INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Myocardial Injury after Percutaneous Coronary Intervention for In-Stent Restenosis Versus *de novo* Stenosis

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Abstract

Objective Periprocedural myocardial injury (PMI) remains a relatively common complication even after successful procedures. In-stent restenosis (ISR) may be involved in lesion-related factors for PMI. We compared the incidence of PMI between patients with ISR and those with *de novo* stenosis.

Methods The study population consisted of 121 patients with coronary artery disease who had been treated with statins and subsequently underwent angiographically successful percutaneous coronary intervention (PCI). Blood samples for troponin I were collected 18 to 24 hours after PCI. PMI was defined as an increase in the troponin I levels greater than 0.15 ng/mL. Major PMI was defined as an increase in the troponin I levels greater than 0.75 ng/mL.

Results There were 34 patients with ISR and 87 patients with *de novo* stenosis. The incidence of PMI was similar between the two groups (47.1 % vs. 55.2 %, p=0.42). Among the patients with ISR, the incidences of PMI were 33.3 %, 60.0 % and 66.7 % in patients with focal ISR, diffuse ISR and diffuse proliferative ISR, respectively, although these differences were not statistically significant. The incidence of major PMI was significantly less frequent in patients with ISR than those with *de novo* stenosis (5.9 % vs. 25.3 %, p=0.03). A multivariate logistic regression analysis showed that ISR [odds ratio (OR) 0.22, 95% confidence interval (CI) 0.03-0.90; p=0.03] and the maximum inflation pressure (OR 1.15, 95% CI 1.04-1.30; p=0.009) were independent predictors of major PMI.

Conclusion Our results suggest that while PMI occurs in patients with ISR as commonly as those with *de novo* stenosis, major PMI occurs less frequently in patients with ISR.

Key words: periprocedural myocardial injury, in-stent restenosis, percutaneous coronary intervention

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Introduction

Percutaneous coronary intervention (PCI) is a well-established treatment of coronary artery disease (1-3). Periprocedural complications such as acute closure or flow-limiting dissection have decreased significantly with technological advances. However, periprocedural myocardial injury (PMI) remains a relatively common complication even after successful procedures (4, 5). Some studies have shown that PMI is associated with subsequent mortality and other poor clinical outcomes (6-8). It is therefore clinically important to clarify lesion-related factors. Previous studies have shown that plaque burden, lesion eccentricity or thrombus is associated with the development of PMI. However, little is known regarding the development of PMI on in-stent restenosis (ISR). ISR remains an unresolved limitation of PCI (9-11), and it is often treated with repeated PCI (12, 13). Because there are some differences in the tissue characteristics between ISR and *de novo* stenosis (14, 15), ISR may be involved in lesion-related factors for PMI. To elucidate this issue, we compared the incidence of PMI between patients with ISR and those with *de novo* stenosis.

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Materials and Methods

Study population

The study population consisted of 121 patients with coronary artery disease (CAD) who had been treated with statins and subsequently underwent angiographically successful PCI between March 2012 and July 2013 at Hiroshima University Hospital. The main objective of this study was to clarify the effects of ISR on PMI. Several previous studies have shown favorable effects of statins on PMI (16, 17). Therefore, only patients who had been treated with statins prior to PCI were included in the current study. The indications for PCI were: symptomatic CAD or documented myocardial ischemia on a treadmill exercise test or myocardial scintigraphy; and diameter stenosis of >75% on coronary angiography. Procedural success was defined as residual diameter stenosis of <25% and Thrombolysis in Myocardial Infarction (TIMI) grade of 3 on the final angiogram (18). Exclusion criteria included: acute coronary syndrome; prior myocardial infarction in the territory associated with the target vessel; severe renal insufficiency (serum creatinine >2.0 mg/dL); small vessel disease (<2 mm); abnormal value of creatine kinase before PCI; transient no-flow/slow-flow during PCI; or occlusion of the major branch (>1 mm) after PCI.

Quantitative coronary angiography and PCI procedure

Coronary angiograms for quantitative coronary angiography (QCA) were obtained after intracoronary infusion of isosorbide dinitrate (2.0 mg), and evaluated using the QCA analysis software program (QCA-CMS v.6.0, Medis, Leiden, Netherlands). All PCI procedures in the catheterization laboratory were performed according to standard techniques. PCI was performed through the radial, brachial or femoral artery by experienced cardiologists. The strategy of PCI, such as the stent type, size or length, was left to the discretion of the operator. In principle, patients with in-stent restenosis were treated with balloon angioplasty, and patients with *de novo* stenosis were treated with stent deployment. The angiograms were reviewed offline by two independent cardiologists, and ISR was classified as follows according to the previous report (19):

・Focal ISR: lesions are ≦10 mm in length and are positioned at the unscaffolded segment, the body of the stent, the proximal or distal margin (but not both) or a combination of these sites

・Diffuse intrastent ISR: lesions are >10 mm in length and are confined to the stent without extending outside the margins of the stent

・Diffuse proliferative ISR: lesions are >10 mm in length and extend beyond the margin of the stent.

PMI

Blood samples for lipid, glucose and inflammatory profiles were collected at fasting before PCI from the peripheral vein. The blood samples for troponin I were collected 18 to 24 hours after PCI. Troponin I levels were measured using a commercially available assay kit. The upper limit of the normal value (ULN) of this assay was 0.05 ng/mL. PMI was defined as an increase in the troponin I levels greater than 0.15 ng/mL (3 times the ULN) (20). Major PMI was defined as an increase in the troponin I levels greater than 0.75 ng/mL (15 times the ULN).

Statistical analysis

Continuous variables are shown as the mean ± SD, and categorical variables are presented as frequencies and percentages. Continuous variables were compared using Student's *t*-test or the Mann-Whitney U-test. Categorical variables were compared using the chi-square test or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to evaluate the relation between major PMI and other variables. Differences were considered to be significant if the p value was <0.05. Statistical analysis was conducted using the JMP 11 software program (SAS Institute, Tokyo, Japan).

Results

Patient characteristics

There were 34 patients with ISR and 87 patients with *de novo* stenosis. ISR was found on a bare metal stent (BMS) in 14 patients and on a drug-eluting stent (DES) in 20 patients. The patient characteristics of the two groups are shown in Table 1. There was no significant difference in the coronary risk factors, such as hypertension or diabetes mellitus, between the two groups. Previous myocardial infarction occurred more frequently in patients with in-stent restenosis than those with *de novo* stenosis (47.1 % vs. 18.4 %, p= 0.001). All patients were treated with statins, and there was no significant difference in the medications between the two groups except for a lower use of clopidogrel in patients with ISR.

Lesion characteristics and PCI procedure

The lesion characteristics and PCI procedure of the two groups are shown in Table 2. In patients with ISR, the previously deployed stent size was 3.05±0.45 mm. The angiograms showed focal ISR in 18 patients, diffuse ISR in 10 patients and diffuse proliferative ISR in 6 patients. There was no significant difference in the culprit lesion location or PCI procedure, such as maximum balloon size or maximum inflation pressure, between patients with ISR and those with *de novo* stenosis. Before PCI, patients with ISR had a significantly shorter lesion length than those with *de novo* stenosis (14.6±7.0 mm vs. 22.2±11.7 mm, p<0.001), however, the minimum lumen diameter and diameter stenosis were similar between the two groups. After PCI, patients with ISR had a significantly smaller minimum lumen diame-

Table 1. **Patient Characteristics.**

	Patients with in-stent restenosis (n=34)	Patients with *de novo* stenosis (n=87)	p value
Age (years)	71.1 ± 9.8	70.8 ± 8.4	0.95
Male gender	22 (64.7%)	70 (80.5%)	0.07
Hypertension	28 (82.4%)	79 (90.8%)	0.32
Hyperlipidemia	25 (73.5%)	64 (73.6%)	0.82
Diabetes	23 (67.6%)	51 (58.6%)	0.36
Smoking	19 (55.9%)	60 (69.0%)	0.25
Prior myocardial infarction	16 (47.1%)	16 (18.4%)	0.001
Prior coronary intervention	34 (100%)	51 (58.6%)	< 0.001
Serum creatinine (mg/dL)	1.03 ± 0.25	0.96 ± 0.26	0.13
LDL cholesterol (mg/dL)	82.6 ± 25.4	86.8 ± 25.7	0.42
HDL cholesterol (mg/dL)	54.3 ± 16.8	49.3 ± 12.5	0.12
Fasting plasma glucose (mg/dL)	114.5 ± 28.4	126.6 ± 44.0	0.08
Hemoglobin A1C (%)	6.3 ± 0.9	6.1 ± 1.0	0.23
C reactive protein (mg/dL)	0.14 ± 0.28	0.19 ± 0.37	0.46
Medications			
Aspirin	33 (97.1%)	86 (98.9%)	0.92
Clopidogrel	23 (67.6%)	86 (98.9%)	< 0.001
ACE-Is	3 (8.8%)	13 (14.9%)	0.55
ARBs	20 (55.8%)	52 (59.8%)	0.92
Beta blockers	15 (44.1%)	33 (37.9%)	0.53
Calcium channel blockers	16 (47.1%)	56 (64.4%)	0.08
Statins	34 (100%)	87 (100%)	NA

LDL: low-density lipoprotein, HDL: high-density lipoprotein, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin Ⅱ type 1 receptor blocker

Table 2. **Lesion Characteristics and PCI Procedure.**

	Patients with in-stent restenosis (n=34)	Patients with *de novo* stenosis (n=87)	p value
Culprit lesion location			
Left anterior descending artery	15 (44.1%)	48 (55.2%)	0.27
Left circumflex artery	8 (23.5%)	18 (20.7%)	0.73
Right coronary artery	11 (32.4%)	21 (24.1%)	0.36
PCI procedure			
Number of stents	-	1.3 ± 0.5	-
Stent size (mm)	-	3.09 ± 0.49	-
Total stent length (mm)	-	27.5 ± 14.6	-
Maximum balloon size (mm)	3.10 ± 0.49	3.12 ± 0.53	0.86
Balloon size with maximum inflation pressure (mm)	3.10 ± 0.49	3.06 ± 0.54	0.70
Maximum inflation pressure (atm)	17.3 ± 5.2	18.1 ± 5.2	0.43
Pre-PCI procedure			
Lesion length (mm)	14.6 ± 7.0	22.0 ± 11.7	< 0.001
Minimum lumen diameter (mm)	0.70 ± 0.39	0.80 ± 0.41	0.22
Reference vessel diameter (mm)	2.36 ± 0.80	2.52 ± 0.73	0.33
Diameter stenosis (%)	70.8 ± 13.3	69.5 ± 11.6	0.61
Post-PCI procedure			
Minimum lumen diameter after PCI (mm)	2.09 ± 0.55	2.66 ± 0.61	< 0.001
Reference vessel diameter after PCI (mm)	2.55 ± 0.43	2.95 ± 0.67	< 0.001
Diameter stenosis after PCI (%)	18.3 ± 12.0	10.2 ± 6.9	< 0.001

PCI: percutaneous coronary intervention

ter (2.09±0.55 mm vs. 2.66±0.61 mm, p<0.001) and a significantly larger diameter stenosis (18.3±12.0 % vs. 10.2± 6.9 %, p<0.01) compared to patients with *de novo* stenosis.

Lesion characteristics and PMI

The troponin I levels after PCI in patients with ISR and those with *de novo* stenosis were 0.35±0.96 ng/mL and 0.61±1.17 ng/mL, respectively (Table 3, Fig. 1). The incidence of PMI was similar between the two groups (47.1 % vs. 55.2 %, p=0.42) (Fig. 2, left panel). Among the patients with ISR, the incidence of PMI was similar between patients with BMS and those with DES (53.3 % vs. 42.1 %, p= 0.76). The incidences of PMI were 33.3 %, 60.0 % and 66.7 % in patients with focal ISR, diffuse ISR and diffuse prolif-

Table 3. Biomarkers for Myocardial Injury before and after PCI Procedure.

	Patients with in-stent restenosis (n=34)	Patients with *de novo* stenosis (n=87)	p value
Pre-PCI procedure			
Creatine kinase (IU/L)	129.5 ± 84.4	121.5 ± 91.3	0.65
Creatine kinase-MB (IU/L)	8.9 ± 4.2	9.6 ± 3.3	0.50
Post-PCI procedure			
Creatine kinase (IU/L)	126.6 ± 117.1	117.5 ± 99.6	0.69
Creatine kinase-MB (IU/L)	10.9 ± 6.4	10.4 ± 5.5	0.70
Troponin I (ng/mL)	0.35 ± 0.96	0.61 ± 1.17	0.22

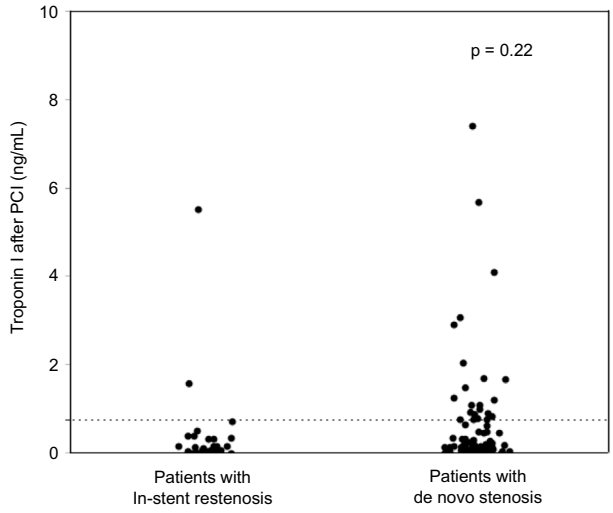

Figure 1. Troponin I levels after percutaneous coronary intervention (PCI) in patients with in-stent restenosis and those with *de novo* stenosis. The dotted line shows a cut-off value for major periprocedural myocardial injury (PMI).

erative ISR, respectively, although these differences were not statistically significant. The incidence of major PMI was significantly less frequent in patients with ISR than those with *de novo* stenosis (5.9 % vs. 25.3 %, p=0.03) (Fig. 2, right panel).

Predictors of major PMI

A univariate logistic regression analysis showed that ISR [odds ratio (OR) 0.18, 95% confidence interval (CI) 0.03-0.68; p=0.008), the maximum inflation pressure (OR 1.17, 95% CI 1.06-1.31; p=0.001) and the lesion length (OR 1.05, 95% CI 1.01-1.09; p=0.009) were predictors of major PMI (Table 4). A multivariate logistic regression analysis including these variables showed that ISR (OR 0.22, 95% CI 0.03-0.90; p=0.03) and the maximum inflation pressure (OR 1.15, 95% CI 1.04-1.30; p=0.009) were independent predictors of major PMI.

Discussion

In the present study, we demonstrated the following: 1) PMI occurred in patients with ISR as commonly as those with *de novo* stenosis, while major PMI occurred less frequently in patients with ISR and 2) ISR and the maximum inflation pressure were independent predictors for major PMI.

PMI is relatively common after PCI due to various factors that can be broadly categorized as patient-related factors, lesion-related factors, and procedure-related factors (4). Previous studies have shown that patient-related factors include diabetes mellitus, chronic kidney disease or systemic inflammation, and lesion-related factors include plaque burden, lesion eccentricity or thrombus. Because distal embolization of microparticles released from the target lesion is the main cause of PMI (4, 21), the tissue characteristics of the target lesion are likely to play an important role in the development of PMI.

Pathologic studies using specimens retrieved with atherectomy catheters have shown that the tissue of ISR is dominated by the presence of α-actin positive smooth muscle cells and an abundant proteoglycan matrix (12, 13). In an intravascular ultrasound study, Hoffman et al. evaluated the mechanisms of ISR and showed that chronic stent recoil was minimal, and late lumen loss and ISR were the result of neointimal tissue proliferation (22). The current understanding, according to clinical and experimental studies, is that neointimal tissue proliferation is the main mechanism of ISR. In the present study, 34 patients with ISR were successfully treated with repeated balloon angioplasty. This acute response to balloon angioplasty would reflect the tissue characteristics peculiar to ISR. Nevertheless, PMI occurred in patients with ISR as commonly as those with *de novo* stenosis. Several clinical studies have evaluated the mechanisms of balloon angioplasty for ISR (23, 24). Gordon et al. concluded that lumen enlargement after balloon angioplasty was entirely due to neointimal tissue compression or extrusion out of the stent rather than to additional stent expansion using QCA (23). Mehran et al. demonstrated that 56% of the lumen gain after balloon angioplasty was secondary to further stent expansion, whereas 44% resulted from neointimal tissue extraction using intravascular ultrasound (24). The distribution of these mechanisms is possibly dependent on the PCI procedure such as the balloon size used, inflation pressure or cross-sectional area of the previously deployed stent. However, neointimal tissue extraction remains a major mechanism of balloon angioplasty for ISR. Theoretically, neointimal extraction can occur through tissue

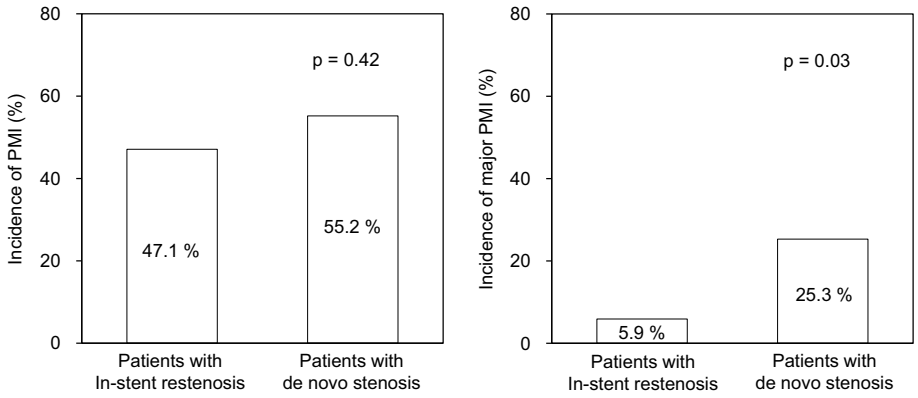

Figure 2. **The incidence of periprocedural myocardial injury (PMI) was similar between patients with in-stent restenosis (ISR) and those with *de novo* stenosis (left panel). The incidence of major PMI was significantly less frequent in patients with ISR than those with *de novo* stenosis (right panel).**

Table 4. **Univariate and Multivariate Logistic Regression Analyses for Major Periprocedural Myocardial Injury.**

Variables	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Age	0.99	0.95 - 1.05	0.83			
Male gender	0.71	0.27 - 2.04	0.51			
Hypertension	3.56	0.66 - 66.3	0.56			
Hyperlipidemia	0.84	0.32 - 2.39	0.74			
Diabetes	0.46	0.18 - 1.13	0.09			
Smoking	1.10	0.43 - 2.94	0.85			
Prior myocardial infarction	0.91	0.30 - 2.44	0.86			
Serum creatinine	1.82	0.32 - 9.75	0.49			
LDL cholesterol	0.99	0.97 - 1.007	0.23			
HDL cholesterol	0.98	0.94 - 1.01	0.24			
Fasting plasma glucose	0.99	0.97 - 1.0002	0.054			
Hemoglobin A1C	0.81	0.46 - 1.31	0.41			
C reactive protein	0.84	0.11 - 2.80	0.80			
In-stent restenosis	0.18	0.03 - 0.68	0.008	0.22	0.03 - 0.90	0.03
Maximum balloon size	0.95	0.39 - 2.24	0.90			
Balloon size with maximum inflation pressure	0.78	0.31 - 1.83	0.57			
Maximum inflation pressure	1.17	1.06 - 1.31	0.001	1.15	1.04 - 1.30	0.009
Lesion length	1.05	1.01 - 1.09	0.009	1.02	0.98 - 1.06	0.38
Minimum lumen diameter	0.69	0.21 - 2.08	0.52			
Reference vessel diameter	0.98	0.52 - 1.75	0.94			
Diameter stenosis	1.004	0.97 - 1.04	0.83			

OR: odds ratio, CI: confidence interval, LDL: low-density lipoprotein, HDL: high-density lipoprotein

mobilization into the distal small coronary arteries (distal embolization) as well as tissue compression, tissue extrusion out of the stent or tissue redistribution within the stent. These results suggested that neointimal tissue itself was often released in response to balloon angioplasty, and was associated with the development of PMI.

Recent studies and meta-analyses have revealed that PMI assessed by troponins is associated with increased mortality (25, 26). PMI remains an unresolved problem of PCI. Previous studies have shown several possible strategies to prevent PMI (21). In addition to lipid-lowering effects, beneficial effects of statins include improved endothelial function, reduced oxidative stress and increased atherosclerotic plaque stability (27). Atorvastatin treatment prior to PCI was shown to reduce PMI compared with controls in both the ARMYDA trial and NAPLES II trial (16, 17). In the present study, even though all 34 patients with ISR were treated with statins, PMI occurred in approximately half of the patients. These results suggested the limited effect of statins to prevent PMI even in patients with ISR. Intracoronary adenosine (28), intracoronary beta blockers (29), ischemic preconditioning (30) and remote ischemic preconditioning (31) are other attractive options to prevent PMI in patients with *de novo* stenosis, and should also be examined in patients with ISR.

The present study demonstrated that major PMI occurred less frequently in patients with ISR compared to those with *de novo* stenosis. Because the patient-related factors, such as diabetes, were similar between the two groups, this finding was possibly due to lesion- or procedure-related factors. The multivariate logistic regression analysis showed that ISR and the maximum inflation pressure were independent predictors of major PMI, although the lesion length was not. Stent deployment can provide an acute lumen gain more or less

through plaque compression on *de novo* stenosis. In particular, atherosclerotic plaque containing a large necrotic core leads to the high risk of large embolization during PCI (32, 33), which is subsequently associated with major PMI. In fact, recent pathologic or coronary imaging studies have shown that this atherosclerotic change can occur even on ISR (neoatherosclerosis) (34, 35). Nakazawa et al. showed that in-stent neoatherosclerosis was found in both BMS and DES in autopsy cases, and it was found earlier in DES compared to BMS (34). Ikenaga et al. recently reported a case of neoatherosclerosis on ISR assessed using coronary angioscopy and optical coherence tomography (35). However, neoatherosclerosis on ISR is not as common as atherosclerosis on *de novo* stenosis. These lesion-related differences may be associated with the lower incidence of major PMI in patients with ISR.

There are several limitations associated with the present study. First, we excluded patients with renal insufficiency; therefore, our results may not be extrapolated to all patients undergoing PCI. Second, we did not evaluate the impact of PMI on the long-term prognosis. Third, we did not routinely assess the plaque morphologies. Further studies using intravascular ultrasound or optical coherent tomography will contribute to the understanding of PMI on ISR (34). Finally, the small sample size is a major limitation and a larger, prospective study should be performed to confirm our findings.

Conclusion

In conclusion, PMI occurred in patients with ISR as commonly as those with *de novo* stenosis, however, major PMI occurred less frequently in patients with ISR. Cardiologists should recognize that PMI can occur commonly even in patients with ISR despite the simple procedure.

The authors state that they have no Conflict of Interest (COI).

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