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

Jian Li, MDa,*, Man-Tao Guo, MDab, Xiao Yang, MDa, Fang Gao, MDa, Na Li, MDa, Ming-Gang Huang, MDa

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
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/m². 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. The iodine contrast medium (370mgI/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) × 0.49–0.7mL. After the injection of contrast medium, 40mL of normal saline solution was immediately flushed at the same rate.

The acquisition parameters were: gantry rotation speed of 0.275 s/rot, 100kVp 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 SURESubtraction Coronary (Canon Medical Systems) to obtain subtracted-CCTA images. 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 (0.014mSv/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/m², and the heart rate was 58.45 ± 4.89 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 mGycm, 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 reformnation on CCTA image of the LCX is non-interpretable due to heavy artifacts of the stent. While the stent was removed using SURESubtraction postprocessing and coronary lumen was clearly showed on subtracted CCTA, no ISR was depicted.
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.

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).

**Table 1**

| 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 (5.50%)              |
| 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.

**Table 2**

| Measure                      | CCTA     | Subtracted-CCTA | P value |
|------------------------------|----------|-----------------|---------|
| Imaging quality              | Scores   | 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.

The 50-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 SURESubtraction 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.
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 diagnosis, 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.\cite{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.\cite{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.\cite{18,19}

Previous studies have reported diagnostic improvement with subtracted-CCTA for patients with server calcification,\cite{20–22} only limited reports of ISR with typical materials of stent.\cite{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-breath 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.\cite{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 3 | The diagnose of ISR using CCTA. |
| 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 | 1 | 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.

| Table 4 | The diagnose of ISR using subtracted-CCTA. |
| Subtracted-CCTA | 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.
Data curation: Jian Li, Mantao Guo, Xiao Yang, Fang Gao.
Software: Fang Gao.
Writing – original draft: Jian Li.
Writing – review & editing: Na Li, Minggang Huang.

References
[1] Lee MS, Banka G. In-stent restenosis. Interv Cardiol Clin 2016;5:211–20.
[2] Canfield J, Totary-Jain H. 40 years of percutaneous coronary intervention: history and future directions. J Pers Med 2018;8:33.
[3] Brilakis ES, Mashayekhi K, Tsuchikane E, et al. Guiding principles for chronic total occlusion percutaneous coronary intervention. Circulation 2019;140:420–33.
[4] Juan YH, Huang YC, Sun Z, et al. The evolution and investigation of native coronary arteries in patients after coronary stent implantation: a study by 320-detector CT angiography. Int J Cardiovasc Imaging 2014;30(suppl):13–24.
[5] Nakashiki R, Motoyama S, Leipsic J, et al. How accurate is atherosclerosis imaging by coronary computed tomography angiography? J Cardiovasc Comput Tomogr 2019;13:254–60.
[6] Nogourani MK, Moradi M, Khajouei AS, et al. Diagnostic value of intraluminal stent enhancement in estimating coronary in-stent restenosis. J Clin Imaging Sci 2020;10:12.
[7] Pugliese F, Weissink AC, Van Mieghem C, et al. Dual source coronary computed tomography angiography for detecting in-stent restenosis. Heart 2008;94:848–54.
[8] Fuchs A, Kuhl JT, Chen MY, et al. Feasibility of coronary calcium and stent image subtraction using 320-detector row CT angiography. J Cardiovasc Comput Tomogr 2015;9:393–8.
[9] Zhu Z, Razeto M, Matthews J, et al. Accurate registration of coronary arteries for volumetric CT digital subtraction angiography. Proc SPIE 8768, International Conference on Graphic and Image Processing (ICGIP 2012) 2013;876834.
[10] Ourselin S, Styner MA, Razeto M, et al. Accurate, fully-automated registration of coronary arteries for volumetric CT digital subtraction angiography. ProcSPIE 9034, Medical Imaging 2014;90343F.
[11] Tian J, Tang YD, Qiao S, et al. Two-year follow-up of a randomized multicenter study comparing a drug-coated balloon with a drug-eluting stent in native small coronary vessels: the RESTORE small vessel disease china trial. Catheter Cardiovasc Interv 2020;95(suppl):587–97.
[12] Yamaguchi T, Ichikawa K, Takahashi D, et al. A new contrast enhancement protocol for subtraction coronary computed tomography requiring a short breath-holding time. Acad Radiol 2017;24:38–44.
[13] Yoshioka K, Tanaka R, Nagata K, et al. Modified subtraction coronary CT angiography method for patients unable to perform long breath-holds: a preliminary study. Acad Radiol 2016;23:1170–5.
[14] Takamura K, Fujimoto S, Kawaguchi Y, et al. The usefulness of low radiation dose subtraction coronary computed tomography angiography for patients with calcification using 320-row area detector CT. J Cardiovasc Imaging 2019;73:38–64.
[15] Abdulla J, Pedersen KS, Budoff M, et al. Influence of coronary calcification on the diagnostic accuracy of 64-slice computed tomography coronary angiography: a systematic review and meta-analysis. Int J Cardiovasc Imaging 2012;28:943–53.
[16] Kay FU. Dual-energy CT and coronary imaging. Cardiovasc Diagn Ther 2020;10:1090–107.
[17] Albrecht MH, De Cecco CN, Schoepf UJ, et al. Dual-energy CT of the heart current and future status. Eur J Radiol 2018;105:110–8.
[18] Meijer FJA, Schuif JD, de Vries J, et al. Ultra-high-resolution subtraction CT angiography in the follow-up of treated intracranial aneurysms. Insights Imaging 2019;10:2.
[19] Ma G, Yu Y, Duan H, et al. Subtraction CT angiography in head and neck with low radiation and contrast dose dual-energy spectral CT using rapid kV-switching technique. Br J Radiol 2018;91:20170631.
[20] Amanuma M, Kondo T, Sano T, et al. Subtraction coronary computed tomography in patients with severe calcification. Int J Cardiovasc Imaging 2015;31:1635–42.
[21] Fuchs A, Kuhl JT, Chen MY, et al. Subtraction CT angiography improves evaluation of significant coronary artery disease in patients with severe calcifications or stents-the C-Sub 320 multicenter trial. Eur Radiol 2018;28:4077–85.
[22] Vilades Medel D, Leta R, Alomar Serralach X, et al. Reliability of a new method for coronary artery calcium or metal subtraction by 320-row cardiac CT. Eur Radiol 2016;26:3208–14.
[23] Amanuma M, Kondo T, Sano T, et al. Assessment of coronary in-stent restenosis: value of subtraction coronary computed tomography angiography. Int J Cardiovasc Imaging 2016;32:661–70.