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Performance of ultra-low-dose CT for the evaluation of coronary calcification: a direct comparison with coronary calcium score

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AIM: To evaluate the diagnostic performance of ultra-low-dose computed tomography (ULDCT) in comparison to standard coronary calcium score (CCS) acquisition for the evaluation of coronary artery calcification (CAC).

MATERIALS AND METHODS: Standard CCS acquisition and ULDCT were performed in patients referred for coronary CT angiography for the evaluation of coronary artery disease. CAC in ULDCT was graded subjectively using a four-point scale (from 0, no calcification, to 3, severe calcification) for the complete study and for each individual coronary segment. The summation of all individual coronary segment scores generated an ULDCT total CAC score. ULDCT results were compared to standard Agatston score and sensitivity and specificity of ULDCT were calculated.

RESULTS: CCS and ULDCT were performed in 74 patients, with a mean DLP of 77.7 mGy·cm (±12.1) and 9.3 mGy·cm (±0.6), respectively ($p<0.001$). Coronary calcification was detected in 47 patients (63.5%) in standard CCS acquisition (median Agatston score of 41; interquartile range [IQR]:0263), in comparison to 42 patients (56.8%) in ULDCT ($p<0.001$). The sensitivity and specificity of the ULDCT total CAC score ≥1 was 80.9% and 85.2%, respectively, with an accuracy of 82.4%. The area under the receiver operating characteristic curve for the presence of CAC was 0.87.

CONCLUSION: ULDCT shows good sensitivity, specificity, and overall accuracy for the detection of coronary calcification with a markedly lower radiation dose in comparison to CCS. ULDCT is unlikely to miss coronary calcification in individuals with at least moderate calcium load (Agatston score >100).

Introduction

Coronary calcium score (CCS) is a powerful predictor of cardiovascular events and it is a valuable tool for risk stratification of asymptomatic individuals.[1] Conversely, the data regarding its use in symptomatic patients is less robust, particularly in those referred to coronary computed

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tomography (CT) angiography (CCTA). Although small, the radiation dose associated with this test has been highlighted,[2] and strategies to reduce the radiation burden to patients referred for CCTA have suggested the exclusion of CCS as part of the imaging protocol.[3,4]

More recently, several studies have attempted to combine new reconstruction algorithms to low-dose chest CT imaging to generate diagnostic images of the thorax with low radiation doses.[5,6] In patients undergoing CT lung cancer screening, assessment of coronary calcification has been successfully performed using low-dose chest CT, with excellent correlation with conventional electrocardiographic (ECG)-gated CCS.[7]

The use of iterative reconstruction (IR) combined with very low tube output may allow dramatic reduction in radiation dose still maintaining diagnostic image quality. This has been demonstrated for the evaluation of the lung parenchyma and for the detection of lung nodules[8–10]; however, the evaluation of coronary calcification in ultra-low-dose CT (ULDCT) images and its correlation with conventional CCS has not been formally compared. Quantification of coronary artery calcification (CAC) using ULDCT could obviate the need of CCS acquisition in patients referred to CCTA. Therefore, the present study was undertaken to evaluate the diagnostic performance of ULDCT in comparison to standard CCS acquisition for the evaluation of CAC.

Materials and methods

Patient population

Between August and December 2015, 86 consecutive patients referred to CCTA for the evaluation of suspected or known coronary artery disease (CAD) in which imaging of the chest was also requested were included. Patients with prior revascularisation or those in which a coronary calcium scan was not performed were excluded. This retrospective observational study was approved by the local research ethics board and the need for patients' written informed consent was waived.

Imaging protocols

All studies were performed with the use of a 64-row multidetector CT system (Ingenuity CT; Philips Healthcare, Best, The Netherlands). Helical ULDCT acquisition was performed without ECG gating and using a tube potential of 80 kVp and a tube current–time product of 15 mAs, covering the entire chest in end-inspiration without intravenous contrast medium. Images were reconstructed using IR (iDose4; Philips Healthcare) at level 3, with contiguous 2.5 mm thick sections a cardiac-centered field of view of 220 cm, to match CCS reconstruction parameters.

Coronary calcium scan acquisitions were performed using prospective ECG-triggering, a tube potential of 120 kVp and a weight-adapted tube current–time product (80–120 mAs), covering from the carina to below the heart in end-inspiration. Images were reconstructed with a section thickness of 2.5 mm and using conventional filtered back projection.

After CCS acquisition, patients without contraindications and with a heart rate (HR) of ≥60 beats/min received an oral beta-blocker (metoprolol, 50–150 mg) approximately 1 hour prior to CCTA in order to achieve a target HR of <60 beats/min.[11] Additional intravenous metoprolol was used in boluses of 5 mg (up to 20 mg) as needed immediately prior to CCTA acquisition. In addition, all patients without contraindications received 5 mg sublingual nitroglycerin 1–2 minutes prior to the contrast-enhanced scan.

CCTA acquisition was performed with the use of 100–120 kVp, 600–800 mA, with a minimum gantry rotation time of 350 milliseconds. Prospective ECG triggering or retrospective ECG gating was used depending on the HR prior image acquisition: prospective ECG triggering was selected for patients with a regular HR of <55 beats/min; retrospective ECG-gating was selected for the remainder. Images were reconstructed at 75% of the R–R interval, with a section thickness of 0.6 mm and 50% overlap. *z*-Axis coverage was planned according to the CCS acquisition: 15 mm above the section showing the cranial-most coronary artery and 15 mm below the heart.

Image analysis

All reconstructed images were stored in a digital picture archiving and communications system (Pixviewer 6.0, Pixeon Medical Systems) and were reviewed and post-processed using a dedicated cardiac workstation (View-forum; Philips, Best, The Netherlands).

Two radiologists blinded to the standard CCS acquisition evaluated independently the presence or absence of coronary calcification in ULDCT. Coronary calcification in ULDCT was described as present or absent and then it was graded subjectively using a four-point scale (simplified scoring method: 0, no calcification; 1, mild calcification; 2, moderate calcification; and 3, severe calcification)[7] for the entire study and for each individual coronary segment (coronary segmentation was done according to the SCCT guidelines for the interpretation and reporting of coronary CT angiography).[12] Based on a subjective evaluation, coronary calcification was classified as mild when few tiny discontinuous calcified plaques were visualised in a coronary segment. Severe coronary calcification was assigned to continuous densely calcified plaques in a coronary segment. Coronary calcification was classified as moderate when densely discontinuous calcified plaques were observed in a coronary segment (Fig 1). Differences were solved by consensus. A global ULDCT CAC score was also generated by summing up all individual coronary segment scores (0–3 for each coronary segment). The standard Agatston CCS was divided into the categories of 0, 1–100, 101–400, and >400.

ULDCT images were also evaluated for the identification of the proximal and distal coronary anatomy to estimate the *z*-axis coverage of the CCTA. Based on the CCS, *z*-axis coverage of the CCTA is determined by subtracting 15 mm to the most cranial image showing a coronary artery and by adding 15 mm to the most caudal image showing a coronary

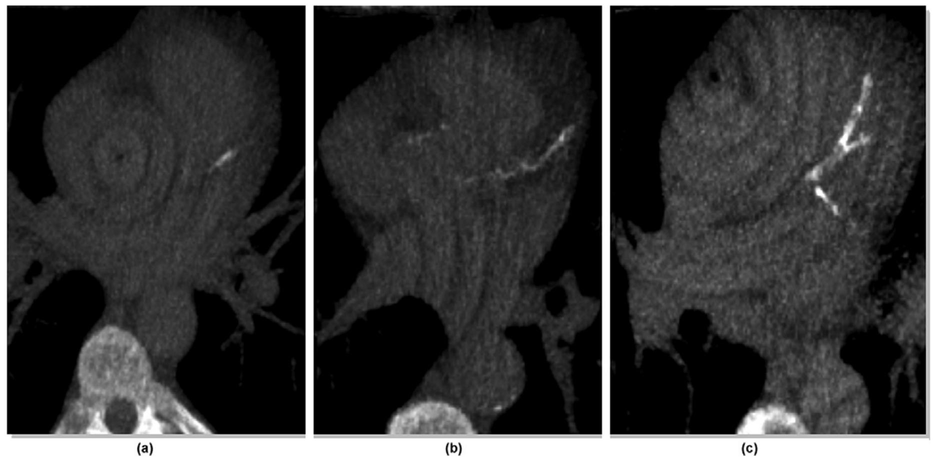

Figure 1 ULDCT maximum intensity projection images from three different patients demonstrating (a) mild (score of 1), (b) moderate (score of 2) and (c) severe (score of 3) coronary calcification.

artery based. In each patient, the image position of the most cranial and caudal limits of the coronary arteries were recorded in ULDCT and compared to the same image positions in the CCS scan.

The dose–length product (DLP) of each component of the study, including ULDCT, CCS acquisition, and CCTA, as well as the DLP for the entire study were recorded. A chest conversion factor of 0.014[13] was used to generate the effective dose (ED), as follows:

$$ED = 0.014 \times DLP.$$

Signal and noise were measured in both ULDCT and CCS acquisition by placing a 3–5 mm^2 circular region of interest (ROI) in the ascending aorta at the level of the origin of the coronary arteries; the mean and standard deviation (SD) of the ROI CT attenuation were recorded and the signal-to-noise ratio (SNR) was calculated by dividing the mean attenuation by the SD from each image.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) released 2009. PASW Statistics for Windows, Version 18.0. SPSS, Chicago, IL, USA) and Stata software, version 11 (StataCorp, College Station, TX, USA). Continuous variables were described using mean ± SD or median (interquartile range, IQR) for continuous variables according their distribution and categorical variables using frequency and percentage. Spearman's rank correlation test was used for assessment of linear association between continuous variables. The DLP from each acquisition was compared between the two methods (UDCT and standard CCS) using Student's *t*-test.

The diagnostic performance of ULDCT for the detection and quantification of coronary calcium was assessed by calculating sensitivity, specificity, and accuracy of the simplified scoring method in comparison to standard Agatston CCS categories. Receiver-operating characteristic (ROC) curves were generated, with adjustment to the SNR.

Inter-reader agreement was assessed by using the intraclass Kendall's tau-a for continuous measures (global scoring method) and the weighted k statistic for ordinal measures (simplified scoring method). The k-values were interpreted as follows: poor (<0.7), fair (between 0.7 and 0.8), good (between 0.8 and 0.9), and high (≥0.9). p-Values of <0.05 were considered to be statistically significant.

Results

Standard CCS acquisition and ULDCT were performed in 74 patients, including 43 male (58.1%), with a mean age (±SD) of 62.8 (±10.3). Most patients were referred for the evaluation of suspected CAD, with an average of one to two risk factors for CAD (Table 1). Oral beta-blockers were used in 45 (61%) of patients for heart rate control prior to CT imaging and the mean HR (±SD) during CCTA acquisition was 56 (±7) beats/min.

Image noise at the level of the aortic root was significantly higher in ULDCT (63.2±23.9 HU) in comparison to CCS acquisition (18.5±4.7 HU; p<0,001).

Simplified scoring method

Coronary calcification was detected in 47 patients (63.5%) in standard CCS acquisition, with a median Agatston

Table 1
Characteristics of the participants.

Parameter	
Mean age	62.7±10.3
Men	43 (58)
Body mass index	27.5±4.2
Arterial hypertension	37 (50)
Diabetes	13 (17)
Smoking status	
Never smoker	52 (70)
Former smoker	15 (20)
Current smoker	7 (10)
Cardiovascular disease family history	39 (52)
Hypercholesterolaemia	27 (36)

Values are mean ± SD or n (%).

Table 2
Coronary calcification as detected by ULDCT in comparison to standard coronary calcium acquisition.

ULDCT Score	Agatston CCS = 0	Agatston CCS = 1–100	Agatston CCS = 101–399	Agatston CCS ≥400
ULDCT = 0	23	8	1	0
ULDCT = 1	4	12	11	4
ULDCT = 2	0	0	1	6
ULDCT = 3	0	0	0	4

CCS, coronary calcium score; ULDCT, ultra-low-dose computed tomography.

score of 41 (IQR: 0–263), in comparison to 42 patients (56.8%) in ULDCT ($p<0.001$). The overall visual assessment of CAC using the simplified scoring method exhibited good agreement with categorised Agatston scores, with a weighted k = 0.86 (95% confidence interval [CI]: 0.81–0.92). ULDCT missed CAC in nine patients and overcalled calcification in four patients (Table 2). In those classified as having moderate or severe calcification (grades 2 or 3), coronary calcium was missed in only one patient by ULDCT (Table 2). Inter-reader reproducibility for the simplified CAC scoring method was good, with a weighted k = 0.89 (95% CI: 0.83–0.93).

Global ULDCT CAC score

Using the Spearman's rank correlation test to evaluate the association between the global ULDCT CAC score and CCS, a strong correlation coefficient was observed (0.906; $p<0.001$). Inter-reader reproducibility of the global ULDCT CAC score was fair. The probability of concordance of standard CCS between observer "a" and observer "b" was 65% (intraclass Kendall's tau-a= 0.65; 95% CI: 0.56, 0.74).

Diagnostic performance of CAC Detection by ULDCT

The sensitivity and the specificity of the ULDCT total CAC score for the detection of any CAC (CCS ≥1) was 80.9% and 85.2%, respectively, with an accuracy of 82.4%. The area under the ROC curve for the presence of CAC was 0.87, with no statistically significant difference when adjusted to ULDCT SNR (0.89; p=0.28; Fig 2).

CCTA z-axis coverage

The most cranial and caudal images of the coronary artery tree were identified in all ULDCT studies. The use of ULDCT images to plan the z-axis coverage of CCTA acquisition would result in inclusion of all coronary artery segments.

Radiation dose

The mean (±SD) DLP and ED for the standard CCS acquisition was 77.7 (±12.1) mGy·cm and 1.09 (±0.17) mSv, respectively, and 9.3 (±0.6) mGy·cm and 0.13 (±0.01) mSv for the ULDCT, respectively ($p<0.001$).

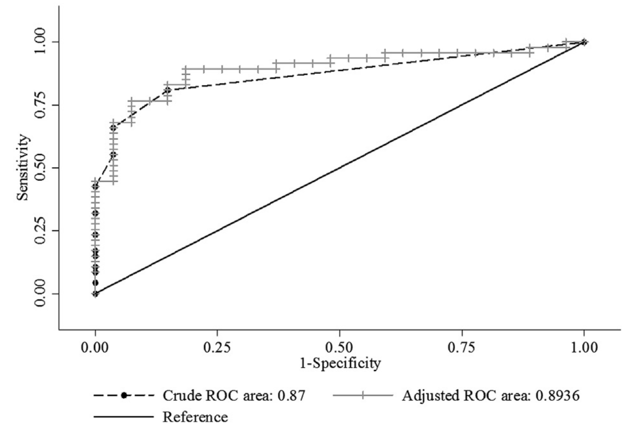

Figure 2 ROC curve for the detection of CAC using ULDCT. The area under the ROC of 0.87 indicates very good performance of ULDCT.

Discussion

The present study demonstrated that ULDCT had good sensitivity and specificity for the detection and classification of CAC in comparison to standard CCS acquisition. With a radiation dose similar to frontal and lateral chest radiography, ULDCT was able to match CCTA scan range acquisition when planned using standard CCS acquisition, despite a significant increase in image noise. As the utility of CCS before CCTA has been questioned, ULDCT could be a reasonable alternative for planning the CCTA scan range while still detecting coronary calcification.

The National Institute for Health and Care Excellence (NICE) evidence-based recommendations on assessing and diagnosing chest pain of recent onset in adults (CG95) recommends CCTA if the clinical assessment indicates typical or atypical angina.[14] CCS is not recommended as a standalone method for the evaluation of symptomatic patients. As the utility of CCS when used prior to CCTA has been a matter of debate, as it only rarely alters management, ULDCT could offer a very low radiation dose alternative to standard CCS acquisition for both detecting CAC and planning the CTA scan range. The present results confirm this hypothesis demonstrating a dramatically reduced radiation dose while maintaining a very good diagnostic performance for CAC detection. The guidelines for conventional coronary artery calcium scoring recommend a target radiation dose of 1–1.5 mSv.[15] Using currently available hardware and newer acquisition techniques, some reports showed that the radiation dose from a single CAC CT examination can vary significantly (effective dose range, 0.8–10.5 mSv),[2] which is considerably higher than that provided by ULDCT.

With the advent of IR techniques and low tube voltage coronary imaging, the radiation dose of CCTA has dropped significantly to a point in which the dose related to CCS acquisition would be responsible for up to 50% of the total dose of the combined studies. Although similar techniques can be used to reduce radiation dose from CCS, the standard protocol uses 120 KVp and traditional image reconstruction, namely filtered back projection, for coronary calcium quantification. Nonetheless, recent publications have explored the use of IR for reducing radiation dose of ECG-triggered CCS acquisitions. Willemink *et al.*[5] evaluated the maximally achievable CT dose reduction for CCS using IR. The authors demonstrated that it is possible to achieve a dose reduction in CCS acquisition of up to 80% while maintaining reclassification levels within 15% if the highest IR levels are used. Although neither the highest possible IR level nor stratified current–time product by weight were used, the present results show that it is possible to assess coronary calcification with good correlation with conventional CCS risk categories based on ULDCT. The use of a higher IR level might have mitigated the number of false positives in the present study, as higher IR levels result in less noise compared to lower levels. Modification of scanning acquisition parameters and IR level would be particularly useful in larger/obese patients, when higher noise is expected. Future studies are required to address the impact of a tailored protocol based on patient size on the accuracy and radiation dose of CAC quantification with ULDCT.

The fact that CAC can be quantified using helical, non-ECG-gated, low-dose CT imaging is in line with several other reports in the literature, particularly with those studies involving lung cancer screening. In the setting of lung cancer screening, several studies and at least one meta-analysis have demonstrated the very good diagnostic performance of low-dose CT acquisition for quantification of CAC.[7,16,17] In addition, the studies by Chiles *et al.* and Shamesh *et al.*[7,18] demonstrated that moderate and high coronary calcification, assessed either by an ordinal[7,18] or a visual[7] scoring system were associated with cardiovascular mortality, suggesting that a simplified CAC quantification method can be used by non-cardiothoracic radiologists for addition cardiac risk stratification and treatment.[18] The present study also demonstrated that a simple CAC score is feasible and shows good diagnostic performance when applied in ULDCT studies. A similar result was obtained using an ordinal method[19] (data not shown). In this context, a multisocietal guideline for coronary artery calcium scoring of non-contrast non-cardiac chest CT has been issued.[20] The authors suggest that it is prudent to report CAC at all chest CT examinations, irrespective of the indication.[20] The present study suggests that this recommendation would also be valid for ULDCT studies.

Non-ECG-gated chest CT has the potential to miss small coronary calcifications in a few individuals with low CCS, reducing the negative predictive value of this method, and this issue can be amplified in ULDCT studies due to excessive image noise. A systematic review and meta-analysis examined the correlation between CCS in non-ECG-gated chest CT and conventional ECG-gated coronary calcium imaging.[17] The authors reported a pooled correlation coefficient of 0.94 (95% CI: 0.89–0.97), with high heterogeneity among studies (I^2: 89.1%). Pooled concordance between four categories of CCS using two studies was 0.89 (0.83–0.95), with low heterogeneity (I^2: 0%). Interestingly, the frequency of false-negative calcium scores in non-ECG-gated chest CT varied from 0 to 14%. Despite the higher image noise in ULDCT, a similar result was found, with 12% of false-negative ULDCT studies (nine out of 74 individuals). Xie *et al.*,[17] also demonstrated that a zero CCS in non-ECG-gated CT indicates low cardiovascular risk; although this method cannot reliably exclude coronary calcification. It should be noted that false-negative studies are most commonly observed in patients with low CCS. In the present study, only one patient with negative calcification in ULDCT had a CCS >100. Willemink *et al.*[5] demonstrated that increased levels of IR resulted in more patients being reclassified to a lower cardiovascular risk category. Only three patients in their study had a false-negative result and all of them had conventional CCS only slightly above 0. The impact from missing such small calcified plaques in clinical management is not well known, but it could be important in younger individuals (when lower levels of coronary calcification would translate to higher percentile scores).

There is heightened medical and public concern regarding potential carcinogenic effects of diagnostic imaging, including CCS.[3] It is the role of the radiologist to perform studies with the least amount of radiation dose required to acquire diagnostic imaging studies. The mean radiation dose of the National Lung Cancer Screening trial CT acquisition was 1.4 mSv.[7] The present results add to the knowledge in this field by demonstrating that the diagnostic performance of chest CT imaging with even lower doses than used in major lung cancer screening trials is feasible. In addition, despite high image noise due to the very low dose protocol, the high inter-reader reproducibility of CAC quantification, with a weighted kappa of 0.89, was very encouraging.

Limitations

The present study has limitations that deserve attention. First, as it was a retrospective study, the scan range parameters provided by the ULDCT to plan CCTA acquisition could not be used. Nonetheless, the initial and final image positions determined using ULDCT images were almost exactly the same as the initial and final CCTA images, determined based on standard CCS. Second, the number of patients included in the present study was relatively small. On the other hand, the number of patients in each Agatston CCS category was relatively well balanced, which allowed the authors to explore the performance of ULDCT for the most important tasks, which are detection of any calcium and detection of at least a moderate calcium load (Agatston score >100). Third, different IR levels for ULDCT image reconstruction were not explored, and therefore, whether the use of a different IR level would perform better for coronary calcium detection could not be determined. Fourth, a fixed tube current protocol was used, and it is possible that a weight-adapted protocol could have resulted in better image quality, and therefore, better accuracy of the CAC scoring method, particularly in situations in which higher image noise is expected, such as in large/obese adults. The aim of the study, on the other hand, was to test a simple strategy using the lowest possible dose parameters, independently of patient characteristics. For a similar reason, the performance of the standard Agatston score algorithm in ULDCT was not evaluated. Calculation of the standard Agatston calcium score would require an additional step, with dedicated software and/or workstation. In addition, as the tube voltage used in the present study was 80 kVp, further modifications in the Agatston scoring algorithm would be required. For the sake of simplicity, the present study examined a method that would be readily available to all radiologists.

In conclusion, ULDCT shows good sensitivity, specificity, and overall accuracy for the detection of coronary calcification with a markedly lower radiation dose in comparison to standard CCS. In addition, ULDCT enables CCTA coverage to be planned with almost identical performance in comparison to CCS and may become a simple and viable alternative to standard CCS acquisition in patients referred to CCTA for which radiation dose would be a major concern.

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