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**CLINICAL RESEARCH**  
Imaging

# Accuracy of low-dose computed tomography coronary angiography using prospective electrocardiogram-triggering: first clinical experience

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## Aims

To evaluate the accuracy of low-dose computed tomography coronary angiography (CTCA) using prospective ECG-triggering for the assessment of coronary artery disease (CAD).

## Methods and results

A total of 30 patients (19 males, 11 females, mean age  $58.8 \pm 9.9$  years) underwent low-dose CTCA and invasive coronary angiography (CA) [median 2 days (0, 41)]. Before CT scanning, intravenous beta-blocker was administered in 18 of 30 patients as heart rate (HR) was  $>65$  b.p.m., achieving a mean HR of  $55.7 \pm 7.9$  b.p.m. CAD was defined as coronary artery narrowing  $\geq 50\%$ , using CA as standard of reference. The estimated mean effective radiation dose was  $2.1 \pm 0.7$  mSv (range: 1.0–3.3), yielding 96.0% (383/399) of evaluable segments. On an intention-to-diagnose-base, all non-evaluative segments were included in the analysis. Vessels with a non-evaluative segment and no further finding were censored as false positive. Patient-based analysis revealed sensitivity, specificity, positive predictive value, and negative predictive value of 100, 83.3, 90.0, and 100%, respectively. The respective values per vessel were 100, 88.9, 85.7, and 100%, respectively.

## Conclusion

Prospective ECG-triggering allows low-dose CTCA and provides high diagnostic accuracy in the assessment of CAD in patients with stable sinus rhythm and a low heart rate.

## Keywords

CT coronary angiography • Diagnostic accuracy • Low dose • Prospective ECG-triggering • Image quality

## Introduction

The implementation of 64-multidetector computed tomography (CT) has been a milestone for the introduction of CT coronary angiography (CTCA) as diagnostic tool for non-invasive assessment of coronary artery stenoses in the clinical routine.<sup>1–7</sup> Throughout all technical advances, the two main challenges still remain motion-free depiction of coronary arteries and reduction of radiation exposure to the patient. Although new developments such as dual-source technology<sup>8–14</sup> and latest scanner generations

with 256<sup>15</sup> and more slices<sup>16</sup> may help reducing motion artefacts, the issue of radiation is not solved by these technical advances. In fact, in a preliminary study using 256 slices, radiation administered to the patient has been reported as high as 33 mSv.<sup>15</sup> In view of the ongoing debate on the radiation burden of CTCA and its risk of cancer induction,<sup>17</sup> any suggestion to successfully reduce radiation dose is important. Introduction of tube modulation by electrocardiogram has reduced radiation from over 20 mSv<sup>4</sup> to 10–15 mSv,<sup>2</sup> and optimized protocols have achieved doses as low as  $<8$  mSv.<sup>18</sup>

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The most promising approach for dose reduction seems to be the use of a new scanning protocol applying prospective ECG triggering, where radiation is administered only at one predefined end-diastolic time point instead of during a whole phase of the cardiac cycle.<sup>19</sup>

A recent report has demonstrated the clinical feasibility of such low-dose CTCA with prospective triggering to achieve diagnostic image quality despite reduction of radiation dose by almost an order of magnitude.<sup>20</sup> However, no data on the accuracy of CTCA by prospective triggering compared with invasive CA are available so far.

Thus, the purpose of our study was to investigate the accuracy of low-dose CTCA using prospective ECG triggering for the assessment of coronary stenoses in comparison with invasive CA.

## Methods

### Study population

The present study evaluated patients with suspected chronic stable coronary artery disease (CAD). We decided to aim at including 30 patients into the final analysis of this preliminary report, although no formal sample size calculation was performed due to the pilot nature of this study. Among 112 consecutive patients referred for elective invasive CA, 70 patients deemed ineligible due to known significant CAD. Four of the remaining 42 patients refused to give the consent and eight were excluded due to allergy to iodinated contrast agent ( $n = 1$ ), nephropathy (creatinine levels  $>150 \mu\text{mol/L}$  or  $>1.7 \text{ mg/dL}$ ) ( $n = 4$ ), non-sinus rhythm, known premature ventricular, or supra-ventricular beats ( $n = 3$ ). The 30 patients included in our final analysis were referred for the following symptoms: dyspnoea ( $n = 3$ ), typical angina pectoris ( $n = 9$ ), atypical chest pain ( $n = 10$ ), pathological exercise test, or ECG ( $n = 11$ ). All patients underwent both invasive CA and CTCA. The study protocol was approved by the local ethics committee and written informed consent was obtained from patients included in the study.

### Data acquisition and post-processing

All patients received a single dose of 2.5 mg isosorbiddinitrate sublingual (Isoket, Schwarz Pharma, Monheim, Germany) 2 min prior to the scan. In addition, intravenous metoprolol (2–20 mg) (Beloc, AstraZeneca, London, UK) was administered, if necessary to achieve a target HR of  $<65 \text{ b.p.m.}$  prior to the start of the scan. The HR was monitored and HR variability was assessed as the standard deviation of the HR throughout the scan as reported previously.<sup>21</sup> For CTCA, 80 mL of iodixanol (Visipaque 320, 320 mg/mL, GE Healthcare, Buckinghamshire, UK) at a flow rate of 5 mL/s followed by 50 mL saline solution was injected into an antecubital vein through an 18-gauge catheter. Bolus tracking was performed with a region of interest placed into the ascending aorta, and image acquisition was started 4 s after the signal density reached a threshold of  $\sim 120$  Hounsfield units (HU).

All CTCA examinations were performed with a LightSpeed VCT XT scanner (GE Healthcare) and prospective ECG triggering,<sup>19</sup> using a commercially available protocol (SnapShot Pulse, GE Healthcare) and the following scanning parameters as previously reported:<sup>20</sup> slice acquisition acquisition  $64 \times 0.625 \text{ mm}$ , smallest X-ray window (only 75% of the RR-cycle), z-coverage 40 mm with an increment of 35 mm, gantry rotation time 350 ms, body mass index (BMI) adapted tube voltage (100 kV: BMI  $<25 \text{ kg/m}^2$ ; 120 kV: BMI  $\geq 25 \text{ kg/m}^2$ ) and effective tube-current (450 mA: BMI  $<22.5 \text{ kg/m}^2$ ; 500 mA: BMI

22.5–25  $\text{kg/m}^2$ ; 550 mA: BMI 25–27.5  $\text{kg/m}^2$ ; 600 mA: BMI 27.5–30  $\text{kg/m}^2$ ; 650 mA: BMI  $>30 \text{ kg/m}^2$ ). The CT scan was performed from below the tracheal bifurcation to the diaphragm, choosing three to four scan blocks (field of view 11–14.5 cm). By restricting the scan to the smallest possible window at only one distinct end-diastolic phase of the RR-cycle (i.e. 75%), we ascertained the lowest achievable effective dose delivery.

The effective dose from CTCA was calculated as the product of the dose-length product (DLP) times a conversion coefficient for the chest ( $k = 0.017 \text{ mSv/mGy cm}$ ) as previously suggested.<sup>22</sup> The CTCA images were reconstructed with a slice thickness of 0.6 mm, using a medium-soft tissue convolution kernel (standard). In case of vessel wall calcifications, additional images were reconstructed using a sharp-tissue convolution kernel (detail) and preferably analysed using a bone window setting (window width: 1500 HU; window level: 500 HU) to compensate for blooming artefacts. All images were transferred to an external workstation (AW 4.4, GE Healthcare).

### Computed tomography image analysis

Coronary arteries were segmented as suggested by the American Heart Association.<sup>23</sup> The right coronary artery was defined to include segments 1–4, the left main artery and the left anterior descending (LAD) artery to include segments 5–10, and the left circumflex artery (CX) to include segments 11–16; the intermediate artery was designated as segment 16, if present. All segments with a diameter of at least 1.5 mm at their origin were included. Two readers semi-quantitatively assessed independently the overall image quality on a four-point scale (1, excellent, no motion artefacts; 2, good, minor artefacts; 3, adequate, moderate artefacts; 4, non-evaluative, severe artefacts) as previously reported.<sup>14</sup> Scores 1–3 were considered as diagnostic, score 4 as non-diagnostic. Step artefacts at junctions of different image blocks may not necessarily lead to misinterpretations. However, as a hidden lesion within the artefact cannot be excluded with absolute certainty, we have categorized any step artefact as non-evaluative. Both readers assessed all coronary vessels for the presence of haemodynamically significant stenoses, defined as narrowing of the coronary luminal diameter  $\geq 50\%$ . In case of multiple lesions in one segment, the segment was classified by the worst lesion. For any disagreement in data analysis between the two observers, consensus agreement was achieved.

### Invasive coronary angiography

Invasive CA was performed according to standard techniques, and multiple views were stored on a CD-ROM. An experienced observer blinded to the results from CTCA evaluated the angiograms. The coronary arteries were subdivided according to the same model used for the CT angiography images<sup>23</sup> and were quantitatively assessed with the use of an automated edge-detection system (Xcelera 1.2; Philips Medical Systems, Best, the Netherlands) as reported previously.<sup>24</sup> In brief, quantitative CA measurements were performed in two image planes and included the diameter of the reference vessel (proximal and distal to the stenosis), the minimal luminal diameter, and the extent of stenosis (defined as the diameter of the reference vessel minus the minimal luminal diameter, divided by the reference diameter and multiplied by 100%). For biplane assessment, diameters obtained in both image planes were averaged. Coronary arteries were included in the analysis if luminal diameter was at least 1.5 mm; excluding those vessels distal to complete occlusions. Each vessel was scored as being normal or significantly stenosed (defined as a diameter reduction of  $\geq 50\%$ ).

## Statistical analysis

Quantitative variables were expressed as mean  $\pm$  standard deviation and categorical variables as frequencies, median (25th, 75th percentiles) or percentages.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated; invasive CA was considered the standard of reference. The 95% confidence intervals (CI) were calculated from binomial expression per vessel and per patient. We took into account the clustered nature of the data (i.e. the fact that the 90 vessel were not independent but instead clusters of vessels in 30 patients). For these analyses, a proportion-procedure for survey data of the Stata software (StataCorp 10.0, College Station, USA) with patient as primary sample unit was performed to address dependencies between the vessels.<sup>25</sup>

## Results

Computed tomography coronary angiography and CA were successfully performed in all 30 patients (19 males, 11 females, age  $58.8 \pm 9.9$  years) [median 2 days (0, 41)]. Twelve patients were on beta-blocker therapy as part of their baseline medication. Using CTCA, additional intravenous beta-blocker was administered in 18 patients for HR control prior to CTCA (median  $4.5 \text{ mg}^{1,20}$  yielding a mean HR of  $55.7 \pm 7.9$  b.p.m. (range: 35–70 b.p.m.) and a mean HR variability of  $1.5 \pm 0.9$  b.p.m. (range: 0.3–3.7 b.p.m.). The mean BMI was  $27.0 \pm 4.9 \text{ kg/m}^2$  (range: 21.9–42.5  $\text{kg/m}^2$ ). The mean DLP was  $125.8 \pm 43.1 \text{ mGy cm}$  (range: 58.3–192.7  $\text{mGy cm}$ ) resulting in an estimated mean effective radiation dose of  $2.1 \pm 0.7 \text{ mSv}$  (range: 1.0–3.3  $\text{mSv}$ ). Of the 480 theoretically possible segments in 30 patients with 16 coronary segments, 52 were missing due to anatomical variants and 29 had a diameter of  $<1.5 \text{ mm}$  at their origin (by both methods). Thus, 52 segments were missing for reasons not associated with the methodology as these segments did simply not exist. The remaining 29 segments were categorized as lower than 1.5 mm and thus not evaluable by the gold standard invasive CA. Thus, the missing data do not seem to introduce a selection bias.

### Image quality with computed tomography coronary angiography

Image quality of 383/399 segments (96.0%) in 26/30 patients was diagnostic (score 1–3); excellent image quality (score 1) was rated in 133 segments (33.3%), good (score 2) in 146 segments (36.6%), and adequate (score 3) in 104 segments (26.1%). Sixteen segments (4.0%) in four of 30 patients were non-diagnostic (score 4) and were considered as false-positive. Two of these four patients had correctly identified lesions in other segments, re-categorizing these two as true positive patients. Table 1 shows demographic data and overall image quality.

### Diagnostic accuracy of computed tomography coronary angiography in comparison with invasive coronary angiography

In 18 patients and 36 vessels, 66 coronary artery stenoses were recognized with invasive CA. Single-vessel disease was present in eight patients, two-vessel disease in two patients, and three-vessel

**Table 1** Patient demographics, overall image quality

Number of patients	30
Mean age $\pm$ SD (years)	$58.8 \pm 9.9$
Female/male	11/19
Mean BMI $\pm$ SD ( $\text{kg/m}^2$ )	$27.0 \pm 4.9$
Mean HR $\pm$ SD (b.p.m.)	$55.7 \pm 7.9$
Mean HR variability $\pm$ SD (b.p.m.)	$1.5 \pm 0.9$
Mean effective radiation dose $\pm$ SD (mSv)	$2.1 \pm 0.7$
Overall image score <sup>a</sup>	$2.01 \pm 0.96$
Score 1 (%)	33.3 (133/399)
Score 2 (%)	36.6 (146/399)
Score 3 (%)	26.1 (104/399)
Score 4 (%)	4.0 (16/399)

SD, standard deviation; HR heart rate; b.p.m., beats per minute.

<sup>a</sup>Image quality scores: 1, excellent; 2, good; 3, adequate; 4, not evaluative.

disease in eight patients. Figure 1 demonstrates an example of coronary artery stenosis detection by CTCA and CA.

Low-dose CTCA correctly detected CAD in all patients ( $n = 18$ ) and in all vessels ( $n = 36$ ) with lesions. Invasive CA revealed no CAD in 12 patients. CAD has been correctly ruled out by CTCA in 10 of 12 patients and in 48 of 54 vessels without coronary stenoses. Two patients were categorized as false positive. Six vessels were found to be false positive due to massive calcification ( $n = 2$ ) or due to non-evaluative image quality caused by motion artefacts ( $n = 4$ ). Of note, there was no false-negative finding, neither per vessel nor per patient (Table 2).

On a per-vessel analysis, there was 100% (36/36) sensitivity, 88.9% (48/54, 95% CI: 0.77–1.00) specificity, 85.7% (36/42, 95% CI: 0.70–1.00) PPV, and 100% (48/48) NPV.

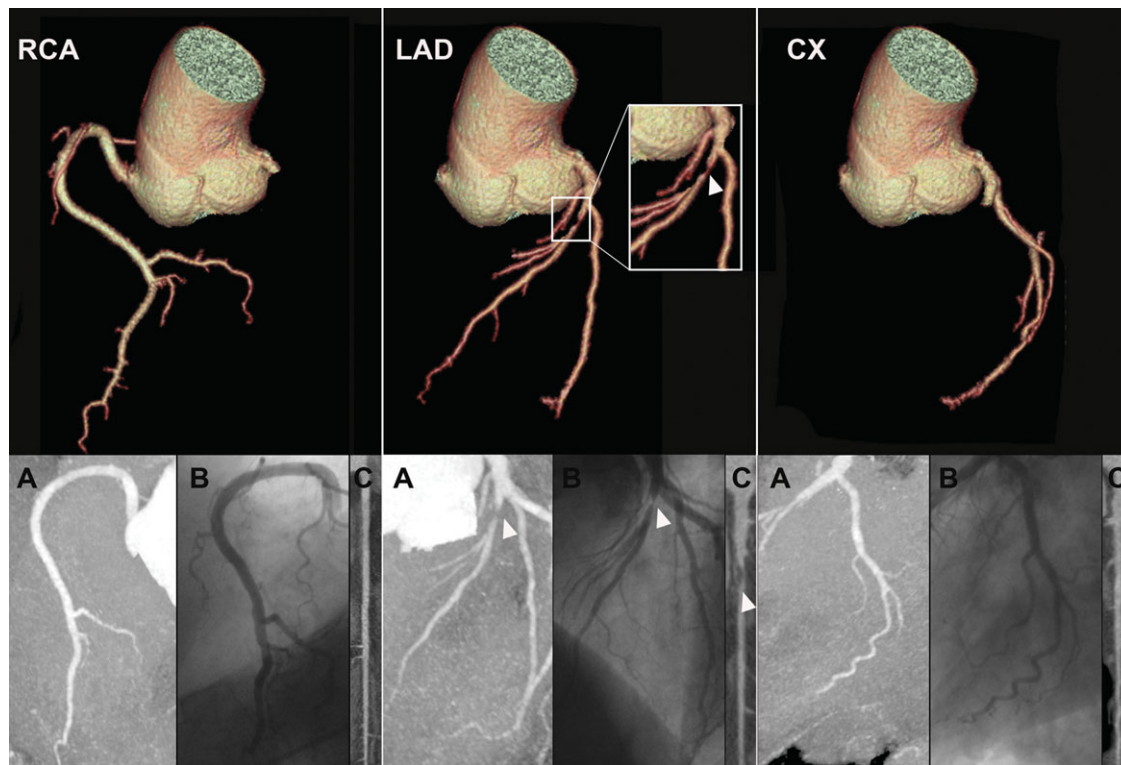
On a per-patient analysis, there was 100% (18/18) sensitivity, 83.3% (10/12, 95% CI: 0.62–1.00) specificity, 90.0% (18/20, 95% CI: 0.76–1.00) PPV, and 100% (10/10) NPV (Table 2).

## Discussion

The present study is the first to demonstrate the accuracy of low-dose CTCA using prospective ECG-triggering for the assessment of CAD in comparison with the reference standard invasive CA.

Radiation exposure to patients in CTCA has remained a source of concern, even after successful reduction down to 9.4  $\text{mSv}$  in 64-slice MDCT<sup>26</sup> and to 7.8  $\text{mSv}$  in dual source CT<sup>18</sup> by applying ECG-gated tube modulation and retrospective triggering. The present protocol using prospective ECG-triggering allows to further substantially reduce the effective radiation dose down to  $2.1 \pm 0.7 \text{ mSv}$ , which compares favourably to the average of 7  $\text{mSv}$  typically reported for a diagnostic invasive CA.<sup>22</sup> Our results confirm the previously reported feasibility<sup>20</sup> and document a high accuracy of low-dose CTCA, comparing well to results from retrospectively gating with 64-slice CT or dual-source CT.<sup>3–7,27,28</sup>

Interestingly, the NPV was excellent both on a per-patient and on per-vessel base. This is important as the main strength and the main clinical role of CTCA is thought to be exclusion of



**Figure 1** Low-dose CT and invasive coronary angiography in a 42-year-old male patient with atypical chest pain. Right coronary artery (RCA), left anterior descending artery (LAD) artery and circumflex artery (CX) illustrated as volume-rendered images. (A) maximum intensity projections, (B) invasive coronary angiography images, and (C) stretched multiplanar reconstructions. The arrow head indicates a non-calcified significant stenosis in the proximal LAD.

**Table 2** Diagnostic accuracy

	Patient based	Vessel based
Stenoses in CA	18	36
Stenoses in CTCA	20	42
TP	18	36
FP	2	6
TN	10	48
FN	0	0
Sensitivity (%)	100	100
Specificity (%) (95% CI)	83.3 (0.62–1.00)	88.9 (0.77–1.00)
PPV (%) (95% CI)	90.0 (0.76–1.00)	85.7 (0.70–1.00)
NPV (%)	100	100

CA, coronary angiography; CTCA, CT coronary angiography; TP, true positives; FP, false positives; TN, true negatives; FN, false negative; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

CAD in low-to-intermediate probability populations.<sup>29</sup> The present study supports that low-dose CTCA can reliably rule out CAD.

A criticism often raised against CTCA studies has been the inclusion of high prevalence populations. This may also apply to our study. However, validation of a new CTCA protocol for the

assessment of CAD requires comparison against the standard of reference, namely invasive CA. The latter, however, is affected by a small but distinct procedure-related morbidity (1.5%) and mortality rate (0.15%),<sup>30</sup> precluding its use for purely scientific purposes in a low-probability population for ethical reasons. This may introduce a bias as patients with normal CTCA findings would not undergo invasive CA, which reduces true negative findings, resulting in an apparent decline in specificity.<sup>31</sup> Therefore, we have included only patients who were referred for invasive CA due to clinical suspicion, which may explain the relatively high prevalence of CAD in our study. This strengthens the validity of our results with excellent NPV as in low-prevalence populations with more true positive findings the NPV is generally higher.<sup>32</sup>

In addition, patient groups which we generally perceived as most suitable for CTCA are typically younger and have less coronary calcifications. This would improve image quality and reduce false-positive findings. The large field of view in 256 or 320 multislice CT scanners allows acquisition of the whole coronary tree within one cardiac cycle eliminating any stair-step artefacts. Preliminary data confirm that the concept of prospective ECG triggering is applicable in latest scanner generations. Thus, although prospective ECG-triggering is still in its infancies, this scanning protocol has the potential to become a new standard.

We acknowledge the following limitation to our pilot study. First, we included a relatively small number of only 30 patients.

However, the results appear valid as we have used an intention-to-diagnose strategy to achieve a clinically relevant end-point, i.e. findings on a per-patient and per-vessel analysis. Furthermore, HR control is mandatory for prospective ECG triggering,<sup>20</sup> explaining the frequent beta-blocker administration in this study, though the median dose of 4.5 mg<sup>1,20</sup> intravenous metoprolol in our study compares well with previous reports.<sup>2–4,7,21,33</sup> Nevertheless, as all patients turned out to have normal ejection fraction, we may have introduced a bias towards lower heart rates and/or eligibility for larger doses of intravenous metoprolol allowing to reach the target heart rate of <65 b.p.m. in each patient. Furthermore, by excluding patients with known coronary lesions, we may have introduced a bias towards younger age. This may result in less calcifications and also better ability to follow breath hold commands. Finally, CTCA with prospective ECG-triggering does not allow functional assessment of the left ventricle. This, however, is generally assessed primarily with other modalities such as echocardiography or a gated nuclear exam if hybrid imaging is performed.<sup>34</sup>

In conclusion, prospective ECG-triggering allows to acquire low-dose CTCA at radiation doses below those of invasive CA providing high diagnostic accuracy in the assessment of CAD in patients with stable sinus rhythm and a low heart rate.

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## CLINICAL VIGNETTE

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### Giant Kawasaki coronary artery aneurysm: cardiac imaging evolution

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We present the evolution of cardiac imaging findings in a female Caucasian teenager with a diagnosis of Kawasaki's disease since age 5. She had remained asymptomatic throughout most of her life although stress myocardial perfusion imaging had shown myocardial ischaemia in the anterior and anterior septal left ventricular wall (Panel A) at age 11. Low-radiation dose 64-slice CT coronary angiography (CTA) performed for non-invasive disease surveillance at age 13 showed giant coronary artery aneurysms (Panel B) in the proximal left anterior descending coronary artery (LAD), as well as in the proximal and mid-right coronary artery (RCA), the two former of which showed wall calcification and thrombus formation, however, without flow-limiting stenosis. Functional analysis based on cine-CT reconstructions showed left ventricular function deficits in good correlation with prior myocardial perfusion imaging. On the basis of the CTA results, chronic anticoagulation therapy was initiated. The patient started developing a smoking habit at age 13. At age 15, she complained about exertional retrosternal pain. Echocardiography with Doppler flow evaluation of the coronary arteries was performed but deemed inconclusive due to heavy vessel wall calcifications within the giant coronary aneurysms. Subsequently, ultra-low radiation dose dual-source coronary CTA was performed, which showed essentially unchanged appearance of the RCA aneurysms (Panels B–E). However, the LAD aneurysm showed extensive progression of thrombus with interval near-complete occlusion (Panels C, G, and H) and only faint contrast enhancement of the LAD beyond the aneurysm. Invasive catheter angiography (Panels F and I) was subsequently performed with the intent of revascularization, which confirmed the findings at CTA and showed extensive collateralization of the LAD lesion. However, the nature of the lesion was deemed too complex for successful interventional revascularization, and an indication for surgical coronary artery bypass grafting was established.

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