Evaluation of neointimal coverage in patients with coronary artery aneurysm formation after drug-eluting stent implantation by optical coherence tomography

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Background. The vessel healing in patients with coronary artery aneurysms (CAA) that form after drug-eluting stent (DES) implantation is not clear. This study aims to assess the vessel healing in patients with CAA formation after DES implantation.

Methods. From June 2008 to August 2011, follow-up coronary angiography was conducted on 1160 patients who underwent percutaneous coronary intervention (PCI). The average period of follow-up was about (18.9±13.1) months. A total of 175 patients who underwent DES implantation into de novo lesions and who underwent coronary angiography and optical coherence tomography (OCT) examination during follow-up were identified. Patients were divided into the CAA group (n=31) and non-CAA group (n=144) based on the results of the coronary angiography. The cardiac events including angina and acute myocardial infarction were noted; in addition, the neointimal thickness and the frequency of strut malapposition and strut uncoverage were also noted.

Results. A greater proportion of incomplete neointimal coverage (17.17% vs. 1.90%, \( P < 0.001 \)) and strut malapposition (18.20% vs. 1.38%, \( P < 0.001 \)) were observed in the CAA group. The neointimal thickness in the CAA group was significantly thinner than that in the non-CAA group ((146.6±94.8) µm vs. (192.5±97.1) µm, \( P < 0.001 \)), as detected via OCT. Patients with CAA formation had a higher frequency of cardiac events including angina pectoris (25.81% vs. 6.25%, \( P = 0.001 \)) and acute myocardial infarction (9.68% vs. 0.13%, \( P = 0.002 \)) and thrombosis (16.13% vs. 0.69%, \( P < 0.001 \)). The longitudinal length of the CAA in the cardiac event group was significantly longer than in the no cardiac event group ((20.0±9.07) mm vs. (12.05±5.38) mm, \( P = 0.005 \)).

Conclusion. CAA formation after DES implantation is frequently associated with cardiac events as a result of stent malapposition and incomplete neointimal coverage.

SOME STUDIES HAVE REPORTED THAT CORONARY ARTERY ANEURYSM (CAA) OCCURRED IN 0.3% TO 6.0% OF PATIENTS AFTER STENT IMPLANTATION.\(^1\)\(^,\)\(^2\) THE POTENTIAL CAUSES ARE DELAYED ENDOTHELIALIZATION, INFLAMMATION, ANTIMITOLOBITE EFFECTS OF THE DRUG, AND HYPERSENSITIVITY REACTIONS TO THE DRUG AND THE POLYMER.\(^3\)\(^,\)\(^4\) BASED ON THE FOLLOW-UP INTRAVASCULAR ULTRASOUND (IVUS) EXAMINATION, CAA FORMATION AFTER DES IMPLANTATION CAN ENLARGE THE EXTERNAL ELASTIC MEMBRANE AND INCREASE LATE STENT MALAPPOSITION.\(^6\)\(^,\)\(^7\) HOWEVER, IVUS CANNOT ASSESS THE NEOINTIMAL COVERAGE AFTER STENT IMPLANTATION BECAUSE OF ITS LIMITED RESOLUTION. THEREFORE, THE STATUS OF NEOINTIMAL COVERAGE IN PATIENTS WITH CAA FORMATION AFTER DES IMPLANTATION REMAINS TO BE DETERMINED.

Optical coherence tomography (OCT) is a new imaging modality with a higher resolution, approximately 10-fold better than that of the IVUS image. OCT can assess vessel healing more clearly and accurately during the follow-up of DES evaluation compared with IVUS.\(^8\)\(^,\)\(^9\) THE CURRENT STUDY AIMS TO ASSESS THE VESSEL HEALING IN PATIENTS WITH CAA FORMATION AFTER DRUG-ELUTING STENT (DES) IMPLANTATION.
n=144), based on the baseline and follow-up quantitative coronary angiography (QCA). The exclusion criteria included congestive heart failure, renal insufficiency (serum creatinine >1.8 mg/dl), left main disease, target vessel diameter ≥4.0 mm, and a history of revascularization. All patients provided written informed consent prior to coronary angiography and OCT examination.

Coronary angiography and PCI
Coronary angiography was performed using a 6 French catheter through the femoral or radial artery. Heparin (100 U/kg) was administered conventionally, and imaging was performed after administering 200 µg of intracoronary nitroglycerin. PCI was performed in a standard manner, and the lesion was completely covered by stents. The types of DES implantation included the Cypher stent (sirolimus-eluting stent, Cordis, USA), Endeavor stent (zotarolimus-eluting stent, Medtronic, USA), Firebird stent (sirolimus-eluting stent, Microport, China), Partner stent (sirolimus-eluting stent, Lepu, China), and Excel stent (sirolimus-eluting stent, JW, China). The stents were successfully implanted without complication, and all patients were prescribed oral aspirin (100 mg/d) for life and clopidogrel (75 mg/d) for at least one year. The patients underwent coronary angiography examination in the period of follow-up. Coronary angiograms (including baseline, intervention and follow-up) were analyzed by two doctors in the angiographic core laboratory who were blind to the research. QCA was performed with an automatic edge-detection system (MEDIS, CMS 4.0, Leiden, the Netherlands). CAA was defined as a localized angiographic dilation of the vessel lumen (50% of the adjacent reference vessel) at late angiography, closely related to the underlying DES or its edges(Figure 1).2,10

OCT imaging acquisition and analysis
An M3 OCT system (LightLab Imaging, USA) with an automatic pullback speed of 1.5 mm/s was used in the current study. The images included the entire length of the stent and a segment of at least 5 mm extending beyond the stent edges. The OCT images were analyzed off-line by two independent doctors blinded to the research. LightLab Imaging Inc. provided the software. A single OCT cross-sectional still frame from each 1 mm segment was selected for quantitative analysis throughout the entire length of the stent. The still frames were selected based on the appearance of the stent struts and the lack of OCT motion or other image artifacts. Each stent strut in the still frame was observed to determine if the strut was a malapposition or a complete coverage. If neointimal coverage on the strut was observed, its average thickness was measured. The presence of strut malapposition and gaps between the vessel wall and strut, as well as strut uncoverage, neointimal thickness, stent area, corresponding vessel lumen area and thrombosis were noted.

Definition of malapposition, neointimal coverage and thrombosis
Malapposition is defined as the separation of at least one stent strut from the intimal surface of the arterial wall not overlapping a side branch, and the gap between the strut and the vessel wall should exceed 150 µm (Figure 2A).11,12 Complete neointimal coverage is defined as all the stent strut covered by visible neointima (Figure 2B), strut uncoverage is confirmed if no visible neointimal coverage on the strut is found (Figure 2C). Thrombosis is defined as an irregular mass with dorsal shadowing protruding from the lumen (Figure 2D).13

Statistical analysis
Continuous variables are expressed as the mean ± standard deviation (SD) and are compared using an independent samples t test. Categorical variables are the absolute number and percentage and are compared using χ² statistics or the Fisher’s exact test. A multivariable Logistic regression analysis was performed to assess the independent predictors for positive coronary remodeling. The independent variables in the model included age, history of diabetes mellitus, history of hypertension, history of hypercholesterolemia, history of smoking, stent number, stent diameter, and stent length. A P value <0.05 was considered statistically significant. Statistical evaluation was performed using dedicated software (SPSS 11.5 for windows, SPSS, Chicago, IL, USA).

RESULTS
Table 1 shows the baseline characteristics of the two groups. The demographic baseline and coronary risk factors are similar between the two groups except that the number of smoking patients in the CAA group is higher than in the non-CAA group (74.19% vs. 49.92%, P=0.008). The period of follow-up was longer in the CAA group compared with the non-CAA group ((24.68±13.29) m vs. (17.72±12.71) m, P=0.007). Patients with CAA formation after DES implantation had a higher frequency of cardiac events. Events occurred in 21 patients during follow-up, 11

Figure 1. Coronary angiography and analysis. A: Coronary angiography before intervention. B: Coronary angiography after DES implantation. C: CAA formation at late follow-up.
in the CAA group and 10 in the non-CAA group, including angina pectoris (25.81% vs. 6.25%, \( P = 0.001 \)) and acute myocardial infarction (9.68% vs. 0.13%, \( P = 0.002 \)). In addition, more thrombosis were detected in CAA group (16.13% vs. 0.69%, \( P < 0.001 \)).

OCT examination was conducted after coronary angiography without complication. OCT readily detected an irregular vessel lumen and malapposition with a prominent cavum backside the stent struts (Figure 3). The optical coherence tomography results (Table 2) indicate a higher proportion of uncoverage (17.17% vs. 1.90%, \( P < 0.001 \)) and malapposition struts (18.2% vs. 1.38%, \( P < 0.001 \)) in the CAA group compared with the non-CAA group. In addition, the neointimal thickness in the CAA group is significantly less than in the non-CAA group ((146.6±94.8) µm vs. (192.5±97.1) µm, \( P < 0.001 \)), as detected by OCT.

Patients with cardiac events were also analyzed as a group, as shown in Table 3. The percentage of incomplete neointimal coverage ((17.36±12.79)% vs. (1.05±0.51)%, \( P < 0.001 \)) and malapposition struts ((22.26±14.47)% vs. (1.85±0.62)%), \( P < 0.001 \) is higher in the CAA group than in the non-CAA group. The neointimal thickness in the CAA group is significantly less than in the non-CAA group ((145.2±88.6) µm vs. (193.40±114.61) µm, \( P < 0.001 \)). More thrombosis was detected in the CAA group using OCT, but there were no significant differences between the two groups (\( P = 0.149 \). Table 4 shows the results of cardiac events in CAA group. The longitudinal length of CAA in the event group is significantly longer than in the no event group ((20.0±9.07) mm vs. (12.05±5.38) mm, \( P = 0.005 \)). The percentage of stent malapposition ((25.69±19.01)% vs. (12.77±7.36)%, \( P = 0.003 \)) and incomplete neointimal coverage ((20.82±17.39)% vs. (12.43±8.24)%, \( P = 0.027 \)) in the group with cardiac events is significantly higher than in the no cardiac events group.

The age, history of diabetes mellitus, hypertension, hypercholesterolemia, smoking, stent number, stent diameter, and stent length of the CAA and non-CAA groups were compared. The multivariable Logistic regression analysis reveals that smoking (\( P = 0.004 \), \( OR 4.413, 95\% CI 1.624–11.995 \)) correlated with CAA formation after DES implantation. These data are summarized in Table 5.

**DISCUSSION**

The main findings of the current analysis are as follows: (1) CAA formation after DES implantation increases the frequency of stent malapposition and incomplete neointimal coverage; (2) CAA was associated with cardiac events, including angina pectoris and acute myocardial infarction.
Owing to the varying clinical presentations, CAA is usually detected at the time of repeat angiography for recurrent symptoms or the routine angiographic follow-up according to the clinical research protocol. IVUS not only readily detects the stent malapposition with a prominent distance to the vessel wall but also measures the external elastic lamina area and volume. According to the IVUS research, CAA is frequently associated with adverse clinical events as a result of DES restenosis and thrombosis. However, the neointimal coverage was not assessed in IVUS clinical trials because IVUS could not clearly and accurately detect neointimal coverage. Owing to the greater spatial resolution, OCT can assess the neointimal coverage and apposition accurately after DES implantation, and stent apposition and neointimal coverage may be a useful surrogate parameter for determining late stent thrombosis and stent safety. OCT studies have reported that DES implantation for ST elevation myocardial infarction had a higher frequency of stent malapposition and incomplete neointimal coverage during follow-up, but lacking of data from CAA formation after DES implantation. In the current study, the stent malapposition and neointimal coverage in patients with CAA formation were assessed using OCT, and a higher proportion of struts with incomplete neointimal coverage and malapposition were found. Struts with incomplete neointimal coverage and malapposition indicate poor vessel healing after DES implantation and the high risk of stent thrombosis. Moreover, the neointimal thickness is significantly less in patients with CAA formation. The potential mechanism is that neointimal hyperplasia is depressed when the stent struts do not contact with the vessel wall. Clinical trials have indicated that stent malapposition and incomplete coverage are associated with late stent thrombosis. In our study, a higher percent of patients with stent malapposition and incomplete neointimal coverage in the CAA group had acute myocardial infarction or angina pectoris compared with the non-CAA group. This result shows that CAA formation after DES implantation increases the cardiac events in long-term follow-up.
An additional phenomenon that has been observed in patients with CAA formation is the irregular vessel lumen with cavum backside the stent struts. The vessel remodeling can lead to the change of hydromechanics and create a blood whirlpool in the cavum at the segment of the CAA. This is also a risk factor of stent thrombosis. We also find that cardiac events readily occurred in the patients with a longer longitude of CAA. It indicates that the more diffused the CAA formation the more risk of cardiac events. The average time between the first and second coronary angiography in the CAA group is (24.68±13.29) months, and most patients were taking a single aspirin as antiplatelet therapy when CAA was diagnosed because dual antiplatelet therapy was modified after one year. Notwithstanding some patients with CAA formation are without clinical symptoms, they still belong to the high-risk group of cardiac events. Therefore, lifelong dual antiplatelet therapy such as aspirin and clopidogrel, is necessary for those patients in order to reduce the risk of stent thrombosis. However, there is no consensus regarding CAA treatment, and further study is needed to assess the strategy.

The mechanism of CAA is still unclear even though previous reports described local hypersensitivity and chronic inflammation. The polymer carrier of DES can also induce an inflammatory reaction of the arterial wall. CAA formation is a slow pathophysiologic procedure, and it is important to detect CAA at an early stage. Late positive remodeling after stent implantation has been assessed by IVUS and late stent malapposition was frequently observed, although the relationship between CAA and late stent malapposition remains to be determined. Hong et al reported that the predictors of late stent malapposition include the total stent length, primary stenting in acute myocardial infarction, and chronic total occlusion lesions; however, all factors are correlated with the characteristics of the lesion and PCI. Smoking is a proven risk factor for cardiovascular disease and is associated with restenosis and late thrombosis. Smoking can induce an endothelium function disorder as well as chronic inflammation around the stent and the vessel wall response to the pathological procedure. The age, risk factors of coronary disease, and stent characteristics were compared to assess the predictors for CAA, and the result reveals that smoking is a predictor for positive remodeling. The result also indicates the importance of smoking cessation in patients who underwent DES implantation.

The current study has several limitations. First, it is a single center study that involved a small sample. A study involving larger patient populations from various centers is warranted to confirm the results. Second, the limited penetration of the current OCT cannot accurately detect the components of deep structures, especially the external elastic membrane of the vessel; hence the whole profile of the cavum backside stent is not clear. In addition, OCT cannot detect a very thin intimal coverage (<10 μm) although it is the highest resolution technique available at the present time. This may increase the frequency of suspected uncovered stent struts during OCT imaging analysis that do have a very thin intimal covering.

In conclusion, CAA formation after DES implantation is frequently associated with cardiac events as a result of stent malapposition and incomplete neointimal coverage.

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