Deteriorative Effect of Smoking on Target Lesion Revascularization After Implantation of Coronary Stents With Diameter of 3.0 mm or Less

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Background Although smoking cessation is widely encouraged because of the associated risk of cardiovascular events, the impact of smoking on target lesion revascularization (TLR) after percutaneous coronary intervention (PCI) is controversial. Therefore, the present study retrospectively investigated the effect of smoking on TLR after plain-old balloon angioplasty (POBA; n=376) and stenting (STENT; n=434) in patients undergoing secondary coronary angiography at a single center.

Methods and Results A smoker was defined as current smoking or quitting within 2 years of the first PCI. In the POBA group, the predictors for TLR, as calculated by multiple logistic regression analysis, were a complex type of lesion ($p<0.0001$) and the left anterior descending artery (LAD) as affected vessel ($p<0.05$). In the STENT group, the predictors were the final % diameter of stenosis after stenting, measured by quantitative coronary arteriography ($p<0.0005$), LAD ($p<0.01$), and smoking ($p=0.049$). When the STENT group was divided into 2 groups according to the diameter of the implanted stent, smoking was a predictive factors for TLR in the group that received relatively small stents (diameter ≤ 3.0 mm) ($p<0.02$), but not in the group that received larger stents (diameter ≥ 3.5 mm).

Conclusion Smoking has a deteriorative effect on TLR after implantation of relatively small coronary stents with a diameter of 3.0 mm or less. (Circ J 2005; 69: 227–231)

Key Words: Percutaneous coronary intervention (PCI); Restenosis; Smoking; Target lesion revascularization (TLR)

Smoking is widely known as a major coronary risk factor and it is also well known that the overall percentage of active smokers is highest in Japan among the developed countries.¹ Based on the many studies reporting the toxic effects of smoking,² the Japanese Circulation Society (JCS) declared an anti-smoking campaign³ in order to prevent not only primary, but also secondary cardiac events, which includes target lesion revascularization (TLR), after percutaneous coronary intervention (PCI).

However, the impact of smoking on clinical restenosis, particularly TLR, is controversial^{4–9} such as the ‘smoker’s paradox’ reported in the United States.⁴ The clinical treatment, such as the rate of performing secondary coronary angiography (CAG) during the chronic phase,¹⁰ the overall percentage of smokers,¹ and the attitude toward smokers by physicians are very different between Japan and the United States⁴ and so the aim of the present study, conducted in

Japan, was to clarify the impact of smoking on TLR after conventional PCI with equal treatment of smokers by retrospectively analyzing the pooled data from a single center of patients who underwent secondary CAG during the chronic phase (second study).

One of the problems of investigating the effect of smoking on the cardiovascular system is that there are various classifications of smoking status and the definition of a smoker is inconsistent.^{4–9} In the present study, we defined smoking status as (1) smoker, including cessation within the 2 years prior to the first PCI and (2) nonsmoker, similar to the definition used by Cohen et al⁴

Methods

Patient Population

We retrospectively analyzed the data from patients with ischemic heart diseases (IHD), including acute myocardial infarction (AMI), unstable angina pectoris (UAP), stable angina pectoris (SAP), recent and old myocardial infarction (RMI and OMI), or silent myocardial infarction (SMI), who underwent conventional PCI (plain-old balloon angioplasty (POBA) or stenting) that was successful ($<50\%$ diameter stenosis (%DS) as measured by quantitative coronary arteriography (QCA) after PCI) from August 1997 to November 2002 and who then underwent a second study and repeat PCI at The Jikei University Hospital. Patients who underwent an elective second study were included in the SAP

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Preliminary results of this study were announced at the 67th annual meeting of the Japanese Circulation Society held in Fukuoka.¹¹

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Table 1 Impact of Smoking on Target Lesion Revascularization (TLR) in the Plain-Old Balloon Angioplasty (POBA) and Stenting (STENT) Groups

	TLR (-)	TLR (+) [†]	Single regression			Multiple regression
			Exp (B)	CI	p value	p value
POBA (n=376)						
Age (years)	61.4	62.3	1.010	0.985–1.036	0.425	0.0001 0.037
Male sex (%)	87.8	89.5	0.844	0.410–1.739	0.646	
HL (%)	64.9	65.7	0.967	0.602–1.553	0.888	
HT (%)	66.4	63.5	1.139	0.710–1.826	0.589	
Sm (%)	56.8	57.1	0.987	0.626–1.556	0.956	
DM (%)	42.4	51.4	0.696	0.443–1.094	0.117	
BMI	23.9	24.0	1.012	0.934–1.098	0.768	
ACS (%)	13.7	18.1	0.716	0.391–1.312	0.279	
Simple type (%)	56.3	57.8	2.646	1.630–4.294	0.0001	
Lesion (LAD) (%)	43.2	61.0	0.487	0.307–0.771	0.0021	
Balloon size (mm)	2.94	2.94	0.998	0.620–1.606	0.993	
Post PCI %DS (%)	28.1	26.6	0.992	0.974–1.009	0.347	
STENT (n=434)						
Age (years)	61.3	59.1	0.979	0.955–1.004	0.095	0.049 0.010
Male sex (%)	87.7	92.0	0.615	0.252–1.498	0.284	
HL (%)	71.9	74.9	0.852	0.483–1.503	0.579	
HT (%)	64.1	67.1	0.864	0.511–1.459	0.584	
Sm (%)	57.4	69.7	0.578	0.339–0.984	0.043	
DM (%)	45.4	56.6	0.638	0.388–1.051	0.078	
BMI	24.1	24.1	1.002	0.917–1.094	0.968	
ACS (%)	33.0	27.5	1.27	0.733–2.20	0.394	
Simple type (%)	48.5	43.5	1.264	0.730–2.186	0.403	
Lesion (LAD) (%)	49.3	64.5	0.530	0.317–0.885	0.015	
Stent size (mm)	3.24	3.17	0.443	0.196–1.001	0.051	
Total S length (mm)	16.7	18.5	1.023	0.996–1.051	0.098	
Stent/artery ratio	1.14	1.24	1.598	0.966–2.643	0.068	
Post PCI %DS (%)	8.03	12.5	1.027	1.008–1.047	0.006	0.00054

[†]TLR (+)=39% in POBA, 17.4% in STENT.

ACS, acute coronary syndrome; BMI, body mass index; CI, confidence interval; %DS, % diameters stenosis; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; PCI, percutaneous coronary intervention; Sm, smoker; Total S length, total stented segment length.

group even though their clinical symptoms were grade III of the Braunwald classification of UAP. The patients were divided into POBA and stenting (STENT) groups because the strategies of the primary and secondary PCI and the mechanism of restenosis were different.^{12,13} The POBA group included patients who underwent only balloon angioplasty for the first PCI. Lesions dilated by cutting balloon angioplasty alone were not included. The STENT group included patients who had coronary stents implanted despite pre- or post-balloon angioplasty during the PCI. Also included were patients who underwent either POBA or stenting after debulking with directional coronary atherectomy or rotational atherectomy. Ticlopidine (200mg/day) was administered for approximately 1 month after stenting if it had no adverse effects. A second study and/or repeat PCI (TLR) were performed between 30 days and 10 months after the first PCI. The patients who were stable usually underwent stress radionuclide scintigraphy (RI) before the second study in order to detect ischemia and to determine myocardial viability. All of the physicians treated all patients routinely, but encouraged the smokers to stop smoking. Cases of chronic total occlusion were excluded because of their low rate of success with PCI and the high incidence of restenosis. TLR was performed when the patient was admitted as an emergency case of AMI, RMI or UAP with chest pain, or electively when admitted with stable chest pain and/or positive RI for SAP, SMI, and OMI. Accordingly, 376 consecutive cases (the follow-up ratio was 88.7%) were enrolled in the POBA group and 434 consecutive cases (92.1%) comprised the STENT group.

PCI Procedure

Approximately 70% of the PCI procedures were performed under the guidance of intravascular ultrasonography (IVUS), and implantation of a stent was provisional¹¹ because of the difficulty of treating in-stent restenosis (ISR), even though the rate of clinical events within 6 months of stenting is similar to that for balloon angioplasty.¹² Therefore, in small vessels, stenting was avoided as much as possible unless there was a major coronary dissection, protrusion of the atherothrombus, recoil after balloon angioplasty, or restenosis after POBA for the first PCI. When the minimal lumen cross-sectional area (CSA) of the target lesion (MLA) was greater than 4.5 mm² and/or the MLA exceeded the average of the proximal and distal reference lumen areas after balloon angioplasty, the PCI was completed and defined as optimal POBA. If optimal POBA was not achieved, a bare-metal coronary stent (eg, Palmaz-Schatz, GFX, S6, Multi-Link, NIR or BX-Velocity) was implanted. The size of the implanted stent was usually selected according to the size of the vessel distal to the lesion. An optimal stenting was considered to be a gain of more than 6.0 mm² in the minimum stent lumen CSA and/or in the average of the proximal and distal reference lumen areas after stenting.

Statistical Variables

In order to statistically investigate the impact of smoking on TLR, the following variables at PCI were examined: patient characteristics (age, sex,¹⁴ body mass index (BMI)¹⁵) and coronary risk factors such as hyperlipidemia (HL),

Table 2 Impact of Smoking According to the Size of Implanted Stent

	TLR (–)	TLR (+) [†]	Single regression p value	Multiple regression p value
<i>Stent ≤3.00 mm (n=258)</i>				
Age (years)	61.9	61.6	0.804	
Male sex (%)	85.5	93.9	0.129	
HL (%)	73.5	79.6	0.381	
HT (%)	62.5	65.3	0.716	
Sm (%)	55.5	73.4	0.024	0.0189
DM (%)	52.0	59.2	0.367	
BMI	24.1	23.8	0.618	
ACS (%)	29.7	26.4	0.664	
Simple type (%)	50.9	43.6	0.412	
Lesion (LAD) (%)	48.5	65.2	0.0372	
Stent size (mm)	2.985	2.948	0.0377	
Total S length (mm)	15.8	16.5	0.494	
Stent/artery ratio	1.10	1.14	0.449	
Post PCI %DS (%)	7.59	12.1	0.0211	0.0139
<i>Stent ≥3.5 mm (n=176)</i>				
Age (years)	60.4	54.4	0.0087	
Male sex (%)	90.6	88.9	0.786	
HL (%)	69.8	66.7	0.743	
HT (%)	66.0	70.4	0.659	
Sm (%)	60.0	63.0	0.753	
DM (%)	37.1	51.9	0.151	
BMI	24.2	24.8	0.304	
ACS (%)	36.9	29.6	0.466	
Simple type (%)	45.8	41.7	0.7085	
Lesion (LAD) (%)	50.3	63.0	0.227	
Stent size (mm)	3.586	3.583	0.959	
Total S length (mm)	17.7	22.3	0.0421	
Stent/artery ratio	1.18	1.41	0.0394	
Post PCI %DS (%)	8.58	13.2	0.0983	

[†]Target lesion revascularization = 19.2% for stents ≤3 mm and 14.8% for stents ≥3.5 mm.

See Table 1 for abbreviations.

hypertension (HT), smoking (Sm), and diabetes mellitus (DM). A smoker was defined as a current smoker and/or those who had quit within 2 years of the first PCI. HL, HT, and DM were diagnosed from the patient's clinical history and each value was measured according to the guideline of the relevant society. The clinical course (acute coronary syndrome (ACS), such as AMI and UAP, or stable course, such as SAP, RMI, OMI, and SMI), the diseased vessel (left anterior descending artery (LAD)⁵ or others included in the bypass graft), the lesion type (simple (A and B₁ type) or complex (B₂ and C), according to the AHA/ACC Task Force Report¹⁶), calculated data of QCA immediately after PCI (post PCI %DS),¹⁷ balloon size in the POBA group, and stent size, total stented segment length (total S length),¹⁸ and the ratio of the number of stents in the target lesion (stent/artery ratio) in the STENT group. The %DS was calculated after PCI using QCA Dicomex (Siemens, USA). The %DS before PCI in the non-TLR group was not significantly different from that in the TLR group in both the POBA and STENT groups. In the POBA group, the mean value of %DS at the second study in the TLR group (88.4%) was significantly increased compared with the non TLR group (28.1%) ($p<0.001$) and we got a similar result in the STENT group (78.3% and 28.3%, $p<0.001$). Because the increase in the %DS in the TLR group correlated with TLR, the %DS at the second study was not used as a statistical variable.

Statistical Analysis

The measured values are expressed as the mean value. In order to verify the significance of each variable to TLR,

each variable was analyzed by single logistic regression analysis. If there were multiple significant variables, those were analyzed by multiple logistic regression analysis and statistical significance was verified at $p<0.05$.

Results

Although our definition of a smoker was different, the ratios of smokers (56.9% in POBA and 59.5% in STENT group; Table 1) were higher than the average ratio of active smokers in Japan reported by Ministry of Health, Labor and Welfare,¹ which is less than 50% and progressively reducing year by year.

As shown in Table 1, the lesion type (complex type, $p<0.0001$) and diseased vessel (LAD, $p=0.037$) were significant TLR-related factors in the POBA group, but Sm ($p=0.956$) was not. In addition, when the POBA group was divided according to the size of balloon, Sm was not a significant factor (data were not shown). The post PCI %DS ($p=0.00054$), LAD ($p=0.010$), and Sm ($p=0.049$) were significant TLR-related factors in the STENT group.

In order to further investigate the deteriorative effect of smoking on TLR after stenting, the STENT group was divided into 2 groups according to the size of the implanted stent (small stent group: ≤3.0 mm (ie, 2.5 and 3.0 mm); large stent group: ≥3.5 mm (ie, 3.5, 4.0, 4.5, and 5.0 mm)). Sm was a significantly predictive factor for TLR in the small stent group ($p=0.0189$, Table 2), but not in the large stent group ($p=0.753$, Table 2).

Discussion

The objective of the present study was to clarify the impact of smoking on TLR after conventional PCI with equal treatment of smokers, because it is a controversial issue⁴⁻⁹ and there are many differences in the clinical and social backgrounds of patients in Japan and the United States.^{1,10} The major finding of this study was that, under equal treatment, smoking was not associated with a lower rate of TLR in either the POBA or STENT group (Table 1), refuting previous studies,⁴⁻⁶ but smoking did have a deteriorative effect on TLR after implantation of relatively small stents, indicating a differential impact of smoking according to the size of stent (Tables 1,2).

Definition of Smoking Status

In the present retrospective study, a smoker who had ceased smoking within 2 years of the first PCI was also defined as a smoker because it is our experience that the relapse rate after quitting smoking is very low if the subject can achieve 2 years of complete cessation. We defined smokers and non-smokers according to their smoking history at the time of the first PCI, which is similar to Cohen et al⁴ but the definition of a smoker and the classification of smoking status are a major problem and limitation of the present study, compared with a previous report⁹ This problem also applies to many reports on the effect of smoking on the cardiovascular system because the definitions of smoking status have not been standardized and thus are inconsistent between reports and between scientific associations, including the JCS.³ However, this inconsistency arises because of the many unknown biological effects of both smoking and smoking cessation on the cardiovascular system² and because there are no quantitative criteria and/or biological markers of smoking compared with other coronary risk factors such as DM, HT, dyslipidemia, and obesity. The dose-dependent toxic effect of smoking on the risk of cardiovascular events is also inconsistent.² Passive smoking has been recently highlighted^{2,19} by the report that approximately 30% of passive smokers have a risk of a cardiovascular event.² It has been reported that the serum concentration of cotinine is a concentration-dependent marker of IHD²⁰ and therefore, passive smoking^{2,19} and/or a biomarker, such as cotinine,²⁰ have to be taken into consideration when the smoking status is classified. In the present study, we simply defined smoking as one of 2 states, similar to Cohen et al⁴ but in the future, as the unknown biological effects of smoking and smoking cessation are progressively elucidated, a more precise classification of smoking will be needed.

Deteriorative Effect of Smoking on TLR After Implantation of Relatively Small Coronary Stents

The present study refuted previous reports of a negative impact of smoking on TLR.⁴⁻⁶ The 'smoker's paradox'⁴ is considered to be mainly caused by a reduction in the clinical symptoms of restenosis in smokers and a lower rate of smokers in the second study, in view of the cost-effectiveness, so that, despite clinical symptoms, the physicians selected a more intentional medical treatment to encourage smoking cessation. Modifying the PCI procedure from POBA to primary stenting, which reduced both the acute procedural success and the rate of restenosis, was also considered a reason for the discrepancy.

In the present study, patients were treated equally

despite their smoking status and so approximately 90% of them underwent a second study. Our rate of stenting (approximately 1.15-fold cases of POBA) was not particularly high in this era of stenting because at our center stent implantation at first PCI is provisional, based on a previous report.¹² An increase in the threshold of angina in smokers was not clear in the present study because of our undefined descriptions of SAP and UAP and the inaccurate ratio of SMI. However, the increase in the mean value of %DS at the time of the second study correlated with TLR in both the POBA and STENT groups (see Methods). In addition, the impact of smoking on TLR differed between the POBA and STENT groups (Table 1) and according to the size of the stent (Table 2). These differential and deteriorative effects of smoking cannot be explained by the reduction in clinical symptoms of restenosis in smokers. Therefore, among the patients who underwent a second study who were given equal treatment, the deteriorative effect of smoking on TLR would be caused by a direct biological effect on the diseased lesion and/or vessels, which would be mainly related to promotion of intimal growth through vessel injury²¹ caused by the stenting, something that does not occur with POBA alone. Because a direct biological effect on the diseased lesion through vessel injury was considered to be a cause of TLR, the pressure and duration of balloon inflation and the effect of the pre- and/or the post balloon angioplasty, particularly in STENT group, had to be taken into consideration. However, because stents were implanted provisionally, according to the achievement of optimal PCI, and similar clinical outcomes for direct stenting and stenting with pre-dilatation have been reported,²² those data were not evaluated. Thus, particularly for smokers, another device that dilates the stents to give a lower %DS, or implantation of a drug-eluting stent that inhibits neointimal growth, is needed to reduce TLR after the implantation of a stent into relatively small vessels.

Conclusion

In the present study, in order to determine the relationship between smoking and TLR, the impact of smoking on TLR after PCI for IHD was retrospectively analyzed in a small cohort in a single center where stents are implanted provisionally. Smoking did not have a beneficial effect on TLR after conventional PCI among the patients undergoing a second study under equal treatment, but exerts a deteriorative effect after implantation of a stent in a relatively small coronary vessel. Thus, to prevent primary and secondary IHD, in accordance with the Anti-Smoking Declaration of the JCS,³ smokers must stop smoking.

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