Positive Distal Vessel Remodeling After Initial Balloon Dilatation of Chronic Total Occlusions and Staged Stenting in a Selected Group of Patients

Wei-Jung Lo, MD[a], Yu-Cheng Hu, MD[a], Wei-Jhong Chen, MD[a], Yu-Wei Chen, MD[a], Chih-Hung Lai, MD[a,b], Jie-Shou Su, MD[a,b], Tsun-Rui Liu, MD[a,b], Wen-Lieng Lee, MD, PhD[a,b], Wei-Chun Chang, MD[c]

[a]*Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan*
[b]*Institute of Clinical Medicine, National Yang-Ming Chiao-Tung University School of Medicine, Taipei, Taiwan*
[c]*Ministry of Health and Welfare Feng-Yuan Hospital, Taichung, Taiwan*
Drs Wei-Jung Lo and Yu-Cheng Hu contributed equally to the writing of this article.

Abstract

Background: It is not uncommon to see that immediately upon opening of chronic total occlusions (CTOs) the distal coronary vessels are too small and diffusely diseased to be stented. As coronary vessel size depends on flow and arterial remodeling takes time, the available arterial size may be underestimated if assessed immediately after opening a CTO. This study aimed to investigate the positive remodeling of distal coronary arteries after successful balloon angioplasty of CTOs.

Methods: Patients who received successful balloon angioplasty (POBA) for CTO, in whom no stenting was intended due to very small vessel size and diffuse lesions at the index PCI were prospectively studied. Angiographic follow-up was conducted within 1-3 months. The angiographic characteristics of the CTO and coronary artery one segment downstream were measured at baseline, immediately post-POBA and at angiographic follow-up.

Results: A total of 28 patients were studied. After a mean follow-up of 2.3 ± 1.9 months, it was found that the vessel lumen one segment distal to the CTO had become significantly enlarged, as compared with immediately post-POBA (2.0 ± 0.6 mm vs. 1.7 ± 0.6 mm, P = 0.004) despite a binary angiographic restenosis of 60.7%, and reocclusion of 21.4% in these patients. All but one of these lesions could be successfully treated percutaneously, with the size and length of the stents significantly larger and shorter than those that would have been chosen if stenting had been done at the index PCI.

Conclusion: Positive remodeling of coronary arteries distal to the CTOs does occur after initial successful POBA. The optimal stent size and length are better determined in a staged manner in a selected group of patients.

Keywords: arterial remodeling, percutaneous coronary intervention, chronic total occlusion

Received: Sep. 22, 2021; Accepted: Sep. 23, 2021
Address for correspondence: Wei-Chun Chang, MD
Department of Internal Medicine, Ministry of Health and Welfare Feng-Yuan Hospital; No. 100, An-Kan Road, Feng Yuan Dist., Taichung 42055, Taiwan
Tel: +886-952528753; Email: xiauochunchun@gmail.com

1. Introduction

Chronic coronary total occlusion (CTO) is frequently seen in the cath labs, with the incidence ranging from 30% to 50% in patients undergoing coronary angiography for significant coronary artery disease.[1] CTOs remain a significant challenge for interventional cardiologists because of the low success and high reocclusion/restenosis rates after balloon angioplasty (POBA).[2] Stenting of coronary CTOs, especially with drug-eluting stents (DES), significantly reduces re-occlusion and restenosis and is routinely considered in current practice.[3,4] However, it is not uncommonly seen that immediately after opening CTOs, the distal vessels are too small and diffusely diseased to be stented with confidence, even with the smallest available stents. Using an oversized stent carries the risk of distal edge dissection or vessel rupture, and full metal jacketing brings its own concerns.[5,6]

Physiological wall shear stress is an important factor in maintaining normal endothelial function and participates in arterial remodeling.[7,8] It is proportional to blood viscosity and blood flow but inversely proportional to the cube of the vessel radius.[8] Since the vessel size depends on flow to maintain shear stress in the physiological range and positive remodeling takes time after restoration of antegrade blood flow following successful opening,[9] the coronary artery size may be underestimated upon opening of CTOs and even intravascular ultrasound evaluation tends to underestimate it. The coronary vessel size, and therefore the stent size and length, might be better determined at follow-up angiography after revascularization has been established for some time but before re-occlusion occurs. Positive vessel remodeling has previously been reported in the literature.[10]

The purpose of this study was to investigate whether and to what extent positive remodeling of distal coronary arteries occurred after successful POBA of CTOs in which the treated vessels were too small and diffusely diseased to be stented at the index percutaneous coronary intervention (PCI). The safety of delaying stenting until a more reasonable choice of stent size, length and numbers could be made for a in the second-stage PCI was also studied.

2. Methods

From January 2005 to July 2009, patients who received successful POBA of CTO in native coronary arteries, in which no stenting was intended due to very small vessel size and diffuse lesions at the index PCI, were recruited and prospectively studied. Angiographic follow-up was scheduled within 1-3 months to allow for arterial remodeling but ostensibly before re-occlusion occurred. This study protocol was approved by the institutional review board for human research of this hospital.

In this study, CTOs were defined as the complete obstruction of a native coronary artery with no luminal continuity and a TIMI flow of grade 0. The duration of coronary occlusion had to be greater than 3 months, as estimated from clinical events including myocardial infarction (MI), sudden onset or worsening of symptoms, or previous angiography. Patients were excluded if the CTO was not in the native coronary artery or in a vessel supplying only a minor territory of myocardium, or if the CTO was within or in contingency with a previously placed stent. Patients were excluded if they refused scheduled angiographic follow-up. All patients provided written informed consent to the procedure.

2.1. Intervention procedure

Patients were medicated according to general cardiac principles, including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, nitrates, and statins, throughout the study period. These medications were kept constant throughout unless contraindicated. All PCIs were performed following standard practice at our cath lab. Patients were pretreated with aspirin and clopidogrel, or a

minimum of 300 mg loading dose of clopidogrel was administered before the procedure if not pretreated. During the procedure, heparin was administered to maintain the activated clotting time (ACT) > 300 seconds or ~200 seconds if a GP IIb/IIIa inhibitor was used. After successful wiring of the CTO lesions, the occluded segments were dilated with balloons using a maximal size no larger than that estimated from proximal and distal reference to obtain as normal a final TIMI flow as possible and to avoid diffuse dissections at the same time. If the final blood flow was TIMI II or higher, the treated segment and the proximal and distal reference vessels < 2.25 mm (smaller than the smallest available DES in the market) and the diseased segment was diffuse (> 55 mm; longer than twice the length of the longest 2.25 mm DES), no stenting was considered at the index PCI. Patients were fully informed on the PCI results and were invited to participate in this study if they agreed to scheduled angiographic follow-up.

Follow-up CAG and second-stage PCI were also done following standard practice. Angioplasty and stenting were performed according to the follow-up angiographic findings. Only segments that were ≥ 50% restenotic were stented, using the maximum possible sizes estimated from the proximal and distal reference vessels and stents were limited to segments where they were imperative. Full metal jacketing with small stents was avoided and intravascular ultrasound was done at the discretion of operators.

After the second intervention, all patients were continuously medicated and followed up at the out-patient clinic and the outcomes were recorded.

2.2. Quantitative coronary angiographic (QCA) analyses

Coronary angiograms were done at baseline, immediately after the index PCI, and at angiographic follow-up. The angiographic measurements were made on a viewing workstation with software for quantitative analysis of angiograms (Horizon Cardiology 11, vers. TCS3.1 HF5, Medcon, a McKesson Company, Tel Aviv, Israel). The angiographic characteristics of both the CTO and the coronary artery one segment distal were measured by reviewing the session cine thoroughly and were recorded at baseline, immediately post-POBA and during angiographic follow-up. The CAD vessel numbers were defined as the number out of the three major coronary vessels that were ≥ 70% diameter stenotic.

The lesion length was defined as the estimated length of the occlusion from the point of total occlusion to the most proximal point of the distal vessel visualized by collateral filling with contrast. The distal vessel size was defined as the size of the vessel one segment distal to the CTO lesion. Binary angiographic restenosis (BAR) was defined as a diameter stenosis of > 50% at angiographic follow-up, while re-occlusion was defined as a minimal lumen diameter (MLD) of zero with a TIMI 0 flow at the previously dilated site on angiographic follow-up.

2.3. Statistical analysis

Categorical variables are presented as frequencies with percentage. Continuous variables are expressed as mean ± standard deviation (SD). Changes in vessel size on angiographic follow-up were measured by paired student's *t*-test. A p value < 0.05 is considered statistically significant. All statistical procedures were performed using SPSS software (SPSSversion15.0, SPSS Inc, Chicago, IL).

3. Results

3.1. Patient characteristics

A total of 28 patients, 26 males and 2 females, with a mean age of 63 ± 13 years were studied. The baseline clinical characteristics are shown in Table 1. 60.7% of them had hypertension, 39.3% diabetes, 64.3% hyperlipidemia and 60.7% smoking history. 67.9% of them had multiple vessel diseases. The LDL-cholesterol averaged 132 ± 47 mg/dl.

Table 1. Demographic data of all patients

No. of patients	N = 28
Age (years)	63 ± 13
Sex (M/F)	26/2
Body height (cm)	165 ± 7.0
Body weight (kg)	70.7 ± 11.8
Hypertension (N) (%)	17 (60.7)
Diabetes (N) (%)	11 (39.3)
Hyperlipidemia (N) (%)	18 (64.3)
Smoking history (N) (%)	17 (60.7)
Family history of CAD (N) (%)	1 (3.6)
Previous PCI (N) (%)	10 (35.7)
Previous coronary bypass (N) (%)	0 (0)
Old myocardial infarction (N) (%)	6 (21.4)
Old CVA (N) (%)	1 (3.6)
PAOD (N) (%)	1 (3.6)
Congestive heart failure (N) (%)	11 (39.3)
COPD (N) (%)	1 (3.6)
LVEF (%)	40.2 ± 17
Total Cholesterol (mg/dl)	198 ± 52
HDL-cholesterol (mg/dl)	43 ± 8
LDL-cholesterol (mg/dl)	132 ± 47
Triglyceride (mg/dl)	134 ± 59
BUN (mg/dl)	24 ± 19
Serum creatinine (mg/dl)	1.5 ± 1.0
Admission diagnosis	
Stable angina (N) (%)	13 (46.4)
Acute coronary syndrome (N) (%)	7 (25.0)
Congestive heart failure (N) (%)	8 (28.6)
CAD vessel number (%)	
Single vessel disease (N) (%)	9 (32.1)
Two vessel disease (N) (%)	14 (50.0)
Three vessel disease (N) (%)	5 (17.9)

Data expressed as mean ± SD; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; PAOD: peripheral arterial occlusive disease.

3.2. Procedural characteristics and angiographic findings

Angiographic and procedural variables are summarized in Table 2. Almost all of the CTOs were located at the left anterior descending (60.7%) or right coronary arteries (35.7%). The CTO segment was 27.0 ± 20.5 mm in length and vessel size preceding CTO was only 1.6 ± 0.6 mm at the baseline. All lesions had bridging collaterals. After the index PCI with POBA, the MLD increased to 1.3 ± 0.5 mm with a residual stenosis of 41 ± 15%. The final TIMI flow was grade II in 4 (14.3%) cases and III in the remaining 24 (85.7%) cases. The distal vessel size one segment distal to the CTO site was only 1.7 ± 0.6 mm. The patient was maintained on previous medications and strictly on dual antiplatelets.

After a mean angiographic follow-up of 2.3 ± 1.9 months, the vessel size became 2.0 ± 0.7 mm in size. The MLD at the CTO sites decreased significantly from that immediately post POBA at the index PCI (1.0 ± 0.6 mm vs. 1.3 ± 0.5 mm, P = 0.003; Figure 1, upper panel). However, the lumen size of the vessel one segment distal to the CTO site became significantly larger as compared with that immediately post-POBA (2.0 ± 0.6 mm vs. 1.7 ± 0.6 mm, P = 0.004; Figure 1, lower panel) despite angiographic re-stenosis occurring in 17 and re-occlusion in 6 of these patients. All of these restenotic/ re-occlusive lesions could be successfully re-treated with PCI. Using more proximal vessel segments as reference, the diameter of stents implanted at the CTO site was 2.8 ± 0.3 mm. The implanted stent length was 35.5 ± 15.0 mm and a total of 1.4 ± 0.7 overlapping stents were deployed for the lesion. The average stent deployment pressure was 14.6 ± 3.6 atm. The final MLD was 2.4 ± 0.5 mm with a mean residual stenosis of 18.4 ± 9.5%. No major complications occurred at the second-stage PCIs.

3.3 Clinical follow-up

All patients were followed up at our outpatient clinic except one who was lost to follow up. During a mean 11.8 ± 10.3 months

Table 2. Angiographic and procedural characteristics (N = 28)

Locations of chronic total occlusion	
LAD (N)(%)	17 (60.7)
LCX (N)(%)	1 (3.6)
RCA (N)(%)	10 (35.7)
Baseline	
CTO lesion length (mm)	27.0 ± 20.5
Preceding-CTO vessel diameter (mm)	1.6 ± 0.6
MLD (mm)	0.0 ± 0.0
Diameter stenosis (%)	100 ± 0
Bridging collaterals	28 (100)
First intervention	
POBA segment length (mm)	34.2 ± 11.7
Maximum pressure (atm)	11.3 ± 3.5
MLD at CTO site (mm)	1.3 ± 0.5
Residual stenosis at CTO site (%)	41 ± 15
Distal segment vessel size (mm)	1.7 ± 0.6
Distal blood flow	
TIMI 0 (N) (%)	0 (0)
TIMI 1 (N) (%)	0 (0)
TIMI 2 (N) (%)	4 (14.3)
TIMI 3 (N) (%)	24 (85.7)
CAG follow-up	
Months	2.3 ± 1.9
Preceding-CTO vessel diameter (mm)	2.0 ± 0.7
MLD (mm) at CTO site	1.0 ± 0.6
Restenosis at CTO site (N) (%)	17 (60.7)
Reocclusion at CTO site (N) (%)	6 (21.4)
Distal segment vessel size(mm)	2.0 ± 0.6
Distal blood flow	
TIMI 0 (N) (%)	2 (7.1)
TIMI 1 (N) (%)	1 (3.6)
TIMI 2 (N) (%)	3 (10.7)
TIMI 3 (N) (%)	23 (82.1)
Re-intervention (N) (%)	23 (82.1)
POBA (N) (%)	1 (4.5)
POBA segment length (mm)	20
Proximal RVD (mm)	2.5
Maximum pressure (atm)	14
Final MLD (mm)	1.5
Residual stenosis (%)	15
Stent (N) (%)	22 (78.6)
Stented segment length (mm)	35.5 ± 15.0
Stent diameter (mm)	2.8 ± 0.3
Number of stents per lesion	1.4 ± 0.7
Proximal RVD (mm)	2.8 ± 0.6
Maximum pressure (atm)	14.6 ± 3.6
Final MLD (mm)	2.4 ± 0.5
Residual stenosis (%)	18.4 ± 9.5

Continuous variables are expressed as mean ± SD; CTO: chronic total occlusion; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; RVD: reference vessel diameter; MLD: minimal luminal diameter; POBA: plain old balloon angioplasty; TIMI: thrombolysis in myocardial infarction trial.

of clinical follow-up, there were no patient deaths, one (3.6%) patient developed restenosis and suffered from a new myocardial infarction, three (10.7%) required a new revascularization procedure, and three (10.7%) patients were re-admitted due to congestive heart failure. Major adverse cardiovascular events (MACE) occurred in a total of five (17.9%) patients.

4. Discussion

4.1. CTO and PCI

CTO lesions are usually complex and characterized by long obliterations with new tissue formation, organized thrombus, atheroma and calcifications.[11] CTOs present great challenges to interventional cardiologists and the long-term results are difficult to maintain even after successful opening. The use of stents, especially DES, significantly reduces re-stenosis and re-occlusion risks, and is current routine practice.[3,4] Studies have indicated that the successful opening of CTOs is associated with improved quality of life, left ventricular function, less need for bypass surgery and reduced mortality.[12,13] Advances in new concepts, techniques and novel devices (bilateral injections, new wires, parallel wiring, IVUS-guided PCI, retrograde approach etc) have resulted in more and more PCIs for these lesions in contemporary practice.[14,15] However, it is not uncommon to find that upon opening of CTOs the distal vessels are too small and too diffusely diseased to be stented with confidence, even with the smallest available stents. If left unstented, the risk of re-closure is high.[2] Using an oversized stent, on the other hand, carries the risk of distal edge dissection and vessel rupture.[5] Full metal jacketing with long and small stents is also associated with a higher rate of stent thrombosis, restenosis and re-interventions.[16,17] Since the arterial vessel size is flow dependent and positive remodeling after balloon angioplasty takes time,[9] we, therefore, hypothesized that positive remodeling of the distal vessel after successful initial POBA of CTO lesions might permit a more

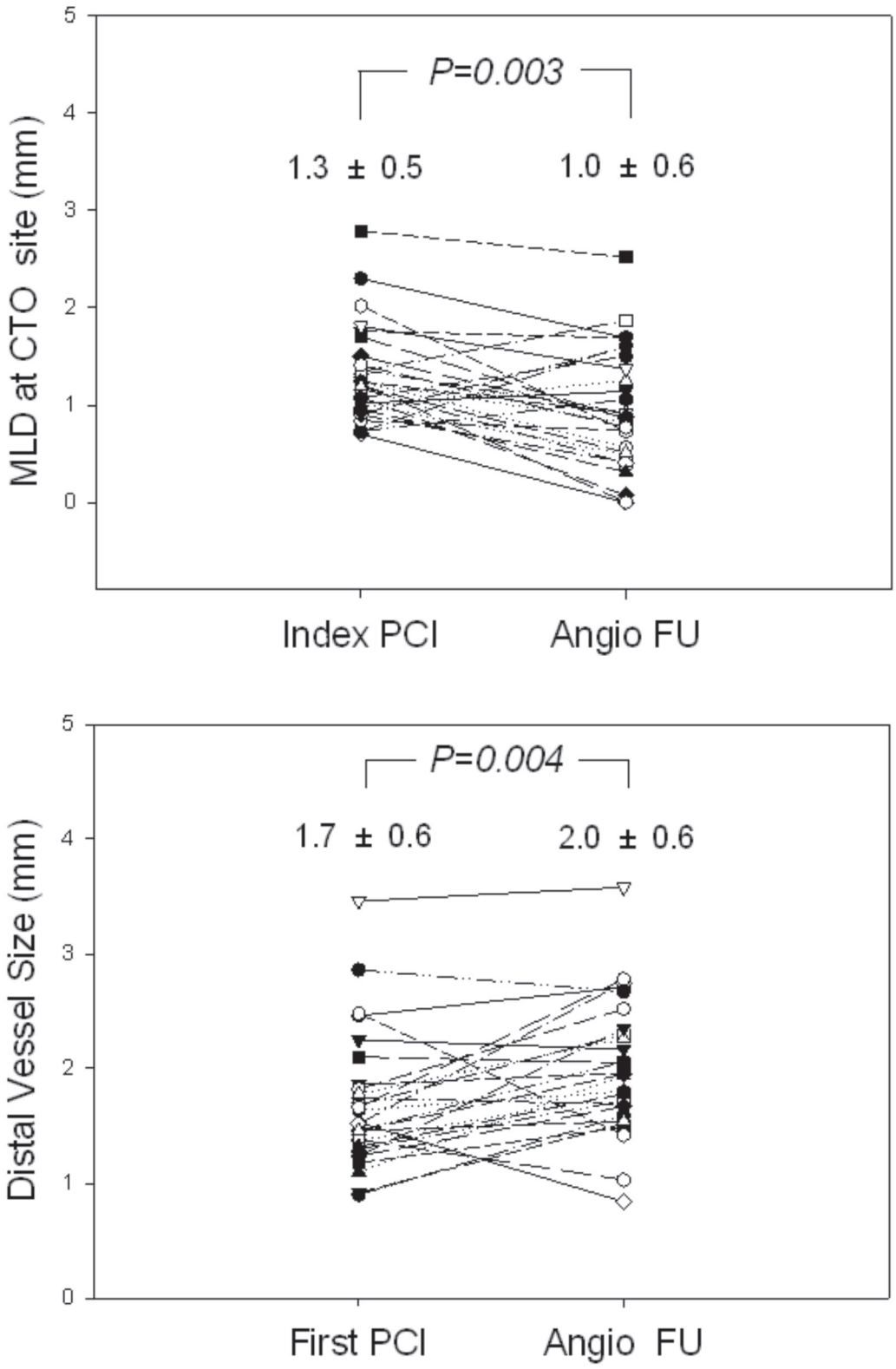

Figure 1. The changes in minimal lumen diameter (MLD) at the CTO site (upper panel) and in vessel size one segment distal to the CTOs (lower panel) at the angiographic follow-up.

appropriate choice of stents in a staged manner. Positive distal vessel remodeling has previously been reported in the literature,[10] however, in that study angiographic follow-up was made at one year or longer, and not in the range of weeks after the index procedure. Whether vessel remodeling will occur and allow proper stenting in the shortest possible time after index POBA of a CTO vessel in which no stenting is possible due to too small vessel sizes, remains undetermined.

4.2. Wall shear stress and vessel remodeling

Physiological wall shear stress is a major factor in maintaining normal artery structure and function.[7,8] Arterial shear stress in the physiological range keeps the endothelial cells fusiform and aligned, and maintains normal endothelial functions like suppressing endothelial proliferation or production of vasoconstrictors, adhesion molecules and inflammatory mediators, while promoting production of vasodilators and antioxidants.[7,8] When arterial wall is exposed to low shear stress, such as at the outer walls of vessel bifurcation, it is prone to the development of atherosclerosis. Given Poiseuille flow, wall shear stress is proportional to the product of blood viscosity and blood flow but inversely proportional to the cube of the vessel radius. In order to keep shear stress within the physiological range, the arteries change the vessel diameter in adaptation to changes in the blood flow and such changes are related to endothelial function.[9] Vascular remodeling after POBA is determined by the severity and depth of arterial injury, extent of inflammation, blood flow, pressure and the wall stress.[18] The phenomenon of late stent mal-apposition after PCI treatment of acute myocardial infarction may, in part, be caused by vascular remodeling.[19,20] Our study results did confirm that positive remodeling of distal vessel beds took place in the short follow-up period after successful restoration of antegrade blood flow, despite a high incidence of restenosis and even a few cases of re-occlusion. As the re-occlusion was still soft in most cases, the vessel must have been kept patent for some period of time before occlusion recurred, and hence allowed positive remodeling to take place. During the second-stage PCI, all restenotic and re-occlusive lesions could be successfully re-treated and stented. No re-PCI complication (edge dissection, vessel rupture or no reflow) was encountered after deploying a mean stent length of 35.5 ± 15.0 mm with a diameter of 2.8 ± 0.3 mm. This would not be possible if stenting were done at the index PCI. As a result, a more rational use of DES in deferred stenting was realized in real world practice, and this has been reported before. In the study by Okuya et al, positive distal vessel remodeling was identified and novel predictors for late lumen enlargement (small distal vessel sizes, in the LAD, no moderate or severe calcification) were reported.[21] However, in this study all CTO segments could be and were stented at the index procedure.

4.3. Antiplatelets after PCI for CTO

Dual antiplatelets, but not aspirin in combination with coumadin or dipyridamole, have been shown to effectively reduce the risk of stent thrombosis after placement of BMS or DES.[22,23] However, dual antiplatelets were not used or tested in the era of simple POBA.[22,23] Today, strong evidence has proved the benefits of dual antiplatelets in acute ST-elevation myocardial infarction and non-ST-elevation acute coronary syndrome. As plaque ruptures, underlying tissue factor exposure and resultant thrombus formation play central roles in acute or sub-acute vessel closures after POBA. Dual antiplatelets, by combining agents with different mechanisms, might effectively reduce these risks. This hypothesis was tested in the current study, amid concerns of a high re-occlusion rate, given that the treated segments were long, small and diffusely diseased. After an average of 2.3 months of medical treatment, re-occlusion did occur in 21% of our patients, but most of these re-occlusions were soft and re-interventions and stenting could be carried out successfully. Therefore, the safety of delayed stenting in our study was assured and this deferral

strategy was well justified. In the current study, a significant proportion of the patients' angiographic follow up occurred more than a month after the index PCI due to different causes. If all the angiographic follow-up could have been done earlier, the re-occlusion rate would have been much lower and patency of the vessels further secured. In recent years, triple antiplatelets (with additional cilostazol) were used in elective and primary PCI and shown to reduce the early MACE rate.[24,25] Whether the use of triple antiplatelets in settings like ours could further reduce the risk of re-occlusion before second intervention is unknown but seems promising.

4.4 Limitations

The study patient number was relatively small. However, this was a prospective study and exclusively limited to patients whose coronary vessels were too small and diffusely diseased to be stented with confidence after successful POBA of CTO lesions at the index PCI. The angiographic and clinical results, even in limited patient numbers, convinced us that positive remodeling did occur and more rational use of DES could be made in the second session. Secondly, no routine IVUS measurements were done in the current study, neither at the index PCI nor at the angiographic follow-up. However, even if IVUS study were done, scaffolding of diffusely diseased and angiographically small vessels would have still mandated full metal jacketing with small stents and would not be reasonable or practical. Choosing the proximal and distal landing zones would also be very difficult under these circumstances. Furthermore, as vessel remodeling of arteries takes time, even IVUS measurements immediately after POBA at the index PCI could never accurately measure the vessel anatomies to come.

5. Conclusions

Positive remodeling of coronary arteries distal to the CTOs does occur after successful POBA. The optimal stent sizes, lengths and numbers are better determined in a staged manner if the post-POBA vessels are too small and diffusely diseased to be stented with confidence. In these circumstances it is well justified to abstain from placing stents after POBA. Deferred stenting is rational and safe if patients receive dual antiplatelets and angiographic follow-up can be ensured in a reasonably short period of time.

References

1. Christofferson RD, Lehmann KG, Martin GV, et al. Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol* 2005;95(9):1088-91.
2. Tamai H, Berger PB, Tsuchikane E, et al. Frequency and time course of reocclusion and restenosis in coronary artery occlusions after balloon angioplasty versus Wiktor stent implantation: results from the Mayo-Japan Investigation for Chronic Total Occlusion (MAJIC) trial. *Am Heart J* 2004;147(3):E9.
3. Kandzari DE, Rao SV, Moses JW, et al. Clinical and angiographic outcomes with sirolimus-eluting stents in total coronary occlusions: the ACROSS/TOSCA-4 (Approaches to Chronic Occlusions With Sirolimus-Eluting Stents/Total Occlusion Study of Coronary Arteries-4) trial. *JACC Cardiovasc Interv* 2009;2(2):97-106.
4. Colmenarez HJ, Escaned J, Fernandez C, et al. Efficacy and safety of drug-eluting stents in chronic total coronary occlusion recanalization: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55(17):1854-66.
5. Liu X, Tsujita K, Maehara A, et al. Intravascular ultrasound assessment of the incidence and predictors of edge dissections after drug-eluting stent implantation. *JACC Cardiovasc Interv* 2009;2(10):997-1004.
6. Sharp AS, Latib A, Ielasi A, et al. Long-term follow-up on a large cohort of "full-metal jacket" percutaneous coronary intervention procedures. *Circ Cardiovasc Interv* 2009;2(5):416-22.
7. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA* 1999;282(21):2035-42.
8. Chatzizisis YS, Coskun AU, Jonas M, et al. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. *J Am Coll Cardiol* 2007;49(25):2379-93.
9. Vita JA, Holbrook M, Palmisano J, et al. Flow-induced

arterial remodeling relates to endothelial function in the human forearm. *Circulation* 2008;117(24):3126-33.
10. Gomez-Lara J, Teruel L, Homs S, et al. Lumen enlargement of the coronary segments located distal to chronic total occlusions successfully treated with drug-eluting stents at follow-up. *EuroIntervention* 2014;9(10):1181-8.
11. Jaffe R, Leung G, Munce NR, et al. Natural history of experimental arterial chronic total occlusions. *J Am Coll Cardiol* 2009;53(13):1148-58.
12. Valenti R, Migliorini A, Signorini U, et al. Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. *Eur Heart J* 2008;29(19):2336-42.
13. Hannan EL, Racz M, Holmes DR, et al. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation* 2006;113(20):2406-12.
14. Rathore S, Katoh O, Matsuo H, et al. Retrograde percutaneous recanalization of chronic total occlusion of the coronary arteries: procedural outcomes and predictors of success in contemporary practice. *Circ Cardiovasc Interv* 2009;2(2):124-32.
15. Weisz G, Moses JW. Contemporary principles of coronary chronic total occlusion recanalization. *Catheter Cardiovasc Interv* 2010;75 Suppl 1:S21-7.
16. Sallam M, Spanos V, Briguori C, et al. Predictors of re-occlusion after successful recanalization of chronic total occlusion. *J Invasive Cardiol* 2001;13(7):511-5.
17. Tin-Hay EL, Poh KK, Lim YT, et al. Clinical predictors of stent thrombosis in the "real world" drug-eluting stent era. *Int J Cardiol* 2010;145(3):422-5.
18. Birnbaum Y, Fishbein MC, Luo H, et al. Regional remodeling of atherosclerotic arteries: a major determinant of clinical manifestations of disease. *J Am Coll Cardiol* 1997;30(5):1149-64.
19. Ako J, Morino Y, Honda Y, et al. Late incomplete stent apposition after sirolimus-eluting stent implantation: a serial intravascular ultrasound analysis. *J Am Coll Cardiol* 2005;46(6):1002-5.
20. Hong MK, Mintz GS, Lee CW, et al. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation* 2006;113(3):414-9.
21. Okuya Y, Saito Y, Takahashi T, et al. Novel predictors of late lumen enlargement in distal reference segments after successful recanalization of coronary chronic total occlusion. *Catheter Cardiovasc Interv* 2019;94(4):546-552.
22. Raymond C, Menon V. Dual antiplatelet therapy in coronary artery disease: a case-based approach. *Cleve Clin J Med* 2009;76(11):663-70.
23. Hamdalla H, Steinhubl SR. Oral antiplatelet therapy for percutaneous coronary revascularization. *Catheter Cardiovasc Interv* 2007;69(5):637-42.
24. Singh I, Shafiq N, Pandhi P, et al. Triple antiplatelet therapy vs. dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: an evidence-based approach to answering a clinical query. *Br J Clin Pharmacol* 2009;68(1):4-13.
25. Chen KY, Rha SW, Li YJ, et al. Triple versus dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation* 2009; 119(25):3207-14.