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Association of microvascular dysfunction with clinical outcomes in patients with non-flow limiting fractional flow reserve after percutaneous coronary intervention

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ABSTRACT

Background: We sought to investigate prognostic implication of microvascular dysfunction as assessed by the index of microcirculatory index (IMR) in patients without residual obstructive CAD with non-flow limiting fractional flow reserve (FFR) (>0.80) following percutaneous coronary intervention (PCI).
Methods: A total of 570 patients who had both post-PCI FFR and IMR values were included in the present analysis; of these, 65 patients had FFR $\leq$ 0.80 and 505 had FFR > 0.80. Of the 505 patients with FFR > 0.80, 137 had high IMR and 368 had low IMR. The primary outcome of the present analysis is a composite of all-cause death, spontaneous myocardial infarction, or target-vessel revascularization. Impaired microvascular function was defined as IMR $\geq$ 25 (high IMR).
Results: During a median follow-up duration of 4.0 years, those with FFR > 0.80 and low IMR demonstrated lower rate or primary outcome event than those with FFR $\leq$ 0.80 (hazard ratio 0.49 [95% confidence interval 0.27–0.92], p = 0.026) and those with FFR > 0.80 and high IMR (hazard ratio 1.60 [0.99–2.16], p = 0.056). The patients with FFR > 0.80 and IMR $\geq$ 25 had similar rate of primary outcome event compared with those with FFR $\leq$ 0.80 (p = 0.49).
Conclusion: Microvascular dysfunction following PCI is not rare and is associated with adverse events even in the setting of a non-flow limiting FFR; these results suggest that when performing coronary physiologic assessment following PCI, interrogating not only the epicardial vessel, but also the microvasculature is useful for the risk stratification in patients undergoing PCI.

1. Introduction

Physiologic assessment of coronary artery lesions following percutaneous coronary intervention (PCI) is recently attracting attention as a tool to evaluate residual coronary disease and to predict clinical events after PCI. Significant residual ischemia after angiographically successful PCI (defined as FFR $\leq$ 0.80 and/or iFR $\leq$ 0.89) occurs in a significant portion of patients and is associated with more frequent adverse events [1]. Recent prospective studies suggest that physiology-guided optimization can reduce residual ischemia [2] and lead to better clinical outcome [3]. However, despite the success of PCI in reducing ischemia by treating epicardial artery narrowing, microvascular dysfunction (MVD) is observed in around one quarter of patients after PCI, identifying patients with a worse clinical outcome [4]. In the present analysis,

Abbreviations: FFR, fractional flow reserve; IMR, the index of microcirculatory index; MI, myocardial infarction; MVD, microvascular dysfunction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

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we focus on the prognostic implication of MVD in the absence of a residual flow limiting epicardial disease following PCI, comparing the rate of adverse cardiac events in patients with MVD as assessed by the index of microcirculatory index (IMR) and a non-flow limiting FFR (>0.80) versus patients with no MVD and non-flow limiting FFR and patients with a flow limiting FFR (FFR $\leq$ 0.80) as reference.

2. Methods

The present study was an additional analysis of the international registry where we included 572 stable patients who underwent IMR measurement using a pressure sensor/thermistor-tipped guidewire immediately after elective and successful PCI from 2009 to 2013 from 8 hospitals in 4 countries (Australia, Belgium, Japan, and United States) [4]. We excluded patients with acute coronary syndrome, previous myocardial infarction (MI) in the target vessel, a previous bypass graft to the target vessel, recent MI, and patients with a target vessel in which IMR post-PCI could not be successfully measured. Further details of the methods have been described previously [4]. In the registry, an FFR value post PCI was missing in 2 patients who were therefore excluded from the present analysis. In the original report from this registry, we included periprocedural MI as a part of the primary outcome (i.e., all-cause death, any MI or target vessel revascularization). However, since there was a strong correlation between high IMR and periprocedural MI, the prognostic significance of high IMR based on the primary outcome

Table 1
Clinical characteristics.

	FFR > 0.80, low IMR (n = 368)	FFR > 0.80, High IMR (n=137)	FFR $\leq$ 0.80 (n = 65)	*p* value
Age, years	66 ± 9	67 ± 9	66 ± 10	0.70
Male	302 (82%)	112 (82%)	55 (85%)	0.87
BMI	25.3 ± 3.9	25.6 ± 4.7	26.4 ± 4.9	0.19
Diabetes Mellitus	131 (36%)	56 (41%)	27 (42%)	0.43
Hypertension	260 (71%)	98 (72%)	49 (75%)	0.74
Dyslipidemia	241 (66%)	100 (73%)	46 (71%)	0.24
Smoking	93 (25%)	41 (30%)	16 (25%)	0.54
Prior myocardial infarction	24 (7%)	13 (10%)	3 (5%)	0.37
Prior PCI	44 (12%)	19 (14%)	8 (12%)	0.85
Reduced LVEF (<50%)	37 (10%)	13 (10%)	4 (6%)	0.61
Target Vessels				<0.001
LAD	244 (66%)	83 (61%)	59 (91%)	
LCX	59 (16%)	16 (12%)	3 (5%)	
LM	1 (0.3%)	0 (0%)	0 (0%)	
RCA	64 (17%)	38 (28%)	3 (5%)	
Lesion Length, mm	15.2 ± 8.1	15.6 ± 9.5	16.2 ± 9.4	0.69
MLD, mm	1.3 ± 2.1	1.2 ± 0.4	1.1 ± 0.4	0.54
Reference Diameter	2.7 ± 0.6	2.8 ± 0.6	2.5 ± 0.5	0.002
%Diameter Stenosis	56 ± 12%	59 ± 11%	56 ± 15%	0.047
No. of Stents	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.5	0.56
DES use	318 (86%)	116 (85%)	59 (91%)	0.50
Stent Length, mm	25.8 ± 11.0	26.9 ± 12.2	27.3 ± 13.8	0.52
Stent Diameter, mm	3.1 ± 0.4	3.2 ± 0.4	3.1 ± 0.4	0.13
Multi-vessel disease	55 (15%)	25 (18%)	10 (15%)	0.65
Side branch occlusion*	12/330 (4%)	5/126 (4%)	2/59 (3.4%)	0.98
Slow flow†	4/331 (1%)	3/126 (2%)	0/59 (0%)	0.40
Post-PCI troponin elevation (times 99th percentile URL)	5.7 ± 15.1 1.5 [0.5, 3.5]	8.9 ± 14.3 1.3 [0.5, 6.0]	3.6 ± 10.8 1.0 [0.5, 2.3]	0.021
Post-PCI troponin >URL	218 (59%)	82 (60%)	31 (48%)	0.20
Medications				
β-blockers	154 (42%)	60 (44%)	31 (48%)	0.66
ACE inhibitor or ARB	221 (60%)	74 (54%)	50 (77%)	0.008
Statin	266 (72%)	104 (76%)	55 (85%)	>0.99
Calcium channel blockers‡	142 (41%)	46 (35%)	20 (33%)	0.40
Nitrates‡	99 (28%)	34 (26%)	15 (25%)	0.81
Coronary Physiological Indicies				
Pre-PCI CFR	2.7 ± 1.7 2.3 [1.6, 3.3]	2.3 ± 1.4 2.0 [1.2, 2.9]	2.1 ± 1.2 1.9 [1.3, 2.6]	0.008
Pre-PCI IMR_{true}	20.7 ± 13.3 17.2 [11.3, 26.8]	34.0 ± 26.2 26.0 [19.8, 44.3]	17.5 ± 9.6 16.5[10.7, 21.6]	<0.001
Pre-PCI FFR	0.69 ± 0.12 0.73 [0.65, 0.78]	0.70 ± 0.13 0.73 [0.64, 0.79]	0.60 ± 0.13 0.62 [0.50, 0.71]	<0.001
Post-PCI CFR	4.1 ± 2.3 3.5 [2.3, 5.3]	2.3 ± 0.9 2.2 [1.7, 2.7]	3.1 ± 1.6 2.5 [1.9, 4.0]	<0.001
Post-PCI IMR	15.0 ± 4.7 14.9 [10.9, 18.3]	39.5 ± 16.3 35.0 [29.8, 43.1]	17.2 ± 12.0 12.2 [9.6, 21.5]	<0.001
Post-PCI FFR	0.89 ± 0.05 0.88 [0.85, 0.93]	0.90 ± 0.05 0.90 [0.86, 0.95]	0.75 ± 0.05 0.77 [0.74, 0.79]	<0.001

Values are mean ± SD, median [interquartile range], or n (%). ACE, Angiotensin-converting enzyme; ARB, Angiotensin II Receptor Blockers; BMI, body mass index; CFR, coronary flow reserve; DES, drug-eluting stent; FFR, fractional flow reserve; IMR, the index of microcirculatory index; LAD, left anterior descending artery; LCX, left circumflex; LM, left main, LVEF, left ventricular ejection fraction; RCA, right coronary artery; MLD, minimum lumen diameter; PCI, percutaneous coronary intervention. *†‡Data were not available for 55*, 54† and 30‡ patients. Pre-PCI IMR_{true} was available in 446 patients; pre-PCI CFR in 467; pre-PCI FFR in 565 patients; and post-PCI CFR in 502 patients.

was largely driven by periprocedural MI. There has been still controversy about the definition of periprocedural MI and its clinical relevance. Therefore, in the present analysis, we exclude periprocedural MI from the primary outcome and defined it as a composite of all-cause death, spontaneous myocardial infarction (MI), or target-vessel revascularization (TVR). A flow-limiting FFR value was defined as FFR $\leq$ 0.80 and impaired microvascular function was defined as IMR $\geq$ 25 (high IMR). The study was approved by an institutional review committee from each site, and the study protocol was in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

Categorical variables were expressed as numbers and/or percentages and compared using Fisher's exact test. Continuous data are expressed as mean ± SD (or median [interquartile range] for coronary physiological indices and the degree of troponin elevation) and compared using Student *t* test or Mann-Whitney *U* test as appropriate. The cumulative incidence of clinical events was estimated by the Kaplan-Meier method and compared by the log-rank test. Hazard ratio (HR) with 95% confidence interval (CI) was analyzed using the Cox proportional hazard model. Adjusted HR for primary outcome was calculated in a multivariable model with adjustment for potential confounding factors [4], including age, sex, body mass index, diabetes mellitus, hypertension, dyslipidemia, prior MI, prior PCI, smoking, reduced ejection fraction, lesion location, multivessel disease, DES use, number of stent, stent length, and stent diameter. SPSS version 24 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) and R programming language version 3.1.4 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

3. Results

A total of 570 patients who had both post-PCI FFR and IMR values were included in the present analysis (mean age 66 ± 10, 82% male); of these, 65 patients had an FFR $\leq$ 0.80 and 505 had anFFR > 0.80. Of the 505 patients with FFR > 0.80, 137 had high IMR and 368 had low IMR. Clinical characteristics and outcomes are summarized in Table 1. The LAD was more often the target vessel in patients with FFR $\leq$ 0.80. Patients with high IMR had relatively larger reference lumen diameter and greater percent diameter stenosis than those with low IMR and those with FFR $\leq$ 0.80. During a median follow-up duration of 4.0 years, those with negative post-PCI FFR and low IMR demonstrated lower rate of primary outcome event (a composite of death, spontaneous MI, and TVR) than those with FFR $\leq$ 0.80 and those with FFR > 0.80 and high IMR post PCI. The patients with FFR > 0.80 and high IMR post PCI had similar rate of primary outcome event compared with those with post-PCI FFR $\leq$ 0.80 (Fig. 1). The higher rate of primary outcome events in patients with FFR $\leq$ 0.80 was mainly driven by higher rate of TVR, whereas patients with high IMR and FFR > 0.80 had numerically higher rate of events than patients with low IMR and FFR > 0.80 across all the components of primary outcomes without any statistical significance of each (Table 2). The rate of non-target revascularization was higher in patients with FFR $\leq$ 0.80 than the other 2 groups. There was no significant difference in the rate of non-target revascularization between the high and low IMR groups. The multiple variable Cox hazard model for the primary outcome event showed a consistent result; the risk was highest in patients with FFR $\leq$ 0.80, followed by patients with FFR > 0.80 and high IMR, and lowest in patients with FFR > 0.80 and low IMR. When using patients with low IMR and FFR > 0.80 as a reference, adjusted HR were 1.44 (95 %CI 0.85–2.45) in patients with high IMR and FFR > 0.80, and 2.91 (95 %CI 1.47–5.75) in patients with FFR $\leq$ 0.80.

4. Discussion

The present study investigated prognostic implication of MVD in the absence of flow limiting FFR following PCI, comparing the risk of adverse cardiac events including death, spontaneous MI

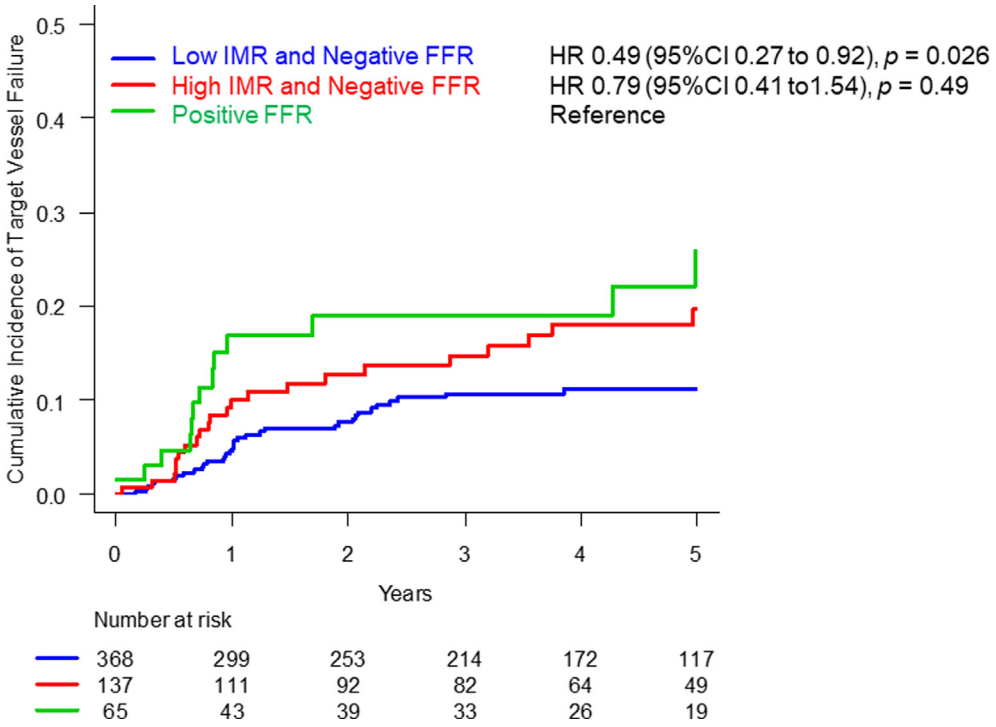

Fig. 1. Target vessel failure defined as a composite of death, myocardial infarction or target-vessel revascularization according to IMR among patients with non-flow limiting FFR (FFR > 0.80) compared with those with flow-limiting FFR (FFR $\leq$ 0.80). The group with microvascular dysfunction (IMR $\geq$ 25) exhibited as similar incidence of adverse cardiovascular events compared with those with FFR > 0.80, while those with low IMR and FFR > 0.80 showed better clinical outcomes.

Table 2
Clinical outcomes.

	FFR > 0.80, low IMR (n = 368)	FFR > 0.80, High IMR (n = 137)	FFR ≤ 0.80 (n = 65)
Primary Outcome: Death, MI, or TVR	44 (12.0%) 3.0% PPY Reference HR 0.49 (0.27–0.92), p = 0.026	26 (19.0%) 4.6% PPY HR 1.60 (0.99–2.61), p = 0.056 HR 0.79 (0.41–1.54), p = 0.49	13 (20.0%) 5.7% PPY HR 2.03 (1.09–3.77), p = 0.026 Reference
Death, or MI	22 (6.0%) HR 0.81 (0.28–2.37) Reference	15 (10.9%) HR 1.46 (0.48–4.44) HR 1.80 (0.93–3.48)	4 (6.2%) Reference HR 1.23 (0.42–3.59)
Death	16 (4.3%) HR 0.60 (0.20–1.80) Reference	10 (7.3%) HR 0.97 (0.30–3.08) HR 1.67 (0.56–5.02)	4 (6.2%) Reference HR 1.61(0.73–3.56)
MI	6 (1.6%) HR 0.86 (0.10–7.22) Reference	5 (3.6%) HR 2.00 (0.23–17.21) HR 2.33 (0.71–7.66)	1 (1.5%) Reference HR 1.17 (0.14–9.79)
TVR	25 (6.8%) HR 0.37 (0.18–0.77) Reference	14 (10.2%) HR 0.56 (0.25–1.27) HR 1.52 (0.79–2.93)	10 (15.4%) Reference HR 2.72 (1.30–5.69)
Non-TVR	39 (10.6%) HR 0.37 (0.20–0.67) Reference	17 (12.4%) HR 0.42 (0.21–0.85) HR 1.15 (0.65–2.04)	15 (23.1%) Reference HR 2.71 (1.49–4.95)

Values are n (%) and hazard ratio (95% confidence interval). FFR, fractional flow reserve; HR, hazard ratio; IMR, the index of microcirculatory index; MI, myocardial infarction; PCI; percutaneous coronary intervention; PPY, per patient year; TVR, target vessel revascularization.

and TVR between subgroups based on post-PCI IMR and FFR, and found that there was a risk stratification of adverse cardiac events with the risk being highest in patients with FFR ≤ 0.80, followed by patients with high IMR and FFR > 0.80 and lowest in patients with low IMR and FFR > 0.80. The results of the present study suggest that MVD is associated with adverse clinical events even after successful relief of epicardial artery narrowing (post-PCI FFR > 0.80). MVD following PCI precludes sufficient coronary flow and myocardial perfusion, which may contribute to plaque proliferation, and neointima and thrombus formation, resulting in a higher incidence of MI and TVR. Another possible explanation is that coronary lesions associated with microvascular embolization and subsequent microvascular dysfunction following PCI may contain greater plaque burden and more unstable plaque resulting in a higher rate of future adverse events. Indeed, as we previously reported, patients with elevated post-PCI IMR had a higher incidence of periprocedural MI assessed by troponin elevation (HR 1.59 [95 %CI 1.11–2.28]) [4]. In addition, the post-PCI FFR value can be falsely high when there is significant acute microvascular dysfunction (i.e., high IMR value) as it blunts the vasodilator response leading to a decrease in maximal myocardial flow. Additionally, patients with MVD may have ongoing angina [5,6] which may lead to recurrent catheterization and repeat revascularization. In the present study, numerically higher incidence rate of spontaneous MI or TVR was observed in patients with non-flow limiting FFR and high IMR than patients with low IMR; however, it did not achieve statistical significance. A further study with a larger sample size is needed to confirm our findings and hypotheses.

The microvascular dysfunction observed after PCI may not be an acute procedure-related event, but may exist before PCI in many cases, due to pre-existing conditions such as diabetes mellitus, amyloid or hypertrophic cardiomyopathy. In the present study, those with post-PCI high IMR had high pre-IMR_{true} than the others, suggesting observed microvascular dysfunction was not only acquired by PCI but also preexisted before PCI. Previous study from the WISE showed that among women without obstructive coronary artery disease, abnormal nuclear magnetic resonance spectroscopy test consistent with myocardial ischemia predicted cardiovascular outcome, notably higher rates of anginal hospitalization and repeat catheterization [5]. Lee et al reported that among 230 patients with FFR > 0.80, those with overt microvascular dysfunction defined as high IMR (≥23) and low coronary flow reserve (≤2.0) (n = 16) had worse outcomes than those without, and the overt microvascular dysfunction, diabetes mellitus, and multivessel disease are independent prognostic factors in patients with non-flow limiting FFR [7]. A recent international and prospective cohort study by the Coronary Vasomotor Disorders International Study (COVADIS) Group showed that patients with ischemic sings/symptoms and MVD in the absence of obstructive CAD were at substantial risk of major adverse events (7.7% per patient year), especially hospitalization for unstable angina, and that previous history of CAD was the most significant independent predictor of the adverse events [6]. These results suggest that MVD even not related to revascularization is prognostically important, especially in patients with CAD, supporting the interrogation of microvascular function in patients undergoing PCI. The etiology of abnormal function and the difference in their prognostic importance require further investigation.

Some limitations in the present study should be considered when interpreting the findings. First, the present study was a post hoc analysis with a relatively small number of patients. Therefore, the findings are hypothesis generating in nature. Second, there were only 10 patients who had FFR ≤ 0.80 and IMR ≥ 25 post PCI in the present study cohort; of these, 3 patients had a primary outcome event during a follow-up period. Due to the limited number of patients and events, we did not subdivide patients with FFR ≤ 0.80 according to the IMR value. The prognostic significance of high IMR in patients with flow limiting FFR post PCI should be further investigated in future research. Third, neither the patients nor the physicians were blinded to the physiologic values. Finally, pre-PCI IMR_{true} was not available in all patients, therefore we could not fully investigate its clinical importance in relation to post-PCI IMR.

5. Conclusion

MVD following PCI is not rare and is associated with adverse events even in the setting of a non-flow limiting FFR; these results suggest that when performing coronary physiologic assessment

following PCI, interrogating not only the epicardial vessel, but also the microvasculature is useful for the risk stratification in patients who underwent PCI.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [T. Murai. has received fees from Abbott Vascular Japan and Phillips-Volcano Japan for educational events. Dr Fearon reports research grants from Medtronic and Abbott and consulting with HeartFlow and CathWorks. The other authors report no conflicts.].

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