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Myocardial Infarction as a Presentation of Clinical In-Stent Restenosis

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Background In-stent restenosis is considered to be a gradual and progressive condition and there is scant data on myocardial infarction (MI) as a clinical presentation.

Methods and Results Of 2,462 consecutive patients who underwent percutaneous coronary intervention between June 2001 and December 2002, clinical in-stent restenosis occurred in 212 (8.6%), who were classified into 3 groups: ST elevation MI (STEMI), non-ST elevation MI (NSTEMI) and non-MI. Of the 212 patients presenting with clinical in-stent restenosis, 22 (10.4%) had MI (creatine kinase (CK) ≥2×baseline with elevated CKMB). The remaining 190 (89.6%) patients had stable angina or evidence of ischemia by stress test without elevation of cardiac enzymes. Median interval between previous intervention and presentation for clinical in-stent restenosis was shorter for patients with MI than for non-MI patients (STEMI, 90 days; NSTEMI, 79 days; non-MI, 125 days; p=0.07). Diffuse in-stent restenosis was more frequent in MI patients than in non-MI patients (72.7% vs 56.3%; p<0.005). Renal failure was more prevalent in patients with MI than in those without MI (31.8% vs 6.3%, p=0.001). Compared with the non-MI group, patients with MI were more likely to have acute coronary syndromes at the time of index procedure (81.8% vs 56.8%, p=0.02).

Conclusion Clinical in-stent restenosis can frequently present as MI and such patients are more likely to have an aggressive angiographic pattern of restenosis. Renal failure and acute coronary syndromes at the initial procedure are associated with MI. (*Circ J* 2006; **70:** 1026 – 1029)

Key Words: Angiography; Angioplasty, Restenosis; Stents; Thrombosis

Compared with balloon angioplasty, implantation of coronary stents has significantly decreased restenosis[1–5] but in-stent restenosis caused by neointimal hyperplasia can occur in 20–30% of cases following bare metal stent implantation[6–10] and clinical in-stent restenosis or ischemia-driven revascularization for significant restenosis (≥50%) occurs in 10–15% following implantation of bare metal stents. This process usually occurs within 1 year of the index procedure and is believed to have a benign presentation with recurrent angina and/or evidence of ischemia on a stress test. However, there is scant data of an acute event such as myocardial infarction (MI) presenting as clinical in-stent restenosis. We sought to determine the incidence and type of MI, as well as clinical and angiographic characteristics of patients presenting with clinical in-stent restenosis (namely, any recurrent ischemia occurring in the stented segment) from our single center experience.

Methods

Study Patients

Of 2,462 consecutive patients who underwent percutaneous coronary interventions (PCI) with bare metal stents between June 2001 and December 2002, 212 (8.6%) were found to have clinical in-stent restenosis, which was defined as angiographic stenosis >50% within 5 mm of the stented segment for patients presenting for an angiogram for clinical evidence of ischemia (viz. angina or positive stress test). Patients presenting within 30 days of index procedure, with recurrent in-stent restenosis or restenosis following balloon angioplasty only, and patients presenting with MI clearly attributable to non-restenotic lesion or vessel were excluded. The antiplatelet regimen after the initial stent deployment was aspirin 325 mg daily indefinitely, and clopidogrel 75 mg daily for 4 weeks following a loading dose of 300 mg on the day of the procedure. The average follow-up period was 205±23 days (median 124 days). Based on the presenting symptoms and findings, the patients were divided into 3 groups: ST elevation MI (STEMI), non-ST elevation MI (NSTEMI), and non-MI groups. Patients with elevation of creatinine kinase (CK) 2-fold more than the normal reference with elevated MB fraction were considered to have a MI. Patients with STEMI were to have >1 mm ST-segment elevation in ≥2 contiguous leads. The NSTEMI group had elevated cardiac enzymes as above, without ST-segment elevation on the ECG. Renal failure was defined as baseline serum creatinine >2.0 mg/dl. The angiographic pattern of in-stent restenosis was analyzed as classified by Mehran et al.[11] Clinical and angiographic characteristics were compared among the 3 groups. Informed consent was given by each patient and the study protocol was approval by the institutional review board.

Statistical Analysis

Quantitative data are presented as mean value±1 SD or

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Table 1 Clinical Characteristics

	STEMI	NSTEMI	Non-MI	p value
Age (years)	64.4±9	67.4±14	64.6±12	0.70
Male, n (%)	8 (80)	12 (100)	124 (65)	0.03
Diabetes, n (%)	2 (20)	6 (50)	69 (36)	0.35
Hypertension, n (%)	8 (80)	12 (100)	164 (86)	0.32
Hyperlipidemia, n (%)	10 (100)	10 (83)	183 (96)	0.08
Smoking, n (%)	9 (90)	10 (83)	131 (68)	0.22
Renal failure, n (%)	2 (20)	5 (42)	12 (6)	0.001*
Vessels treated, n (%)				
LAD	5 (50)	2 (17)	69 (36)	
LCX	1 (10)	5 (41)	41 (21)	0.46
RCA	3 (30)	3 (25)	58 (30)	
SVG	1 (10)	2 (17)	14 (7.4)	
Presentation at the time of index PCI, n (%)				0.02*
Stable effort angina	2 (20)	2 (17)	82 (43)	
Acute coronary syndromes	8 (80)	10 (83)	108 (57)	
Stent length (mm)	28.7±17.3	20.8±13.0	20.9±10.3	0.23
Stent diameter (mm)	3.1±0.3	3.2±0.6	3.1±0.5	0.68
Median interval to event (range) (days)	90 (31–1,296)	79 (40–1,450)	125 (31–1,433)	0.07
Diameter stenosis (%)	98.9±3.1	91.1±9.5	86.0±12.9**	<0.005
Ejection fraction (%)	32.5±13.9	43.1±12.5	49.5±12.6**	<0.005

*Comparison was made between combined MI and non-MI groups, **p<0.005 vs STEMI.
STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; MI, myocardial infarction; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; SVG, saphenous vein graft; PCI, percutaneous coronary intervention.

Table 2 Angiographic Patterns of In-Stent Restenosis

	MI total (n=22)		Non-MI (n=190)	p value*
	STEMI (n=10)	NSTEMI (n=12)		
Focal, n (%)	1 (10.0)	5 (41.7)	83 (43.7)	0.14
Diffuse intrastent, n (%)	1 (10.0)	0 (0)	59 (31.1)	0.009
Diffuse proliferative, n (%)	3 (30.0)	4 (33.3)	34 (17.9)	0.15
Total occlusion, n (%)	5 (50.0)	3 (25.0)	14 (7.4)	0.005

*Comparison between combined MI and non-MI groups.
See Table 1 for abbreviations.

median (range), and qualitative data as frequencies. Continuous variables were compared using analysis of variance or Kruskal-Wallis analysis. Bonferroni-Dunn method was used for post-hoc analyses. Categorical variables were examined by chi-square test or Fisher's exact test. All probability values are two-tailed and p-value <0.05 was considered statistically significant. Statistical analysis was performed with StatView 5.0 (Abacus Concepts Inc, Calabasus, CA, USA).

Results

Clinical and Angiographic Characteristics

Of the 212 patients with clinical in-stent restenosis, 22 (10.4%) presented with MI (Table 1) and of these, 10 (4.7%) had STEMI and 12 (5.7%) had NSTEMI. The remaining 190 (89.6%) patients had angina or evidence of ischemia by stress test without elevation of cardiac enzymes. Of these patients, 22 patients (11.6%) also had isolated elevation of troponin I ≥2 ng/ml without elevation of CK or the MB fraction or ECG changes, but were not classified as having MI in our study. Renal failure was more prevalent in patients with MI than in those without MI (31.8% vs 6.3%, p=0.001). Compared with the non-MI group, patients with MI were more likely to have acute coronary syndromes at the time of index procedure (81.8% vs 56.8%, p=0.02). Median interval between previous intervention and presentation for clinical in-stent restenosis was 90 days in the STEMI, 79 days in NSTEMI and 125 days in non-MI groups (p=0.07). Of the 22 patients with MI, premature cessation of clopidogrel within 4 weeks was noted in 2 patients (9.1%). At the time of MI, 10 patients (45.5%) were on single antiplatelet therapy (either with aspirin or with clopidogrel) and of these the average interval between the index procedure and presentation as MI was 253±344 days (median 137 days).

The mean stent diameter was similar among the 3 groups. The mean stent length was 24.1 mm overall, without statistical significance among the groups (STEMI, 28.7±17.3 mm; NSTEMI, 20.8±13.0 mm and non-MI, 20.9±10.3 mm; p< 0.23). Total occlusion of the target lesion occurred more frequently in patients who presented with STEMI (50%) than in those with NSTEMI (25%) or without MI (7.4%).

Angiographic Pattern of In-Stent Restenosis

The angiographic pattern of in-stent restenosis was significantly different between the MI group in total and the non-MI group (Table 2). Patients with MI had a more aggressive type of in-stent restenosis. Total occlusion with Thrombolysis in Myocardial Infarction flow grade 0 appeared to be more frequent in patients with STEMI whereas focal restenosis appeared more frequently in patients with NSTEMI. Of the 22 patients with MI, 11 (50%) had an angiographically visible thrombus. An angiogram from a patient with STEMI is shown in Fig 1, with the pattern suggesting profuse in-stent restenosis rather than late stent thrombosis as a cause of MI in this case.

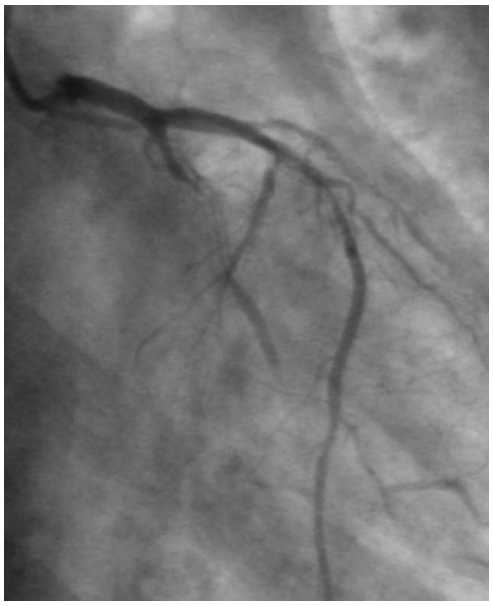

Fig 1. Coronary angiogram in the right anterior oblique view from a 63-year-old man with ST elevation myocardial infarction. The ECG shows ST elevation in the I and aVL leads, and the angiogram reveals diffuse in-stent restenosis of the left circumflex stent with Thrombolysis in Myocardial Infarction grade I flow.

Treatment

Most in-stent restenosis lesions were treated with balloon angioplasty followed by brachytherapy. AngioJet rheolytic thrombectomy (Possis Medical, Minneapolis, MN, USA) was performed prior to balloon angioplasty in 1 patient in the STEMI group because of significant thrombus burden.

There was differential use of brachytherapy, with 30% of patients with MI treated with adjunctive brachytherapy as opposed to 66% of patients who did not present with MI. There were several reasons for not using brachytherapy in all patients, namely, presence of thrombus at the lesion and resistance of operators to use brachytherapy for acute events, failure to cross the catheter to the lesion and nonavailability of a radiation physicist for emergency procedures.

In-Hospital Mortality

In-hospital deaths occurred in 3 patients with NSTEMI, giving an overall mortality of 1.4%. The first patient was a 64-year-old man with a history of bypass surgery and endstage renal artery disease on hemodialysis, who presented with cardiogenic shock and respiratory failure 2 months after stenting of a saphenous vein graft to the circumflex artery. He underwent successful intervention for in-stent restenosis in the vein graft, but died 4 days later from pneumonia.

Another patient was a 73-year-old man who was admitted with NSTEMI and respiratory failure requiring intubation. He underwent successful balloon angioplasty for in-stent restenosis of the dominant left circumflex artery 50 days after the initial procedure, but died 10 days later from extensive pneumonia.

The third patient was a 67-year-old male with endstage renal disease, who developed cardiogenic shock during hemodialysis 3 months after initial stent placement in the dominant circumflex artery. He underwent successful repeat intervention of the circumflex lesion. At the time of presentation, he was also suffering from acute bilateral lower extremity ischemia, for which emergency common femoral and iliac thrombectomy was performed. The patient died shortly after surgery from intractable cardiogenic shock.

Discussion

In our series of 212 consecutive patients who presented with clinical in-stent restenosis, MI occurred in 10.4% patients (4.7% with STEMI, 5.7% with NSTEMI). There are scant data on MI as a presentation of clinical in-stent restenosis. In their study of 234 patients who underwent intervention for in-stent restenosis, Bossi et al reported that 3.5% of the patients had MI on presentation,[12] and Walters et al reported NSTEMI in 12% of patients and STEMI in 8% of patients who presented with clinical in-stent restenosis.[13] The incidence of MI in our study may have been underestimated because only patients who returned to Lahey Clinic Medical Center with recurrence of ischemia are included in this study. In addition, the number may underestimate the actual incidence because of our more stringent definition of MI. Only patients who have CK $\geq$2–fold greater than baseline with elevated MB were included. The main reason to use such a definition was to exclude patients who present with acute coronary syndrome with minor enzyme elevations. We also excluded patients presenting within 30 days of the index procedure for repeat revascularization because of the possibility of stent thrombosis as a cause of MI. In our study, 11.6% of the patients in non-MI group had elevation of troponin I $\geq$2 ng/ml. If these patients are included as MI, the incidence of MI would be 20.8%, similar to that reported by Walters et al.

Mechanisms of MI in Clinical In-Stent Restenosis

The mechanism of late MI associated with stenosis of the stented segment is unclear. In-stent restenosis occurs because of gradual progressive smooth muscle cell proliferation resulting in neointimal hyperplasia within the stent,[14,15] whereas MI is a result of rapid plaque growth with ulceration or plaque rupture and sudden compromise of the vessel lumen. The most likely explanations for MI is late stent thrombosis because of incomplete neointimal coverage of the stent, early termination of antiplatelet therapy, and increased thrombogenic tissue factor in the neointimal tissue with a higher propensity of thrombosis.[16] Intracoronary angioscopy studies have shown that complete coverage of a stent by neointimal tissue takes 3 months or longer.[17,18] In our study, the median interval between the index procedure and presentation as clinical in-stent restenosis was 90 days in STEMI patients, and 79 days in NSTEMI patients. These data call for prolonged dual antiplatelet therapy even after PCI with bare-metal stents.

The observed association of renal failure and acute coronary syndromes at the time of index procedure with MI is in line with previous reports on stent thrombosis. Iakovou et al identified renal failure as a predictive factor of thrombosis after implantation of drug-eluting stents.[19] In a study of bare-metal stents by Heller et al, a discharge diagnosis of MI was associated with an increased incidence of stent thrombosis.[20] These results support the theory that stent thrombosis is a major cause of late MI.

According to previous reports, the incidence of late stent thrombosis defined as stent thrombosis occurring >30 days post procedure ranges from 0.4% to 0.8%.[20–22] The incidence of late MI in our study population was 0.9%, which

is slightly higher than those reports. Although the primary cause of the late MI would be late stent thrombosis, the somewhat higher incidence of MI in the present report suggests mechanisms other than that.

Another potential explanation for MI could be the restenosis itself. Stent restenosis is associated with more aggressive neointimal hyperplasia compared with restenosis following balloon angioplasty alone, which occurs predominantly because of elastic recoil. This profuse in-stent restenosis may then be associated with diminished flow in the vessel leading to MI (Fig 1). In contrast, restenosis associated with balloon angioplasty has a lower incidence of MI.[3] We found that patients with STEMI were more likely to have total occlusion (50%) and an aggressive in-stent restenosis pattern (40% had diffuse or proliferative) compared with the NSTEMI group (25% and 33%, respectively) supporting the hypothesis that aggressive restenosis may be associated with MI.

Study Limitations

This is a retrospective analysis from a single center. The patient subset was limited to those who had recurrent symptoms and did not include patients with silent restenosis or ischemia. Angiographical analysis was performed visually by 2 experienced operators and not by an independent core laboratory with quantitative analysis. Finally, intravascular ultrasound data were not available, which would be useful for evaluating the cause of stent thrombosis, such as underdilataion of the stent, as well as detecting unstable plaque in the adjacent non-stented segment. However, we believe this study still provides a "real world" view of the incidence of MI as a presentation of clinical in-stent restenosis.

Conclusion

The present study shows that clinical in-stent restenosis can frequently present as a MI. Patients with MI are more likely to have renal failure and acute coronary syndromes at the initial procedure. Angiographically, patients with MI tend to have an aggressive pattern of restenosis and total occlusion of the target lesion. With the advent of drug-eluting stents, it will be interesting to see if the derease in restenosis and possible change in the pattern of restenosis will translate into a reduction in MI.[23,24] In the meantime, there may be a role for aggressive secondary prevention treatments, including longer duration of antiplatelet therapy, to reduce the incidence of these recurrent events.[25,26]

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