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 <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 ≥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 <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 ≥25 had similar rate of primary outcome event compared with those with FFR ≤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.

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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 < 0.80 and/or iFR < 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]. How-
ever, 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, 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 ≤ 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

### Table 1

| Clinical characteristics | FFR > 0.80, Low IMR (n=368) | FFR > 0.80, High IMR (n=137) | FFR ≤ 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 ± 2.3                    | 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 Diameter, mm       | 25.8 ± 11.0                  | 26.9 ± 12.2                  | 27.3 ± 13.8      | 0.52   |
| Stent Length, 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 | 8.9 ± 14.3 | 3.6 ± 10.9 | 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<sup>2</sup>     | 99 (28%)                     | 34 (26%)                     | 15 (25%)         | 0.81   |
| **Coronary Physiological Indicies** |                          |                              |                  |        |
| Pre-PCI CFR              | 2.7 ± 1.7                    | 2.3 ± 1.4                    | 2.1 ± 1.2        | 0.008  |
| Pre-PCI IMR<sub>min</sub> | 2.3 [1.6, 3.3]               | 2.0 [1.2, 2.9]               | 1.9 [1.3, 2.6]   | <0.001 |
| Pre-PCI FFR              | 20.7 ± 13.3                  | 34.0 ± 26.2                  | 17.5 ± 9.6       | <0.001 |
| Pre-PCI FFR              | 17.2 [11.3, 26.8]            | 26.0 [19.8, 44.3]            | 16.5 [10.7, 21.6]| <0.001 |
| Pre-PCI FFR              | 0.69 ± 0.12                  | 0.70 ± 0.13                  | 0.69 ± 0.13      | <0.001 |
| Post-PCI CFR             | 0.73 [0.65, 0.78]            | 0.73 [0.64, 0.79]            | 0.62 [0.50, 0.71]| <0.001 |
| Post-PCI CFR             | 3.5 [2.3, 5.3]               | 2.2 [1.7, 2.7]               | 2.5 [1.9, 4.0]   | <0.001 |
| Post-PCI IMR             | 15.0 ± 4.7                   | 39.5 ± 16.3                  | 17.2 ± 12.0      | <0.001 |
| Post-PCI FFR             | 14.9 [10.9, 18.3]            | 35.0 [29.8, 43.1]            | 12.2 [9.6, 21.5] | <0.001 |
| Post-PCI FFR             | 0.89 ± 0.05                  | 0.90 ± 0.05                  | 0.75 ± 0.05      | <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<sub>min</sub> was available in 446 patients; pre-PCI CFR in 467; pre-PCI FFR in 565 patients; and post-PCI CFR in 502 patients.
on the primary outcome 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 ≤ 0.80 and impaired microvascular function was defined as IMR ≥ 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’s 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 ≤ 0.80 and 505 had an FFR > 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 ≤ 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 ≤ 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 ≤ 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 ≤ 0.80 (Fig. 1). The higher rate of primary outcome events in patients with FFR ≤ 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 ≤ 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 ≤ 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 ≤ 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...
Clinical outcomes.

Those with post-PCI high IMR had high pre-IMR true than the others, amyloid or hypertrophic cardiomyopathy. In the present study, acute procedure-related event, but may exist before PCI in many patients. In the present study, numerically higher incidence rate of spontaneous MI or TVR was observed in patients with non-flow limiting lesions associated with microvascular embolization and subsequent microvascular dysfunction following PCI may contain additional and prospective cohort study by the Coronary Vasomotor Disorders International Study (COVADIS) Group showed that patients with ischemic signs/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 MVD 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

| Table 2 |
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| 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%) | 26 (19.0%) | 13 (20.0%) |
| | 3.0% PPY | 4.6% PPY | 5.7% PPY |
| HR 0.49 (0.27–0.92), p = 0.026 | HR 1.60 (0.99–2.61), p = 0.056 | HR 2.03 (1.09–3.77), p = 0.026 |
| Death, or MI | 22 (6.0%) | 15 (10.9%) | 4 (6.2%) |
| | Reference | HR 1.46 (0.48–4.44) | Reference |
| HR 0.81 (0.28–2.37) | HR 1.80 (0.93–3.48) | HR 1.23 (0.42–3.59) |
| Death | 16 (4.3%) | 10 (7.3%) | 4 (6.2%) |
| | Reference | HR 0.97 (0.30–3.08) | Reference |
| HR 0.60 (0.20–1.80) | HR 1.67 (0.56–5.02) | HR 1.61 (0.73–3.56) |
| MI | 6 (1.6%) | 5 (3.6%) | 1 (1.5%) |
| | Reference | HR 2.00 (0.23–17.21) | Reference |
| HR 0.86 (0.10–7.22) | HR 2.33 (0.71–7.66) | HR 1.17 (0.14–9.79) |
| TVR | 25 (6.8%) | 14 (10.2%) | 10 (15.4%) |
| | Reference | HR 0.56 (0.25–1.27) | Reference |
| HR 0.37 (0.18–0.77) | HR 1.52 (0.79–2.93) | HR 2.72 (1.30–5.69) |
| Non-TVR | 39 (10.6%) | 17 (12.4%) | 15 (23.1%) |
| | Reference | HR 0.42 (0.21–0.85) | Reference |
| HR 0.37 (0.20–0.67) | HR 1.15 (0.65–2.04) | 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.
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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References
[1] G. Rimac, W.F. Fearon, B. De Bruyne, F. Ikeno, H. Matsuo, Z. Piroth, et al., Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis, Am Heart J. 183 (2017) 1–9.
[2] D. Collison, TARGET FFR: A randomized trial of physiology-guided PCI optimization, Presented at: TCT October 16 (2020) 2020 (abstr).
[3] Patel M, Jeremias A, Davies J, et al. One-year outcomes of patients with residual physiologic ischemia after percutaneous coronary intervention: the DEFINE PCI trial, Presented at: TCT 2020. October 15, 2020. (abstr).
[4] Nishi T, Murai T, Ciccarelli G, Shah SV, Kobayashi Y, Derimay F, et al. Prognostic Value of Coronary Microvascular Function Measured Immediately After Percutaneous Coronary Intervention in Stable Coronary Artery Disease: An International Multicenter Study. Circ Cardiovasc Interv. 2019:e007889. doi: 10.1161/CIRCINTERVENTIONS.119.007889.
[5] B.D. Johnson, L.J. Shaw, S.D. Buchthal, C.N. Bairey Merz, H.W. Kim, K.N. Scott, et al., Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE), Circulation. 109 (2004) 2993–2999.
[6] H. Shimokawa, A. Suda, J. Takahashi, C. Berry, P.G. Camici, F. Crea, J. Escaned, et al., Clinical characteristics and prognosis of patients with microvascular angina: an international and prospective cohort study by the Coronary Vasomotor Disorders International Study (COVADIS), Group. Eur Heart J. (2021), https://doi.org/10.1093/eurheartj/ehab282, May 26:ehab282.
[7] J.M. Lee, J.H. Jung, D. Hwang, J. Park, Y. Fan, S.H. Na, et al., Coronary Flow Reserve and Microcirculatory Resistance in Patients With Intermediate Coronary Stenosis, J Am Coll Cardiol. 67 (2016) 1158–1169.