Original Investigation

Modified Subtraction Coronary CT Angiography Method for Patients Unable to Perform Long Breath-Holds:

A Preliminary Study

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Rationale and Objectives: Severe calcifications of the coronary arteries are still a major challenge in coronary computed tomography (CT) angiography (CCTA). Subtraction CCTA using a 320-detector row CT scanner has recently been introduced for patients with severe calcifications. However, the conventional subtraction CCTA method requires a long breath-holding time of approximately 20–40 seconds. This is a major problem in clinical practice because many patients may not be able to perform such a long breath-hold. We explored a modified subtraction CCTA method with a short breath-holding time to overcome this problem.

Materials and Methods: This study was approved by our institutional review board, and all patients gave written informed consent. A total of 12 patients with a coronary calcium score of >400 were enrolled in this study. All patients were unable to hold their breath for more than 20 seconds. Modified subtraction CCTA was performed using the bolus-tracking method. The acquisition protocol was adjusted so that the mask scan was acquired 10 seconds after the postcontrast scan during a single breath-hold. The subtraction image was obtained by subtracting the mask image data from the postcontrast image data. The breath-holding times were recorded. Enhancement of the coronary arteries in the subtraction images was assessed. Subjective image quality was evaluated in a total of 32 segments using a 4-point scale.

Results: The mean breath-holding time was 12.8 ± 0.8 seconds (range, 12–14 seconds). The average CT number in the coronary arteries was 288.6 ± 80.5 Hounsfield units (HU) in the subtraction images. Average image quality was significantly increased from 2.1 ± 0.9 with conventional CCTA to 3.1 ± 0.7 with subtraction CCTA ($P < 0.001$). With subtraction CCTA, the number of non-diagnostic segments was significantly reduced from 53% to 19% ($P = 0.001$).

Conclusions: This preliminary study has shown that our modified subtraction CCTA method allows the breath-holding time to be shortened to <15 seconds. This may substantially improve the success rate of subtraction CCTA by reducing artifacts and allowing this technique to be applied to patients who are unable to perform a long breath-hold.

Key Words: Computed tomography; coronary CT angiography; coronary artery calcification; subtraction.

INTRODUCTION

One of the major challenges in coronary computed tomography (CT) angiography (CCTA) is the presence of severe calcifications in the coronary arteries, which frequently reduces diagnostic accuracy and may even make it impossible to evaluate the presence of stenosis (1–3).

Subtraction CCTA has recently been introduced using first- and second-generation 320-detector row CT technology (4–7). In subtraction CCTA, scanning is performed twice to acquire both a precontrast (mask image) and a postcontrast image

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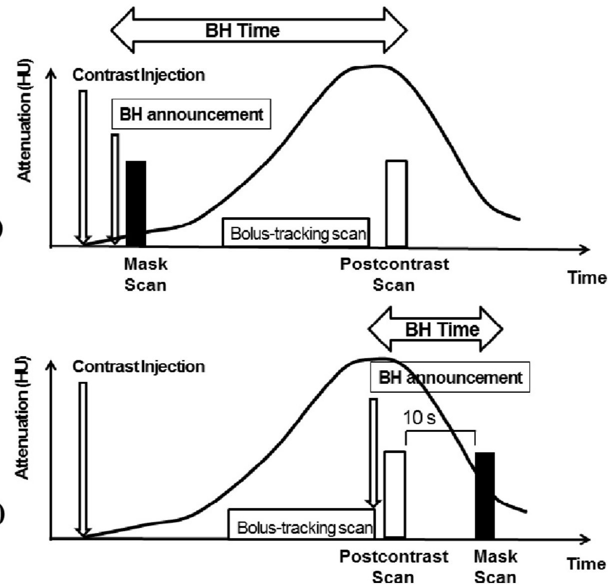

Figure 1. Overview of the conventional and modified subtraction coronary computed tomography angiography (CCTA) methods. **(a)** Conventional subtraction CCTA: The bolus-tracking technique is used. The mask image is obtained immediately after the breath-hold announcement is issued. Subsequently, the postcontrast scan is triggered when the CT number in the ascending aorta reaches 150 Hounsfield units (HU). The breath-holding (BH) time is the interval between the end of the breath-hold announcement and the end of the postcontrast scan. **(b)** Modified subtraction CCTA: The bolus-tracking technique is used. The postcontrast scan is triggered when the CT number in the ascending aorta reaches 150 HU. The mask scan is acquired 10 seconds after the postcontrast scan. The BH time is the interval between the end of the breath-hold announcement and the end of the mask scan.

datasets. To minimize misregistration artifacts due to differences in the breath-hold position, the two scans should preferably be acquired during a single breath-hold (4). In the conventional subtraction CCTA protocol, the scan for obtaining the mask image (mask scan) is acquired immediately after contrast injection, with the postcontrast scan acquired after the contrast medium has reached the coronary arteries (Fig 1a). In this protocol, a long breath-holding time of approximately 20–40 seconds is required between the mask and the postcontrast scans (4–7).

The long breath-holding time required in the conventional subtraction CCTA protocol is a major problem because it excludes patients who are unable to perform a long breath-hold. We hypothesized that the breath-holding time for subtraction CCTA could be shortened by acquiring the mask scan after the postcontrast scan (Fig 1b) rather than before (Fig 1a). As a result, this modified approach may allow imaging of patients who are ineligible for conventional subtraction CCTA because of limited breath-hold capability. We report our initial experience with this modified acquisition protocol for subtraction CCTA in patients unable to perform a long breath-hold.

MATERIALS AND METHODS

From patients clinically referred for CCTA because of suspected or known coronary artery disease, 12 consecutive patients (5 men and 7 women, average age 71.5 ± 7.7 years) with a coronary calcium score (Agatston score) of >400 and unable to perform a breath-hold of >20 seconds were enrolled in the current feasibility study. The coronary calcium-scoring scan had been performed before CCTA. All 12 patients were excluded from conventional subtraction CCTA because of their limited breath-hold capability. Exclusion criteria were known allergy to iodinated contrast media, estimated glomerular filtration rate of <45 mL/min/1.73 m^2, arrhythmia, previous cardiac surgery, evidence of acute coronary syndrome, aortic stenosis, intolerance to beta-blockers, and body mass index >40 kg/m^2.

The study was approved by our institutional review board, and all patients gave written informed consent.

Axial imaging was performed using a second-generation 320-detector row CT scanner (Aquilion One ViSION Edition; Toshiba Medical Systems, Otawara, Japan). All patients were imaged using prospective electrocardiographic (ECG) gating. The tube voltage was 120 kV, and the target noise for the tube current was set at 28 Hounsfield units (HU). The acquisition phase window (padding) was 65–80% of the RR interval for patients with a heart rate of ≤60 bpm and 35–80% of the RR interval for patients with a heart rate of >60 bpm. The coverage of both the postcontrast and mask scan was up to 16 cm. Images were reconstructed with a 512×512 matrix and 0.5-mm slice thickness using kernel FC44 with iterative reconstruction (Adaptive Iterative Dose Reduction 3D [AIDR 3D]; Toshiba Medical Systems) at the standard setting. Before scanning, 8 patients with a heart rate greater than 65 beats/minute received intravenous beta-blockade (landiolol hydrochloride; Ono Pharmaceutical, Osaka, Japan; 0.125 mg/kg).

Modified subtraction CCTA was performed with iodinated contrast agent (iohexol 350; Daiichi Sankyo Company, Tokyo, Japan) injected intravenously at a rate of $0.07 \times$ body weight (kg) mL/s in 9 seconds, followed by a 30-mL saline chaser bolus. The bolus-tracking method was used to determine the postcontrast scan start time. When the CT number in the ascending aorta reached 150 HU, a breath-hold announcement was issued automatically. The duration of the breath-hold announcement was 4 seconds in Japanese, which is identical to the default setting in English, but could be different in other languages. Two seconds after the end of the announcement, a prospective ECG-gated scan at 0.275 seconds/rotation was triggered by the R wave to acquire the postcontrast image. Then, the mask scan (same protocol as the postcontrast scan) was acquired 10 seconds after the postcontrast scan during the same breath-hold. Therefore, the breath-holding time in this method extended from the end of the breath-hold announcement to the end of the mask scan (Fig 1b). The breath-holding time was recorded for all patients.

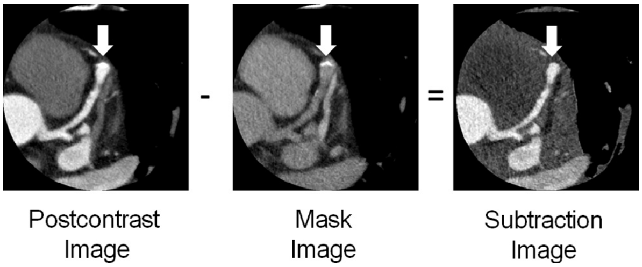

Figure 2. Concept of the modified subtraction coronary computed tomography angiography (CCTA) method. The modified subtraction CCTA image dataset is obtained by subtraction of the mask image dataset from the postcontrast image dataset. Although the coronary arteries show mild enhancement in the mask image, they are adequately opacified in the subtraction image. The small calcification is eliminated (*arrow*).

The effective radiation dose was estimated based on the dose-length product (mGy × cm) using the following formula: effective radiation dose = dose-length product × k, where $k = 0.014$ mSv × mGy^{-1} × cm^{-1}.

For image reconstruction, the optimal cardiac phase in which motion artifacts were minimal was identified visually on the postcontrast images. The same cardiac phase was used for the mask images.

Subtraction was performed using a dedicated algorithm "volumetric CT digital subtraction angiography" (Toshiba Medical Systems). The subtraction images were obtained by subtracting the mask images from the postcontrast images (Fig 2). To assess whether the modified subtraction CCTA protocol provides images that are adequate for diagnostic evaluation, both coronary artery contrast opacification and subjective image quality were evaluated.

To determine coronary artery contrast opacification in the subtraction images, intraarterial enhancement was evaluated as attenuation in HU. It was measured in each patient using the mean of three regions of interest (ROI) placed at the origin of the right coronary artery and left main trunk, respectively (8). The ROIs were set as large as possible. In each patient, the procedure was repeated for the postcontrast and mask images, using ROIs at the same locations, but coronary walls, plaques, and calcifications were avoided.

In addition, subjective image quality assessment was performed. The coronary arteries were divided into segments according to the American Heart Association classification (9). Only segments with severe calcification were evaluated, whereas stented segments were excluded. Severe calcifications were defined as more than one quadrant calcification on a cross-sectional image of conventional CCTA (6). Image quality was evaluated for each calcified segment on conventional and subtraction CCTA images using a 4-point scale (5,6,10,11): 1 (unintepretable; evaluation not possible), 2 (poor image quality; severe artifact limiting adequate evaluation [low reader confidence]), 3 (fair image quality; some artifact present, but interpretation possible [moderate reader confidence]), and 4 (good image quality; good image quality without artifact [high reader confidence]). Scores 1 and 2 were considered to reflect non-diagnostic image quality. The evaluation was performed by two experienced radiologists with more than 10 years of experience. Discrepancies were settled by consensus.

TABLE 1. Patient Characteristics (n = 12)

Characteristics	Values
Age (years)	71.5 ± 7.7
Male (*n*)	5 (42%)
Body mass index (kg/m^2)	25.4 ± 4.4
Coronary risk factors (*n*)	
Hypertension	7 (58%)
Diabetes	3 (25%)
Hypercholesterolemia	6 (50%)
Smoking	2 (17%)
Previous myocardial infarction	4 (33%)
Previous PCI	4 (33%)
Coronary calcium score (Agatston score)	
Range	425.9–1774.7
Mean ± SD	893.3 ± 428.4
HR at postcontrast scan (beats/min)	56.1 ± 10.6
HR at mask scan (beats/min)	56.3 ± 7.9
Use of beta-blockade (*n*)	8 (67%)
Estimated effective radiation dose (sum of postcontrast and mask scans, mSv)	5.2 ± 2.2
Breath-holding time (seconds)	12.8 ± 0.8
CT number of coronary arteries (HU)	
Postcontrast image	397.8 ± 79.9
Mask image	97.8 ± 22.8
Subtraction image	288.6 ± 80.5

CT, computed tomography; HU, Hounsfield units; HR, heart rate; PCI, percutaneous coronary intervention; SD, standard deviation.

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation. The average image quality scores between conventional CCTA and subtraction CCTA was compared using paired t test. The diagnostic image quality versus non-diagnostic image quality frequencies were compared using a McNemar's test. Interobserver agreement was assessed with kappa statistics. P values of <0.05 were considered statistically significant.

RESULTS

The modified subtraction CCTA protocol was successfully performed in all 12 patients. Patient characteristics are specified in Table 1. The average breath-holding time was 12.8 ± 0.8 seconds (range, 12–14 seconds). All patients were able to perform this breath-hold. Heart rates during the postcontrast and mask scans were on average 56.1 ± 10.6 beats/minute and 56.3 ± 7.9 beats/minute, respectively.

The used padding was 65–80% of the RR interval in seven cases and 35–80% of the RR interval in five cases. The estimated effective radiation dose for the modified subtraction

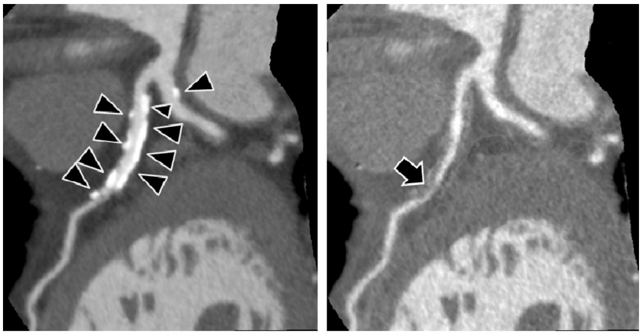

Figure 3. A 73-year-old man with suspected coronary artery disease. **(a)** Postcontrast image. Curved planar reformation image of the left anterior descending artery. Multiple nodular and linear calcifications are observed (*arrowheads*). **(b)** Subtraction image. Curved planar reformation image at the same location as in **(a)**. All calcifications are eliminated and moderate stenosis can be seen (*arrow*).

CCTA protocol (sum of the postcontrast and mask scans) was 5.2 ± 2.2 mSv (range, 2.7–10.0 mSv).

In the postcontrast images, the coronary arteries were well enhanced, with an average CT number of 397.8 ± 79.9 HU (range, 270.0–553.6 HU). In the mask images, the coronary arteries showed mild enhancement, with an average CT number of 97.8 ± 22.8 HU (range, 56.5–128.1 HU). In the subtraction images, the coronary arteries were adequately opacified, with an average CT number of 288.6 ± 80.5 HU (range, 112.4–411.8 HU). Opacification of <250 HU was seen in two patients, however.

A total of 32 segments with severe calcification were available for analysis of subjective image quality. Six stented segments were excluded from the analysis. The average image quality of conventional CCTA in these segments was 2.1 ± 0.9. A total of 17 (53%) segments were judged as non-diagnostic, which was caused by severe calcification in 15 segments and both severe calcification and motion artifacts in two segments. The interobserver kappa score for image quality score was 0.809. The average image quality of subtraction CCTA was 3.1 ± 0.7, which was significantly higher than conventional CCTA ($P < 0.001$). A total of six (19%) segments were judged non-diagnostic, which was caused by misregistration artifact in all affected segments. The percentage of segments with non-diagnostic image quality of subtraction CCTA was significantly lower than conventional CCTA ($P = 0.001$). The interobserver kappa score for image quality score was 0.787.

An example case is shown in Figure 3.

DISCUSSION

This preliminary study has shown that a modified subtraction CCTA method allows the breath-holding time to be shortened to <15 seconds without compromising image quality. With this modified approach, subtraction CCTA was successfully performed in patients unable to perform a breath-hold of >20 seconds and thus otherwise considered ineligible for subtraction CCTA. Despite the presence of mild enhancement in the mask scan, average coronary artery opacification in the subtraction images was adequate for diagnostic evaluation. Moreover, subjective image quality of modified subtraction CCTA was significantly improved as compared to conventional CCTA.

One of the major problems in CCTA is the presence of severe calcifications, which can cause blooming artifacts as well as beam-hardening artifacts. These factors reduce diagnostic accuracy and may make it difficult to assess luminal stenosis. In the present study, we evaluated a population prone to artifacts specifically due to calcium; 53% segments were judged non-diagnostic due to severe calcification in CCTA. Subtraction CCTA using a first- or second-generation 320-detector row scanner has been shown to provide improved diagnostic accuracy over conventional CCTA in patients with severe coronary artery calcifications (5–7). Particularly, specificity and positive predictive values for calcified lesions are higher for subtraction CCTA as compared to conventional CCTA (6,11,12). Recently, it has also been reported that subtraction CCTA is not only useful in case of severe calcifications but may also enhance the evaluation of coronary stents (11–13).

However, subtraction CCTA requires a long breath-holding time. This is because the two acquisitions required for subtraction are ideally obtained within a single breath-hold to minimize misregistration artifacts. Two previous feasibility studies, both using the test injection method for contrast administration, reported breath-holding times in the range of 20–40 seconds (5,6). In another feasibility study that used the bolus-tracking method, the breath-holding time was approximately 25 seconds, and the authors reported that subtraction CCTA could not be performed in some patients despite the administration of supplemental oxygen (7). As a consequence, patients unable to perform a breath-hold of around 30 seconds are frequently excluded from subtraction CCTA. This is an important limitation of subtraction CCTA in clinical practice because patients who are unable to perform a long breath-hold are typically older and have a greater likelihood of extensive calcifications.

Keeping in mind that precisely these patients may actually benefit the most from subtraction CCTA, reduction of the breath-holding time seems crucial. Recently, Kidoh et al used a test injection protocol to optimally time the pre- and postcontrast scans and shorten the breath-hold time to <20 seconds (14). However based on this particular scan protocol, it seems that further reduction of breath-hold time is unlikely (14). In the present preliminary study employing a modified subtraction CCTA approach, we have shown that by reversing the scan order in combination with bolus-tracking, the breath-holding time can be further shortened to approximately 13 seconds. This shortened breath-holding time represents a substantial reduction as compared to all previously reported methods (5–7,14), offering several important advantages.

First, the short breath-holding time makes subtraction CCTA a feasible option for patients with limited breath-hold capability. Consequently, the modified subtraction CCTA may extend the clinical application of subtraction to a wider number of patients, including patients who with conventional subtraction CCTA would have been excluded.

Second, a long breath-holding time increases the likelihood of misregistration artifacts due to changes of heart rate between postcontrast scan and mask scan. Close temporal proximity of the two scans on the other hand will minimize such artifacts. Therefore, the technical success rate should also be improved with the modified protocol.

This substantial reduction in the breath-holding time was achieved by acquiring the mask scan 10 seconds after the postcontrast scan, unlike previous acquisition methods in which the mask scan has always been acquired before the postcontrast scan. A potential concern of this reversed and shortened acquisition order is the presence of remaining coronary enhancement in the mask scan. Although the coronary arteries showed indeed mild enhancement in the mask image, the difference with the postcontrast scan was as such that they were still adequately opacified in the subtraction image. The average CT number of the coronary arteries in the subtraction images was approximately 280 HU, which is well in line with the SCCT (Society of Cardiovascular Computed Tomography) guidelines, which recommend an opacification of 250 HU (15). However, it is important that various parameters, such as cardiac output, can influence the geometry of the contrast bolus and thus affect the attenuation in the coronary arteries on subtraction CCTA images. Actually, it should be noted that intraarterial opacification below 250 HU was observed in two cases (16.7%). Inadequate intraarterial enhancement is one of the major limitations of the modified subtraction CCTA protocol. Increased transit time due to decreased cardiac output may cause inadequate coronary artery opacification on the subtraction images. Therefore, patients with heart failure or those with aortic or mitral valve disease should be imaged with caution. It is recommended to optimize the imaging methods including the contrast injection protocol and the time between the postcontrast scan and mask scan.

Another major limitation of subtraction CCTA in general is the increased radiation dose. The average radiation dose of the present study was 5.2 ± 2.2 mSv. Use of a different conversion factor, as suggested by Huda et al, would have resulted in an even higher estimate (16). The radiation dose of subtraction CCTA is higher than for conventional CCTA because subtraction CCTA requires to scan twice. Therefore, this method should be performed after careful consideration of the benefits versus risks for each individual case.

An important limitation of the current study is the small number of patients and evaluated coronary artery segments. The purpose of this small investigation was to obtain initial experience with our modified subtraction CCTA protocol and demonstrate its feasibility in patients unable to perform long breath-holds. As a next step, we will explore the diagnostic accuracy of the modified subtraction CCTA in patients with severe coronary artery calcifications and limited breath-holding capability by comparing to invasive coronary angiography.

CONCLUSIONS

The results of this preliminary study have shown that our modified subtraction CCTA method allows the breath-holding time to be shortened to <15 seconds. This shortening may substantially improve the success rate of subtraction CCTA by reducing artifacts and allowing this technique to be applied to patients who are unable to perform a long breath-hold.

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