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The usefulness of subtraction coronary computed tomography angiography for in-stent restenosis assessment of patients with CoCr stent using 320-row area detector CT

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Abstract

The aim of this study was to assess in-stent restenosis (ISR) of coronary artery for patients with CoCr stent using subtraction coronary computed tomography angiography (CCTA) with one-breath-hold scan on 320-row area detector CT, invasive coronary angiography (ICA) as clinical standard.

Patients who were referred for CCTA from January 2020 to May 2021 were retrospectively analyzed. Pre-contrast and CCTA was performed with dedicated one-breath-hold subtraction scan protocol and post processing to get subtracted-CCTA image without stent. Subjective image qualities and diagnosable rate were analyzed for CCTA and subtracted-CCTA respectively. The ISR degree of each stent was evaluated both on CCTA and subtracted-CCTA images. The receiver-operating characteristic curve with sensitivity, specificity, accuracy of CCTA, and subtracted-CCTA in the diagnosis of ISR were calculated with ICA as reference.

Forty patients with 85 CoCr coronary stents of 3 to 3.5 mm diameter with ICA confirmation within 1 month were finally included. Subtracted-CCTA showed more diagnosable segments of stent (91.76% [78/85]) than those of CCTA (50.59% [43/85]) ($P < .001$). The subjective image quality score of CCTA was 2.23 ± 1.32 while 3.41 ± 0.90 on subtracted-CCTA ($P < .001$). Both subtracted-CCTA and CCTA showed high consistency with ICA (Kappa = 0.795 and 0.918 respectively). The area under the curve was 0.607 for CCTA and 0.757 for subtracted-CCTA ($P < .001$) for stent based diagnose, respectively. The sensitivity, specificity, accuracy of CCTA, and subtracted-CCTA were 90.0%, 97.0%, 95.3%, and 87.5%, 100.0%, 97.43%, respectively.

Subtracted-CCTA showed improved diagnose performance for ISR, which potentially reduce further follow-up ICA procedures for patients with CoCr stents.

Abbreviations: CCTA = coronary computed tomography angiography, CT = computed tomography, CTDIvol = CT dose index, DLP = dose length product, ICA = invasive coronary angiography, ISR = in-stent restenosis.

Keywords: coronary computed tomography angiography, in-stent restenosis, invasive coronary angiography, subtraction

1. Introduction

Percutaneous coronary intervention is the most common treatment procedure performed worldwide in patients with coronary artery disease, especially for those patients need stent for revascularization.[1–3] Normally, patients previously treated with stent often have high possibilities to show atherosclerotic burden of non-treated coronary segments. If both have severe or tandem calcifications and stents, performance of coronary computed tomography angiography (CCTA) further reduced.[4–6] The gold standard for the evaluation of in-stent restenosis (ISR) in clinical is invasive coronary angiography (ICA). However, most of patients are willing to have non-invasively and efficiently assessment of ISR. Previous studies revealed the diagnostic performance of ISR using conventional CCTA was not satisfied even with improvement of image qualities using new scanner detectors.[7] With development of deformable registration algorithm, subtracted-CCTA could successfully remove stents and calcification from CCTA in order to better lumen visualization, and several studies investigated the performance of subtraction for calcification and stents with typical metal materials.[8–10] Recently, with government medical insurances policy changes to encourage using national vendors of stent with lower price, more and more patients were treated with Rapamycin-eluting coronary CoCr stents system in China.[11] Therefore, the aim of this study was to assess diagnostic performance of ISR using subtracted-CCTA for patients with CoCr stent, using ICA as reference standard.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Materials and methods

2.1. Patient population

Patients with previous stents treatment history who were referred for CCTA from January 2020 to May 2021 were retrospectively included. The inclusion criteria were: with Rapamycin-eluting coronary CoCr stent and ICA within 1 month. The exclusion criteria were: contraindications for iodinated contrast material, history of cardiac surgery, arrhythmia, heart failure, aortic stenosis, intolerance to beta-blockers and body mass index >35 kg/m^2. This study was approved by the institutional review board.

2.2. CCTA protocol

Both pre-contrast scan and contrast CCTA scan of each patient were performed using a 320-row area detector CT (Aquilion ONE Vision Edition, Canon Medical Systems Corp., Otawara, Japan). Patients received an oral beta-blocker (metoprolol, 20–50 mg) up to 3 hours before the scan, for those with a heart rate ≥65 bpm additionally received beta-blocking medication prior to scanning. One-breath-hold protocol was applied for pre-contrast and post-contrast scan. Therefore, test bolus was scanned at first. The test bolus was injected for 2 seconds, followed by a 0.9% saline solution for another 5 seconds. During the subsequent 8 seconds of waiting, a 5 seconds breath-holding instruction was performed. Then pre-contrast and post-contrast were scanned. And the time elapsed for 6 seconds between pre-contrast and post-contrast CCTA scanning. Patients were asked to hold breath during both pre- and post-contrast scanning for once. The main bolus injection for 7 seconds was automatically started, followed by injection of a saline solution for 7 seconds.[12,13] The iodine contrast medium (370 mgI/mL, iopamidol 370, Bayer AG, Germany) was injected via antecubital vein at a rate of body weight (kg) × 0.07, the total amount of main bolus injection injected was weight (kg) × 0.49–0.7 mL. After the injection of contrast medium, 40 mL of normal saline solution was immediately flushed at the same rate.

The acquisition parameters were: gantry rotation speed of 0.275 s/rot, 100 kVp for tube voltage, tube current using automatic exposure control function with a target image noise level of standard deviation 28. The scan range was set to the minimum size that included the coronary arteries in their entirety. In all patients, the prospective one-beat CTA mode targeting the mid-diastole was used with the cardiac phase for scanning set to 75% to 80% of the R–R interval. Adaptive iterative dose reduction (Canon Medical Systems) with kernel FC43 was applied for image reconstruction of slice thickness 0.5 mm with interval 0.25 mm.

Both pre- and post-contrast images were imported to the dedicated post-processing software of $^{\text{SURE}}$Subtraction Coronary (Canon Medical Systems) to obtain subtracted-CCTA images.[14] Stent showed high attenuation on both images which could be served as marker point for rigid registration, meanwhile the deformable registration based on mask of heart were further applied to get rid of motion and deformation of heart between pre- and post-contrast images. Finally, the heart, coronary, and stent were successfully registered. With subtraction process, stent was removed by subtracting 3D data of pre-contrast image from post-contrast images. The software provided semi-manual mode for radiologist to make sure best registration of 2 images.

2.3. Subjective image quality assessment

Subjective image quality was assessed using a 4-point scale both on CCTA and subtracted-CCTA images. The grading scales are: uninterpretable: evaluation not possible; poor: severe artifacts limited adequate evaluation of the segment (low reader confidence); moderate: some artifacts present but interpretation possible (moderate reader confidence); good: good image quality without artifacts (high reader confidence). Scores of 1 or 2 were considered as unreadable image quality, whereas scores of 3 and 4 were with diagnosable image quality. Two radiologists with 5 (M.H.) and 11 years (X.Y.) of experiences in cardiac radiology assessed all images. Any discrepancy between the observers was settled by consensus.

2.4. Radiation exposure

The effective radiation dose was estimated with CT dose index (CTDIvol) and the dose length product (DLP) multiplied by a conversion coefficient for the chest (0.014 mSv/mGy/cm), CTDIvol and DLP of each patient was recorded. The total dose of each patient was calculated for the sum of pre-contrast and post-contrast scan.

2.5. ICA procedure

In all patients, diagnostic ICA (Artis Zee, Siemens Healthineers, Forchheim, Germany) was performed within 30 days after CCTA examination by certified interventional cardiologists. Each stent segment was evaluated with 2 different DSA angles for accurate diagnose of ISR, <50% diameter stenosis as mild, 50% to 75% stenosis as moderate, >75% stenosis as severe stenosis.

2.6. Statistical analysis

Statistical analysis was performed with SPSS version 17 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). The subjective image quality scores were compared using a Wilcoxon signed-rank test, the diagnosable rate was analyzed using McNemar test. The consistency of subtracted CCTA and conventional CCTA with ICA for stenosis evaluation was assessed by Kappa test. To assess diagnostic performance of CCTA and subtracted CCTA, sensitivity, specificity, and diagnostic accuracy versus ICA as standard of references were calculated. A P value <.05 was considered statistically significant.

3. Results

Forty patients with 85 CoCr stents were finally included. The mean age of patients were 64.67 years (range, 46–82 years) with mean body mass index 24.96 kg/m^2, and the heart rate was 58.45 ± 2.89 bpm (Table 1). The diameter range of stent was 3.0 to 3.5 mm with length range is 18 to 23 mm. The mean radiation dose was 18.1 ± 2.12 mGy, 240.12 ± 48.43 mGy cm, 3.36 ± 0.67 mSv for CTDIvol, DLP, and effective dose respectively. Images of a 59-year-old man with left circumflex coronary (LCX) CoCr stent implantation (3 mm diameter and 36 mm length) were illustrated in Fig. 1. The curved planar reformation on CCTA image of the LCX is non-interpretable due to heavy artifacts of the stent. While the stent was removed using $^{\text{SURE}}$Subtraction postprocessing and coronary lumen was clearly showed on subtracted CCTA, no ISR was depicted.

Table 1

Patient characteristics.

Characteristics	Value
Age, yrs	
Mean ± SD	64.67 ± 10.59
Range	42–86
Sex (n)	
Men	23 (57.50%)
Women	17 (42.50%)
Body mass index	24.96 ± 2.97
Number of coronary stents implanted	85
CCTA HR beats/min	
Mean ± SD	58.45 ± 2.89
Range	52–63
Coronary risk factors (n)	
Hypertension	29 (72.50%)
Diabetes	23 (57.50%)
Cholesterolemia	22 (7.50%)
Smoking	21 (52.5%)
Mean ± SD	3.08 ± 0.42
Range	2.32–4.86

CCTA = coronary computed tomography angiography, HR = heart rate, SD = standard deviation.

The interobserver insistences of subjective image quality were 0.896 and 0.915 for CCTA and subtracted-CCTA respectively, the subjective image qualities of subtracted-CCTA were significantly better than that of CCTA (2.23 ± 1.32 vs 3.41 ± 0.90, $P < .001$) (Table 2). Subtracted-CCTA images showed 91.76% (78/85) segments were diagnosable, which was significantly higher than CCTA (50.59% [43/85]). There were 7 target segments of subtracted-CCTA classified as non-diagnosable due to misregistration artifacts of deformable registration algorithm.

Table 2

Subjective imaging quality and diagnosable rate.

Measure	CCTA	Subtracted-CCTA	*P* value
Imaging quality			
Scores (mean ± SD)	2.23 ± 1.32	3.41 ± 0.90	<.001
Interobserver kappa scores	0.896	0.915	
Diagnosable rate			
Diagnosable segments	50.59%(43/85)	91.76%(78/85)	<.001
Non-diagnosable segments	48.41%(42/85)	8.24%(7/85)	

CCTA = coronary computed tomography angiography, SD = standard deviation.

There were 43 diagnosable segments of CCTA, 36 (83.7%) of them were diagnosed correctly with ICA as reference. Among them 30 segments without ISR were observed, 28 segments were confirmed with ICA, while remaining 2 segments were confirmed by ICA as mild and severe stenosis. Three segments with mild stenosis of CCTA, 1 segment was consistence with ICA, while 2 segments were without ISR revealed by ICA. One mild stenosis was misdiagnosed as moderate ISR using CCTA. There were 9 segments were severe stenosis with conventional CCTA, among them 7 were confirmed of ICA, 2 segments were moderate stenosis (Table 3).

For 78 diagnosable segments of subtracted CCTA, 73 (93.6%) were successfully diagnosed using ICA as standard. Forty-nine segments showed no ISR using subtracted CCTA, only one was confirmed with ICA as mild stenosis. There were 13 segments with mild ISR, only one was no ISR revealed by ICA. There segments with moderate stenosis were observed, 2 confirmed as mild stenosis with ICA. Thirteen segments were diagnosed as severe using subtracted CCTA, 11 of them confirmed by ICA while 2 were moderate restenosis (Table 4).

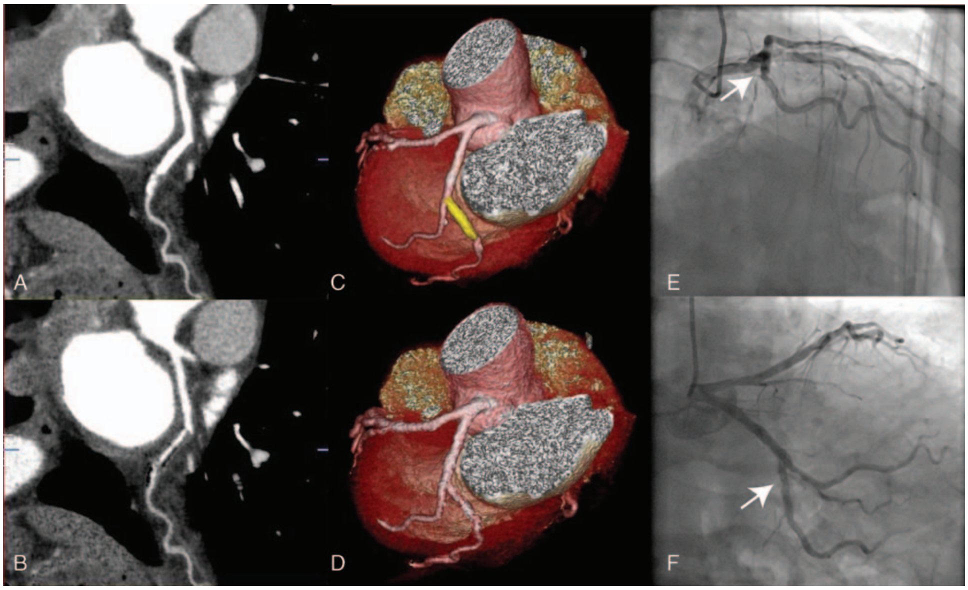

Figure 1. A 59-year-old man with left circumflex coronary (LCX) stent implantation (diameter: 3 mm, length: 36 mm, Rapamycin-eluting coronary CoCr stents, Shanghai MicroPort Medical [Group] Co. Ltd., China). (A) CCTA. The curved planar reformation (CPR) image of the LCX is non-interpretable (arrow) for coronary lumen due to heavy artifacts of the stent. (B) Subtracted-CCTA. CPR at the same position as in (A). The stent was removed using ^{SURE}Subtraction postprocessing and clearly showed coronary lumen, no ISR is depicted (arrow). (C) and (D) were corresponding volume rendering image for CCTA and subtracted-CCTA respectively. The yellow part of LCX in (C) indicated implanted stent. (E) and (F) Invasive coronary angiography (ICA) with 2 angels. No stenosis was demonstrated in the LCX.

Table 3

The diagnose of ISR using CCTA.

	ICA				
CCTA	No stenosis	Mild stenosis	Moderate stenosis	Severe stenosis	Sum
No stenosis	28	1	1	0	30
Mild stenosis	2	1	0	0	3
Moderate stenosis	0	1	0	0	1
Severe stenosis	0	0	2	7	9
Sum	30	3	3	7	43

CCTA = coronary computed tomography angiography, ICA = invasive coronary angiography, ISR = in-stent restenosis.

Receiver-operating characteristic curve results indicated the area under the curve was 0.607 (0.434–0.779) for CCTA and 0.757 (0.580–0.934) for subtracted CCTA ($P < .001$) for stent-based diagnose, respectively. The sensitivity, specificity, accuracy of CCTA and subtracted-CCTA were 90.0%, 97.0%, 95.3% respectively, and 87.5%, 100.0%, 97.43%, respectively.

4. Discussion

The results in this study revealed that for patients with Rapamycin-eluting coronary CoCr stents, stent-based diagnosable rate, and diagnosis accuracy of ISR significantly improved by subtracted CCTA.

Although CCTA is the indispensable method for coronary artery lumen assessment easily and noninvasively for coronary artery disease, there are remain limitations for its diagnostic accuracy especially for patients with calcification and stents, which are high-absorption materials lead to partial volume effects or blooming artifacts for difficult evaluation of coronary lumen.[15] It is expected to eliminate high-density areas other than contrast enhancement for best to evaluate coronary lumen. High energetic (kev) image from dual energy CT could potentially reduce artifacts from stent, but with limitation effect.[16,17] The ideal solution is expected to get rid of stent and its artifacts completely and to show lumen clearly. Subtraction has been reported useful to eliminate calcification or coils in the head and neck, lower extremities for evaluating arteries by performing subtraction of pre-contrast image from post-contrast image.[18,19]

Previous studies have reported diagnostic improvement with subtracted-CCTA for patients with server calcification,[20–22] only limited reports of ISR with typical materials of stent.[8,23] This study focused on investigation of subtracted-CCTA for ISR of national Rapamycin-eluting coronary CoCr stents in China. Although, in order to minimize motion-related misregistration, one-breathe hold was applied, patients who were capable for 25 seconds and heart-rate lower 65 bpm were included, 7 stents showed misregistration in total 85 stents. The possible reason for misregistration was significant deformation between pre- and post-contrast scanning.

The non-diagnosable stents reduced from 42 to 7 for subtracted-CCTA, which was consistence with previous reports.[23] For these stents, due to blooming artifacts radiologist' diagnose confidence of CCTA was low and with potential higher possibilities for positive ISR to avoid false negative as far as possible. However, with successfully elimination of stent with subtraction, diagnose confidence significantly improved. This study applied grade analysis of stenosis, majorly dependent on confidence of radiologist. With confidence improvement of subtracted-CCTA, diagnose performance apparently improved.

There were several limitations in this study. First, patients with stent implantation within 3 to 6 months were included in this study which might lead to fewer stents showed ISR. Second, only Rapamycin-eluting coronary CoCr stents with 3.0 to 3.5 diameter and 18 to 23 mm length were analyzed, the results did not reflect stents with other materials and size which might result in much more server artifacts for misdiagnose of ISR. Furthermore, more patients with stent implantation much longer time and diverse types of stents should be recruited for deeply studied. Third, high heart-rate and obese patients need to be further investigated. Fourth, quantitative stenosis degree of CCTA and subtracted-CCTA both on diameter and area should be calculated for further diagnose performance evaluation. Finally, the presence of ISR might not indicate hemodynamic ischemia of myocardium, further functional assessment of myocardium should be considered as gold standard to assess the functional value of subtracted-CCTA compare with CCTA, such as CT derived fractional flow reserve (CT-FFR).

5. Conclusion

The subtracted-CCTA with one-breath-hold scanned on 320-row area detector improved diagnostic performance of ISR, which potentially reduce further ICA procedures for patients with CoCr stents.

Table 4

The diagnose of ISR using subtracted-CCTA.

Subtracted-CCTA	ICA				
	No stenosis	Mild stenosis	Moderate stenosis	Severe stenosis	Sum
No stenosis	48	1	0	0	49
Mild stenosis	1	12	0	0	13
Moderate stenosis	0	2	1	0	3
Severe stenosis	0	0	2	11	13
Sum	49	15	3	11	78

CCTA = coronary computed tomography angiography, ICA = invasive coronary angiography, ISR = in-stent restenosis.

Author contributions

Conceptualization: Jian Li, Minggang Huang.
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