR	0.93±0.07	0.93±0.07	0.93±0.07	0.945
$FFR_{0.8}$	0.68±0.06	0.74±0.03	0.64±0.04	<0.001
Tmn (seconds)	0.35 (0.25-0.75)	0.54 (0.33-1.02)	0.31 (0.20-0.52)	0.008
IMR (U)	30.7 (20.1-63.4)	43.5 (28.6-74.3)	24.8 (16.8-37.0)	0.012
IMR_{true} (U)	24.6 (13.4-43.4)	32.0 (24.6-56.3)	16.7 (11.6-24.5)	0.007
Pw (mm Hg)*	31±9	31±9	30±9	0.793
Pw/Pa	0.34±0.09	0.37±0.10	0.32±0.08	0.100
Pv (mm Hg)†	14±6	15±6	13±5	0.148
Tip sensor position down the vessel (mm)	86±17	86±12	86±21	0.997
Q-wave after PCI (%)	25 (52.1)	11 (52.4)	14 (51.9)	1.000
Peak CK-MB	155 (48-258)	190 (46-364)	145 (49-236)	0.510
Peak TnI	32.14 (14.54-66.69)	34.18 (15.77-146.74)	27.61 (12.3-64.24)	0.003
LV ejection fraction (%)	50±7	50±8	49±7	0.706

Values are shown as mean±SD or median (interquartile range) or n (%). *Pw was measured in 40 patients, †Pv was measured in 32 patients. Pa: aortic pressure, Pd: distal pressure, FFR: fractional flow reserve, Tmn: mean transit time, IMR: index of microcirculatory resistance, Pw: coronary wedge pressure, Pv: right atrial pressure, PCI: percutaneous coronary intervention, CK-MB: creatine kinase-myocardial band, TnI: troponin I, LV: left ventricular

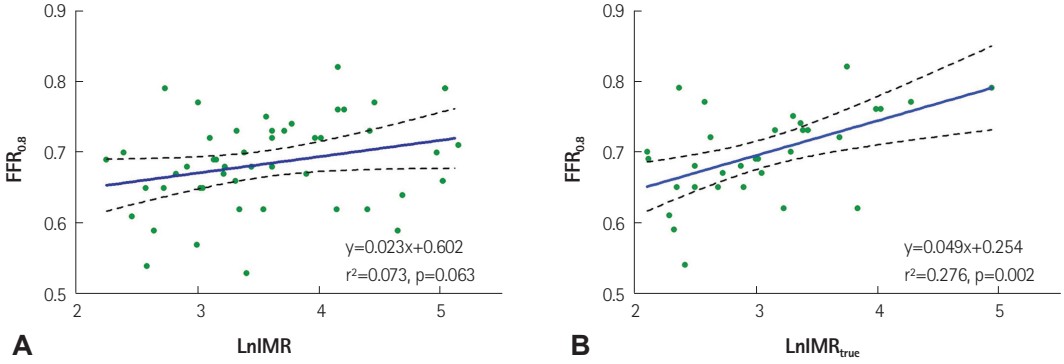

Fig. 1. Scatter plots between the $FFR_{0.8}$ and the log-transformed IMR (LnIMR) (A), and the log-transformed IMR_{true} ($LnIMR_{true}$) (B). The dashed lines represent the 95% confidence intervals for the regression line (solid). FFR: fractional flow reserve, IMR: index of microcirculatory resistance.

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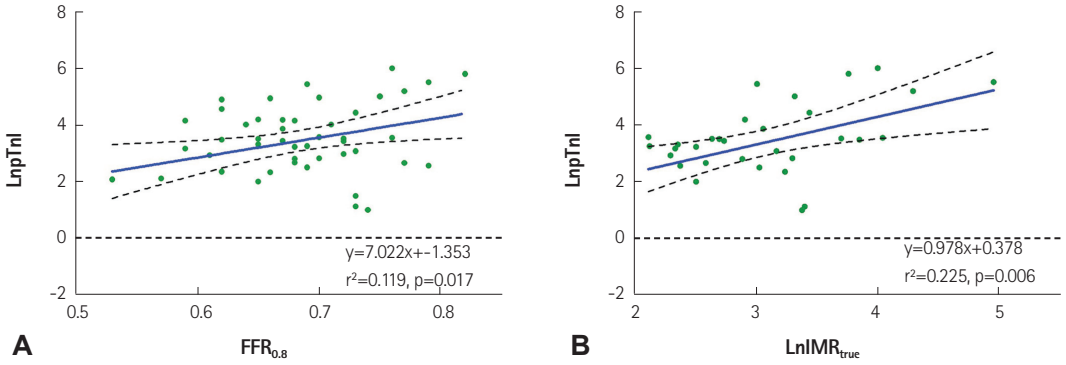

Fig. 2. Scatter plots between the log-transformed peak TnI (LnpTnI) and the $FFR_{0.8}$ (A), and the log-transformed IMR_{true} ($LnIMR_{true}$) (B). The dashed lines represent the 95% confidence intervals for the regression line (solid). FFR: fractional flow reserve, IMR: index of microcirculatory resistance, TnI: troponin I.

Table 4. Multivariate linear regression analyses for the relationship between $FFR_{0.8}$ and the IMR values

	Beta coefficient	p	Adjusted R^2
Model 1			0.108
LnIMR	0.029	0.020	
Age	0.000	0.844	
Male gender	0.045	0.113	
STEMI	-0.010	0.630	
Tip sensor position down the vessel	-0.001	0.072	
Culprit vessel	-0.006	0.550	
Model 2			0.403
$LnIMR_{true}$	0.056	<0.001	
Age	0.000	0.859	
Male gender	0.068	0.028	
STEMI	-0.002	0.933	
Tip sensor position down the vessel	-0.001	0.066	
Culprit vessel	-0.004	0.663	

FFR: fractional flow reserve, IMR: index of microcirculatory resistance, LnIMR: log-transformed index of microcirculatory resistance, $LnIMR_{true}$: log-transformed IMR_{true}, STEMI: ST-segment elevation myocardial infarction

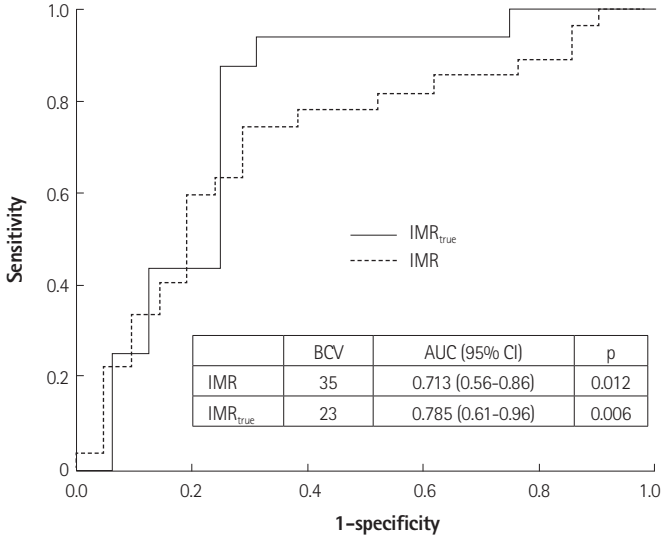

Fig. 3. Receiver-operator characteristic curve analysis for the IMR and the IMR_{true} for the prediction of the $FFR_{0.8} \geq 0.7$. FFR: fractional flow reserve, IMR: index of microcirculatory resistance, BCV: best cut-off value, AUC: area under the curve, CI: confidence interval.

Discussion

In this study, we found a statistically significant positive relationship between the $LnIMR_{true}$ and $FFR_{0.8}$ measured immediately after coronary stenting for AMI. This relationship was maintained after adjustment for relevant covariates. Both the $FFR_{0.8}$ and the $LnIMR_{true}$ also had a positive correlation to the LnpTnI, with statistical significance. Microvascular integrity is considered as a prerequisite of viable myocardium, which in turn, contributes to left ventricular (LV) function and clinical outcomes in patients suffering from AMI.[9][10] With technological advancements, it became feasible to evaluate microvascular function in a catheterization laboratory using an intracoronary pressure wire. Traditionally, FFR has been used to determine the significance of an epicardial coronary artery stenosis in angina patients. Basically, the FFR measured during hyperemia reflects the amount of recruitable microvascular flow, and will decrease as the amount of viable myocardium increases. Thus, the value will be larger in patients suffering from AMI because of a lack of viable myocardium.[11] Conversely, at a given stenosis in the coronary artery, the lower FFR implies a greater amount of viable myocardium remaining. Theoretically we need some degree of stenosis to estimate the quantity of viable myocardium by FFR. Therefore, we created an artificial balloon obstruction within the stented segment after revascularization. What degree of stenosis is optimal for assessing myocardial viability?

Kocaman et al.[12] suggested that the delta FFR (ΔFFR), which was derived by subtraction of the FFR in hyperemia from that in the resting state, may represent the microvascular compensatory func-

tion in response to an epicardial coronary artery stenosis. ΔFFR had the greatest value in the intermediate stenosis (FFR 0.75-0.80). Where the FFR was >0.80 in the resting state, there was not a sufficient compensatory response during hyperemia. Where the FFR was <0.75, there was a blunted response because of the already existing ischemia in the resting state. Artificially creating a stenosis with a balloon to obtain the intermediate obstruction at the resting state gave rise to the notion of $FFR_{0.8}$. The $FFR_{0.8}$ is the value of FFR in a hyperemic state, with the partially inflated balloon used to create the specific normalized FFR value of 0.80 in the resting state. Using this method, Kim et al.[7] demonstrated that the lower $FFR_{0.8}$ value ($FFR_{0.8}$ <0.70) endorsed the larger amount of viable myocardium on cardiac magnetic resonance imaging with the best discriminating value of $FFR_{0.8}$=0.70.

On the other hand, IMR was a well-validated measure of representing microvascular function both experimentally and clinically.[3][13] However, the relationship between $FFR_{0.8}$ and IMR is not well understood. Furthermore, the reference value for the discrimination of viable myocardium against non-viable myocardium has not been adequately investigated. Fearon et al.[14] suggested that the IMR ≤32 was an independent predictor of the recovery of LV function at three months among 29 patients who had undergone primary PCI for STEMI. In another study, where 40 patients with an anterior wall STEMI were enrolled, an IMR value of 33 was suggested as an optimal cut-off value for the improvement of LV function and viable myocardium assessed by positron emission tomography imaging.[6] More recently, a study using CMR showed a higher median IMR value of 35 with microvascular obstruction compared to the value of 27 without obstruction among STEMI patients.[5]

Our study demonstrated that the $LnIMR_{true}$ had a positive correlation with the $FFR_{0.8}$ and this relationship remained even after the adjustment of several relevant covariates. In addition, the relationship between the logarithmic IMR itself and the $FFR_{0.8}$ was found to be significant after considering covariates. Both of those values were associated with the peak TnI. Our best optimal value of IMR predicting $FFR_{0.8}$ ≥0.7 was 35. This value was surprisingly close to the previously suggested values. These results support the notion that myocardial viability might be evaluated using only a pressure-wire either by IMR or $FFR_{0.8}$ in a catheterization laboratory immediately after revascularization for AMI.

Interestingly, one subject had a $FFR_{0.8}$ value of 0.82, which lay above the baseline value of 0.80. He had a high IMR (72 U), Pv (16 mm Hg), Pw (41 mm Hg), and low LVEF (32%), as well as Q wave on the electrocardiography. All of these findings indicated that he had a very large-sized myocardial infarction. The reason for this over-high $FFR_{0.8}$ value after hyperemia could not be fully understood. However, it may be partially explained considering that his large-sized infarction hindered the $FFR_{0.8}$, which declined in response to the hyperemia remaining of the same value of 0.80. Some measurement error had provided a slightly higher value of 0.82.

It is notable that the relationship of the IMR with CK-MB varied across prior studies. We could not locate any relationship between those two values. This might be explained by patient selection, wherein we did not face any time limitations for inclusion. Thus, in those who presented later, CK-MB may have been washed out while TnI remained at a high level due to its slower clearance rate.

Limitations

This study has several limitations to be noted. First, the small number of patients limited our capacity to determine an association among interesting factors, including collateral flow and LV function. Second, there was a lack of comparison with any imaging scan assessing myocardial viability in a direct way. However, those associations had been validated previously, and might be used in an inferred manner. Third, this study was conducted in a single center and the measurements of Tmn were performed by one sole operator. Thus, the findings need to be confirmed by other studies. Forth, the equation for calculating IMR uses Tmn to estimate coronary flow. The inverse correlation of Tmn with absolute flow could only be maintained when the sensor was located ≥6-8 cm from the catheter.[15] We paid attention to the sensor position remaining in the distal third of the vessel. Nevertheless, the IMR measurements could have varied considerably on the sensor and catheter position, as well as the vessel volume. This effect might have accounted for the less robust relationship between the values with limited agreements. The additional balloon obstruction to obtain the $FFR_{0.8}$ might be a cumbersome procedure. However, the $FFR_{0.8}$ can be obtained at any interested point in the coronary artery, even within 6 cm from the catheter, and is not sensitive to vessel volume. These advantages of the $FFR_{0.8}$ enabled us to estimate microvascular function where the IMR proves unsuitable.

In conclusion, there was a positive correlation between the $LnIMR_{true}$ and the $FFR_{0.8}$ in AMI patients with statistical significance. Both of the values were associated with the peak TnI. The $FFR_{0.8}$ and the IMR may prove to be useful surrogate measures of microvascular function after AMI.

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