International Journal of Cardiology 263 (2018) 9–16

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Pathological mechanisms of left main stent failure

Hiroyoshi Mori [a], Sho Torii [a], Emanuel Harari [a], Hiroyuki Jinnouchi [a], Ryan Brauman [a], Samantha Smith [a], Robert Kutys [a], David Fowler [b], Maria Romero [a], Renu Virmani [a], Aloke V. Finn [a,c,*]

[a] CVPath institute, Gaithersburg, MD, United States
[b] Office of the Chief Medical Examiner, Baltimore, MD, United States
[c] University of Maryland, School of Medicine, Baltimore, MD, United States

ARTICLE INFO

Article history:
Received 14 November 2017
Received in revised form 2 February 2018
Accepted 28 February 2018

Keywords:
Left main
Stent
Thrombosis
Bifurcation
And malapposition

ABSTRACT

Background: Despite the increasing use of left main (LM) percutaneous coronary intervention (LM-PCI), there have been no pathological studies devoted to understanding the causes of LM stent failure. We aimed to systematically determine the pathological mechanisms of LM stent failure.

Methods and results: From the CVPath Stent registry, a total of 46 lesions were identified to have LM-PCI. Pathologic stent failure (PSF) was defined as stent thrombosis, restenosis and in-stent chronic total occlusion (CTO). Failed and patent LM stented lesions were pathologically assessed to determine predictors of PSF. Malapposition and uncovered struts were numerically greater in the LM ostium, body, and bifurcation while neointimal thickness was relatively greater in bifurcation and proximal circumflex. In this study cohort, half of the lesions ($n = 23$) showed PSF. Stent thrombosis (ST, $n = 18$) was the major mode of PSF followed by in-stent CTO ($n = 4$) and restenosis (n = 1). Failed lesions showed significantly greater prevalence of malapposition >20% of struts/section (65% vs. 13%, $P < 0.01$), stent struts crossing an ostial side branch >30% of the circumference (48% vs. 13%, $P < 0.01$) and uncovered struts >30% (57% vs. 18%, $P = 0.03$). In multivariate analysis, the prevalence of malapposition >20% was the strongest risk factor for PSF (Odds ratio 8.0, 95% confidence interval 1.8–45.4, $P < 0.01$) followed by struts crossing an ostial side branch >30% (Odds ratio 4.2, 95% confidence interval 0.8–24.7, $P = 0.09$).

Conclusion: Our data demonstrate the main pathological predictors for LM stent failure are malapposition and struts crossing an ostial side branch and suggest that imaging-guided PCI may be important.

1. Introduction

Significant obstructive coronary artery disease of the left main (LM-CAD) was traditionally thought to be contraindication for percutaneous coronary intervention (PCI). Coronary artery bypass grafting (CABG) has been the standard treatment for revascularization in patients with LM-CAD. The emergence of drug-eluting stents (DES) and advances in anti-platelet therapy have increased the popularity of PCI strategies for treatment of LM-CAD in a past decade [1–3]. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) randomized trial showed that major adverse cardiac events following PCI using 1st-generation DES (1st-DES) or CABG for LM-CAD were comparable in low and intermediate SYNTAX score groups [1,4]. Accordingly, current guideline recommended PCI for LM-CAD in the absence of complex and diffuse lesions [5,6]. More recently, two larger international randomized studies compared PCI using 2nd generation DES (2nd-DES) with CABG (EXCEL [$n = 1905$] and NOBLE [$n = 1201$]) have been published [7,8]. In the EXCEL study, the primary end-point (rate of a composite of death from any cause, stroke, or myocardial infarction) at 3 years was not different in patients with low and intermediate SYNTAX scores (15.4% in PCI, 14.7% in CABG, $P = 0.98$) [7]. On the other hand, in the NOBLE study, major adverse cardiac or cerebrovascular events (a composite of all-cause mortality, non-procedural myocardial infarction, any repeat coronary revascularization, and stroke) at 5 years was significantly worse with PCI versus CABG (29% in PCI, 19% in CABG, $P = 0.0066$), which was consistent even in patients with low syntax scores [8].

Although these findings tell us more about the complexity and difficulty of stenting of LM-CAD, a further understanding is needed in order to improve outcomes in patients with LM-CAD requiring PCI. A dedicated pathological analysis of the vascular responses to LM stenting has never been performed but might reveal novel insights into the causes of PSF and whether any of these are modifiable either by improving the stent technology itself or the techniques used to implant stents. In the present

* Corresponding author at: 19 Firstfield Road, Gaithersburg, MD 20878, United States.
E-mail address: afinn@cvpath.org (A.V. Finn).

https://doi.org/10.1016/j.ijcard.2018.02.119
0167-5273/

manuscript, we aimed to systematically study the pathological response of LM stenting focusing on the mechanism of stent failure.

2. Methods

2.1. Patients and lesions

Between 2003 and 2016, the CVPath stent registry had received a total of 1072 lesions from 630 patients. From the CVPath Stent registry, a total of 46 patients were identified to have stent implantation in the LM. Overlapping and consecutively implanted stents were treated as 1 lesion, whereas stents showing gaps of >5 mm were considered separate lesions [9]. Clinical records were reviewed for patient history, duration of implantation, and risk factors if available. Cause of death was categorized into be stent related death (SRD), non-stent related cardiac death (NSRCD) or non-cardiac death (NCD) as previously described [9].

2.2. Histological preparation

Following fixation with 10% neutral buffered formalin, epicardial coronary arteries were removed from the heart and radiographed, decalcified if necessary and the entire stented segments were dehydrated and embedded in methyl methacrylate plastic. The plastic embedded stents were segmented at 3-mm intervals, sectioned at 4 to 6 μm, and stained with hematoxylin and eosin and modified Movat pentachrome stains, as previously described [10].

2.3. Pathological assessment and morphometric analysis

Pathological stent failure (PSF) at autopsy was defined as a composite of stent thrombosis, in-stent restenosis, or chronic total occlusion (CTO). Stent thrombosis was defined as a platelet-rich thrombi involving >1 quadrant of a stented arterial cross-section. In-stent restenosis was defined as >75% cross-sectional luminal area narrowing by neointimal tissue within stent area, with or without atherosclerosis [11]. In-stent CTO was defined when stent lumen is occupied with organizing or organized thrombus as previously described [12]. Length of LM was measured by radiography. Underlying plaque morphology was determined as pathological intimal thickening (PIT), fibroatheroma, thin-cap fibroatheroma (TCFA) and fibrocalcific plaque according to modified AHA classification [13]. Lesion calcification was categorized as none, mild, moderate or severe based on radiographic findings [14].

Isolated LM stenting was defined when the stent did not involve the LM bifurcation while bifurcation involvement was defined when stent crossed the LM bifurcation regardless of stent technique. Two-stent technique included any techniques such as T-stent, V-stent, Culotte stenting and simultaneous kissing stent as long as it involved both vessels of left anterior descending (LAD) and left circumflex (LCX) while simple overlap stenting was included as a one-stent technique. Morphometric analyses were applied in sections within the entire LM and 10 mm of the proximal LAD and proximal LCX, which was performed with image analysis software (Zen2, blue edition, Carl Zeiss, Oberkochen, Germany) following digital scanning. Malapposition (defined when struts are not in contact with the arterial wall with a distance of the strut thickness or greater) was assessed in all lesions while uncovered struts, fibrin deposition, neointimal thickness and luminal narrowing were assessed in the lesions >30 days. Malapposition, uncovered strut and fibrin deposition were expressed as percentage of struts with each finding per a cross section. These were stratified location with the LM (i.e. ostium, body, bifurcation, proximal LAD and proximal LCX) to identify vessel healing in different location.

In each lesion, the degree of malapposition was also expressed as the maximum number or percentage of malapposed struts per cross section. Stent struts crossing an ostial side branch was determined when there was evidence of stent struts jailing either the LCX (if the stent was placed from the LM into the LAD) or the LAD (if the stent was placed from the LM into the LCX), which was expressed as absolute number or percentage of struts per a cross section at the bifurcation site. An illustration demonstrating the definitions for malapposition and stent struts crossing an ostial side branch is shown in Supplemental Fig. 1. Threshold values for each factor were determined which maximized sensitivity and specificity for prediction of PSF by using receiver operative characteristic (ROC) curve. Presence or absence of stent strut protrusion into aorta was assessed by both radiograph and histology. The longitudinal length of protrusion was also measured. Prevalence of medial tear, penetration of necrotic core were evaluated as previously described [9,15]. Stent fracture was assessed by radiography. For lesions >30 days, the maximum number or percentage of uncovered struts per a cross section were expressed in similar manner and also prevalence of uncovered struts >30% was shown as previously described [9]. In-stent atherosclerotic change (neoatherosclerosis) was also assessed as previously described [11].

Additionally, in cases of stent thrombosis, the single most probable cause and the location of the culprit site were determined per lesion based upon the most outstanding pathological findings in agreement with experienced pathologist (RV). Stent struts an ostial side branch (either LAD or LCX) was determined when thrombus was present mainly within the stented portion within the side branch. On the other hand, stent strut protrusion into aorta was selected when thrombus was mainly observed at the protrusion site and attached to stent struts. Major cause of in-stent CTO was determined as previously described [12].

2.4. Statistical analysis

Normality of data was tested with the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation or median value [25th percentile - 75th percentile] as appropriate unless specified. Categorical variables were expressed as number (percentage). Comparisons of continuous variables with normal distribution were tested by student's *t*-test. Comparisons of continuous variables with non-normal distribution were tested by Wilcoxon test. Categorical variables were analyzed by chi-square test or fisher exact test as appropriate. Factors assessed for lesion characteristics, procedure and pathologic features were selected for univariate analysis to predict PSF. The factors whose *P*-value is <0.10 were selected for multivariate analysis. JMP 9 (SAS institute, Cary, NC, USA) was used for statistical analysis. *P*-values of <0.05 were considered statistically significant.

3. Results

PSF was observed in half of the lesions (23 of 46, Supplemental Table 1), and was not different between stent types (i.e. bare metal stent (BMS), 1st-DES, or 2nd-DES). The most frequent mode of PSF in our autopsy registry by far was stent thrombosis (78%) followed by CTO (17%) and restenosis (4%). All the cases with CTO had bypass grafting of the distal vessel. Supplemental Table 2 shows patient characteristics stratified by subjects with failed versus patent lesions. There were no differences in age, gender, coronary risk factors, previous myocardial infarction and previous CABG (coronary artery bypass graft) between the two groups while the cause of death in subjects with failed lesions showed significantly greater stent-related death (SRD) in subjects with failed versus patent lesions. Supplemental Table 3 shows lesion characteristics between failed versus patent lesions. There were no differences in duration, stent type, number and length of stents, LM length, indication for stent implantation, underlying plaque and severity of calcification. Procedural features such as isolated LM stenting and bifurcation involvement with 1-stent or 2-stent techniques didn't differ between failed and patent lesions (Supplemental Table 4).

Supplemental Fig. 2 shows the different pathological responses by location of LM-CAD. Percentage of malapposed struts ([number of malapposed struts] / [total number of struts]) was greatest in the LM ostium followed by the bifurcation and body, and was least in the proximal LAD and LCX (Supplemental Fig. 2A). Similarly, in the lesions >30 days, the percentage of uncovered struts was greatest in the LM ostium followed by body and bifurcation, and was least in the proximal LAD and LCX (Supplemental Fig. 2B) while percent fibrin deposition was greatest within stents located within the ostium and similar in all other locations (Supplemental Fig. 2C). On the other hand, the percentage of luminal narrowing (% stenosis) and mean neointimal thicknesses was greatest in LM bifurcation and proximal LCX, and was less in LM ostium and body (Supplemental Fig. 2D–E).

Pathologic features are shown in Table 1. The maximum number and percentage of malapposed struts were significantly greater in failed versus patent lesions (3 vs. 1, $P = 0.04$; 25% vs. 8%, $P = 0.02$). Similarly, the prevalence of malapposition >20% of struts/section was significantly different (65% vs. 13%, $P < 0.01$). Absolute number and percentage of stent struts crossing an ostial side branch was numerically greater in failed versus patent lesions (4 vs. 1, $P = 0.12$; 33% vs. 10%, $P = 0.10$). When a threshold value of 30% of the circumference of stent struts crossing an ostial side branch was applied, the difference was significant (48% vs. 13%, $P < 0.01$). Any strut protrusion into the aorta was not rare occurring 39%, which was similar between failed and patent lesions. When strut protrusion was major (>30%), it often came with major malapposition (>20%) at left main ostium (8 of 13, 62%). Medial tear was frequently observed in both groups. Necrotic core penetration and stent fracture was not different between groups. For lesions >30 days, uncovered struts were numerically greater and the prevalence of uncovered struts >30% was significantly greater in failed lesions versus patent lesions (57% vs. 18%, $P = 0.03$). Neoatherosclerosis was also numerically greater in failed lesion.

Fig. 1A shows timing and the single most probable cause of stent thrombosis in each lesion while Fig. 1B illustrates the location and causes of stent thrombosis. There was no statistical difference in cause