Clinical usefulness of instantaneous wave-free ratio for the evaluation of coronary artery lesion with prior myocardial infarction: A multi-center study

Shusuke Fukuoka [a], Tairo Kurita [a,*], Akihiro Takasaki [a], Tomoyuki Nakata [b], Naoki Fujimoto [a], Jun Masuda [a], Kozo Hoshino [b], Takashi Tanigawa [c], Sukenari Koyabu [d], Masaaki Ito [a], Kaoru Dohi [a]

[a] Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu, Japan
[b] Department of Cardiology, Nagai Hospital, Tsu, Japan
[c] Department of Cardiology, Matsusaka Central Hospital, Matsusaka, Japan
[d] Department of Cardiology, Owase General Hospital, Owase, Japan

ARTICLE INFO

ABSTRACT

Background: Fractional flow reserve (FFR) is useful for assessing the functional significance of coronary artery stenosis, even in lesions with prior myocardial infarction (pMI). Instantaneous wave-free ratio (iFR) is a vasodilator-free alternative for the physiological assessment of coronary artery stenosis. In addition, iFR shows good diagnostic agreement with FFR and an iFR-guided revascularization strategy was non-inferior to an FFR-guided revascularization strategy. However, the clinical usefulness of iFR for the evaluation of a coronary artery lesions with pMI has not been evaluated.
Methods and Results: A total of 200 lesions from 200 patients (44 pMI territories lesions and 156 non-pMI coronary artery lesions) were analyzed retrospectively. Major adverse cardiac events (MACE) were defined as cardiovascular death, non-fatal MI, unstable angina pectoris, fatal arrhythmia and heart failure during 12 months follow-up after the physiological assessment of coronary artery stenosis. iFR was closely correlated with FFR in pMI and non-pMI lesions (r = 0.81 and 0.72; P < 0.001, respectively). In pMI lesions, an iFR cut-off of 0.89 was optimal against a clinical FFR cut-off of 0.80 according to receiver operating characteristics (ROC) curve analysis, whereas in non-pMI lesions, the iFR cut-off value was 0.92 without statistical significance. In addition, the event rate of MACE was similar between pMI and non-pMI patients during follow-up even in the presence or absence of an PCI procedure.
Conclusions: iFR may be a useful alternative method compared with FFR for clinical decision-making even in pMI patients.

1. Introduction

Fractional flow reserve (FFR) is an invasive physiological index measured in the cardiac catheterization laboratory to assess the functional significance of a coronary artery stenosis [1]. Previous studies showed that FFR-guided percutaneous coronary intervention (PCI) improves clinical outcomes compared with angiography-guided treatment, which led to the guidelines recommendations for FFR-guided PCI [2–5]. Furthermore, the usefulness of FFR in assessing coronary artery stenosis with prior myocardial infarction (pMI) territories has been evaluated by several studies [6,7]. Despite the clinical benefit of FFR-guided PCI, the penetration of FFR-guided PCI remains low in the clinical setting (6–8%) because of the prolongation procedural time and the contraindication to vasodilator drugs administration in patients with asthma, chronic obstructive pulmonary disease, or bradycardia [8,9].

Instantaneous wave-free ratio (iFR) was introduced as a vasodilator-free alternative for the physiological assessment of coronary artery stenosis [10]. Several studies demonstrated a close

correlation between iFR and FFR, with a high accuracy in the diagnostic classification match of the two indices [10–12]. On the other hand, iFR showed a stronger correlation with coronary flow reserve (CFR) compared with FFR [13]. Additionally, the clinical usefulness of iFR for coronary artery lesions with pMI territories has not been well evaluated. In addition, an iFR-guided PCI strategy provided a similar 1-year clinical prognosis to FFR-guided PCI strategy with a reduced rate of adverse procedural signs and symptoms and shorter procedural time [14,15]. The purpose of this study was to investigate the diagnostic and clinical usefulness of iFR for coronary artery lesions with pMI territories.

2. Methods

2.1. Study population

Two-hundred consecutive patients with stable coronary artery disease (CAD) who underwent diagnostic coronary angiogram and physiological assessment with iFR and FFR were retrospectively enrolled from 4 hospitals in Japan from May 2014 and July 2016. The patients were divided into two groups according to the presence or absence of pMI. Patients with pMI were defined as having a documented clinical history of MI more than 6 months before the physiological assessment and iFR and FFR were measured in infarct-related artery of prior MI territories. Patients with any of the following conditions were excluded: (1) previous coronary bypass grafting, (2) hemodialysis, (3) pMI lesion without myocardial viability assessed with echocardiography or cardiac magnetic resonance imaging (MRI), (4) clinical history of MI with a non-target legion for physiological assessment, (5) presence of a chronic total occlusion lesion, (6) tandem lesion in a target artery; a major native coronary artery with ≥2 stenoses separated by a more normal segment, (7) atrial fibrillation, and (8) visible collateral development to the perfusion territory of interest.

The protocol of this study was approved by the ethical committee of Mie University Hospital, and all patients gave their "opt-out" informed consent.

2.2. Assessment of myocardial viability in pMI territories

Assessment of myocardial viability was performed by echocardiography or cardiac MRI. Absence of myocardial viability was defined as pMI territories with a thin wall (<6 mm) and total akinetic wall motion by echocardiography, and transmural extent of hyper-enhancement >50% on late gadolinium enhancement by cardiac MRI [16,17].

2.3. Measurement and analysis of iFR and FFR

iFR and FFR were measured in a single intermediate coronary artery lesion defined as a visually percent diameter stenosis >50% [18].

The iFR and FFR measurements were obtained with the use of a coronary-pressure guidewire. After the administration of a 1–2 mg intracoronary bolus of nitroglycerine, a 0.014-in. pressure sensor-tipped wire (Philips Volcano) was calibrated and introduced into the catheter. At the tip of the catheter, the pressure was equalized to aortic pressure. The wire was advanced through the target lesion and iFR was measured using software embedded in the hemodynamic console (s5x Imaging System; Philips Volcano) in real time. Then, to introduce maximal hyperemia, adenosine triphosphate (ATP) was administered at doses ranging from 160 μg/kg/min through a peripheral vein if needed for a hybrid iFR-FFR strategy [10–12]. After a stable minimum value of FFR was established, a pullback recording was performed to exclude pressure drift.

2.4. Diagnostic strategies and definitions

We evaluated the diagnostic classification agreement with a single iFR strategy and hybrid iFR-FFR strategy in pMI and non-pMI lesions. A hybrid iFR-FFR strategy was proposed, using a deferral iFR value >0.93 and a revascularization iFR value <0.86 and when iFR would fall between 0.86 and 0.93, the value of FFR was adopted [11].

2.5. Patient follow-up

The primary endpoint was major adverse cardiac events (MACE), including cardiovascular death, non-fatal MI, unstable angina pectoris (UAP) requiring revascularization, fatal arrhythmia, and hospitalization for heart failure (HF). When a patient experienced MACE several times, the first event was chosen for analysis. Complete 1-year follow up rate was 99.5% in this study population.

2.6. Statistical analysis

Continuous variables with normal distributions were expressed as mean ± standard deviation (SD), and those without normal distributions were expressed as median and interquartile range. Categorical variables were expressed as percentages. Normality was assessed using Shapiro–Wilk test. Student's *t*-test or Mann–Whitney rank sum test was used to assess statistical significance of continuous variables with and without normally distributed variables, and categorical variables were compared using chi-square test. The receiver-operating characteristic (ROC) curve was used to estimate the diagnostic efficiency of iFR and to identify the most appropriate cut-off value corresponding to FFR 0.80. The diagnostic performance of iFR was assessed using sensitivity, specificity, and diagnostic classification match (the percentage of patients correctly diagnosed by iFR). Comparison between the areas under two independent ROC curves was performed using the method described by Hanley and McNeil [19]. Spearman correlation coefficient was employed to examine the relationship between FFR and iFR. A time-to-event analysis was conducted using Kaplan–Meier analysis. Statistical significance was defined as a P value < 0.05. All data analysis was performed with SPSS version 22 (IBM Inc, Chicago, Illinois, USA) and MedCalc version 17.6 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Patient baseline characteristics

A total of 200 lesions from 200 patients were evaluated including 44 coronary artery lesions with pMI territories (n = 44) and 156 de novo coronary artery lesions without pMI territories (n = 156). Patient baseline characteristics are presented in Table 1. The prevalences of diabetes mellitus (DM), dyslipidemia, prior PCI, and medical therapy including anti-platelet therapy, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, and statins were significantly higher in pMI patients. pMI patients showed a significantly decreased left ventricular ejection fraction (LVEF). The prevalence of right coronary artery lesions was higher and left circumflex artery lesions was lower in pMI patients compared with non-pMI patients.

3.2. Diagnostic characteristics of iFR against FFR

There was no statistically significant difference in the distribution of FFR values in pMI and non-pMI lesions (P = 0.77) (Fig. 1.). A

Table 1
Patient baseline characteristics.

	pMI (n = 44)	Non-pMI (n = 156)	P value
Age, years	74 ± 8	73 ± 10	0.14
Male, n (%)	34 (77)	112 (72)	0.52
Body mass index, kg/m^2	23.7 ± 2.7	23.3 ± 3.5	0.34
Current smoker, n (%)	6 (14)	28 (18)	0.19
Comorbidities			
Hypertension, n (%)	35 (80)	123 (79)	0.92
Diabetes mellitus, n (%)	27 (61)	66 (42)	0.03
Dyslipidemia, n (%)	40 (91)	110 (71)	0.01
Prior percutaneous coronary intervention, n (%)	44 (100)	59 (38)	<0.001
Laboratory Dates			
Triglyceride, mg/dl	139 ± 90	130 ± 78	0.35
LDL-cholesterol, mg/dl	79 ± 29	100 ± 33	<0.001
HDL-cholesterol, mg/dl	53 ± 14	53 ± 17	0.95
Serum-Creatinine, mg/dl	1.0 ± 0.3	0.9 ± 0.3	0.30
HbA1c, %	6.6 ± 1.0	6.2 ± 1.0	0.01
BNP, pg/ml	46 (23–93)	29 (14–56)	<0.05
Coronary anatomy			
Left ascending artery, n (%)	26 (59)	100 (64)	0.54
Left circumflex artery, n (%)	3 (7)	25 (16)	0.12
Right coronary artery, n (%)	15 (34)	26 (17)	0.01
Left main coronary artery, n (%)	0 (0)	5 (3)	0.29
Multi-vessel disease, n (%)	13 (30)	46 (29)	0.99
In-stent restenosis lesion	10 (23)	11 (7)	0.01
Left ventricular ejection fraction, %	53.9 ± 14.2	66.0 ± 7.8	<0.001
Medication			
Anti-platelet therapy, n (%)	44 (100)	93 (60)	<0.001
ACE-inhibitor or ARB, n (%)	37 (84)	93 (60)	0.01
Beta-blocker, n (%)	23 (52)	43 (28)	<0.001
Statin, n (%)	37 (84)	80 (51)	<0.001
Calcium channel blocker, n (%)	22 (50)	78 (50)	0.69
Nitrate, n (%)	15 (34)	30 (19)	0.09

Values are given as mean ± standard deviation, number with percentage or median (interquartile range).
pMI, prior myocardial infarction; LDL, low density lipoprotein; HDL, high density lipoprotein; BNP, brain natriuretic peptide; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

FFR value below 0.80 was reported in 11 (25.0%) of 44 pMI lesions and 46 (29.5%) of 156 non-pMI lesions. The median FFR value of 0.86 in pMI lesions was similar to the median FFR value of 0.85 in non-pMI lesions (P = 0.49). In addition, the median iFR value of 0.94 in pMI lesions was similar to the median iFR value of 0.94 in non-pMI lesions (P = 0.63) (Fig. 2.).

A scatter plot of the relationship between iFR and FFR is shown in Fig. 3. iFR was closely correlated with the FFR in pMI and non-pMI patients (r = 0.81 and 0.72, respectively; P < 0.001). Furthermore, there was no statistical difference in the two correlation coefficients (P = 0.21).

Using an FFR cut-off value of 0.80 to assess significant coronary artery stenosis, a ROC curve revealed that the optimal iFR cut-off values were 0.89 and 0.92 (P < 0.001, respectively), and the area under the ROC curve was 0.92 and 0.87 in pMI and non-pMI lesions, respectively (Fig. 4.). The sensitivity and specificity of iFR for the detection of a cut-off FFR value of less than 0.8 were 78% and 100% in pMI lesions, and 84% and 77% in non-pMI lesions, respectively. In addition, areas under the ROC curves obtained from the pMI and non-pMI lesions showed no significant difference between the two groups (P = 0.42) (see Fig. 4).

3.3. Outcome data

During 12 months of follow-up, 7 of the 200 patients (3.5%) experienced MACE, including 1 fatal arrhythmia, 1 non-fatal MI, 3 UAP requiring revascularization, and 2 HF requiring hospitalization. In patients whose PCI was deferred, 1 of 32 patient (3.1%) with pMI and 4 of 115 patients (3.5%) without pMI experienced MACE (P = 0.70) (Table 2). According to the Kaplan–Meier survival curve, even in the patients with pMI, deferral of PCI using hybrid iFR-FFR strategy provided a similar 1-year prognosis, compared with the patients without pMI (HR 0.87, 95% CI; 0.10–7.76, P = 0.90). In addition, the event rate of MACE was similar between patients with pMI and without pMI even in the patients with a PCI procedure (HR 3.29, 95% CI; 0.21–52.62, P = 0.37) (Fig. 5).

4. Discussion

In this study, we demonstrated that iFR may be a useful alternative method compared with FFR for clinical decision-making even in pMI patients. The findings of the present study were that iFR demonstrated an excellent correlation with FFR despite the presence of pMI, and the optimal iFR cut-off value was 0.89, which was equivalent to the clinical FFR cut-off value of 0.80 in lesions with pMI territories. In addition, we found the prognostic usefulness of hybrid iFR-FFR-guided coronary revascularization, even in the pMI patients.

The iFR cut-off value for detecting FFR less 0.80 was around 0.90 according to several previous studies that included a few pMI patients [10–12]. This is consistent with our result, which
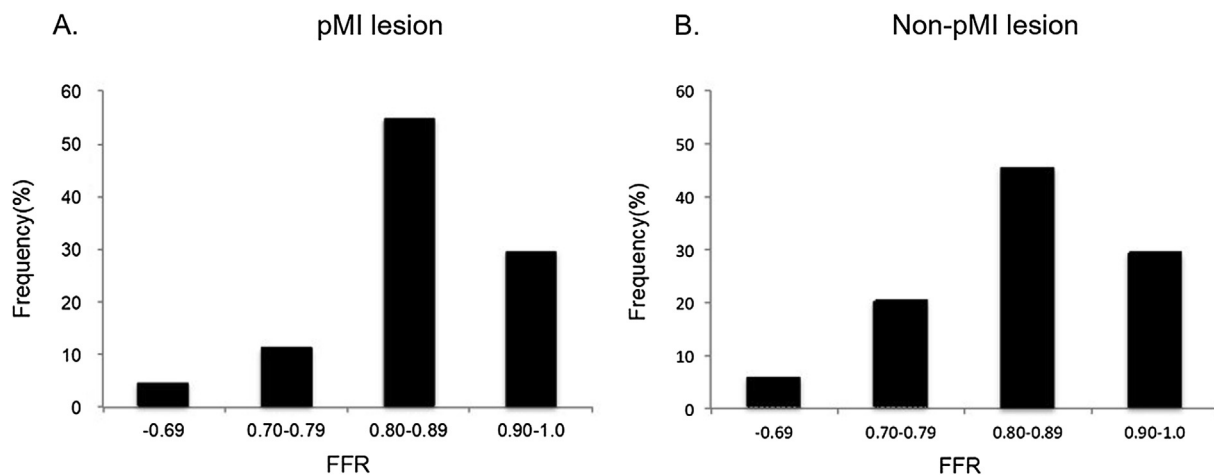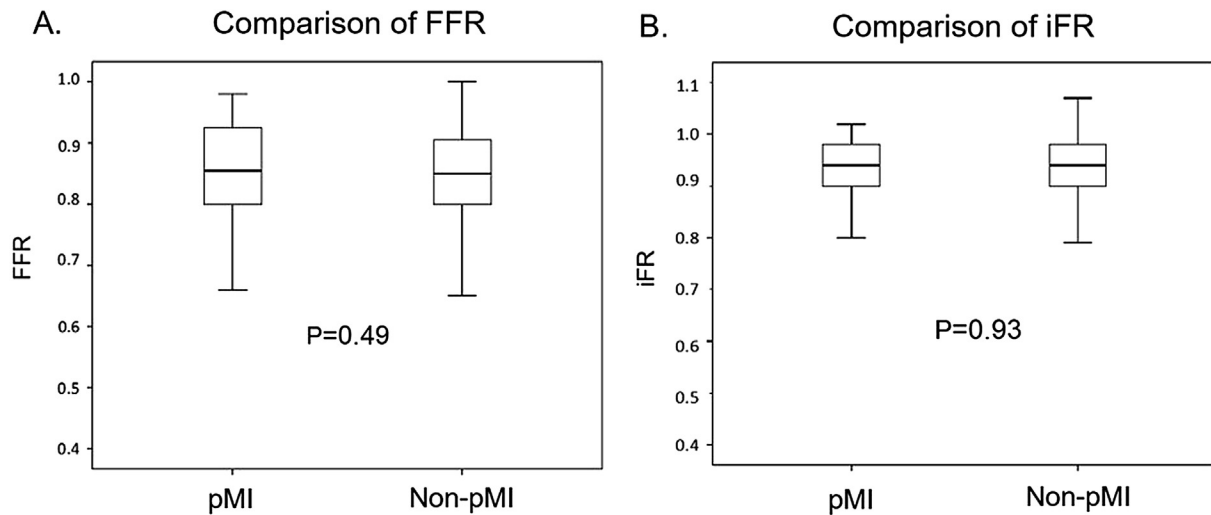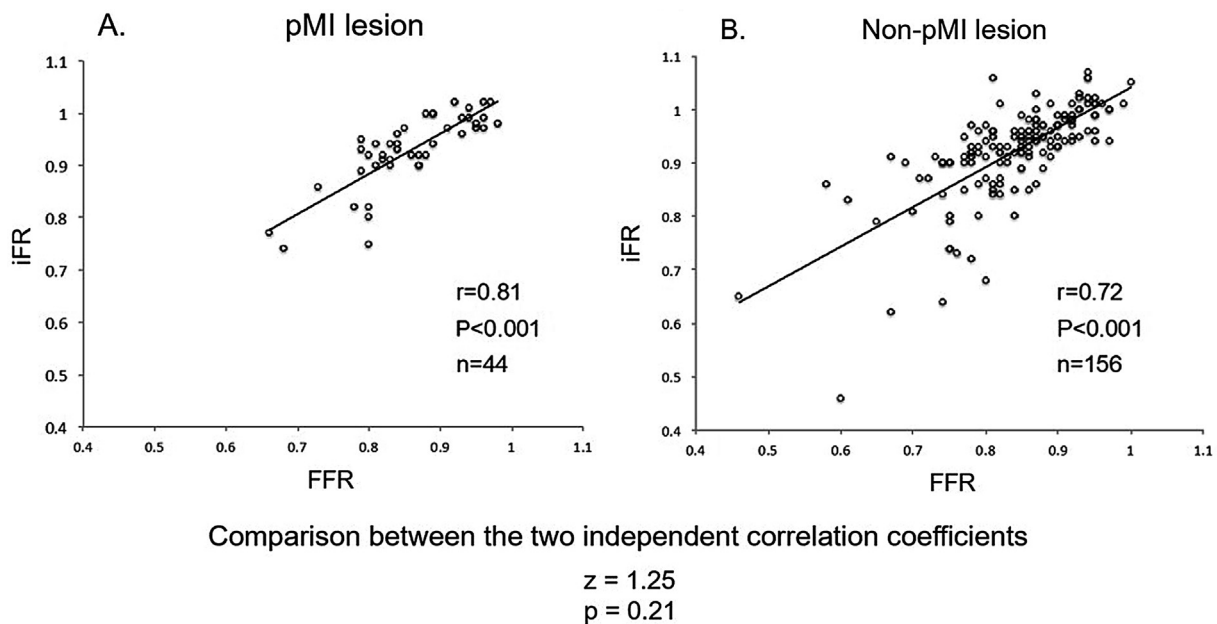

Fig. 1. Distribution of FFR in pMI lesion **(A)** and non-pMI lesion **(B)**. FFR, fractional flow reserve; pMI, prior myocardial infarction.

Fig. 2. Comparison of FFR (**A**) and iFR (**B**) in pMI lesion and non-pMI lesion. iFR, instantaneous wave free ratio; FFR, fractional flow reserve; pMI, prior myocardial infarction.
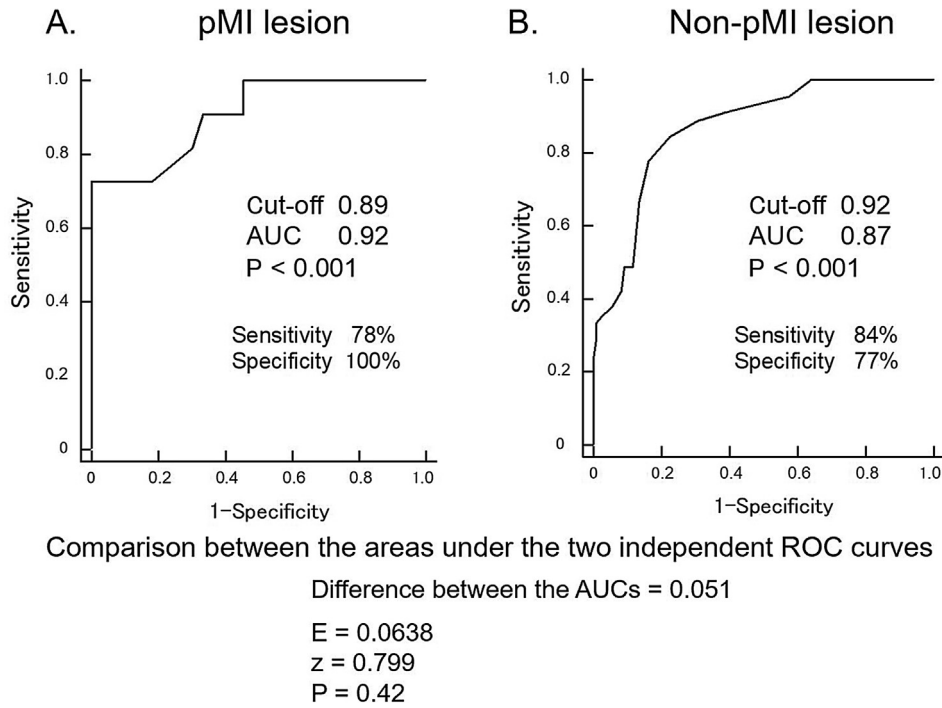

Fig. 3. Correlation between FFR and iFR in pMI lesion (**A**) and non-pMI lesion (**B**). iFR, instantaneous wave free ratio; FFR, fractional flow reserve; pMI, prior myocardial infarction.

demonstrated an iFR cut-off value for detecting FFR less than 0.8 was 0.91 in the entire study population. In addition, we reported an excellent correlation coefficient between FFR and iFR, and the iFR cut-off value for detecting FFR less than 0.80 was 0.89 even in pMI patients in this study. These findings clearly demonstrated the clinical usefulness of iFR for the detection of significant coronary artery stenosis even in lesions with pMI territories.

To maintain constant coronary circulation, auto-regulation is mediated by the resistive vessels [20]. Previous studies demonstrated that pMI patients were significantly associated with high microcirculatory resistance [21,22]. In addition, the index of micro-circulatory resistance (IMR) is independent of epicardial stenosis severity with no correlation with FFR [22,23]. iFR showed stronger correlations with CFR compared with FFR in a previous study, and this finding might suggest the possibility that iFR is influenced by the IMR, which leads to the consideration that the presence of pMI territories might influence the relationship

between the values of FFR and iFR [13]. In acute myocardial infarction (AMI) patients treated by primary PCI, coronary microcirculation begins to recover within 24 h and recovery progresses further by 6 months [24]. The value of IMR for patients without CAD was less than 20 mm Hg/s, and with angina pectoris was around 20 mm Hg/s [25]. Cuculi et al. demonstrated that pMI patients at 6 months after the onset and with preserved myocardial viability showed IMR values were around 20 mm Hg/s [24]. In pMI patients with preserved myocardial viability, post-intervention CFR was restored to values similar to those in patients with angina pectoris [26,27]. According to these findings, the micro-circulation of pMI territories was restored in pMI patients with preserved myocardial viability at 6 months from the onset of AMI. All enrolled pMI patients in this study were more than 6 months after the onset of AMI and with preserved myocardial viability in the pMI territories. Some previous studies demonstrated that FFR was reliable for assessing the functional severity of coronary artery lesions even in

Fig. 4. ROC curves of iFR values for an FFR cut-off value of 0.80 in pMI lesions **(A)** and non-pMI lesions **(B)**. ROC, receiver operating characteristic; iFR, instantaneous wave free ratio; FFR, fractional flow reserve; pMI, prior myocardial infarction.

Table 2
Major adverse cardiac events.

	All patients (n = 200)	Deferral of PCI group (n = 147)		P-value	PCI group (n = 53)		P-value
		pMI (n = 32)	Non-pMI (n = 115)		pMI (n = 12)	Non-pMI (n = 41)	
Major adverse cardiac event	7 (3.5)	1 (3.1)	4 (3.5)	0.70	1 (8.3)	1 (2.4)	0.41
Cardiovascular death	0 (0)	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Non-fetal myocardial infarction	1 (0.5)	1 (3.1)	0 (0)	0.22	0 (0)	0 (0)	–
Unstable AP requiring revascularization	3 (1.5)	0 (0)	2 (1.7)	0.61	1 (8.3)	0 (0)	0.23
Fatal arrhythmia	1 (0.5)	0 (0)	0 (0)	–	0 (0)	1 (2.4)	0.77
Hospitalization for heart failure	2 (1.0)	0 (0)	2 (1.7)	0.61	0 (0)	0 (0)	–

Data given as number and percentage.
pMI, prior myocardial infarction; AP, angina pectoris.
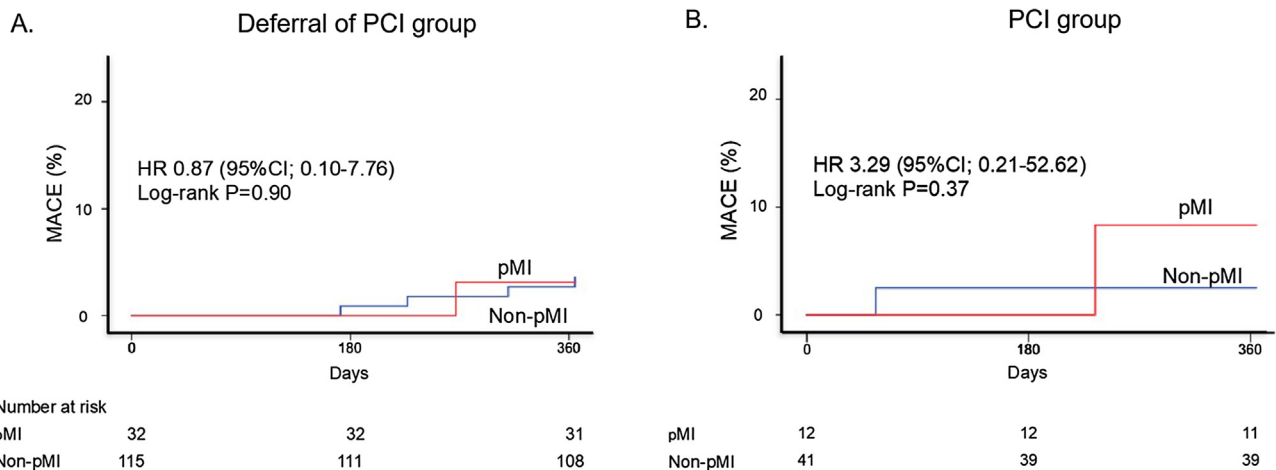
Fig. 5. Kaplan–Meier curves for the primary endpoint of deferral of PCI group **(A)** and PCI group **(B)**. PCI, percutaneous coronary intervention; pMI, prior myocardial infarction; MACE, major adverse cardiac event.

pMI territories with preserved myocardial viability [6,7]. Furthermore, phasic analysis of coronary pressure, flow, and microvascular resistance demonstrated that microvascular resistance is approximately 30–40% lower during the wave-free period compared with whole-cycle microvascular resistance [12]. iFR is calculated by measuring the resting pressure gradient across a coronary lesion during the portion of diastole when microvascular resistance is low and stable [10]. The present study showed that the optimal iFR cut-off was 0.89 for a clinical FFR cut-off of 0.80, which was almost consistent of the optimal cut-off value of 0.91 for lesions without pMI [10–12].

Cardiovascular events risk was strongly associated with age and medical history (e.g. DM, pMI, stroke, UAP, or HF) [28]. As mentioned above, pMI patients are considered as higher-risk patients for the recurrence of CAD and late complications, such as neoatherosclerosis, restenosis, and stent thrombosis [28,29]. However, there was no 1-year prognostic difference between pMI and non-pMI patients in this study. This may have been due to the short observational duration and the fact that the pMI patients had relatively low cardiovascular event risks because of their preserved myocardial viability.

Recent clinical trials including around 30% pMI patients showed that an iFR-guided PCI provided non-inferior prognosis to FFR-guided PCI at 1 year [14,15]. This might be consistent with our results that iFR-guided PCI is a useful procedure for pMI patients.

4.1. Limitations

Several limitations of this study should be acknowledged. First, this study was performed retrospectively using previous records from a routine clinical setting. Second, a reference examination of myocardial ischemia (i.e., stress perfusion images of O-15 water positron emission tomography, myocardial scintigraphy or cardiac MRI) was not performed as a confirmatory test. Third, two modalities including echocardiography and cardiac MRI were used for the quantification of myocardial viability. Fourth, unrecognized small pMI might be present in non-pMI patients [30]. Fifth, the effect of mediation for myocardial microcirculation and differences in medication between the two groups were not considered. Sixth, this study used a hybrid iFR-FFR-guided strategy for decision-making for deferral of PCI or not, because this study analyzed the data before publication of the DEFINE-FLAIR and iFR-SWEDEHEART trial [14,15]. Seventh, location of a stenosis may affect iFR and FFR values, but we could not conduct a study matched these conditions because of few pMI patients. Eighth, this study was conducted with a small patients population and short follow up period.

5. Conclusion

iFR may be a useful alternative method compared with FFR for clinical decision-making even in pMI patients.

Disclosures

Funding

Acknowledgements

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100431.

References

[1] N.H. Pijls, J.A. van Son, R.L. Kirkeeide, B. De Bruyne, K.L. Gould, Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty, Circulation 87 (1993) 1354–1367.

[2] W.F. Fearon, B. Bornshein, P.A. Tonino, et al., Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease, Circulation 122 (2010) 2545–2550.

[3] B. De Bruyne, N.H. Pijls, B. Kalesan, et al., Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease, N. Engl. J. Med. 367 (2012) 991–1001.

[4] M.R. Patel, G.J. Dehmer, J.W. Hirshfeld, P.K. Smith, J.A. Spertus, ACCF/SCAI/STS/ AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography, J. Am. Coll. Cardiol. 59 (2012) 857–881.

[5] S. Windecker, P. kolh, F. Alfonso, et al., ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), Eur. Heart J. 2014 (35) (2014) 2541–2619.

[6] B. De Bruyne, N.H. Pijls, J. Bartunek, et al., Fractional flow reserve in patients with prior myocardial infarction, Circulation 104 (2001) 157–162.

[7] Y. Usui, T. Chikamori, H. Yanagisawa, et al., Reliability of pressure-derived myocardial fractional flow reserve in assessing coronary artery stenosis in patients with previous myocardial infarction, Am. J. Cardiol. 92 (2003) 699–702.

[8] P.B. Dattilo, A. Prasad, E. Honeycutt, T.Y. Wang, J.C. Messenger, Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry, J. Am. Coll. Cardiol. 60 (2012) 2337–2339.

[9] H. Samady, B.D. Gogas, Does flow during rest and relaxation suffice?, J. Am. Coll. Cardiol. 61 (2013) 1436–1439.

[10] S. Sen, J. Escaned, I.S. Malik, et al., Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study, J. Am. Coll. Cardiol. 59 (2012) 1392–1402.

[11] R. Petraco, J.J. Park, S. Sen, et al., Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation, EuroIntervention 8 (2013) 1157–1165.

[12] S. Sen, K.N. Asrress, S. Nijjer, et al., Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study), J. Am. Coll. Cardiol. 61 (2013) 1409–1420.

[13] R. Petraco, T.P. van de Hoef, S. Nijjer, et al., Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve), Circ. Cardiovasc. Interv. 7 (2014) 492–502.

[14] J.E. Davies, S. Sen, H.M. Dehbi, et al., Use of the instantaneous wave-free ratio or fractional flow reserve in PCI, N. Engl. J. Med. 376 (2017) 1824–1834.

[15] M. Götberg, E.H. Christiansen, I.J. Gudmundsdottir, et al., Instantaneous wave-free ratio versus fractional flow reserve to guide PCI, N. Engl. J. Med. 376 (2017) 1813–1823.

[16] A.F. Schinkel, J.J. Bax, V. Delgado, D. Poldermans, S.H. Rahimtoola, Clinical relevance of hibernating myocardium in ischemic left ventricular dysfunction, Am. J. Med. 123 (2010) 978–986.

[17] R.J. Kim, E. Wu, A. Rafael, et al., The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction, N. Engl. J. Med. 343 (2000) 1445–1453.

[18] K.L. Gould, K. Lipscomb, G.W. Hamilton, Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve, Am. J. Cardiol. 33 (1974) 87–94.

[19] J.A. Hanley, B.J. McNeil, The meaning and use of the area under a receiver operating characteristic (ROC) curve, Radiology 143 (1982) 29–36.

[20] S.H. Nellis, A.J. Liedtke, L. Whitesell, Small coronary vessel pressure and diameter in an intact beating rabbit heart using fixed-position and free-motion techniques, Circ. Res. 49 (1981) 342–353.

[21] M.J. Claeys, C.J. Vrints, J.M. Bosmans, B. Krug, P.P. Blocjx, J.P. Snoeck, Coronary flow reserve during coronary angioplasty in patients with a recent myocardial infarction: relation to stenosis and myocardial viability, J. Am. Coll. Cardiol. 28 (1996) 1712–1719.

[22] J.M. Lee, J. Layland, J.H. jung, et al., Integrated physiologic assessment of ischemic heart disease in real-world practice using index of microcirculatory resistance and fractional flow reserve: insights from the international index of microcirculatory resistance registry, Circ. Cardiovasc. Interv. 8 (2015) e002857.

[23] A.S. Yong, M. Ho, M.G. Shah, M.K. Ng, W.F. Fearon, Coronary microcirculatory resistance is independent of epicardial stenosis, Circ. Cardiovasc. Interv. 5 (2012) 103–108.

[24] F. Cuculi, G.L. De Maria, P. Meier, et al., Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction, J. Am. Coll. Cardiol. 64 (2014) 1894–1904.

[25] W. Aarnoudse, G. Fearson WFm Manoharan, et al., Epicardial stenosis severity does not affect minimal microcirculatory resistance, Circulation 110 (2004) 2137–2142.

[26] A. Takaishi, K. Iwasaki, T. Murakami, et al., Coronary flow reserve after coronary intervention is similar in patients with preserved viability in previous myocardial infarction and in those with angina pectoris, J. Int. Med. Res. 32 (2004) 245–257.

[27] M. Bax, R.J. de Winter, K.T. Koch, C.E. Schotborgh, J.G. Tijssen, J.J. Piek, Time course of microvascular resistance of the infarct and noninfarct coronary artery following an anterior wall acute myocardial infarction, Am. J. Cardiol. 97 (2006) 1131–1136.

[28] T. Jernberg, P. Hasvold, M. Henriksson, H. Hjelm, M. thuresson, M. Janzon, Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective, Eur. Heart J. 36 (2015) 1163–1170.

[29] F. Philip, S. Agarwal, M.C. Bunte, et al., Stent thrombosis with second-generation drug-eluting stents compared with bare-metal stents: network meta-analysis of primary percutaneous coronary intervention trials in ST-segment-elevation myocardial infarction, Circ. Cardiovasc. Interv. 7 (2014) 49–61.

[30] T. Omori, T. Kurita, K. Dohi, et al., Prognostic impact of unrecognized myocardial scar in the non-culprit territories by cardiac magnetic resonance imaging in patients with acute myocardial infarction, Eur. Heart J. Cardiovasc. Imag. 19 (2018) 108–116.