A New Contrast Enhancement Protocol for Subtraction Coronary Computed Tomography Requiring a Short Breath-Holding Time

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Rationale and Objectives: We have developed a new contrast enhancement protocol for subtraction coronary computed tomography (SCCTA) requiring a short breath-holding time. In the protocol, test and main boluses were sequentially and automatically injected, and correct timings for pre-contrast and contrast-enhanced scans for main bolus were automatically determined only by the test bolus tracking. Combined with a fixed short main bolus injection for 7 seconds, the breath-holding time was shortened as possible. The purpose of this study was to evaluate whether use of this new protocol produced adequate quality images, taking into account calcified lesions and in-stent lumens.

Materials and Methods: Patients (*n* = 127) with calcium scores of >400 Agatston units or a history of stent placement were enrolled. Breath-holding times were recorded, and image quality was visually evaluated by two observers.

Results: The mean ± standard deviation breath-holding time was 13.2 ± 0.6 seconds. The mean ± SD computed tomography (CT) number of coronary arteries for the pre-contrast scan was sufficiently low [99.2 ± 32.2 Hounsfield units (HU)] and, simultaneously, that for SCCTA was 367.0 ± 77.2 HU. The rate of segments evaluated as unreadable was sufficiently low (3.8%).

Conclusions: Use of the SCCTA protocol was efficient and allowed for a shorter breath-holding time and adequate diagnostic accuracy of SCCTA images, including images of calcified and stent implantation segments.

Key Words: Test bolus tracking method; subtraction coronary CTA; short breath-holding time; coronary calcification; coronary stent implantation.

INTRODUCTION

Subtraction coronary computed tomography angiography (SCCTA) using a 320-detector row computed tomography (CT) scanner was recently developed. This effective method allows calcium to be subtracted from coronary computed tomography angiography (CCTA) images, providing improved diagnostic accuracy over conventional CCTA in patients with severe coronary artery calcification

and stent (1–7). SCCTA uses two CCTA datasets collected pre-contrast and after contrast enhancement. Two types of acquisition protocols have been proposed to acquire the required datasets: the single breath-hold protocol and the two breath-hold protocol. A study by Yoshioka et al. (1) reported that the image quality score using the single breath-hold method was significantly greater than that using the two breath-hold method. Moreover, Tanaka et al. (2) indicated that compared to conventional CCTA, SCCTA performed with the single breath-hold method improved diagnostic accuracy, with SCCTA yielding a significantly reduced number of nondiagnostic segments. Although the breath-holding times (20–40 seconds) of this single breath-hold method has been shortened to approximately 18 seconds using the test bolus method, which enables the prediction of the peak enhancement time by evaluating the enhancement curve of the test bolus (8), the shortened breath-holding time remains to be problematic for some patients who cannot hold their breath for such a long time.

Furthermore, the operation of the test bolus method is complex and time-consuming as the operator has to run an

independent scan plan for monitoring scans, evaluate the peak enhancement time, and then set the time parameter for the main bolus scan plan.

To further reduce the breath-holding time and facilitate the scan protocol for the single breath-hold SCCTA, we developed a new SCCTA protocol using the 320-detector row CT scanner. With this protocol, pre-contrast and contrast-enhanced images are acquired while holding a single breath for approximately 13 seconds and the operation is simplified. The aim of this study was to evaluate whether the proposed protocol achieved successful SCCTA examinations in the short breath-holding time and provided adequate image quality of calcified lesions and in-stent lumens.

MATERIALS AND METHODS

### Contrast Enhancement and Scanning Techniques

The time charts of our proposed protocol for contrast medium injection and CT scanning as well as a typical time enhancement curve at the ascending aorta (AAo) of the injection condition are presented in Figure 1.

The notable aspect of this protocol is the combination of a test bolus injection and a subsequent main bolus injection automatically performed with a specific interval T_I (17 seconds for this protocol). According to a known contrast enhancement principle, the time to peak enhancement is constant irrespective of the injection duration for short durations of 5 seconds and less but is slightly longer for a 7-second injection used in this protocol (9,10). Therefore, it was programmed in this protocol that the main bolus peak arrives with an interval time almost equal to T_I after the peak time of the test bolus (the trigger point), due to the short injection durations of the test and main boluses. As it was reported that the times from contrast medium arrival to peak enhancement are

nearly equal to the injection durations in cases with more than 5 seconds (9), we were able to set the timing for the safety pre-contrast scan before the main bolus arrival (8 seconds after the triggering) in the protocol.

Although the conventional bolus tracking method can be used to determine the trigger point, it cannot predict the timing of peak enhancement. On the other hand, the peak enhancement can be approximated using the test bolus method; however, its operation is complicated as aforementioned. Our proposed test bolus tracking (TBT) method is very unique in that the peak enhancement timings of the main bolus can be automatically set only by tracking the test bolus and then triggering at its peak enhancement, eliminating the complicated operations needed in the test bolus method. Consequently, the breath-holding time was shortened to approximately 13 seconds, owing to the combination of the peak enhancement prediction and the fixed short injection duration of 7 seconds.

Detailed conditions of this protocol are as follows: The test bolus was injected for 2 seconds, followed by a 0.9% saline solution for another 5 seconds. Then, after waiting for 10 seconds, the main bolus injection for 7 seconds was automatically started, followed by injection of a saline solution for 7 seconds. The monitoring scan was at 120 kV and 11 mAs with intervals of 1.0 seconds for the test bolus that was started 8 seconds after the beginning of the test bolus injection. The CT operator then manually pressed the acquisition trigger button at the time of peak enhancement of the test bolus, visually assessing the monitoring images along with enhancement curve measured in the region of interest (ROI) placed on AAo. During the subsequent 8 seconds of waiting, a 5-second breath-holding instruction was performed. The pre-contrast scan was then started automatically, followed by 6 seconds of waiting and performing the contrast-enhanced scan. The scan durations for the pre-contrast and contrast-enhanced scan were
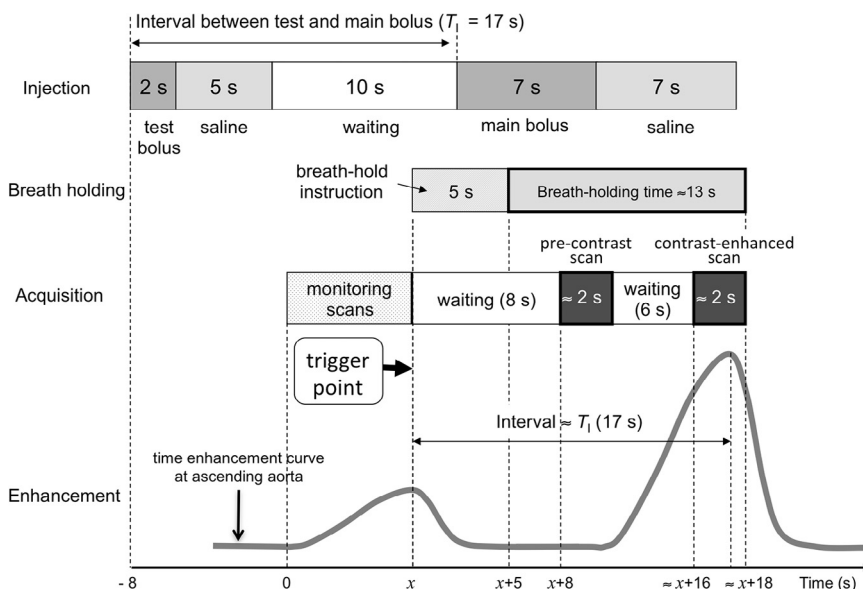
Figure 1. Proposed contrast enhancement protocol for subtraction coronary computed tomography angiography (SCCTA). As the test and main boluses are sequentially and automatically injected with a specific interval (T_I), the correct timings for the pre-contrast and contrast-enhanced scans for the main bolus were automatically determined from the test bolus tracking and triggering at its peak time.

approximately 2 seconds, which varied depending on the heart rate and beat timing of each individual case.

An iodine contrast medium with an iodine concentration of 350 mg/mL (iohexol 350, Daiichi Sankyo Company, Limited, Tokyo, Japan) was delivered via a 20-gauge catheter inserted into an antecubital vein with an injection flow rate dependent upon the patient's body weight in kilogram (main bolus injection: $0.089 \times$ body weight [BW] mL/s).

CCTA

The CT scanner used in this study was a second-generation 320-detector row CT scanner (Aquilion ONE ViSION Edition, Toshiba Medical Systems, Otawara, Japan) with 0.5-mm detector elements and a gantry rotation time of 275 ms. The coronary CT images were reconstructed using 0.5-mm-thick sections and 0.25-mm increments with a reconstruction kernel of FC04 and the iterative reconstruction method AIDR3D (standard setting). All CCTA scans were performed within one heartbeat using the prospective electrocardiogram (ECG)-triggering method. The phase window was set at 70%–80% of the R–R interval. The tube voltage was set at 120 kV, and the target noise for the tube current selection was set at 25 HU. The effective radiation dose was estimated from the dose length product multiplied by a conversion coefficient for the chest (0.014 mSv/mGy/cm) as proposed by the European Working Group for Guidelines on Quality Criteria in CT (11).

Patient Population and Study Protocol

One hundred twenty-seven patients (97 men and 30 women; mean $\pm$ SD age, 68.3 ± 10.0 years) that were referred for CCTA to evaluate known or suspected coronary artery disease between March 2013 and April 2014 were enrolled in this study. These patients were eligible for the subtraction CCTA protocol if they had a coronary calcium score of >400 Agatston units or a stent treatment history. Patients were excluded from the study if they had a cardiac pacemaker, defibrillator, or both implanted; a history of cardiac surgery; atrial fibrillation or extrasystoles at imaging; a scan heart rate higher than 65 beats per minute (bpm); motion artifacts in the coronary artery; had used beta-blockers; or had received nonionic contrast media. This study was reviewed and accepted by the Institutional Review Board before study initiation, and all patients provided informed consent. This study was conducted in accordance with the ethical principles in the Declaration of Helsinki.

Coronary Calcium Scoring

All patients initially underwent low-dose sequential calcium scoring. The tube voltage and target noise were set at 120 kV and 30 HU, respectively, with AIDR3D standard, and the cardiac phase was set at 75%. The coronary calcium score was calculated immediately after acquisition using the Agatston method.

Coronary Subtraction

Image reconstruction of the two CCTA datasets was performed in the optimal cardiac phase for minimizing the motion artifacts of each vessel. These image sets were reconstructed using the half- or full-scan reconstruction. If a motion artifact did not appear, full-scan reconstruction was adopted. The subtraction images were obtained by subtracting pre-contrast scan data from contrast-enhanced scan data. Coronary subtraction was performed using the scanner's embedded software "Volumetric CT Digital Subtraction Angiograph (Toshiba Medical Systems)." The registration process was performed using atlas-based cardiac segmentation and sophisticated rigid and deformable registration algorithms. If misregistration artifacts were visualized, local rigid registration was performed in each spherical ROI, including the artifact.

Image Analysis

All volume datasets were transferred to a workstation (Zio Station, Ziosoft, Tokyo, Japan) for image analysis. Evaluations determined whether pre-contrast and contrast-enhanced images were scanned with optimal timing by measuring the CT number in the major vessels and coronary arteries using axial images. The vessel ROI was placed in the main pulmonary artery (mPA) and AAo of a left atrial appendage level; left atrium of an aortic valve level; and right atrium, right ventricle, and left ventricle of a middle left ventricle level. The coronary artery ROI was placed in the left main artery; the proximal, middle, and distal segments of the right coronary artery; the middle of the left circumflex artery; and the middle of left anterior descending artery. The diameter of the coronary artery ROI was at a minimum more than half of the lumen of the coronary artery.

Curved multiplanar reconstruction images and cross-sectional reconstruction images were generated from the contrast-enhanced and subtraction image datasets. The coronary arteries were divided into 16 segments according to the AHA segment model (12). All segments in the images were evaluated in a window width of 1000 HU with a center of 300 HU. Two observers, each with more than 7 years of CCTA image reading experience and who were blinded to the clinical history, performed the evaluations. Axial slices, curved planar reformation (CPR) images, and cross-sectional images were evaluated. The coronary artery image quality was assessed using a four-point scale on conventional CCTA and SCCTA. The grading scales are (1) uninterpretable: evaluation not possible; (2) poor: severe artifacts limiting adequate evaluation of the segment (low reader confidence); (3) moderate: some artifacts present but interpretation possible (moderate reader confidence); or (4) good: good image quality without artifacts (high reader confidence). Any discrepancy between the observers was settled by consensus. Scores of 1 or 2 were considered to reflect unreadable image quality, whereas scores of 3 and 4 were considered to reflect readable image quality.

Statistical Analysis

Continuous variables are reported as the mean ± SD. Group differences were evaluated using unpaired t tests. Categorical variables are presented as frequencies. Intergroup comparisons were analyzed using χ^2 tests. CT numbers in the scan images and subtraction images were evaluated using one-way analysis of variance followed by Scheffe post hoc tests. Interobserver agreement was assessed based on the proportion of agreement and the values of the kappa coefficient. Image quality scores were compared using McNemar test. A P value < .05 was considered statistically significant. All statistical analysis was performed using SPSS version 20.0 (SPSS, IBM, Tokyo, Japan).

RESULTS

Patient baseline characteristics are presented in Table 1. There was no significant difference in heart rate between pre-contrast and contrast-enhanced scans. The mean ± SD breath-

TABLE 1. Patient Characteristics (N = 127)

Parameter	Value
Age, y	
Mean ± SD (range)	68.3 ± 10 (37–86)
Sex, n (%)	
Males	97 (76.4)
Females	30 (23.6)
Body, mean ± SD	
Length (cm)	162.4 ± 7.9
Weight (kg)	65.1 ± 11
Body mass index	24.6 ± 3.1
Coronary risk factors, n (%)	
Hypertension	94 (74.0)
Diabetes	55 (43.3)
Hypercholesterolemia	75 (59.1)
Smoking	47 (37.0)
Previous myocardial infarction	40 (31.5)
Previous PCI	93 (73.2)
Use of beta-blocker, n (%)	
Propranolol	18 (14.2)
Landiolol	78 (61.4)
Coronary calcium score	
Mean ± SD (range)	1524.4 ± 1641.0 (431–6719)
Pre-contrast CCTA HR, beats/min	
Mean ± SD (range)	53.8 ± 4.6 (39–64)
Contrast-enhanced CCTA HR, beat/min	
Mean ± SD (range)	53.7 ± 4.4 (40–64)
CCTA estimated effective radiation dose (sum of pre-contrast and contrast-enhanced), mSv	
Mean ± SD (range)	5.57 ± 1.32 (1.90–9.43)

CCTA, coronary computed tomography angiography; HR, heart rate; PCI, percutaneous coronary intervention; SD, standard deviation.

holding time was 13.2 ± 0.6 seconds, and the time from the pre-contrast scan to the contrast-enhanced scan was 8.0 ± 0.5 seconds.

The mean CT numbers in the measured points of the pre-contrast and contrast-enhanced images are shown in Figure 2. The CT numbers for the right side of the heart (right atrium, right ventricle, and mPA) in the pre-contrast images were significantly higher than that in the contrast-enhanced images (P < .001), with mPA highest at all measurement points. In addition, the pre-contrast image CT numbers for AAo and coronary artery were sufficiently low. As shown in Figure 3, the scan timings for the enhanced coronary arteries were adequate, with a mean CT number of 469.7 ± 69.7 HU in contrast-enhanced images and 367.0 ± 77.2 HU in subtraction images.

In total, 393 segments were registered by image quality scoring, including 206 segments with calcification and 187 segments with stent implantation segments. There were 134 segments with both stent implantation and calcification. The mean ± SD image qualities of CCTA and SCCTA were 2.5 ± 1.0 and 3.6 ± 0.6 in all segments, respectively. The percentage of segments with unreadable image qualities with CCTA and SCCTA was 50.9% and 3.8%, respectively, and the reasons of all unreadable segments for SCCTA were misregistration. The mean ± SD image qualities of the calcified and stent segments were 2.4 ± 1.0 and 2.6 ± 1.1 for CCTA, respectively, and 3.5 ± 0.5 and 3.5 ± 0.6 for SCCTA, respectively (Table 2). All comparisons between CCTA and SCCTA showed significant differences (P < .001). Representative cases (Fig 4 and Fig 5) depict the improvement in luminal visualization in the SCCTA images. An unreadable case is shown in Figure 6, in which the stent was not properly subtracted.

DISCUSSION

Successful SCCTA examinations with the short breath-holding times of approximately 13 seconds were performed using the TBT method, providing sufficiently low coronary artery CT numbers for the pre-contrast image and sufficiently high CT numbers for the enhanced coronary arteries. The TBT method facilitated an efficient examination operation that eliminated the need to perform an independent test bolus scan before the main bolus scan and the evaluation of the time enhancement curve. Although several papers (5–7) indicated that in SCCTA with long breath-holding times supplemental oxygen has been administered before scanning, it was not necessary in the proposed protocol due to the shortened breath-holding time.

The percentages of unreadable segments in our results (3.8%) was significantly lower than that reported by Yoshioka et al. using single breath-holding times of 20–40 seconds (8.5%) (3). Therefore, the short breath-holding time using our method appeared to contribute to the improvement in image quality and reduction SCCTA misregistration. The reason for all unreadable cases was misregistration. In fact, even when any body
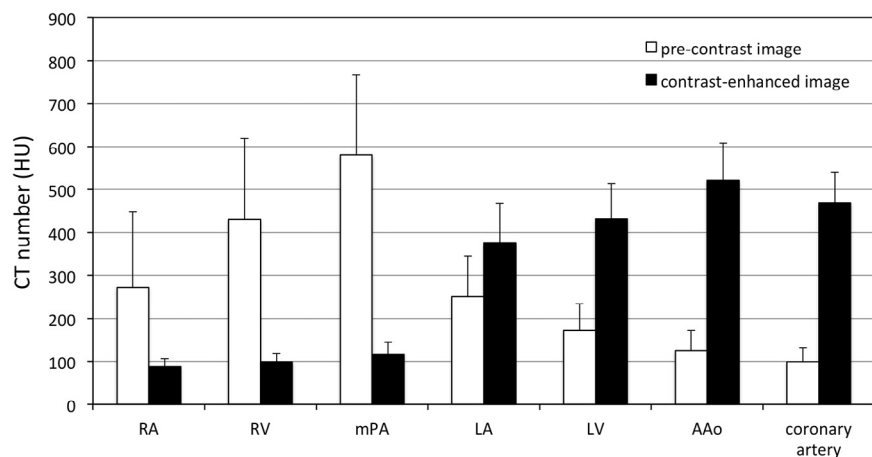
Figure 2. Mean ventricle and vessel computed tomography numbers from pre-contrast and contrast-enhanced images. AAo, ascending aorta; LA, left atrium; LV, left ventricle; mPA, main pulmonary artery; RA, right atrium; RV, right ventricle.
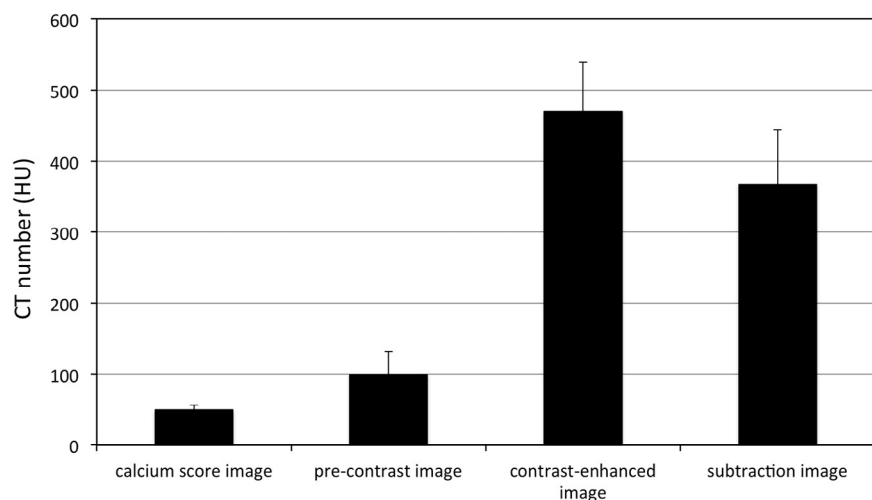
Figure 3. Mean computed tomography numbers of coronary arteries in calcium scan, pre-contrast, contrast-enhanced, and subtraction images.

TABLE 2. Image Quality Scores and Percentage of Segments with Readable Versus Unreadable Image Quality

| Measure	Conventional CCTA	Subtraction CCTA	P value
Image quality score (all)			
Mean ± SD	2.5 ± 1.0	3.6 ± 0.6	<.001
Inter-observer kappa score (95% CI)	0.880 (0.842–0.915)	0.906 (0.860–0.945)	
Segment percentage			
Readable image quality	49.1%	96.2%	<.001
Unreadable image quality	50.9%	3.8%	
Image quality score			
Calcified segment	2.4 ± 1.0	3.6 ± 0.5	<.001
Stent implantation segment	2.6 ± 1.1	3.6 ± 0.6	<.001

CCTA, coronary computed tomography angiography; CI, confidence interval; SD, standard deviation.

movement between the pre-contrast scan and the contrast-enhanced scan was not observed visually, misregistration artifacts occurred in some cases. Therefore, further improvements in the nonrigid registration performance of the subtraction algorithm are required to decrease these artifacts.

We evaluated the stent implantation segment, which has been evaluated in detail in only two recent SCCTA studies (6,7). Maintz et al. have reported that the visibility of a 3-mm stent lumen was approximately 50%–59% with CCTA (13). In our study, the percentage of unreadable stent segment images was significantly improved with SCCTA (50.9% for CCTA and 3.8% for SCCTA). In some stent regions (187 segments), open vessels were detectable even if the regions were estimated as occluded by conventional CCTA (Fig 5). These results strengthen the claim of a recent report in which SCCTA can effectively estimate the stent vessel lumens.
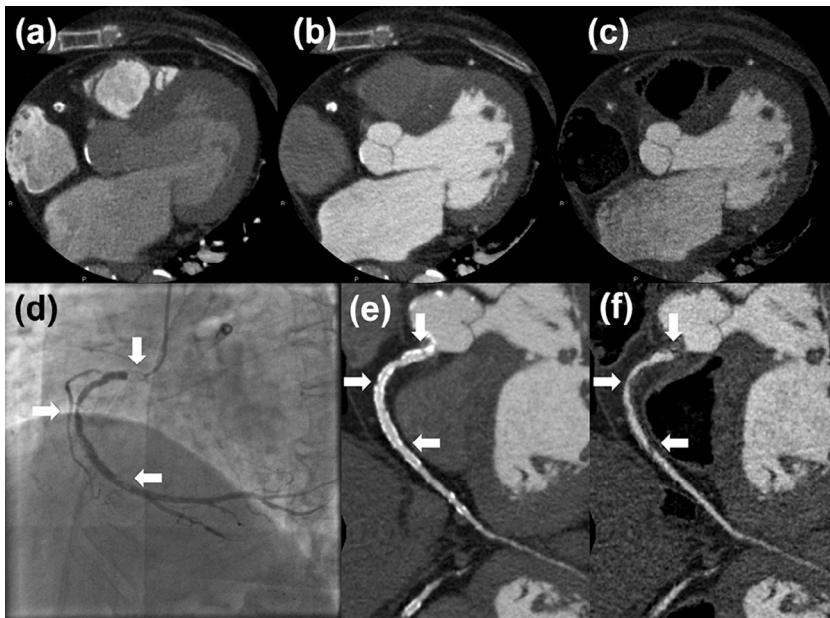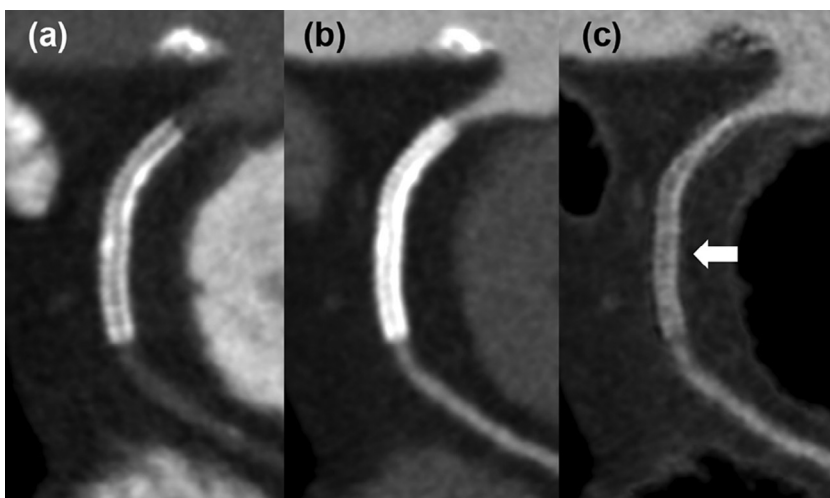
Figure 4. A 63-year-old man with suspected coronary artery disease. **(a)** Axial pre-contrast image; **(b)** axial contrast-enhanced image; **(c)** axial subtraction image; **(d)** invasive coronary angiography; **(e)** conventional coronary computed tomography angiography (CCTA); and **(f)** subtraction CCTA. Stenotic lesions were observed on three segments of the right coronary artery by invasive coronary angiography (*arrows*). Although the stenotic lesions were not clearly visible due to the severe calcifications on the conventional CCTA images, subtraction CCTA clearly depicted the stenosis confirmed by invasive coronary angiography.
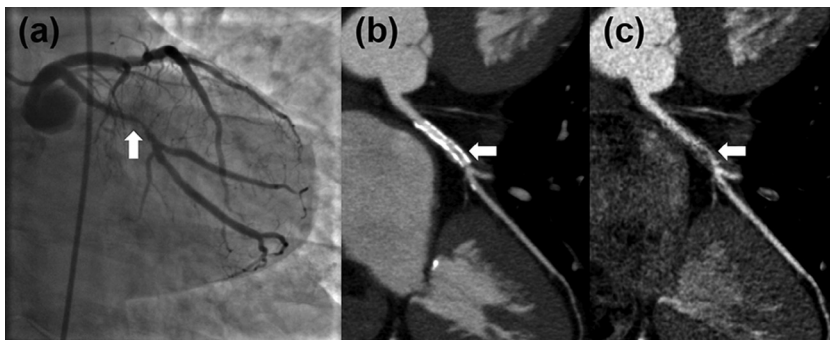
Figure 5. A 63-year-old man with suspected coronary artery disease. **(a)** Invasive coronary angiography; **(b)** conventional coronary computed tomography angiography (CCTA); and **(c)** subtraction CCTA. A 3.0-mm stent (PROMUS Element Plus, Boston Scientific Japan, Tokyo, Japan) was placed in the left circumflex artery. We estimated that the stent intra-lumen was occluded in conventional CCTA (arrows). However, subtraction CCTA showed that the open-vessel lesion was similar to invasive coronary angiography.

Figure 6. A 71-year-old man with suspected coronary artery disease. **(a)** Pre-contrast images; **(b)** contrast-enhanced images; and **(c)** subtraction images. A 2.5-mm stent (Xience PRIME, Abbott Vascular Japan, Minato-ku, Tokyo, Japan) was placed in the right coronary artery. The stent intra-lumen was not visualized on the subtraction image (*arrow*), because the stent was not properly subtracted.

The present study had several limitations. This study only enrolled patients with heart rates of less than 65 bpm. If the scan heart rate was more than 65 bpm, the radiation dose was increased because of the use of a two-heartbeat scan protocol with higher temporal resolution. Moreover, there was the possibility of increasing the occurrence of misregistration artifacts. If an arrhythmia due to extra premature atrial or ventricular contraction occurred during the scan, the scan timing might not be appropriate due to skipping irregular heartbeats. In such a case, the prediction of the peak enhanced time

may fail, similar to that observed with conventional CCTA using the test bolus method. As a corrective action, a pre-contrast scan with earlier timing and an extension of the contrast medium injection time of main bolus are required, leading to an extension of the breath-holding time.

In conclusion, we have described a new contrast enhancement protocol for use with SCCTA, in which the test and main boluses were sequentially and automatically injected with an interval of 17 seconds. By using this protocol, correct timings of the pre-contrast and contrast-enhanced scans were automatically determined by triggering at the test bolus peak, and the breath-holding time was shortened to approximately 13 seconds without the complicated procedures needed for the conventional test bolus method. SCCTA image quality obtained using our new protocol was sufficient to produce diagnostic accuracy with segments harboring not only calcification but also stent implantation.

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