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SHORT COMMUNICATION

Diagnostic accuracy of a modified subtraction coronary CT angiography method with short breath-holding time: a feasibility study

¹KUNIHIRO YOSHIOKA, MD, ¹RYOICHI TANAKA, MD, ¹HIDENOBU TAKAGI, MD, ²KYOUHEI NAGATA, MD, ³TAKUYA CHIBA, RT, ³KOUTA TAKEDA, RT, ³TAKANORI UEDA, RT, ³TSUYOSHI SUGAWARA, RT, ³AKINOBU SASAKI, RT, ³YUTA UEYAMA, RT, ³KEI KIKUCHI, RT and ³TADASHI SASAKI, RT

¹Division of Cardiovascular Radiology, Department of Radiology, Iwate Medical University, Morioka, Japan

²Division of Cardiology, Department of Internal Medicine, Iwate Medical University, Morioka, Japan

³Center for Radiological Science, Iwate Medical University Hospital, Morioka, Japan

Address correspondence to: Dr Kunihiro Yoshioka

E-mail: kyoshi@iwate-med.ac.jp

Objective: To explore the feasibility and diagnostic accuracy of modified subtraction coronary CT angiography (CCTA) with short breath-holding time in patients who have limited breath-hold capability and severe coronary artery calcification.

Methods: 11 patients with a coronary calcium score >400 underwent CCTA using a modified subtraction protocol. All patients were unable to hold their breath for more than 20 s. Subjective image quality using a four-point scale and the presence of significant (>50%) luminal stenosis were assessed for each calcified or stented segment on both conventional CCTA and modified subtraction CCTA images and compared with invasive coronary angiography (ICA) as the gold standard.

Results: The mean breath-holding time was 13.0 ± 0.9 s. A total of 35 calcified or stented coronary segments were evaluated. The average image quality was increased

from 2.1 ± 0.9 with conventional CCTA to 3.1 ± 0.7 with subtraction CCTA ($p < 0.001$). The segment-based diagnostic accuracy for detecting significant stenosis according to ICA revealed an area under the receiver-operating characteristic curve of 0.722 for conventional CCTA and 0.892 for subtraction CCTA ($p = 0.036$).

Conclusion: Modified subtraction CCTA allows the breath-holding time to be shortened to <15 s. As compared with conventional CCTA, modified subtraction CCTA showed improvement in image quality and diagnostic accuracy in patients with limited breath-hold capability and severe calcification.

Advances in knowledge: Modified subtraction CCTA can improve the diagnostic accuracy in patients with a high calcium score and patients who are unable to perform long breath-holds.

INTRODUCTION

The presence of severe coronary calcifications or stents remains one of the major challenges in coronary CT angiography (CCTA) and frequently results in reduced diagnostic accuracy for the evaluation of significant stenosis.^{1,2} Promising results have been reported applying subtraction CCTA using 320-detector row CT scanner in patients with severe calcifications or stents.^{3–8} With subtraction CCTA, coronary calcifications and stents are removed by subtracting mask image data (pre-contrast image data) from post-contrast image data. To minimize misregistration artefact due to differences in the breath-hold position, the required scans (mask and post-contrast scans) should be performed in a single breath-hold.³ Although this method may minimize misregistration artefacts, a long breath-holding time of approximately

20–40 s is required.^{3–8} This long breath-holding time represents a major limitation for subtraction CCTA because it may exclude patients who cannot hold their breath for over 20 s.

Recently, a modified subtraction CCTA method for patients with limited breath-hold capability was reported.⁹ It showed that the modified subtraction CCTA method can shorten the breath-holding time to <15 s. The objective of this study was to assess the feasibility of the modified subtraction CCTA with short breath-holding time. We evaluated the ability of the modified subtraction CCTA to improve calcified and stent segment interpretation compared with conventional CCTA, using invasive coronary angiography (ICA) as the gold standard.

METHODS AND MATERIALS

Patient population

This study received approval from the institutional review board, and written informed consent was obtained from all patients.

11 patients with suspected or known coronary artery disease and a coronary calcium score >400 (Agatston score) were prospectively enrolled in this study. All patients were unable to perform a breath-hold for over 20 s. They were clinically referred for CCTA, followed by ICA. The coronary calcium scoring scan had been performed just before CCTA. All 11 patients were ineligible for conventional subtraction CCTA owing to their limited breath-hold capability.

Modified subtraction coronary CT angiography with short breath-holding time

The scans were obtained with a 320-detector row CT scanner (Aquilion ONE ViSION Edition; Toshiba Medical Systems, Otawara, Japan) with a gantry rotation time of 275 ms. Images were obtained with 0.5-mm thickness by using kernel FC44, iterative reconstruction (Adaptive Iterative Dose Reduction 3D; Toshiba Medical Systems, Otawara, Japan) at standard mode.

Patients with heart rate >65 bpm received i.v. beta blockers (landiolol hydrochloride) (Ono Pharmaceutical, Osaka, Japan) at a rate of 0.125 mg kg^{-1} .

The imaging technique of modified subtraction CCTA with short breath-holding time has been reported previously.⁹ Contrast enhancement was performed with an iodinated contrast medium (iohexol 350) (Daiichi Sankyo Company, Tokyo, Japan) injected intravenously at a rate of $0.07 \times \text{body weight (in kilogram)} \text{ ml s}^{-1}$ in 9 s, followed by a 30-ml saline chaser bolus. The bolus-tracking method was used. When the CT number in the ascending aorta reached 150 HU, a breath-hold announcement was issued automatically. 2 s after the end of the announcement, the prospective electrocardiogram-gated scan was performed to acquire the post-contrast image. Then, the mask scan (with the same protocol as that for the post-contrast scan) followed, 10 s after the post-contrast scan within the same breath-hold. The overview of this imaging protocol is shown in Figure 1. The breath-hold times were recorded for all patients.

The tube voltage was 120 kV and the target noise for the tube current was set to 28 HU at 0.5-mm thickness. The acquisition phase window (padding) was 65–80% for patients with a heart rate ≤ 60 bpm and 35–80% for patients with a heart rate >60 bpm. For calcium scoring, the tube voltage was 120 kV, tube current was 300 mA and the padding was just 75%.

For image reconstruction, the optimal cardiac phase in which motion artefacts were minimal was identified visually on the post-contrast 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, Otawara, Japan). The subtraction images were obtained by subtracting the mask images from the post-contrast images (Figure 2).

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

The effective radiation dose was estimated based on the dose-length product (DLP) (in milligray $\times$ centimetre) using the formula

$$\text{Effective radiation dose} = \text{DLP} \times k$$

where $k = 0.014 \text{ mSv} \times \text{mGy}^{-1} \times \text{cm}^{-1}$.

Invasive coronary angiography

Clinically indicated ICA was performed within 50 days after CCTA using the standard technique. Quantitative coronary analysis (QCA) was performed using a software program (XA v. 7.1) (Medis Medical Imaging System, Leiden, Netherlands). Significant stenosis was defined as $>50\%$ luminal reduction of the maximum stenosis.

Image evaluation

Two experienced observers with more than 10 years' experience performed the evaluation. They were blinded to the results of ICA. Discrepancies were settled by consensus.

A workstation (Ziostation) (Ziosoft, Tokyo, Japan) was used for evaluation and to generate curved planar reformation images from conventional CCTA images and subtraction CCTA images.

Figure 2. The concept of modified subtraction coronary CT angiography (CCTA) method: (a) post-contrast image, (b) mask image and (c) subtraction image. The modified subtraction CCTA image (c) is obtained by subtraction of the mask image (b) from the post-contrast image (a). Although the coronary arteries show mild enhancement in the mask image (b), they are adequately opacified in the subtraction image (c). The linear and spotty calcifications are clearly eliminated (arrowheads). A small misregistration artefact is observed (arrows).

To determine coronary artery contrast opacification in the subtraction images, intra-arterial enhancement was evaluated as attenuation in Hounsfield units. It was measured in each patient by using the mean of three regions of interest placed at the origin of the right coronary artery and left main trunk, respectively.^{9,10} The regions of interest were set as large as possible. The procedure was repeated for the post-contrast and mask images.

Evaluation of image quality and diagnostic accuracy was performed in segments with severe calcifications or stents. Severe calcification was defined as more than one quadrant calcification on a cross-sectional image of conventional CCTA.⁵ Coronary segmentation was performed according to the American Heart Association classification.

The conventional and subtraction CCTA images were evaluated for image quality and the presence of significant stenosis, defined as >50% luminal narrowing. Curved planar reformation images and cross-sectional images were used for evaluation. During this process, both conventional and subtraction CCTA images were used to allow the subtraction CCTA images to be verified with the original contrast-enhanced images. Image quality was evaluated using a four-point scale method^{4,5,8,9,11} on conventional and subtraction CCTA images. Each segment was graded as score = 1 uninterpretable, evaluation not possible; score = 2 poor, severe artefacts limiting adequate evaluation of the segment; score = 3 moderate, some artefact present, but interpretation possible; or 4 good, good image quality without artefact. Scores of 1 or 2 were considered to reflect non-diagnostic quality.

Data and statistical analysis

We evaluated the data on a segment level. The average image quality scores between conventional and subtraction CCTA

images were compared using a paired *t*-test. The diagnostic vs non-diagnostic image quality frequencies were compared using McNemar's test. Interobserver agreement was assessed based on the proportion of agreement and the value of the kappa coefficient.

The conventional and subtraction CCTA diagnostic accuracies (sensitivity, specificity, positive-predictive value and negative-predictive value) for detecting significant stenosis (>50%) were assessed. ICA graded with QCA was used as the gold standard. To assess diagnostic accuracy, the area under the curve (AUC) of the receiver-operating characteristic (ROC) was calculated for both conventional and subtraction CCTA. The ROC analysis was performed using R v. 3.0.1 (The R Foundation for Statistical Computing) and pROC v. 1.7.3.¹² The Venkatraman method was used for the comparison of the two ROC curves. The statistical analysis, except ROC analyses, was performed using PASW® Statistics v. 21 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) for Microsoft Windows. All statistical analyses were performed with a 95% confidence interval (CI).

RESULTS

All 11 patients underwent both subtraction CCTA and ICA successfully. Patient characteristics are listed in Table 1. The average coronary calcium score was 898 ± 458 (range, 426–1775). Segments with stents were excluded from calcium scoring.

The average breath-holding time in this method was 13.0 ± 0.9 s (range, 12–14 s). In the post-contrast images, the coronary arteries were well enhanced, with an average CT number of 411.8 ± 78.7 HU. In the mask images, the coronary arteries showed mild enhancement, with an average CT number of

Table 1. Patient characteristics ($n = 11$)

Characteristics	Values
Age (years)	69.2 ± 10.0
Male (n)	5 (45.5%)
Body mass index (kg m^{-2})	25.9 ± 3.9
Coronary risk factors (n)	
Hypertension	8 (72.7%)
Diabetes	3 (27.3%)
Hypercholesterolemia	7 (63.6%)
Smoking	2 (18.2%)
Previous PCI	3 (27.3%)
Coronary calcium score (Agatston score)	
Mean $\pm$ SD	898 ± 458
Range	426–1775
HR at post-contrast scan (bpm)	59.5 ± 10.7
HR at mask scan (bpm)	59.2 ± 8.4
Use of beta blockade (n)	8 (72.7%)
Estimated effective radiation dose (sum of post-contrast and mask scans) (mSv)	5.5 ± 2.1
Breath-holding time (s)	13.0 ± 0.9
CT number of coronary arteries (HU)	
Post-contrast image	411.8 ± 78.7
Mask image	95.4 ± 21.6
Subtraction image	311.0 ± 64.2

HR, heart rate; PCI percutaneous coronary intervention; SD, standard deviation.

95.4 ± 21.6 HU. In the subtraction images, the coronary arteries were adequately opacified, with an average CT number of 311.0 ± 64.2 HU.

The average tube current was 344.5 ± 106.9 mA (range, 200–550 mA). The padding used was 65–80% in five cases and 35–80% in six cases. The DLPs of calcium scoring and subtraction CCTA (summation of post-contrast and mask scans)

were 115.1 ± 17.6 mGy cm (range, 89.4–146.1 mGy cm) and 392.8 ± 151.6 mGy cm (range, 192.9–714.6 mGy cm), respectively. The estimated effective radiation doses of calcium scoring and subtraction CCTA (summation of post-contrast and mask scans) were 1.6 ± 0.2 mSv (range, 1.3–2.1 mSv) and 5.5 ± 2.1 mSv (range, 2.7–10.0 mSv), respectively. A total of 35 segments, consisting of 29 calcified segments and 6 stent segments, were evaluated. The diameter of the stents was 3.5 mm in one segment, 3.0 mm in three segments and 2.5 mm in two segments. ICA revealed significant stenosis in 7 (63.6%) patients. Significant stenosis was observed in 11 (31.4%) of 35 evaluated calcified or stent segments. The median interval between CCTA and ICA was 27.5 ± 11.1 days (range, 10–49 days)

Conventional coronary CT angiography

The average image quality of conventional CCTA in all segments was 2.1 ± 0.9 (Table 2). A total of 17 (49%) segments were judged non-diagnostic, which was caused by severe calcification in 11 segments, stents in 4 segments and motion artefact in 2 segments. The interobserver kappa score for image quality score was 0.825. The AUC for conventional CCTA was 0.722 (95% CI, 0.563–0.880) for the diagnosis of a segment with stenosis of $>50\%$ as assessed by QCA (Figure 3). Segmental sensitivity, specificity, positive-predictive value, negative-predictive value and accuracy were 90.9, 54.2, 47.6, 92.9 and 65.7%, respectively (Table 3).

Subtraction coronary CT angiography

The average image quality of subtraction CCTA in all segments was 3.1 ± 0.7 (Table 2), which is significantly higher than that of conventional CCTA ($p < 0.001$). A total of 6 (17%) segments were judged non-diagnostic, which was caused by mis-registration artefact in all affected segments. The percentage of segments with non-diagnostic image quality of subtraction CCTA was significantly lower than that of conventional CCTA ($p < 0.001$). The interobserver kappa score for image quality score was 0.803. The AUC for the diagnosis of a segment with stenosis of $>50\%$ as assessed by QCA was 0.892 (95% CI, 0.773–1.000) (Figure 3), which was significantly higher than that for conventional CCTA ($p = 0.036$). Segmental sensitivity, specificity, positive-predictive value, negative-predictive value and accuracy were 90.9, 87.5, 76.9, 95.5 and 88.6%, respectively (Table 3).

Table 2. Image quality scores and percentages of diagnostic vs non-diagnostic image quality

Measure	Conventional CCTA	Subtraction CCTA	<i>p</i> -value
Image quality			
Score (mean ± SD)	2.1 ± 0.9	3.1 ± 0.7	<0.001
Interobserver kappa coefficient	0.825	0.803	
Segment percentages			
Diagnostic image quality	49%	83%	<0.001
Non-diagnostic image quality	51%	17%	

CCTA, coronary CT angiography; SD, standard deviation.

Figure 3. Area under the receiver-operating characteristic curves of conventional coronary CT angiography (CCTA) and subtraction CCTA vs invasive coronary angiography: the area under the curve (AUC) for conventional CCTA is 0.722 [95% confidence interval (CI), 0.563–0.880]. The AUC for subtraction CCTA is 0.892 (95% CI, 0.773–1.000).

Case examples are provided in [Figures 4 and 5](#).

DISCUSSION

This preliminary study has shown that modified subtraction CCTA with short breath-holding time improves diagnostic accuracy compared with conventional CCTA using ICA as a gold

Table 3. Diagnostic accuracy of conventional coronary CT angiography (CCTA) and subtraction CCTA (as per segment analysis) ($n = 35$)

Measure	Conventional CCTA	Subtraction CCTA
True positive	10	10
False positive	11	3
True negative	13	21
False negative	1	1
Sensitivity	90.9%	90.9%
Specificity	54.2%	87.5%
Positive-predictive value	47.6%	76.9%
Negative-predictive value	92.9%	95.5%
Accuracy	65.7%	88.6%
AUC (95% CI)	0.722 (0.563–0.880)	0.892 (0.773–1.000)
Interobserver kappa coefficient	0.814	0.807

AUC, area under the curve; CI, confidence interval.

standard in patients who cannot perform a breath-hold of over 20 s.

One of the major problems in CCTA is the presence of severe calcification and stents, which reduces diagnostic accuracy, sometimes making it impossible to assess the lumen. As a result, clinical guidelines recommend performing CCTA only in patients with a calcium score ≤ 400 .¹³ Subtraction CCTA has been shown to improve diagnostic accuracy over conventional CCTA in patients with a calcium score >400 .^{4,5} Recently, it has also been reported that subtraction CCTA was useful in patients with coronary stents.^{7,8}

However, subtraction CCTA requires a long breath-holding time. In subtraction CCTA, to minimize misregistration artefact due to differences in the breath-hold position, the two scans for obtaining the mask image (mask scan) and post-contrast image (post-contrast scan) should ideally be performed in a single breath-holding.³ A previous study using test injection method reported that breath-holding time is in the range of 20–40 s.⁵ Another study using test injection method reported by Kidoh et al¹⁴ demonstrated that they could shorten the breath-holding time to approximately 20 s. On the other hand, Amanuma et al^{6,7} reported that the breath-holding time was approximately 25 s using bolus-tracking method. They also described that subtraction CCTA could not be performed in some patients despite the administration of supplemental oxygen.⁶

Recently, modified subtraction CCTA with a short breath-holding time using bolus-tracking method was reported. Although this investigation confirmed that this method could shorten the breath-holding time to <15 s while providing diagnostic images, the diagnostic accuracy of the evaluation of significant stenosis itself was not evaluated.⁹ The purpose of this study therefore was to assess the diagnostic accuracy of the modified subtraction CCTA protocol with short breath-holding time in patients with limited breath-hold capability.

In line with the previous report,⁹ the modified subtraction CCTA protocol resulted in subtraction images with sufficient coronary enhancement and improved image quality as compared with conventional CCTA. In addition, a high diagnostic accuracy in detecting significant stenosis was demonstrated. The AUC of modified subtraction CCTA (0.892) was significantly higher than that of conventional CCTA (0.722) ($p = 0.036$). These results indicate that modified subtraction CCTA using short breath-holding method may have adequate accuracy in the diagnosis of significant stenosis at segment level.

This report has some limitations. The first major limitation of this study is the small patient population. Although the present study demonstrates the feasibility of modified subtraction CCTA in segment-based analysis, patient-based or vessel-based analysis cannot be made. As a next step, we will evaluate the diagnostic accuracy of modified subtraction CCTA in a larger patient population. Second, the radiation dose of subtraction CCTA is always higher than that of conventional CCTA, because subtraction CCTA requires scanning twice. Although we chose

Figure 4. A 73-year-old female with suspected coronary artery disease. (a) Conventional coronary CT angiography (CCTA): in the curved planar reformation (CPR) image of the left anterior descending artery, severe calcifications are hampering the assessment of the lumen (arrowhead). (b) Subtraction CCTA: in the CPR image at the same position as in (a), the severe calcifications are eliminated, making it possible to assess the lumen (arrowhead). No significant stenosis is depicted (arrowhead). (c) Invasive coronary angiography: no significant stenosis is demonstrated in the left anterior descending artery (arrowhead).

a tube voltage of 120 kV to avoid beam-hardening artefact in these patients with calcification and stents, the use of lower tube voltage scanning will be effective for radiation dose reduction. Another approach to reducing the radiation dose of subtraction CCTA is to apply a two breath-hold method.³ This method uses the images for calcium scoring as the mask images. An advantage of this technique is that no additional radiation is required for subtraction if calcium scoring is already performed for all patients who undergo CCTA. The main disadvantage of this method is that there is a high likelihood of misregistration artefacts because the two breath-holding positions do not exactly match. Fuchs *et al*¹⁵ reported that misregistration artefacts were

seen in approximately half of the target segments in two breath-hold subtraction CCTA. Third, the mean coronary calcium score in this study was only 898. Further study is needed to explore the feasibility of modified subtraction CCTA in patients with very high calcium scores.

CONCLUSION

The results of this preliminary study show that the modified subtraction CCTA method improves diagnostic accuracy, as compared with conventional CCTA, at segment-based analysis in patients with severe coronary artery calcifications and limited breath-holding capability.

Figure 5. A 70-year-old male with known coronary artery disease. (a) Conventional coronary CT angiography (CCTA): in the curved planar reformation (CPR) image of the posterolateral branch of left circumflex artery, a small-diameter stent (2.5 mm) (MULTI-LINK MINI VISION; Abbot Vascular Japan, Tokyo, Japan) is present, which is non-interpretable (arrow). The distal portion of the branch also cannot be evaluated because of nodular calcifications (arrowhead). (b) Subtraction CCTA: in the CPR image at the same position as in (a), the stent and calcifications are eliminated. In-stent restenosis (arrow) could be ruled out, while severe stenosis in the distal portion of the branch was demonstrated (arrowhead). (c) Invasive coronary angiography is confirming the findings of subtraction CCTA (arrow and arrowhead).

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