ORIGINAL PAPER

Feasibility of morphological assessment of coronary artery calcification with electrocardiography-gated non-contrast computed tomography: a comparative study with optical coherence tomography

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Abstract

To investigate the feasibility of pre-procedural morphological assessment of coronary artery calcification in severely calcified lesions with electrocardiography (ECG)-gated non-contrast computed tomography (CT). Severely calcified coronary arteries in patients who underwent ECG-gated non-contrast CT prior to optical coherence tomography (OCT)-guided percutaneous coronary intervention (PCI) were studied retrospectively. CT and OCT data were co-registered by marking landmark structures such as side branches and reviewed side by side with cross-sectional images. The maximum calcium angle (MCA) and presence of nodular calcification (NC) were evaluated. A total of 496 cross-sections in 16 lesions were included in this analysis. The Pearson correlation coefficient between CT- and OCT-derived MCA was 0.92 (p < 0.001). Bland-Altman plots of OCT-derived MCA in relation to CT-derived MCA showed a mean bias of 4.8 degrees with 95% limits of agreement of − 69.7 to 79.4 degrees. Sensitivity, specificity, and positive and negative predictive values of CT in identifying MCA > 270 degrees were 90.3%, 79.7%, 92.1%, and 97.4%, respectively. Sensitivity, specificity, and positive and negative predictive values of CT in identifying NC were 73.3%, 97.5%, 47.8%, and 99.2%, respectively. ECG-gated non-contrast coronary CT might be helpful to obtain detailed information of severe coronary artery calcification before PCI.

Keywords Coronary artery calcification · Non-contrast computed tomography · Optical coherence tomography · Nodular calcification

Abbreviations

CT	Computed tomography
ECG	Electrocardiography
HU	Hounsfield unit
ICC	Intraclass correlation coefficients
LAD	Left anterior descending artery
MCA	Maximum calcium angle
NC	Nodular calcification
NPV	Negative predictive value
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
PPV	Positive predictive value
RA	Rotational atherectomy

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Introduction

Over the past decade, the rates of coronary revascularization have continued to decline with the advent of drug-eluting stents [1, 2]. However, percutaneous coronary intervention (PCI) for severely calcified lesions remains challenging with increased rates of in-stent restenosis and stent thrombosis, mainly due to insufficient stent expansion [3, 4]. To obtain adequate stent expansion, and subsequently avoid target lesion failure, appropriate lesion modification with balloon and/or rotational atherectomy (RA) is important. Accordingly, accurate evaluation of calcium severity before stent implantation is essential, even in the current era of drug-eluting stents [5].

Optical coherence tomography (OCT) is a powerful imaging modality that provides detailed information on the severity of coronary artery calcification. More specifically, the ability of OCT to accurately evaluate calcium thickness and angle offers reliable prediction of calcium crack formation after balloon angioplasty, leading to optimal stent expansion [6, 7]. However, the invasive nature of this imaging technology limits its application to a broad range of PCI patients; thus, reliable non-invasive methods are required.

Coronary computed tomography (CT) angiography is a non-invasive imaging modality that can enable evaluation of the severity of coronary artery calcification, as well as the extent of luminal narrowing [8, 9]. Recent studies demonstrated that evaluation of coronary artery calcification using coronary CT angiography predicts the need for rotational atherectomy or the success of PCI for chronic total occlusion [10, 11]. These studies suggest that pre-procedural evaluation of coronary artery calcification with cross-sectional coronary CT angiography could improve lesion assessment in a non-invasive manner. Given the ability of non-contrast CT to assess the severity of coronary artery calcification by Agatston scoring [12], we believe that it can provide not only a calcium score but also detailed morphological features of coronary artery calcification without contrast media. Therefore, the current study sought to assess the feasibility of morphological assessment of coronary artery calcification with electrocardiography (ECG)-gated non-contrast CT in comparison with OCT.

Materials and methods

Study population

This was a retrospective, single-center, observational study conducted to evaluate the feasibility of morphological assessment of coronary artery calcification with ECG-gated non-contrast CT in comparison with OCT. We enrolled patients who underwent ECG-gated non-contrast CT within one month before OCT-guided PCI for severely calcified lesions, defined by angiographical radiopacities noted without cardiac motion before contrast injection, in the left anterior descending artery (LAD), from May 2018 to December 2019 at our center. Patients with previous coronary artery bypass grafting, with low image quality of CT or OCT, or without OCT data before stenting, were excluded.

This study protocol conforms to the ethical guidelines of the Declaration of Helsinki. The present study was reviewed and approved by the institutional ethical committee. Due to the retrospective nature of this study, informed consent was obtained in the form of opt-out on the internet.

CT data acquisition and image analysis

All acquisitions were performed using a third-generation dual-source CT scanner (SOMATOM Force; Siemens Healthcare, Forchheim, Germany). CT scout imaging was performed both in the front and side views and followed by non-contrast CT calcium imaging. Non-contrast CT calcium images were acquired at a tube voltage of 120 kV and a rotation speed of 250 ms. CT calcium imaging was performed using ECG triggering sequential mode (i.e. step and shoot method) with the patient holding their breath. Radiation was exposed at 65% of RR interval within the cardiac phase. Tube current was controlled by an automatic exposure control program (reference 80 mAs). CT images were reconstructed at a 0.6-mm slice thickness and 0.3-mm increment using filtered-back projection (Qr36). All images were analyzed with a commercially available workstation (Ziostation2; version 2.4.2.3, Ziosoft Inc., Tokyo, Japan). Radiation exposure was reviewed from patients' dose reports in their medical records. Radiation dose included all of the scout imaging and calcium imaging.

OCT data acquisition and analysis

OCT data were acquired using a frequency-domain OCT system (LUNAWAVE; Terumo, Tokyo, Japan) and imaging catheter (Fast View; Terumo). Contrast media was flushed continuously through the guiding catheter during image acquisition. Motorized pullback OCT imaging was performed at a pullback rate of 40 mm/s. Images were acquired at 180 frames/s and digitally archived. Intracoronary nitroglycerine was administered before scanning. If the catheter could not pass the lesion, OCT was performed after dilation using a small-sized balloon (less than 2.0 mm in diameter) or RA with less than 1.5 mm burr. All OCT data were analyzed using off-line commercially available software (LUNAWAVE; Terumo).

Morphological assessment of coronary artery calcification using CT and OCT

CT and OCT imaging data were co-registered by marking the position of each side branch and reviewed side by side with cross-sectional images. Calcium deposits were evaluated with cross-sectional CT and OCT images at every 1-mm interval from the ostium of the left anterior descending artery (Fig. 1). A representative example of co-registration of CT and OCT data is presented in Fig. 2. In the CT analysis, the window level was set at 200 Hounsfield units (HU) with a window width of 2000 HU. Calcium had a density > 130 HU and was brighter than the surrounding
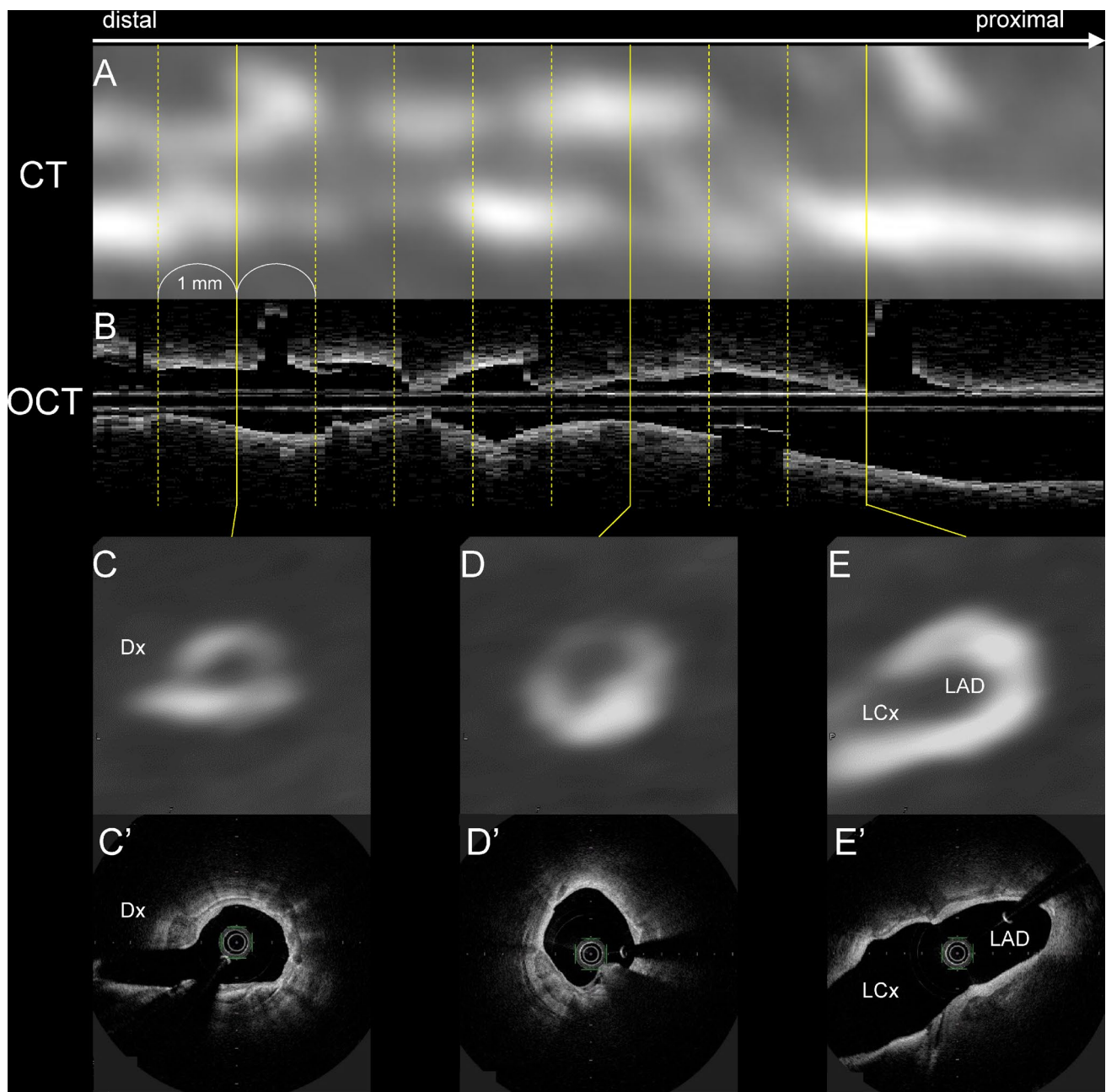
Fig. 1 Co-registration of coronary artery images between CT and OCT. Stretched multi-planer reconstruction image of the coronary artery with ECG-gated non-contrast CT (**A**). Longitudinal view of the coronary artery with OCT (**B**). Cross-sectional images of the coronary vessels with ECG-gated non-contrast CT (**C**–**E**). Cross-sectional images of the coronary vessels with OCT (**C'**–**E'**). CT and OCT imaging data were reviewed side by side and co-registered by marking the position of calcium formation and side branches. Each calcium deposit was evaluated by ECG-gated non-contrast CT and OCT at 1-mm intervals. *CT* computed tomography, *Dx* diagonal branch, *ECG* electrocardiography, *LAD* left anterior descending artery, *LCx* left circumflex artery, *OCT* optical coherence tomography

vessel wall in ≥ 2 independent planes [13]. The maximum calcium angle (MCA) was measured by two dedicated independent investigators (Y.T. and T.T., each with more than 5 years of experience in cardiac CT) using the vessel center, which was specified referring to the adjacent cross-sections, as a reference for angle measurement (Fig. 3). Presence of nodular calcification (NC) derived from CT (CT-NC), which was defined as a hyper-attenuating mass protruding into the center of the vessel (referring to the adjacent cross-section), was evaluated (Fig. 4). In the OCT analysis, calcification was defined as well-delineated, signal-poor regions with sharp borders [14]. NC derived from OCT (OCT-NC) was
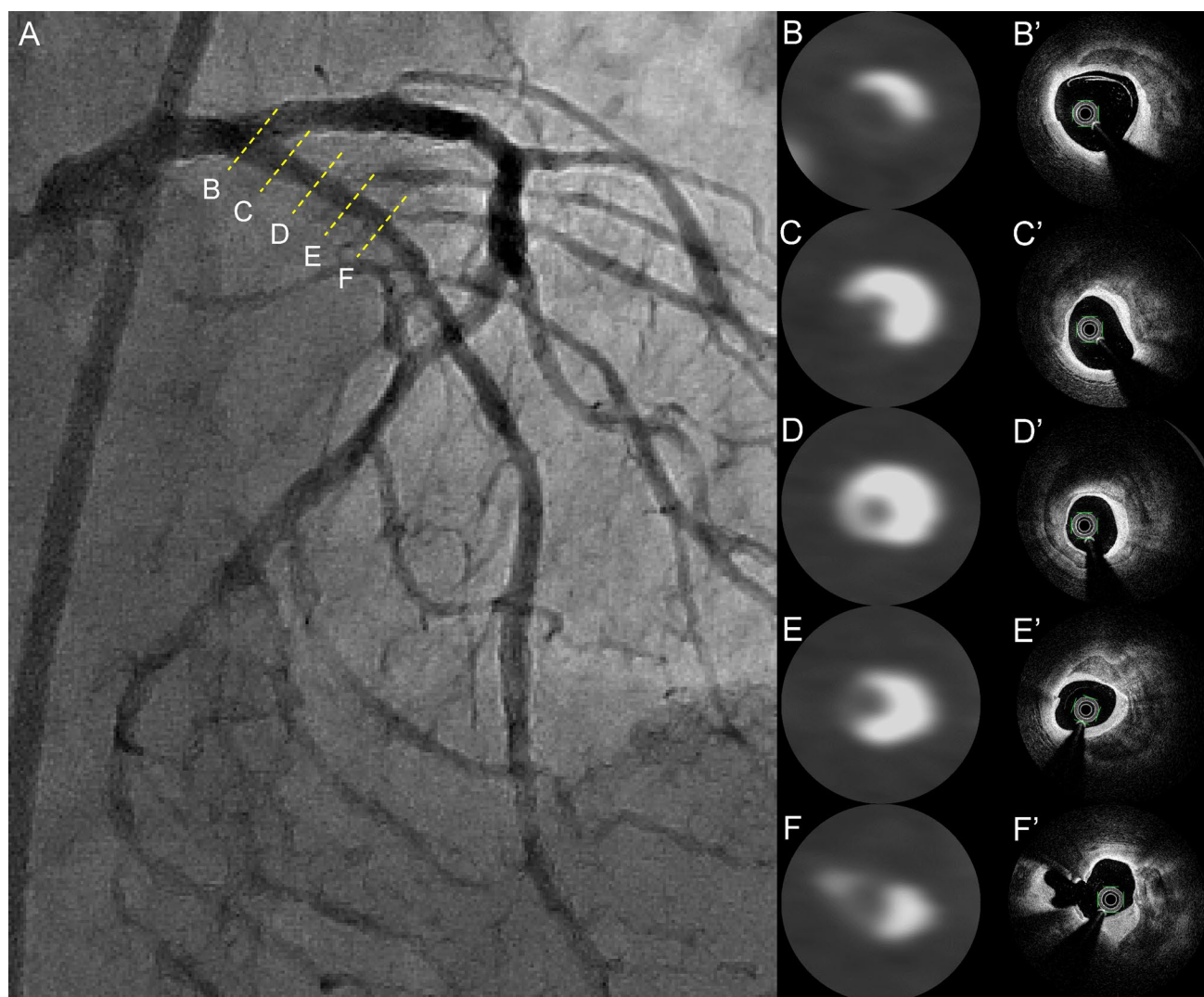
Fig. 2 A representative case of co-registration between ECG-gated non-contrast CT and OCT images. Angiographic imaging of calcified lesions involving the proximal anterior descending artery (**A**). Cross-sectional images of CT (**B**–**F**) are corresponded to OCT (**B′**–**F′**). *CT* computed tomography, *ECG* electrocardiography, *OCT* optical coherence tomography

defined as single or multiple regions of calcium that protrude into the lumen (Fig. 4) [12].

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as means ± standard deviations. Pearson's correlation coefficient was used to compare between CT and OCT-defined MCAs. Bland-Altman and regression analyses were performed to compare the mean differences (bias) and standard deviations between CT and OCT-defined MCA. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for identifying the presence of NC, or MCA > 90, > 180, or > 270 degrees, were calculated. Interobserver agreement

and intraobserver reproducibility of continuous variable measurements were assessed by intraclass correlation coefficients (ICC). The agreement of categorical variables was assessed by Cohen's kappa. Statistical significance was determined by $p < 0.05$. Data analyses were performed using SPSS software version 25.0 (SPSS Inc., Chicago, IL).

Results

Study population

Seventeen patients who underwent ECG-gated non-contrast CT to evaluate the extent of coronary artery calcification within 1 month before OCT-guided PCI were enrolled
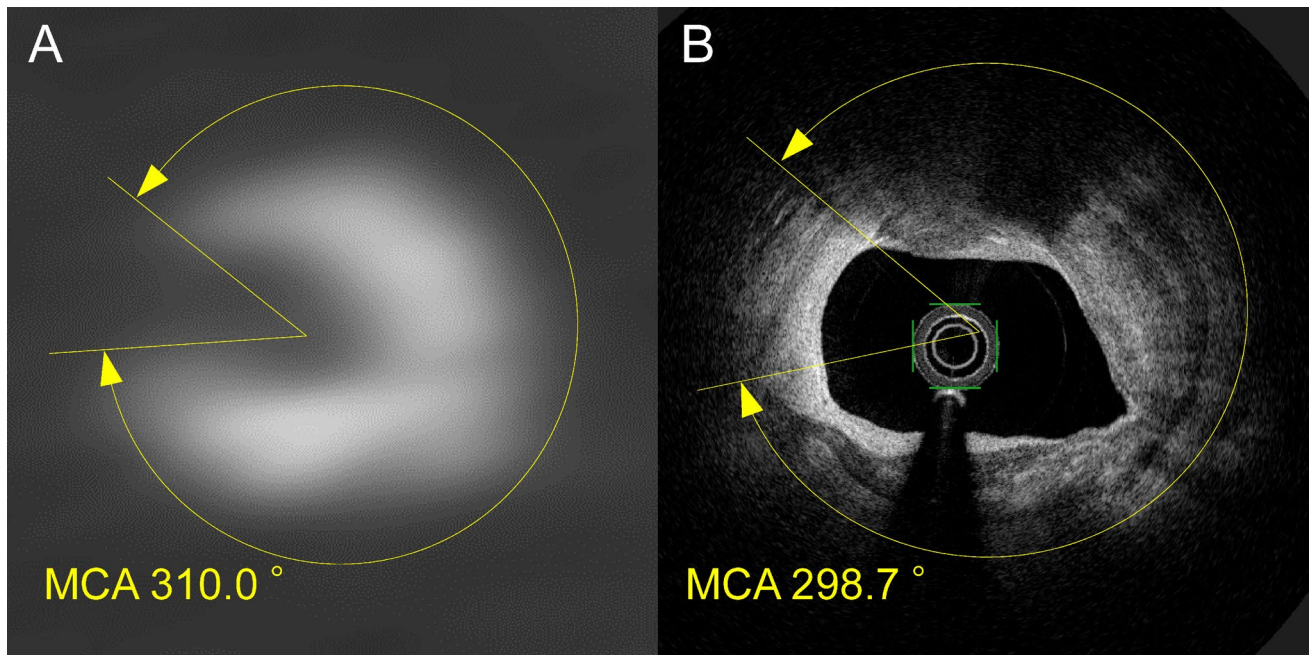
Fig. 3 Measurement of maximum calcium angle using CT and OCT. The maximum calcium angle (MCA) (double-headed yellow arrow) was measured using both CT (**A**) and OCT (**B**). In the presented case, the angles derived from CT and OCT images were 310.0 and 298.7 degrees, respectively. *CT* computed tomography, *OCT* optical coherence tomography

in the current study. One patient with low quality of CT images was excluded. Finally, we analyzed 16 coronary vessels in 16 patients. In these patients, 1 patient underwent 2.0-mm balloon dilatation and 2 patients underwent RA with 1.5 mm burr before OCT. Patient demographics are summarized in Table 1. The radiation parameters of the ECG-gated non-contrast CT are shown in Table 2. The effective dose was 0.69 ± 0.21 mSv, and heart rate at CT scan was 64.9 ± 9.6 beats per minute.

Comparison of MCA between CT and OCT

A total of 573 cross-sectional images in 16 lesions were reviewed in the current study. In the OCT analysis, 67 cross-sections were excluded due to attenuated, undefined OCT plaque, and 10 were excluded due to poor CT image quality in the OCT analysis. Finally, 496 cross-sections were studied. The MCA was 183.3 ± 97.6 degrees and 178.4 ± 92.4 degrees in the CT and OCT analyses, respectively. The average absolute difference in MCA between OCT and CCT was 27.6 ± 26.6 degrees. The Pearson's correlation coefficient was $r = 0.92$ ($p < 0.001$) (Fig. 5A). Bland-Altman plots of OCT-derived MCA in relation to CT-derived MCA showed a mean bias of 4.8 degrees with 95% limits of agreement of -69.7 to 79.4 degrees (Fig. 5B).

Diagnostic accuracy for detecting MCA over 90, 180, and 270 degrees

Cross sections with an MCA over 90, 180, and 270 degrees comprised 83.1% (n = 412), 40.1% (n = 199), and 21.0% (n = 104) of the total cross sections, respectively. Regarding the diagnostic accuracy of non-contrast CT for detecting an MCA over 90 degrees, the sensitivity, specificity, PPV and NPV were 93.6%, 59.5%, 91.9%, and 65.8%, respectively (Fig. 6). For the detection of an MCA over 180 degrees, the sensitivity, specificity, PPV, and NPV were 92.4%, 90.9%, 87.2%, and 94.7%, respectively. Similarly, for detection of an MCA over 270 degrees, the sensitivity, specificity, PPV, and NPV were 90.3%, 79.7%, 92.1%, and 97.4%, respectively (Fig. 6).

The prevalence of nodular calcification

In the cross-sectional analysis, NC was detected in 23 CT cross-sections (4.6%) and 15 OCT cross-sections (3.0%). For the identification of NC derived from OCT, the sensitivity, specificity, PPV, and NPV of non-contrast CT were 73.3%, 97.5%, 47.8%, and 99.2%, respectively.
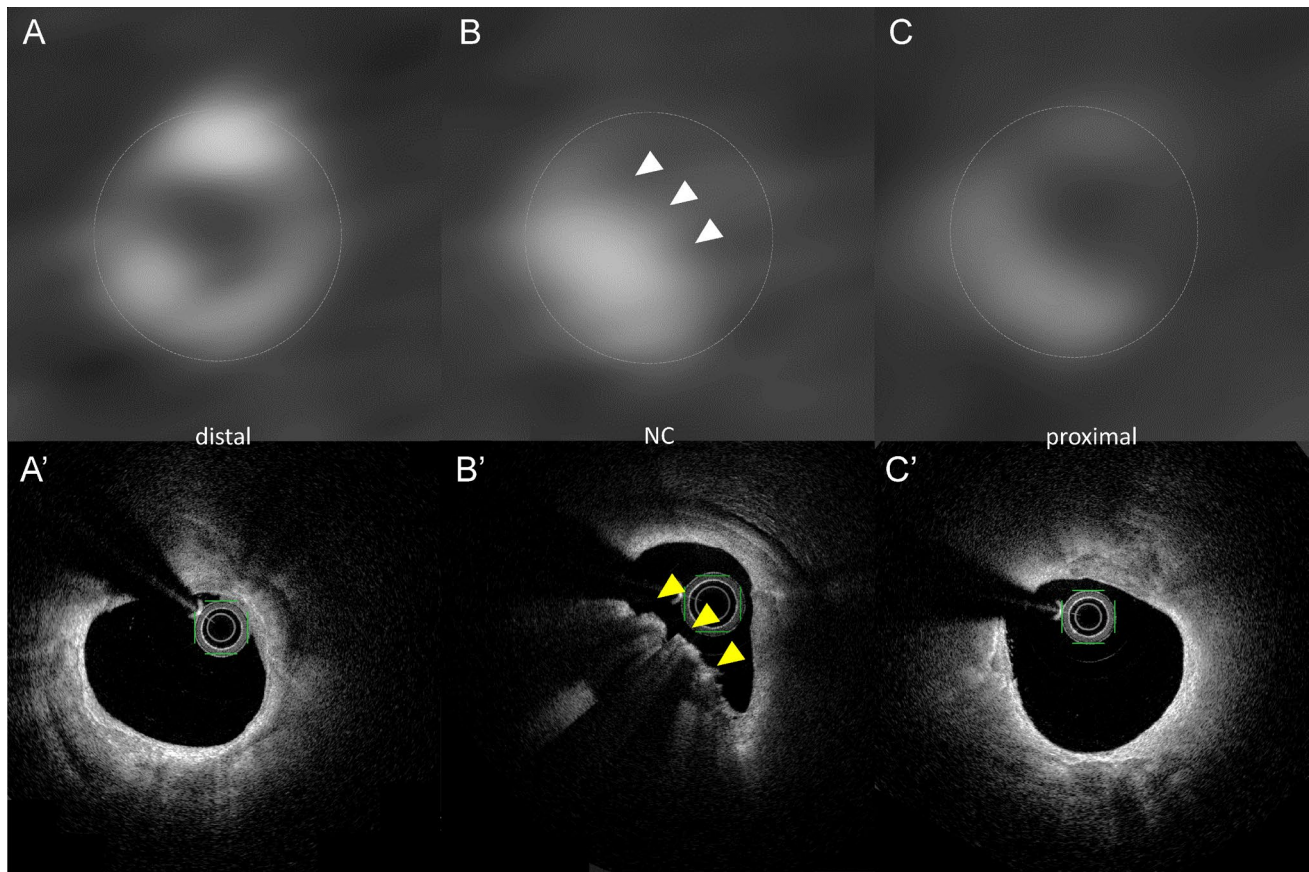
Fig. 4 Definition of nodular calcification derived from CT. Nodular calcification derived from CT (CT-NC) was defined as a hyper-attenuating mass protruding into the center of the vessel (white arrowheads). To specify the center of the vessel, the vessel outer contour (gray dotted line) was assumed referring to the adjacent cross-section (**A**–**C**). Cross-sectional images of OCT were corresponding to CT (**A′**–**C′**). Yellow arrowheads indicate nodular calcification derived from OCT (OCT-NC). *CT* computed tomography, *OCT* optical coherence tomography

Table 1 Patient demographics

Variables	n = 16
Age (years)	72.7 ± 8.1
Male sex [n (%)]	14 (88)
Body height (cm)	161.7 ± 7.1
Body weight (kg)	61.0 ± 10.7
Body mass index	23.3 ± 3.6
Hypertension [n (%)]	15 (94)
Dyslipidemia [n (%)]	14 (88)
Diabetes mellitus [n (%)]	9 (56)
Chronic kidney disease [n (%)]	9 (56)
Smoking history [n (%)]	12 (75)
Prior PCI [n (%)]	9 (56)
Hemodialysis/Renal transplantation [n (%)]	3 (19)

Values are mean ± standard deviation or n (%)

CABG coronary artery bypass grafting, *PCI* percutaneous coronary intervention

Table 2 Radiation dose

Variables	n = 16
Effective dose (mSv)	0.69 ± 0.21
$CTDI_{vol}$ (mGy)	2.85 ± 0.90
DLP (mGy*cm)	49.2 ± 15.2

Values are mean ± standard deviation

$CTDI_{vol}$ volume computed tomography dose index, *DLP* dose length product

Intra- and interobserver variability of MCA measurements and NC detection

Intraobserver and interobserver reproducibility were assessed in CT data sets randomly selected from the 108 cross-sections by two independent experts with more than 5 years of experience in CT analysis. For the intraobserver reliability of MCA assessment, the ICC and absolute difference were 0.940 and 25.2 ± 43.5 degrees, respectively. In
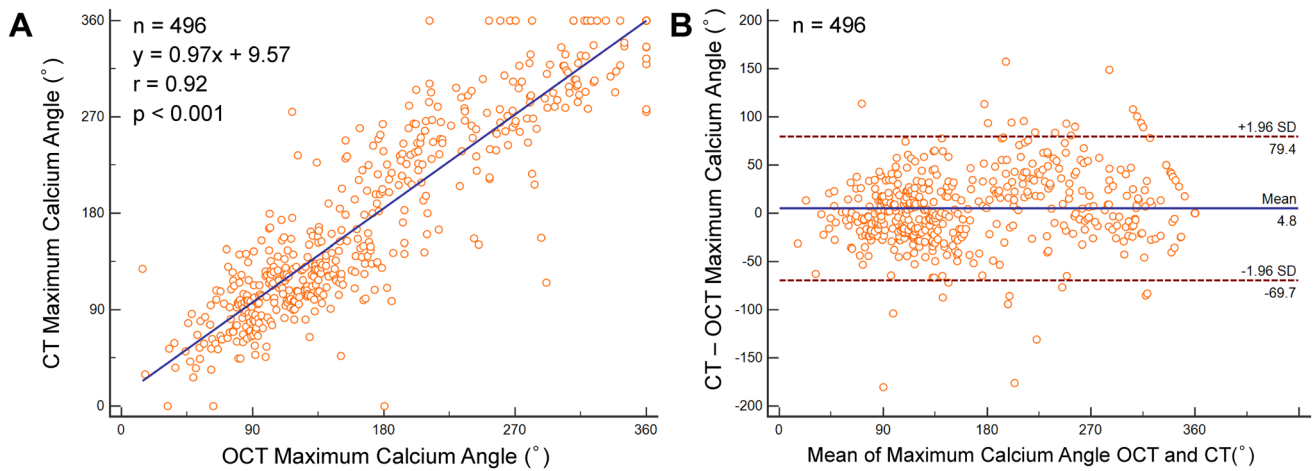
Fig. 5 Comparison of maximum calcium angle between CT and OCT. Scatter plots of the relationship between CT and OCT assessment of the maximum calcium angle (**A**) and Bland-Altman plots of the relative (%) difference between CT and OCT measurements of the maximum calcium angle (**B**). *CT* computed tomography, *OCT* optical coherence tomography, *SD* standard deviation
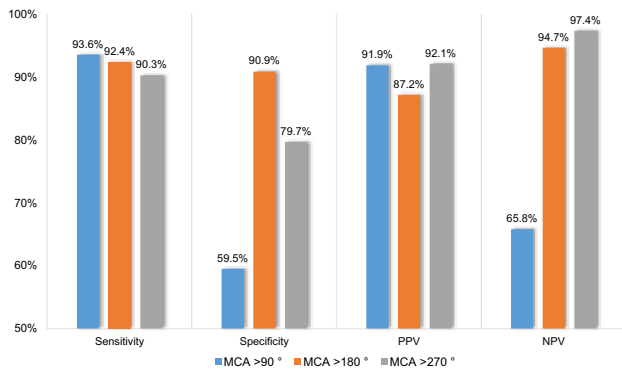

Fig. 6 Diagnostic performance of CT for detecting maximum calcium angles > 90 degrees, 180 degrees, and 270 degrees. *CT* computed tomography, *MCA* maximum calcium angle, *NPV* negative predictive value, *PPV* positive predictive value

the interobserver reliability analysis, the ICC and absolute difference was 0.974 and 21.3 ± 24.7 degrees, respectively. The kappa coefficients of intra and interobserver agreement in detecting CT-NC were 0.80 and 0.66, respectively.

Discussion

In the current study, we report several clinically relevant findings. First, a comparison of cross-sectional images of the coronary artery calcification between the non-contrast CT and OCT demonstrated a significant correlation in the MCA measurements. Further, a reasonable diagnostic accuracy of the non-contrast CT in identification of MCA > 90 degrees (sensitivity 93.6%, specificity 59.5%), > 180 degrees (sensitivity 92.4%, specificity 90.9%), and > 270 degrees (sensitivity 90.3%, specificity 79.7%) was shown. Finally, a good diagnostic accuracy of the non-contrast CT identification of the NC (sensitivity 73.3%, specificity 97.5%) was observed. To the best of our knowledge, the current study is the first to evaluate the feasibility of non-contrast CT in quantifying the coronary artery calcification by using cross-sectional OCT images as a reference standard. Moreover, we studied the diagnostic accuracy of the non-contrast CT in detecting the NC.

Evaluation of the coronary calcium angle is useful when formulating the PCI strategy for severe calcified lesions [5]. Maejima et al. demonstrated that the calcium angle > 227 degrees on OCT was the optimal cut-off for making cracks with RA and ballooning in calcified lesions, with a subsequent adequate stent expansion [6]. Fujino et al. also showed that the calcium angle derived from OCT > 180 degrees was a useful parameter for predicting the stent under-expansion [7]. These studies demonstrated that the OCT evaluation of the calcium angle is valuable for determining the appropriate use of RA and predicting the peri- and post-procedural outcomes. However, occasionally, the OCT catheter cannot pass through the target lesions due to the lumen narrowing and severe tortuosity even after the balloon dilatation, hampering the image acquisition. Accordingly, a non-invasive imaging modality such as non-contrast CT could be beneficial when determining the morphology of coronary artery calcification. Based on the calcium angle derived from non-contrast CT, a decision can be made on whether RA should be performed. Furthermore, some deep calcification with thick intima or lipidic composition cannot be accurately evaluated by OCT. Meanwhile, the use of non-contrast CT can provide detailed images of the coronary artery calcification irrespective of the plaque characteristics. Thus, we consider that the combination of OCT and non-contrast CT can be of great

help when designing an appropriate PCI strategy. Obtaining this information prior to performing cardiac catheterization would facilitate the decisive process concerning an appropriate strategy for severe calcified lesions.

Currently, only limited data on the evaluation of the coronary calcium angle using cross-sectional CT images are available. Cerci et al. demonstrated that quantification of the severity of calcified coronary lesions according to the calcium angle with CT cross-sectional images was associated with the prevalence of significant stenosis [15]. Sekimoto et al. also showed that classification of calcium severity based on the calcium angle determined by CT contributed to predicting the need for RA [10]. Although the authors suggested the usefulness of calcium severity scoring based on cross-sectional CT images, the feasibility of quantifying the calcium angle with cross-sectional CT images has never been thoroughly investigated. Importantly, non-contrast rather than enhanced CT was used when assessing the coronary calcium morphology in the present study. We believe that this is a preferable approach as the use of contrast media may result in an inability to differentiate between the luminal contrast and coronary artery calcification, especially if the calcification and luminal contrast are characterized by similar attenuation. In addition, patients with severe coronary artery calcification are frequently of older age and suffer from renal dysfunction, and the non-contrast CT allows for a precise morphological assessment of the coronary artery calcification without incurring the risk of contrast-induced nephropathy. In the current study, the Bland-Altman plot and linear regression analysis showed that measurements of the calcium angle using the non-contrast CT and OCT exhibit an excellent correlation ($r = 0.92$) with acceptable limits of agreement (− 69.7 to 79.4 degrees). According to previous reports, calcium angle cut-offs of over 180 and 270 degrees were useful for predicting the prognosis after the PCI [7, 10]. The current study demonstrates the excellent sensitivity and specificity of the non-contrast CT in identifying such cut-offs. These findings suggest that the ECG-gated non-contrast CT can be an alternative to OCT when quantifying the coronary calcium angle.

Nodular calcification is pathologically defined as small to moderately sized nodules of calcification that are observed with or without necrotic core components and an intact fibrous cap [16]. It has been characterized with the use of OCT as single or multiple regions of calcium that protrude into the lumen, and strongly correlated with poor prognosis after the PCI [17]. Therefore, detection of NC prior to PCI is considered of great importance for predicting the periprocedural results and long-term prognosis. In the current study, we evaluated the accuracy of the non-contrast CT in detecting NC using OCT as a reference standard. The sensitivity and specificity were 73.3% and 97.5%, respectively. Furthermore, acceptable intra- and inter- observer reproducibility was shown [kappa = 0.66 (inter-observer) and 0.80 (intra-observer)]. This suggests that evaluating the presence of NC using the non-contrast CT is a reasonable diagnostic strategy. Practically, if NC is found on the pre-procedural non-contrast CT, the treatment strategy can be modified to a bypass surgery or a more intensive medical therapy.

Limitations

Several limitations of this study should be addressed. First, this was a retrospective single-center study with a small number of patients. Second, the CT analysis was based on a visual assessment, and the accuracy of lumen detection may be low because the contrast-enhancement was not used. However, even though the non-contrast CT was employed, the vessel outer contour could be determined based on the position and continuity of the coronary vessel and the location of the side branches. Accordingly, the inter- and intra-observer variability in MCA measurements were acceptable. Third, only the LAD was studied in the current study because we consider that the co-registration of non-contrast CT and OCT can be more accurately implemented in arteries with highest number of branches (e.g. LAD). Further investigation is needed to apply this methodology to the left circumflex and right coronary arteries. Fourth, the time interval between the CT and OCT may have resulted in a change in morphological characteristics of the calcium deposits. Finally, OCT was performed after pre-dilation with a ≥ 2.0-mm balloon or RA with a 1.5-mm burr in some cases, which may have affected the calcium angle.

Conclusion

Morphological assessment of the coronary artery calcification with non-contrast CT would be a feasible and accurate diagnostic approach. Thus, pre-procedural non-contrast CT might be helpful in developing tailored strategies for PCI.

Compliance with ethical standards

Conflict of interest Hiromasa Otake has received honoraria from Terumo, but had no role in study design, conduct, or manuscript preparation. The other authors have no conflicts of interest to declare.

Ethical approval This study was conducted in agreement with the Declaration of Helsinki and was approved by the institutional ethics committee.

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