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Distribution characteristics of coronary calcification and its substantial impact on stent expansion: an optical coherence tomography study

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KEYWORDS

- cobalt-chromium stent
- coronary artery disease
- optical coherence tomography

Abstract

Aims: The aim of this study was to evaluate the spatial distribution and magnitude of coronary calcification and to investigate the relationship between measurable components of calcification and stent expansion.

Methods and results: Quantitative OCT analysis was performed in 66 consecutive patients who were successfully treated with OCT-evaluated stenting. Three representative measurements of calcium deposit, including thickness, arc, and depth (distance between lumen surface and calcium), as well as lumen and stent dimensions were assessed and compared. In our study, coronary calcification was detected in 66.7% of patients. The distribution of depth indicated that superficial calcium predominantly existed (mainly located within 0.010 mm from the intima). A positive correlation was observed between thickness and arc ($p<0.05$, $r=0.303$), and negative correlations were found between depth and thickness ($p<0.0001$, $r=-0.548$) and depth and arc ($p<0.005$, $r=-0.444$). Among the measurements of calcifications, depth positively correlated with relative stent expansion ($p=0.0051$, $r=0.406$), whereas thickness and arc did not.

Conclusions: Superficiality is most important for the assessment of coronary calcification, which is associated with the size of coronary calcification (arc and thickness) as well as expandability by stenting procedures. OCT, which allows accurate evaluation of coronary calcification, may be useful for the prediction of the resultant stent expansion of calcified lesions.

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Introduction

According to previous studies, the presence of coronary calcification was associated with worse clinical outcomes due to plaque fracture after angioplasty[1] and stent underexpansion[2]. It remained the biggest issue even after the emergence of drug-eluting stents (DES)[3-6]. Intravascular ultrasound (IVUS) played an important role in the evaluation of coronary calcification during percutaneous coronary intervention (PCI). However, due to limited resolution and inevitable artefacts such as acoustic shadowing and side lobes, only the arc or the "approximate" degree of superficiality of coronary calcifications could be assessed[3,7]. Currently, optical coherence tomography (OCT), another intravascular imaging technique with a higher spatial resolution, has become applicable in the clinical setting. It can visualise and delineate coronary calcification without attenuation or side lobe artefacts[8,9]. Thus, unlike IVUS, we can measure thickness, depth and the arc of the cluster of calcium as well as accurate luminal dimensions[10] using this modality. Considering such performance and superiority[11,12], detailed investigations regarding coronary calcification and its substantial impact on lumen expansion by PCI can be performed and have been demanded. Therefore, the present study was designed to: 1) evaluate geographic and morphological features of coronary calcification, and 2) investigate the relationship between measurable components of calcification and stent expansion in a consecutive series of patients. The results obtained will give us new insights into coronary calcification and vessel expansion.

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Methods

STUDY POPULATION

From August 2011 to May 2013, a total of 818 PCI procedures were performed at our institution. From these, 68 patients who underwent coronary stenting of the native coronary artery as well as OCT evaluation before and after stenting, were consecutively recruited. All patients underwent PCI without IVUS guidance according to the operators' own judgement. Since the purpose was to evaluate the adverse impact of coronary calcification on stent expansion by conventional PCI, two patients who underwent rotational atherectomy before stenting were excluded from the analysis. Three patients underwent OCT-evaluated stenting for two coronary vessels. Thus, 69 lesions were included in the present study.

Patient characteristics, and pre- and post-procedure characteristics were recorded for analysis. Chronic kidney disease was defined by an estimated glomerular filtration rate (eGFR) <60 ml/min^{-1}/1.73 m^{-2}. eGFR was calculated by the Modification of Diet in Renal Disease equation[13], with coefficients modified for Japanese patients as follows: eGFR (ml/min^{-1}/1.73 m^{-2})=194×Cr$^{-1.094}$×age$^{-0.287}$ (×0.739 if female).

OCT IMAGING AND STENTING PROTOCOLS

The C7 XR™ imaging system with the C7 Dragonfly™ imaging catheter (St. Jude Medical, St. Paul, MN, USA) was used in the present study. The imaging catheter was carefully advanced distal to the culprit lesion under fluoroscopic guidance just before PCI. In case the imaging catheter did not cross the target lesion, predilatation using a 1.5 mm balloon and intracoronary nicorandil or isosorbide dinitrate was given. Contrast media was flushed continuously through the guiding catheter during image acquisition, and motorised pullback OCT imaging was performed at a pullback rate of 20 mm/s throughout the lesion. At the discretion of the operator, type of stent, adequate stent diameter, adequate stent length and the endpoint of post-dilation were determined by angiography and OCT imaging. Number of stents, diameter, stent, maximum balloon diameter, maximum inflation pressure and non-compliant balloon usage were recorded. In the present study, the operator made an effort to expand the stent(s) by using a non-compliant balloon when the minimal stent area (MSA) was under 5.0 mm^2, which was a functional threshold for the prediction of DES restenosis[14].

QUANTITATIVE ANGIOGRAPHY

Serial quantitative coronary angiography (QCA) was obtained at pre- and post-intervention assessment. The target lesion was analysed using QCA on a QCA-CMS system, version 7.1 (Medis medical imaging systems bv, Leiden, The Netherlands). Using the external diameter of the contrast-filled guiding catheter as the calibration standard, % diameter stenosis was calculated as minimal lumen diameter divided by the reference diameter.

QUANTITATIVE OCT ANALYSIS

OCT analysis was performed using LightLab OCT imaging proprietary software (LightLab Imaging/St. Jude Medical, Westford, MA, USA) by an independent observer. The assessment range of pre- and post-procedural OCT images was from 5 mm proximal margin to 5 mm distal margin of the stent zone and the corresponding segment to the stent zone prior to stenting. Cross-sectional image analyses by OCT were performed using the measurement software echoPlaque 4 system (INDEC Medical Systems, Santa Clara, CA, USA) as in previous reports[15]. Quantitative OCT analyses included minimal lumen area (MLA), external elastic membrane area (EEMA) at the MLA site, lumen, plaque burden ([EEMA minus lumen] divided by EEMA), minimal stent diameter (MSD) and MSA. Manufacturer-predicted stent diameters and area were derived from the manufacturers' compliance charts. Coronary calcification was defined as a signal-poor or heterogeneous region with a sharply delineated border[16]. In patients with coronary calcification, quantitative assessment of coronary calcification focused on minimum depth (distance from the intima to the surface of calcification), largest arc, and maximum thickness of coronary calcification **(Figure 1)**. In cases with multiple coronary calcifications, the largest coronary calcification was exclusively selected for the analyses. Stent expansion was evaluated in various ways, including relative stent expansion, absolute stent expansion and stent symmetry index. In the present study, it was sometimes difficult to evaluate the reference lumen diameter from the OCT images because of attenuation or limitation of the penetration depth. In addition, all EEMAs could be evaluated at the MSA site. For our purpose, for simple evaluation, relative stent expansion was defined as MSA divided by EEMA at the MSA site. Axial stent symmetry was calculated as the

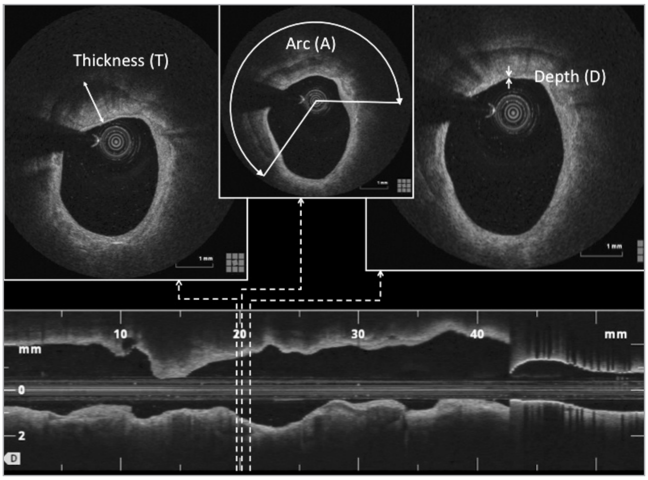

Figure 1. *Quantitative assessment of calcification. A: the arc of coronary calcification; D: the distance from intima to calcification surface; T: thickness of coronary calcification*

minimum stent diameter divided by the maximum stent diameter[17]. Because the difference of MSA was small between IVUS assessment and OCT assessment[10], the absolute stent expansion in the present OCT study was defined as an MSA of over 5.0 mm^2, which was previously reported as a functional threshold for the prediction of DES restenosis from IVUS assessment[14]. Furthermore, malapposition, defined as the axial distance between the strut's surface and the luminal surface, was greater than the strut thickness.

STATISTICAL ANALYSIS

All data were statistically analysed using GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) and are presented as means±standard deviation, or as medians (25th and 75th percentiles) when the distribution was non-normal. Continuous variables were compared by the unpaired Student's t-test or Mann-Whitney U test. Categorical variables were compared using Fisher's exact test. Correlations between variables were analysed by Spearman's rank correlation coefficient. Statistical comparisons among four groups were performed by one-way analysis of variance (ANOVA) and *post hoc* multiple comparison using Tukey's test. Values of $p<0.05$ were considered significant.

Results

INCIDENCE OF CORONARY CALCIFICATION AND UNDERLYING PATIENT AND LESION CHARACTERISTICS

Coronary calcification, as defined in this study, was detected in 46 cases out of 69 lesions (66.7%). We divided the cases by prevalence of coronary calcification into two groups and compared patient and lesion characteristics between the two groups (with coronary calcification versus without coronary calcification) **(Table 1)**. The mean age of the patient population was 68 years and the majority of the patients were male. Patients with coronary calcification had a lower prevalence of acute coronary syndrome and dyslipidaemia than patients without coronary calcification. Coronary calcification was predominantly observed in the left anterior descending artery. There were significant differences in some quantitative parameters, including % diameter stenosis and MLA. Lesions with coronary calcification had less plaque burden and larger MLA compared with those without coronary calcification.

Table 1. Baseline characteristics of the patients.

	Without CC (n=23)	With CC (n=43)	*p*-value
Age, years	68±11	68±10	0.89
Male, n (%)	19 (82.6)	32 (74.4)	1.0
MI or UAP, n (%)	10 (43.5)	6 (14.0)	0.017
Multivessel disease, n (%)	11 (47.8)	28 (65.1)	0.20
Hypertension, n (%)	19 (82.6)	35 (81.4)	1.00
Dyslipidaemia, n (%)	21 (91.3)	28 (65.1)	0.036
Diabetes mellitus, n (%)	6 (26.1)	18 (41.9)	0.28
CKD, n (%)	6 (26.1)	10 (23.3)	1.0
Current smoker, n (%)	5 (21.7)	5 (11.6)	0.30
Angiographic findings			
LAD/LCX/RCA, n	10/0/13	32/3/11	0.017
Reference diameter, mm	2.5±0.6	2.5±0.6	0.73
MLD, mm	0.4±0.2	0.5±0.2	0.15
% diameter stenosis	86.2±8.0	80.8±8.4	0.013
ACC/AHA class (B2, C), n	22	42	0.66
OCT findings			
MLA, mm^2	1.07 [0.79-1.45]	1.64 [1.26-2.18]	0.0064
EEMA at MLA site, mm^2*	11.1±3.7	10.9±3.1	0.76
Plaque burden,% *	88.9 [86.3-91.9]	83.2±6.3	0.0066

All variable data are presented as mean±standard deviation, or as medians (25th and 75th percentiles) when the distribution was non-normal. *Four lesions with calcified nodules were excluded from analysis for EEMA at the MLA site and plaque burden because of poorly delineated borders of EEMA. CC: coronary calcification; CKD: chronic kidney disease; EEMA: external elastic membrane area; LAD: left anterior descending artery; LCX: left circumflex artery; MI: myocardial infarction; MLA: minimal lumen area; MLD: minimal lumen diameter; OCT: optical coherence tomography; RCA: right coronary artery; UAP: unstable angina

DETAILED ASSESSMENT OF CORONARY CALCIFICATION

We measured thickness, arc, and depth of coronary calcification by quantitative assessment of OCT images **(Figure 1)**. **Figure 2** shows the distribution of these three representative parameters. Distribution types were different among the three parameters. Depth and arc demonstrated non-normal distribution, whereas thickness appeared to demonstrate mostly normal distribution. Distribution of depth indicated that superficial calcium predominantly existed (mainly located within 0.010 mm from the intima). The arc had wider variation compared to the other parameters: 30.4% were more than 180 degrees.

The relationship among these three parameters was investigated **(Figure 3)**. The depth of coronary calcification had a moderate negative correlation with the thickness of coronary calcification ($p<0.0001$, $r=-0.548$) and with the arc of coronary calcification ($p<0.005$, $r=-0.444$). A weak positive correlation was observed between the thickness of coronary calcification and the arc of coronary calcification ($p<0.05$, $r=0.303$).

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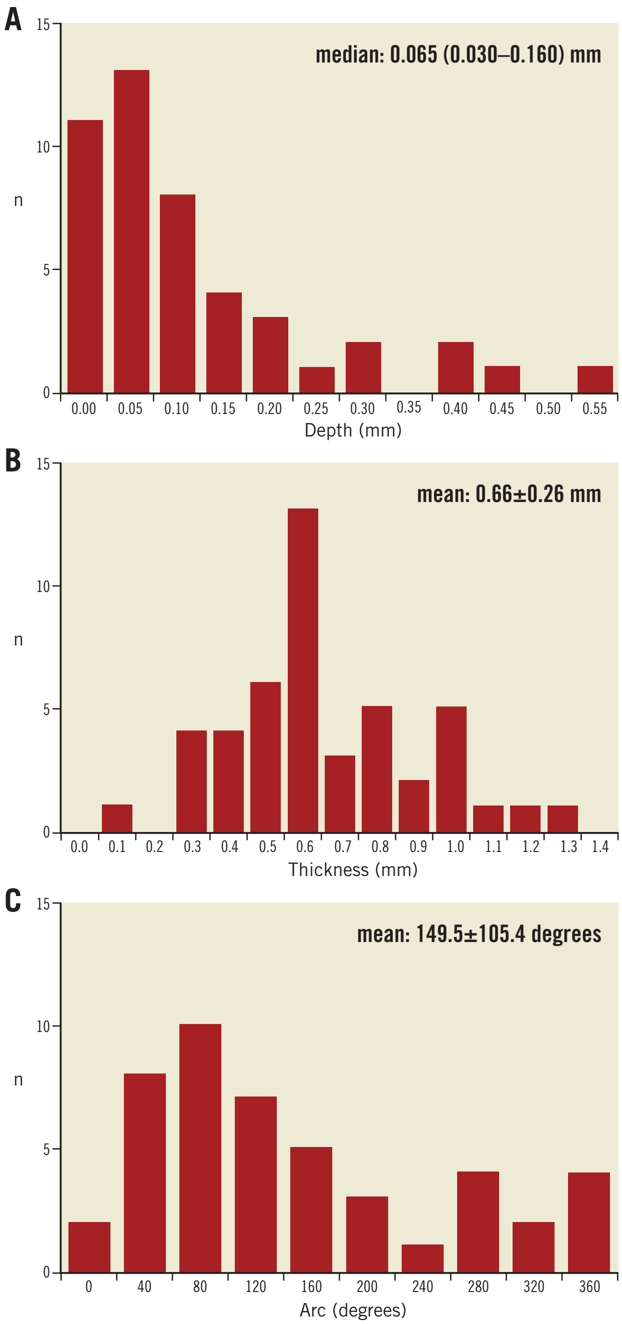

Figure 2. *Distribution of the three representative parameters of calcification in coronary arteries evaluated by OCT.*

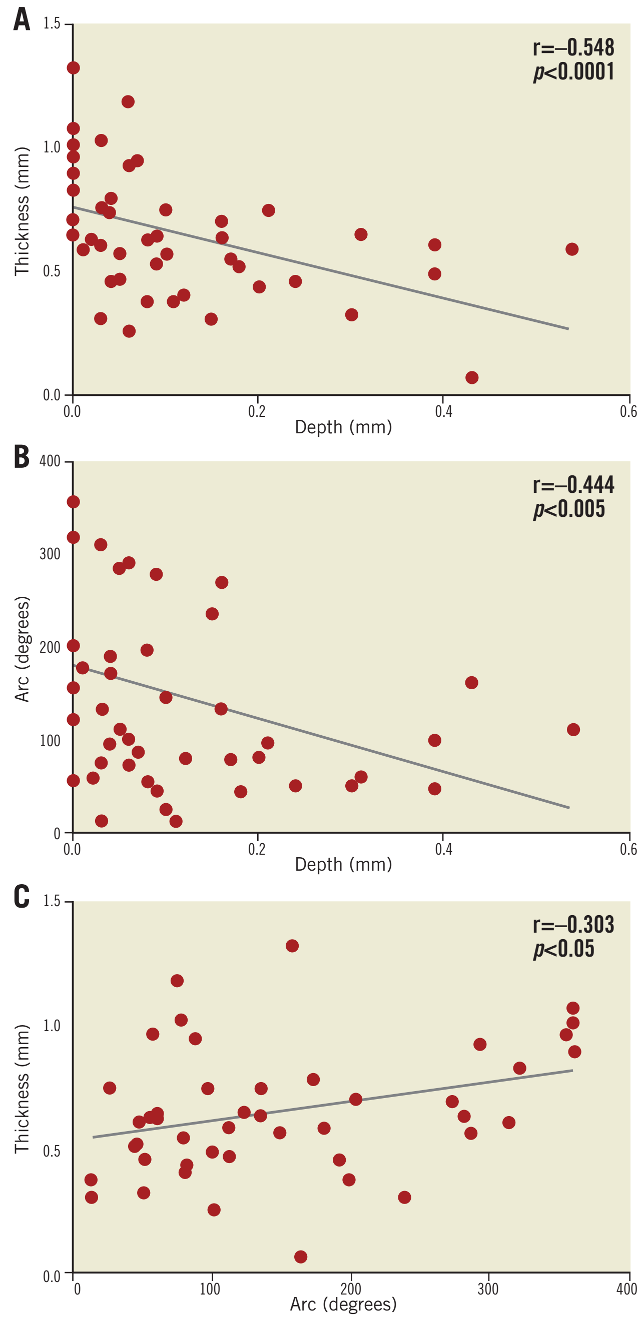

Figure 3. *Relationship between the three parameters of coronary calcification.*

IMPACT OF CORONARY CALCIFICATION ON STENT EXPANSION

Procedural characteristics and parameters of resultant expansion were compared between the two groups **(Table 2)**. Despite similarity in maximum balloon diameter and inflation pressure, the lesions with coronary calcification were more frequently treated with a non-compliant balloon. No significant differences were observed in the OCT-derived parameters of stent expansion except relative stent expansion, which tended to be smaller in those with coronary calcification.

Correlations among the three representative parameters of coronary calcification and relative stent expansion were investigated **(Figure 4)**. A positive correlation was observed between depth and relative stent expansion (p<0.01, r=0.406). However, no correlation was observed between the thickness and the arc and relative stent expansion.

The cases were categorised into three tertile groups by depth (T1: <0.04 mm, T2: 0.04-0.11 mm, T3: >0.11 mm) for further assessment. **Figure 5** demonstrates the comparison of relative stent expansion between each tertile category and the group without coronary calcification. Although no differences were observed in axial stent symmetry, relative stent expansion was different in each depth group. The shallowest group (T1) had significantly lower relative stent expansion than the group without coronary calcification (0.43 vs. 0.49,

Table 2. Procedural characteristics and results.

	Without CC (n=23)	With CC (n=46)	*p*-value
Average/total stent number	1.1/26	1.2/55	0.74
Average stent diameter of each stent, mm	3.1±0.3	3.1±0.4	0.82
Average stent length of each stent, mm	19.4±7.7	20.5±8.1	0.57
Stent			0.35
XIENCE V/PROMUS, n	7	10	
XIENCE PRIME/MULTI-LINK 8, n	11	19	
Others, n	8	26	
Maximum balloon diameter, mm	3.4±0.4	3.4±0.4	0.63
Maximum inflation pressure, atm	13.7±3.8	14.7±3.7	0.31
Non-compliant balloon usage, n (%)	2 (8.7)	15 (32.6)	0.039
MSD, mm	2.6±0.5	2.6±0.6	0.72
MSA, mm²	6.3±2.1	6.1±2.2	0.74
OCT/manufacturer-predicted stent diameter ratio,%	0.84±0.13	0.83±0.20	0.51
OCT/manufacturer-predicted stent area ratio,%	0.81±0.21	0.78±0.19	0.96
Relative stent expansion	0.50±0.10	0.46±0.07	0.05
Absolute stent expansion, n (%)	17 (73.9)	29 (63.0)	0.43
Symmetry index	0.89 [0.86-0.91]	0.87 [0.80-0.92]	0.35
Stent malapposition, n (%)	3 (13.0)	14 (30.4)	0.11

All variable data are presented as mean±standard deviation, or as medians (25th and 75th percentiles) when the distribution was non-normal. Absolute stent expansion was defined as MSA >5.0 mm². Stent malapposition, defined as the axial distance between the strut's surface and the luminal surface, was greater than the strut thickness. Stent symmetry index was defined as minimum stent diameter/maximum stent diameter. CC: coronary calcification; MSA: minimal stent area; MSD: minimal stent diameter; OCT: optical coherence tomography

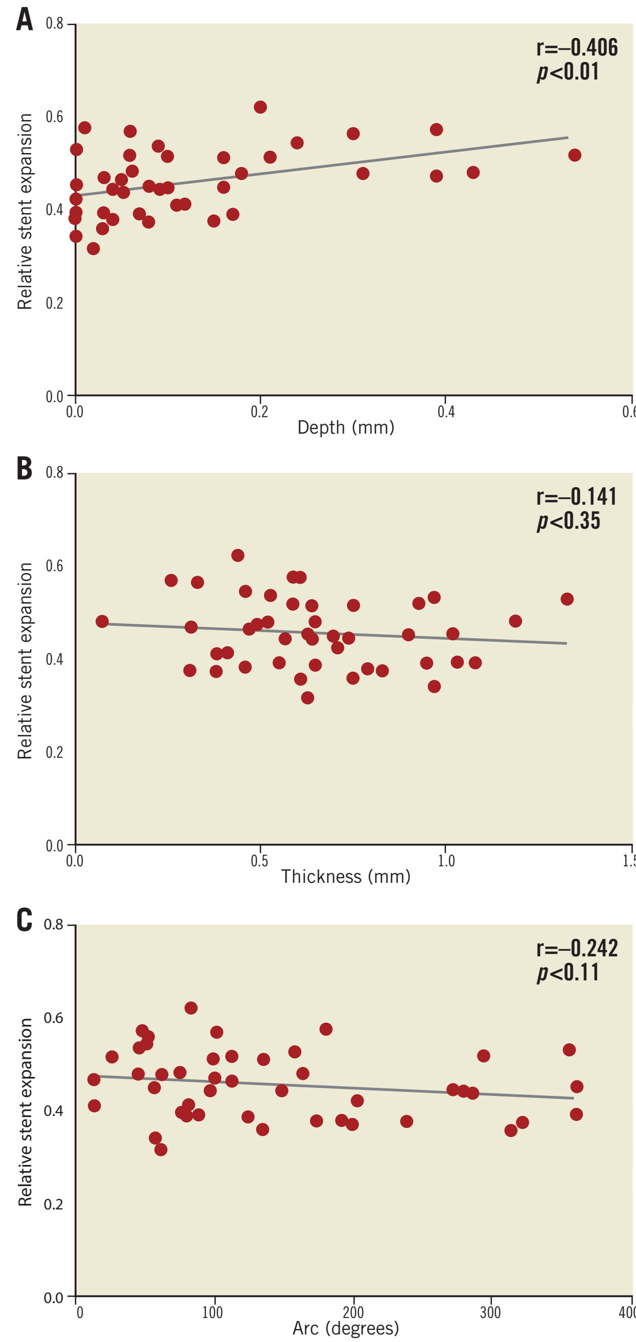

Figure 4. *Correlation between the three parameters of coronary calcification and relative stent expansion.*

p<0.05). A similar tendency was observed in absolute stent expansion; however, these differences were not statistically significant.

Discussion

The results obtained from this OCT study focusing on the nature of coronary calcification and resultant stent expansion can be summarised as follows. In terms of its prevalence or patient characteristics, coronary calcification was: 1) differentiated in two thirds of consecutive PCI cases, 2) observed less frequently in the cases with acute coronary syndrome and dyslipidaemia, and 3) observed more frequently in LAD vessels. Regarding its distribution or lesion characteristics, coronary calcification was located superficially in the majority of cases, and its thickness showed normal distribution. Distribution of the arc varied, but those of <180 degrees were predominant. Furthermore, the lesions with coronary calcification had less plaque burden and larger MLA compared with those without. In terms of relationships among the representative quantitative parameters of coronary calcification, there was: 1) an inverse correlation between its depth and thickness/arc, and 2) a weak positive correlation between its arc and thickness. As seen in the descriptive summary thus far, coronary calcification in the native coronary artery has unique geographic and morphological features. Finally, taking into consideration the impact of coronary calcification on stent expansion, very importantly among the three representative parameters (thickness, arc, depth) of calcification by OCT assessment, depth is the only parameter which is associated with resultant stent expansion. Thickness and arc, which have been considered as potential causes of insufficient expansion for a long time, did not relate to actual stent expansion in our consecutive data set analyses, if we exclude some severely calcified lesions impossible for OCT catheter insertion. These inherent characteristics of coronary calcification and its potential impact on resultant stent expansion should be taken into consideration for the purposes of prediction during OCT-evaluated

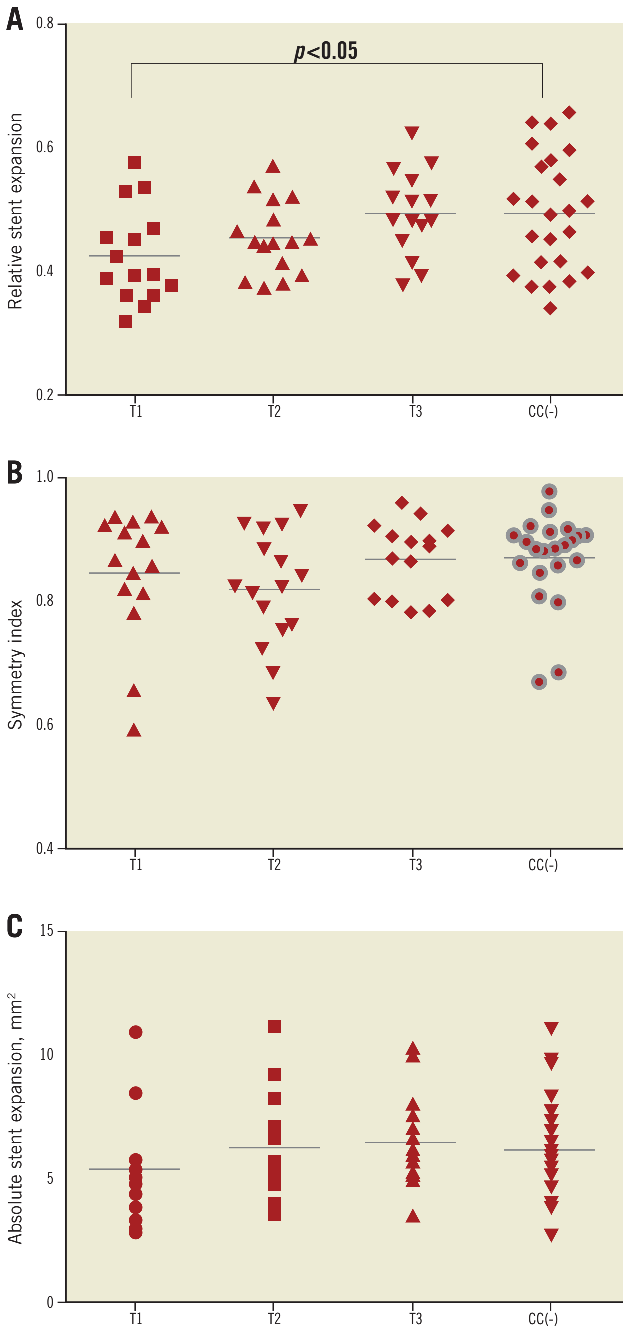

Figure 5. *Comparison of relative stent expansion between each tertile category and the group without coronary calcification. Patients were divided into tertile category (T) according to the distance from the intima to the calcified nodule (T1: <0.04 mm, T2: 0.04-0.11 mm, T3: >0.11 mm). CC (-): without coronary calcification*

stenting. In terms of clinical implications, this result means that the operator should avoid stenting consecutively and should use a scoring balloon or rotational atherectomy before stenting.

CONSISTENCY WITH PREVIOUS RESEARCH

As seen from the results of this study, coronary calcification has unique features. After the development of initial calcification, medial calcification related to vascular smooth muscle cell apoptosis[18] progresses to the intima layer, and occurs preferentially along the elastic lamina[19]. Accordingly, the potential formation processes of coronary calcification, elucidated by previous research, were well supported and explained by the actual findings observed in the current study. In fact, this study clearly demonstrated that the depth of coronary calcification inversely correlated to the arc or the thickness. Such features might confirm that coronary calcification extends inwardly (into the luminal centre) from the media and is distributed like a fan. Shallow calcification tended to be larger compared with deep calcification, a relationship which was clearly proved in this study.

IMPACT OF CORONARY CALCIFICATION ON STENT EXPANSION

As we have described, this study suggested that the "depth" of coronary calcification from the intimal surface is the key factor to predict stent expansion. In other words, lesions with superficial calcium are more difficult to expand. Several potential explanations for this phenomenon can be proposed. First, the depth of calcification could be considered as soft expandable space between the intima and the calcium surface. Thus, deeper calcium tends to have more soft tissue space inside the calcium, which can be expanded more. Second, superficial calcium tends to be thicker and axially wider. The absolute volume of calcium must enhance expandability. However, the thickness and the arc did not independently impact on actual stent expansion. Thus, the first explanation might be fundamental and the primary one as being the mechanism of stent expansion in lesions with coronary calcification.

COMPARISON OF THE PRESENT STUDY WITH OTHER STUDIES

Although many IVUS studies concerning coronary stenting have reported the impact of coronary calcification on clinical outcome, only simple comparisons between two groups that were defined by the presence or absence of coronary calcification were performed in most studies. From a previous IVUS study which assessed coronary calcification in detail and stent expansion, it was suggested that the arc of calcium, calcium location (deep or superficial) and calcium length had no relationship with the stent expansion index[7]. However, it was difficult to compare this IVUS study with the present study. Since procedural protocols (undergoing only direct stenting and avoiding the use of non-compliant balloons) were quite different from the present study, the impact of calcification regarding stent expansion might have been underestimated.

In contrast, another OCT study reported that the amount and extent of coronary calcification were associated with stent expansion[20]. Although these findings were similar to our findings, the mean MSA of another OCT study was smaller than that of the present study (4.96 mm^2 vs. 6.2 mm^2), and the depth of coronary calcification was not evaluated in another OCT study. For these reasons, careful comparison is required between other OCT studies and the present study.

STUDY LIMITATIONS

The present study has several inherent limitations. First, this study was conducted retrospectively and enrolled a relatively small number of patients. Lack of a prospective protocol might have allowed a variety of endpoints of stent expansion among the operators; a uniform stent expansion protocol might be ideal for this type of investigation. Potentially compensating for this, detailed baseline characteristics regarding stent expansion were introduced as much as possible. Second, any long-term clinical events were not observed. This study clearly focused on "acute" results during the primary procedures. Insufficient stent expansion is known to relate to late adverse events[14,21], which can generally be considered as surrogate endpoints. Post-intervention MSA, recognised as a surrogate marker of a major cardiac event, was exclusively measured in this study. Third, the lesion of severe and complex coronary calcification which was suitable for rotational atherectomy had to be excluded from our analysis. These limitations of studies using catheter-based intravascular imaging devices seem inevitable. Fourth, the calcification buried in lipid-rich plaque had a potential to be missed. Because of attenuation, the presence or absence of coronary calcification could not easily distinguish the severity of calcification in our OCT study. Finally, our definition for measuring the arc of coronary calcification, using the centre of the OCT imaging catheter as reference, was different from that used in a previous IVUS study[22], which adopted the lumen centre as reference for calcium arc measurement. For OCT-based analysis, considering its limited penetration depth[23], we do not believe that the latter method is always good. If you use the lumen centre for arc measurement, you have to determine the lumen centre prior to arc measurement every time. The method we introduced in this study is surely more practical, not time-consuming, and reproducible for OCT-evaluated stenting.

Conclusions

Superficiality is most important for the assessment of coronary calcification, which is associated with the size of coronary calcification (arc and thickness) as well as expandability by stenting procedures. OCT, which allows the accurate evaluation of coronary calcification, may be useful for the prediction of the resultant stent expansion of calcified lesions.

Impact on daily practice

Our results show that shallow coronary calcification might relate to insufficient stent expansion. In daily practice, when pre-stenting OCT images show shallow coronary calcification within the zone recommended to implant the stent, the operator should avoid stenting consecutively and should use a scoring balloon or rotational atherectomy before stenting.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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