Eur Radiol (2016) 26:3208–3214
DOI 10.1007/s00330-015-4130-4

CARDIAC

Reliability of a new method for coronary artery calcium or metal subtraction by 320-row cardiac CT

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Received: 25 June 2015 / Revised: 17 November 2015 / Accepted: 19 November 2015 / Published online: 10 December 2015

Abstract
Purpose To investigate the feasibility and diagnostic accuracy of subtraction CTA on patients with highly calcified coronary artery disease (CAD) or previous implanted stents, in comparison with invasive coronary angiography (ICA).
Materials and methods Twenty-three patients were recruited. All conventional and subtraction CTA exams were performed using a 320-row CT. Subjective image quality score was assessed for each segment using a 4-point scale: 1-uninterpretable to 4-good image quality.
Results A total of 129 calcified or stented coronary segments were studied. Mean coronary image quality with conventional CTA was 2.73±0.97 and in subtracted CTA 3.3±0.92 ($p<0.01$). After metal subtraction, image quality in stented coronary segments with >3 mm of diameter improved from 2.69±0.97 to 3.34±0.89 ($p=0.01$) and in those with <3 mm of diameter from 2.11±0.78 to 2.67±0.87 ($p=0.17$). There was an improvement in diagnostic accuracy to detect ICA stenosis >50 % by subtraction CTA compared with conventional CTA (AUC 0.93 to 0.87; $p=0.02$).
Conclusion Subtraction CTA is promising in overcoming limitations of conventional CTA due to calcium or metal artefacts, especially if no motion artefact is present or when stents>3 mm are studied.

Key Points
- *Calcium and metal artefacts are still a limitation for conventional coronary CTA*
- *Diagnostic accuracy is improved by subtraction as compared with conventional CTA*
- *Subtraction CTA is a promising tool to overcome limitations of conventional CTA*

Keywords Cardiac CTA · Subtraction CTA · Artefact · Coronary calcium subtraction · Metal stents

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Introduction

Computed tomography angiography (CTA) of the coronary arteries is a useful non-invasive technique to assess the presence and degree of coronary artery disease (CAD). Recent guidelines on stable CAD [1] and non-ST segment elevation myocardial infarction [2] endorse the use of CTA in symptomatic patients with low to intermediate likelihood of the disease, given the particularly high negative predictive value of the technique. However, in patients with high pre-test likelihood of CAD, the technique is not recommended because of the presumably high amount of calcium in the vessel wall, which interferes with the analysis of the images. This reduces specificity and negative predictive value [3–6] and increases false positive results [7, 8]. Likewise, in stented segments, the visualization of in-stent restenosis remains challenging due to metal artefacts, especially in smaller stents, thus increasing the number of false negative results [9, 10]. The introduction of new-generation CT systems with wide-coverage scanners has made possible obtaining highly accurate non-invasive coronary angiography in a single beat [11, 12]. In spite of these technological advances, improving both spatial and temporal resolution, the presence of small stents or extensive coronary artery calcification are still unsolved relevant issues.

A recently developed new software (SURESubtraction™ Coronary, Toshiba Medical Systems, Otawara, Japan) allows for the removal of the high density signal of calcium and metal stents in the coronary arteries, this improving the diagnostic performance of CTA studies [13].

In this study, we investigate the potential improvement in diagnostic accuracy of subtraction CTA over conventional CTA for the detection and quantification of coronary artery stenosis in comparison with invasive coronary angiography (ICA) as a gold standard, on a series of patients with highly calcified coronary artery plaques or implanted stents.

Methods

Patient population

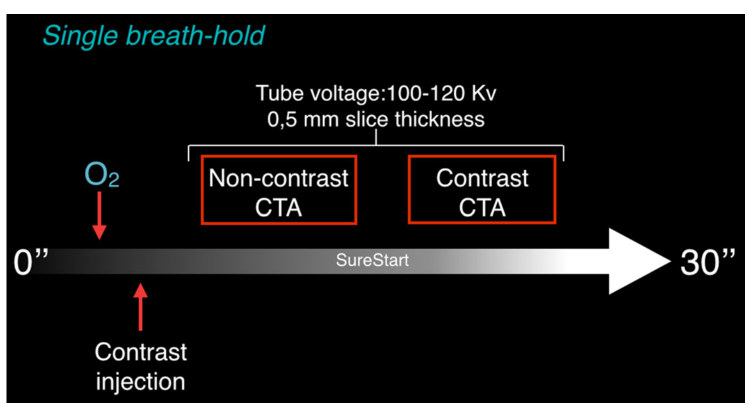
From November 2013 to August 2014, patients with proven CAD at a recent ICA were considered for the study. Selected were those patients with radiological evidence of calcified CAD and/or previous implanted stents. Excluded were those presenting with allergy to iodinated contrast, non-sinus rhythm, creatinine clearance <30 mL/min/m2, intolerance to beta-blockers, inability to perform a 30-second breath-hold, or body mass index >40 kg/m^2. All patients with these conditions agreed to take part in the study and signed an informed consent. Study protocol was approved by the institutional review board of our hospital.

CTA data acquisition

CTA exams were performed using a 320-row CT (Toshiba Aquilion One TM, Toshiba Medical Systems, Otawara, Japan). Patients were treated with low-flow oxygen during the scan and those with heart rate >65 beats/min received intravenous b-blocker therapy before CTA. The acquisition protocol was as follows: at the start of contrast injection, a first scan is obtained, before the arrival of contrast to the left heart chambers, which is followed by a second scan, this triggered by bolus track technique guided by a region of interest at the descending aorta (Fig. 1). Both studies are performed during the same breath-hold and prospectively triggered between 30-80 % of the RR interval using the following parameters: collimation 320×0.5 mm, and rotation time 350 milliseconds. The tube current used was 320-530 and voltage 100 to 120 kV. A contrast dose of 1 ml/kg (Xenetix 350, Guerbet, Aulnay-sous-Bois, France) was used in the contrast study followed by a saline flush of 40 ml, both injected at a rate of 6 ml/s (mean volume of contrast administered was 88.7± 11.7 ml). The effective radiation dose from CTA was calculated as the dose-length product times a conversion coefficient for chest [k=0.014 mSv/(mGy×cm)] [14].

The two datasets are subsequently registered and the non-contrast CTA volume is then subtracted from the contrast CTA volume removing the high-density signal from calcium/metal in the coronary arteries (Fig. 2).

The 11.0 software version (release SP0002) was used, which includes a novel dose reduction technology (Adaptive Iterative Dose Reduction 3D, AIDR 3D, Toshiba Medical Systems) as well as a 6.0 $^{\text{SURE}}$Subtraction™ Coronary software version (release SP0505G; Toshiba Medical Systems). Images were reconstructed at 0.5 mm slice thickness with 0.3 mm overlap. Systolic and diastolic phases (every 5 % of RR interval) with the least motion were routinely reconstructed with standard kernel (FC43). Agatston coronary calcium score was calculated from non-contrast CT scans using the Agatston method [15] and standardized software (VScore, Vitrea Fx 6.4.3; Vital Images, Plymouth, MN). A 16-coronary artery segment model according to the American Heart Association (modified 15-segment model, being segment 16 the intermediate branch) [16] constituted the basis for visual/quantitative assessment of coronary artery stenosis. All data sets were analyzed on an off-line workstation (Vitrea Fx 6.4.3; Vital Images) by blinded to ICA level-3 cardiac



0_2: low-flow oxygen; CTA: Computed Tomography Angiography; Kv: kilovoltage

Fig. 1 Methodology for imaging acquisition for computed tomography angiography subtraction

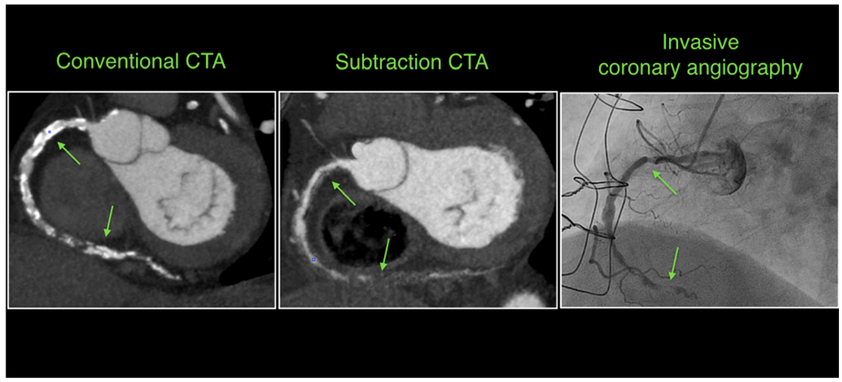


Fig. 2 Example of subtraction in comparison with conventional computed tomography angiography and invasive coronary angiography

computed tomography reader (DVM) [17]. Subjective image quality was assessed for each calcified or stented segment on axial images and curved multiplanar reconstruction using a 4-point scale: 1-uninterpretable, 2-poor image quality, 3-fair image quality and 4-good image quality. Those segments with ≤2 points were deemed as non-diagnostic and considered as corresponding to a significant stenosis for subsequent analyses.

Assessment of diagnostic accuracy

Mean time between ICA and subtraction CTA was 95± 60 days. ICA was performed using standardized angiographic techniques and used as a reference for correlation with conventional and subtraction CTA studies. Coronary artery segments were visually assessed for >50 % stenosis and estimated by quantitative coronary angiography (QCA) in ICA and CTA. Significant coronary stenosis was defined on QCA as a luminal diameter narrowing >50 % of the reference luminal diameter.

Statistical analysis

Continuous variables with a symmetric distribution are expressed as the mean +/- standard deviation and those with an asymmetric distribution as the median and interquartile range. Categorical variables are expressed as counts and percentages. For quantitative variables, a t-test for equal variance

Table 1 Clinical, demographic, and radiological variables of the study group

Variables	Values
Age (years)	63.1±8.9
Gender (% of male)	91
Smokers (%)	85
Hypertension (%)	85
Dyslipidemia (%)	78
Diabetes Mellitus (%)	22
Glomerular filtration rate (ml/min/1.73 m^2)	77.5±12.5
Body mass index (kg/m^2)	31.9±6.2
Previous myocardial infraction (%)	48
Previous percutaneous revascularization (%)	70
Stented segments (% of total analyzed)	20
Previous bypass graft surgery (%)	7
Time between ICA and CTA (days)	95±60
Kilovoltage (Kv)	114±9
Mean CTA estimated effective radiation dose, per exam (mSv)	11.1±2.3
Dose of contrast (ml)	88.7±11.7
Dose of betablockers (mg)	9±6.9
Heart rate at the time of the scan (beats/min)	59±6.9
Agatston score	505±711*
Population percentile of calcification	92±8*
Total volume of coronary calcium (mm^3)	397±544*

* Median ± interquartile range

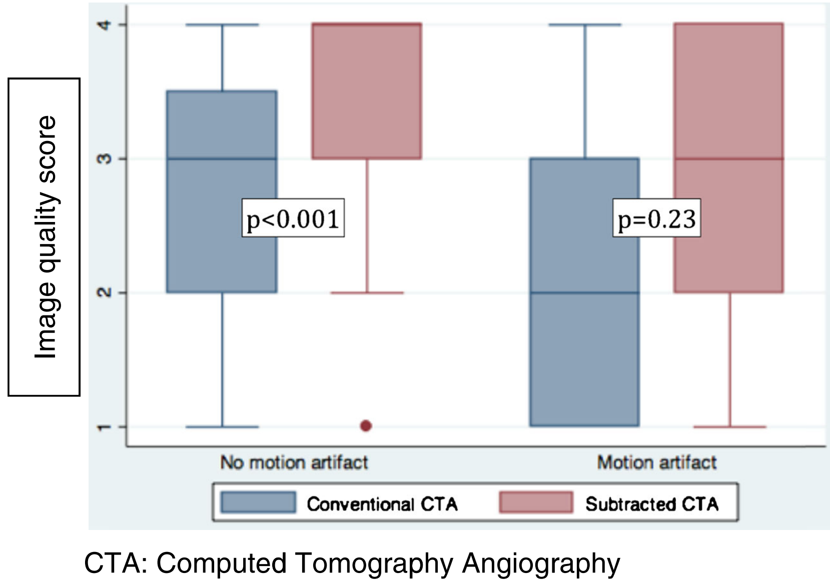


Fig. 3 Image quality of conventional and subtraction computed tomography angiography in studies with/without motion artifact

>2 independent groups was applied. For categorical variables, the Pearson chi-square test was used. Intra-class correlation coefficient was used to assess the correlation between QCA calculated in subtraction CTA and ICA. The receiver operating characteristic (ROC) curve was used as the measure of diagnostic accuracy. Sensitivity, specificity, positive and negative predicting values for both CTA and subtraction CTA were calculated by standard methods [18]. The reference standard for ROC curve analysis was 50 % or greater luminal narrowing at QCA. Area under curve (AUC) for different groups were compared by using a bootstrap confidence intervals for the difference between the AUCs. All p values <0.05, 2-tailed approach, and power of 80 % were used in all tests. Statistical analysis was performed using STATA software, version 12 (StataCorp TX, USA).

Results

A total of 23 patients with 129 calcified or stented coronary segments were studied. Clinical, demographic, and radiological data are showed in Table 1. A high prevalence of

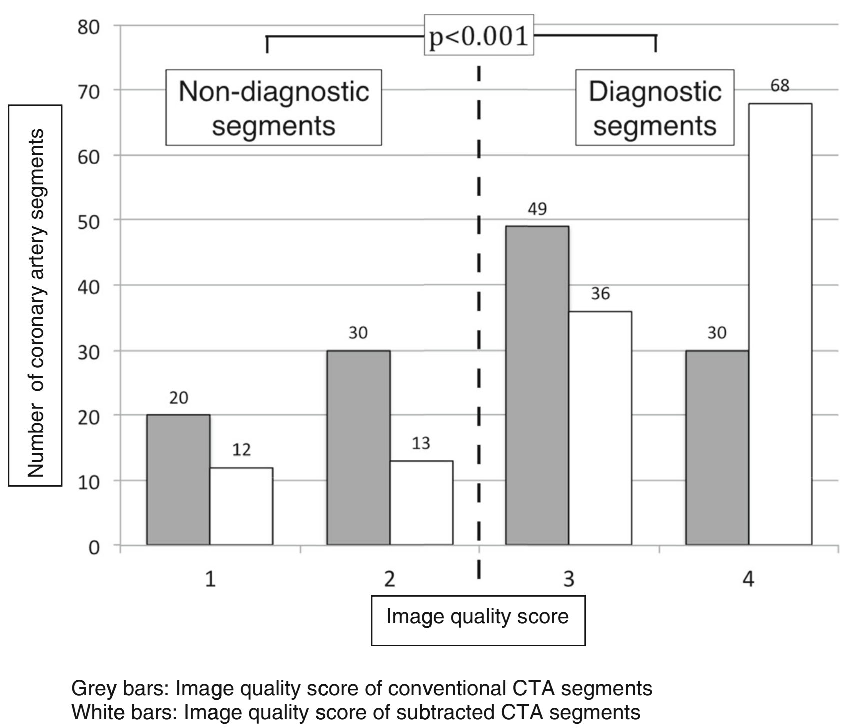


Fig. 4 Classification according to image quality score (1-4) of coronary artery segments form conventional (grey bars) and subtraction (white bars) computed tomography angiography studies

Table 2 Statistical performance of conventional and subtraction computed tomography angiography

	Conventional CTA	Subtraction CTA
Sensitivity (%)	90	97
Specificity (%)	81	88
Positive predictive value (%)	71	80
Negative predictive value (%)	94	98
Accuracy (%)	84	91
AUC (95 % CI) *	0.87 (0.79 – 0.93)	0.93 (0.88 – 0.98)

CTA = Computed Tomography Angiography; AUC = Area Under Curve

***p=0.02**

significant coronary stenosis was found at ICA among the total study group (10/23; 43 %), and, also, when considering the analyzed vessels (17/69; 25 %) and segments (44/129; 34 %). In accordance, median Agatston coronary calcium score was 505 (interquartile range 711) with a mean population percentile of calcification of 92±8.

Mean coronary image quality score with conventional CTA was 2.69±0.99 and in subtracted CTA 3.24±0.97 (p<0.001). Image quality in subtraction CTA was significantly improved in proximal (2.9±0.97 to 3.35±0.93, p=0.016), middle (2.48 ±0.94 to 3.15±0.99, p=0.014) and distal segments (2.54± 1.01 to 3.18±1.04, p=0.005). A total of 32 coronary segments (25 % of total segments) presented with some degree of motion artefact (in non-contrast and/or in contrast scans). In these segments, image quality also improved (from 2.35±1.17 to 2.71±1.19), but not significantly (p=0.23) (Fig. 3).

Non-diagnostic segments with conventional CTA were 38 % (50/129) and after subtraction CTA were 19 % (25/129) (p<0.001) (Fig. 4). Non-diagnostic segments due to motion artefact were more frequent in left circumflex (LCx) (5/28) and right coronary artery (RCA) (5/58) than in the left anterior descending artery (1/41). Patients with non-diagnostic segments more likely presented with motion artefact in non-contrast and/or contrast CT (p=0.013). No other patient-level variable was associated with a non-diagnostic CTA study, including the amount of coronary calcium (p=0.151) and the presence of coronary stents (p=0.856). False-positive results in subtraction CT were associated with the presence of motion artefact (p=0.008).

In 26/129 segments metal stents were present (69.% drug eluting stents, 31.% bare metal stents) with a mean diameter of 2.89±0.41 mm (range 2.25-3.5 mm) and 35.% (9/26) under 3 mm of diameter (mean diameter: 2.41±0.18 mm, range 2.25-2.75 mm). Improvement of image quality after metal subtraction was also significant, from 2.69±0.97 to 3.34± 0.89 (p=0.014) but not in metal stents under 3 mm of diameter (from 2.11±0.78 to 2.67±0.87, p=0.17). Non-conclusive results in segments with metal stents were statistically associated with a motion artefact in non-contrast or contrast CTA (p= 0.013).

Conventional CTA and subtraction CTA statistical performance to detect coronary artery stenosis greater than 50.% is shown in Table 2. There was an improvement in the performance to detect stenosis >50 % by subtraction CTA compared with conventional CTA, with statistical differences in area under the curve (AUC) in ROC curves between the two approaches (p=0.02) (Fig. 5). There was a good correlation

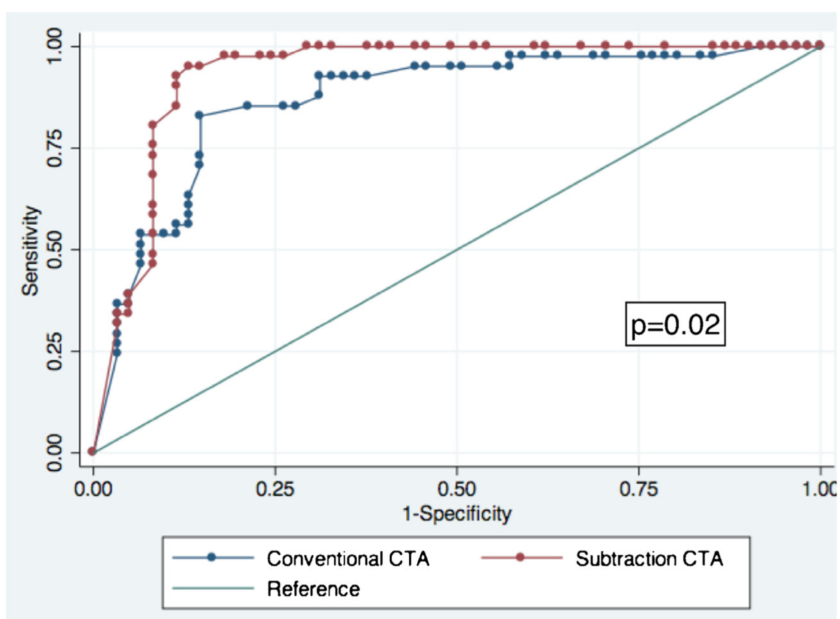


Fig. 5 Comparison of ROC curves of two types of computed tomography angiography

CTA: Computed Tomography Angiography

between ICA and subtraction CTA to detect significant coronary stenosis with a kappa index 0.89 (CI 0.80-0.99; $p<0.001$).

Discussion

The development of methods for coronary subtraction CTA has been feasible by the availability of new-generation multi-detector scanners with a wide coverage of acquisition, as they allow the obtaining of both, non-contrast and contrast scans, in the same breath-hold. This strategy reduces misreading artefacts and improves the image quality of the subtracted CTA [13].

The present study demonstrates the reliability of the acquisition methodology and post-processing algorithm for coronary artery calcium or metal subtraction in patients from current clinical practice selected only on the basis of having severe calcification or previous implanted metal stents.

In comparison with conventional CTA, we have observed a significant improvement of image quality in calcified or stented coronary artery segments whether they are located in the proximal, middle or distal thirds of the coronary tree. Motion artefacts still pose a limitation to the technique, as those segments with motion artefact showed at subtraction a lesser degree of improvement than those without such an artefact.

Subtraction CTA allowed for a significant improvement in diagnostic accuracy by an increased specificity and positive predictive value for the assessment of coronary artery stenosis when compared to conventional CTA. Even so, a few false positive results occurred, mainly due to motion artefact.

In our study, subtraction CTA reduced the number of non-conclusive segments by 19 %. The arteries with higher prevalence of non-diagnostic segments due to motion artefact were LCx and RCA. The epicardial course of these vessels runs along the atrioventricular groove and suffers from a large displacement through the entire cardiac cycle that may explain this result.

In contrast with the only two previously published reports on subtraction CTA [13, 19], our study is the first one to test the performance of this technique in patients with implanted metal coronary stents. The subtraction software works equally well in removing metal artefact from coronary stents, particularly in those larger than 3 mm of diameter. Still, motion artefacts occurring during acquisition may also limit the assessment of stents.

The mean effective radiation dose of the subtraction CTA studies is higher than that of conventional CTA with the equipment used in the study. However, it is similar to doses reported in studies with 64-slice CT systems [14, 20]. We consider this level of radiation as relatively acceptable taking into account the overweight of studied patients, the long phase of the cardiac cycle scanned and, particularly, the learning curve inherent to the technique, this being illustrated by the mean radiation doses of the first and second half of the study group: 12.7±3.1 vs 9±0.63 mSv, respectively. In future trials, the use of a lower kV, a shorter RR scanning phase and narrower z-axis detector coverage could result in a substantial radiation dose saving.

This study has the limitation of a rather small patient population (n=23 with a total of 129 lesions), because it was conceived as a feasibility study of subtraction CTA for the evaluation of improvement in the assessment of highly calcified coronary artery plaques or implanted stents.

Conclusions

Subtraction CTA is a promising tool to overcome limitations of conventional CTA due to calcium and metal artefacts. This study demonstrates an improvement in image quality using this technique, particularly in those exams without motion artefacts or in segments with stents larger than 3 mm. Importantly, diagnostic accuracy for the detection of angiographically significant coronary artery lesions is also improved by subtraction as compared with conventional CTA.

Acknowledgments This study has been performed with technological support from Toshiba Medical Systems- Spain. The scientific guarantor of this publication is Dr. David Viladés Medel. The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article. The authors state that this work has not received any funding. One of the authors has significant statistical expertise (DVM). Institutional Review Board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study. Approval from the institutional animal care committee was not required.

Methodology: prospective, diagnostic study / performed at one institution.

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