Quantifying coronary artery calcification from a contrast-enhanced cardiac computed tomography angiography study

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Aims
We sought to quantify coronary artery calcium (CAC) using a single contrast-enhanced cardiac computed tomography angiography (CCTA) study. CCTA has been successfully used for the assessment of coronary artery stenoses, whereas non-contrast ECG-gated computed tomography (Standard-CAC) is commonly performed to quantify CAC. Thus each scan individually contributes to the total radiation dose.

Methods results
Patients who underwent both Standard-CAC and CCTA scans were identified. Standard-CAC images were scored using the Agatston method. CCTA scans were scored for CAC (CCTA-CAC), whereby CAC was defined as plaque with attenuation 2 SD above the mean attenuation value of the ascending aorta (HUaorta). The correlation between Standard-CAC and CCTA-CAC was determined with the slope used to derive a correction factor for the conversion of CCTA-CAC results to a Standard-CAC Agatston score (AS). To test applicability, the correction factor was assessed in a separate validation cohort of similar demographics. From April 2011 to June 2012, a derivation cohort of 92 patients was identified and analysed. An additional 47 patients were identified for the validation cohort. Correlation between Standard-CAC and CCTA-CAC was excellent (r = 0.96). The slope (y = 2.74 × CCTA-CAC score) derived correction factor from the derivation cohort was used to adjust CCTA-CAC derived scores to an AS (CCTA-CACcorrected = 2.74 × CCTA-CAC). The correction factor was applied to the validation cohort CCTA-CAC results with excellent agreement between CCTA-CACcorrected and Standard-CAC (kappa = 0.93).

Conclusions
Quantification of CAC from a single contrast-enhanced CCTA scan is feasible and correlates well with Standard-CAC. Larger, multicentre studies are needed to validate the universal applicability of CAC quantified using CCTA.

Keywords
Coronary artery calcium • Contrast-enhanced CTA

Introduction
Patients with coronary artery calcium (CAC) are at an increased risk for major adverse cardiovascular events and all-cause mortality.1 Thus, the measurement of CAC is of potential diagnostic and therapeutic importance. Currently, an unenhanced ECG-gated CT examination (Standard-CAC) is the standard method for measuring CAC.2 Although CAC is very specific for the presence of coronary artery disease (CAD), it poorly predicts the presence of obstructive CAD.3 An additional contrast-enhanced cardiac computed tomography angiography (CCTA) study is required to evaluate for coronary artery stenoses. Although CCTA is a well-established modality for the evaluation of CAD, it has not been used to measure CAC quantitatively.

Both CAC and CCTA studies require separate image acquisitions and thus carry radiation burden.4,5 Recent advancements have reduced CCTA radiation doses, but this has not been as effectively accomplished in Standard-CAC scans due to fixed protocol

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requirements. The quantification of CAC and assessment of coronary artery stenosis in a single image acquisition is thus desirable. We sought to develop and validate a method to quantify CAC using CCTA.

Methods

Between April 2011 to October 2011, 100 patients who underwent paired Standard-CAC and CCTA scans were randomly selected for analysis. Patients with a history of coronary revascularization or known CAD, congenital heart disease, or cardiac transplantation were excluded. After exclusions, 92 patients were identified comprising the derivation cohort. After analysis of the derivation cohort, an additional 50 consecutive patients between May 2012 and June 2012 were identified for the validation cohort. Once exclusion criteria as in the derivation cohort were applied, 47 patients were identified and comprised the validation cohort used in the analysis. The local institutional review board approved this study.

Unenhanced CT CAC score and coronary CT angiography

An ECG-gated cardiac CT was obtained as per local clinical routine. Prior to scanning, patients received metoprolol or diltiazem targeting a heart rate to ≤ 60 bpm and sublingual nitroglycerine (0.8 mg) was administered. Using the GE Volume CT scanner (General Electric Healthcare, Milwaukee, WI, USA), a non-contrast enhanced, prospective, ECG-triggered image acquisition (400–800 mA, 120 kVp) was performed at the 70% phase and images were reconstructed with a 2.5 mm slice thickness and 25 cm field of view.

For CCTA, a triphasic contrast (Visipaque 320 or Omnipaque 350, GE Healthcare, Princeton, NJ, USA) bolus protocol was used (100% contrast, 40%/60% contrast/saline, and saline). Prospective ECG-triggered or retrospective ECG-gated images (with X-ray tube modulation) were acquired using the GE Volume CT scanner (64 × 0.625 mm slice collimation, gantry rotation of 350 ms, mA = 400–800, 100 kVp for BMI < 30, 120 kVp for BMI ≥ 30). Prospectively acquired CCTA data sets were reconstructed with a slice thickness of 0.625 mm at 70, 75, and 80% of the R–R interval. With the retrospectively acquired CCTA data sets, the cardiac phase(s) with the least amount of motion were reconstructed with a slice thickness of 0.625 mm and increment of 0.4 mm.

CCTA analysis for CAC

CAC was calculated from CCTA images using the Aquarius iNtuition software (Version 4.4.7, TeraRecon, Inc, San Mateo, CA, USA) by two experienced independent reviewers blinded to all clinical information and Standard-CAC results. For each patient, using axial images, a region of interest (ROI) was placed in the ascending aorta at the level between the origins of the right coronary artery and left coronary artery. The mean aortic attenuation value (HU aorta) and standard deviation (SD) was measured at this level. Using these measures, the threshold for calcium detection was calculated as SD above the mean attenuation in the aorta (HU aorta + 2SD). All other Agatston thresholds, weighting factors, and area calculations remained unchanged.

Using CCTA axial images, each observer manually selected lesions consistent with CAC. Window level and width was adjusted to optimize the differentiation between CAC and luminal contrast. Careful consideration was given to exclude calcified non-coronary structures (such as the aorta, mitral annulus, and aortic valve). The mean values from the two readers were used in the analysis but in cases where there were discrepancies between readers, CCTA-CAC values were resolved through consensus reading. As the reference standard, CAC was measured using the Standard-CAC scan by the same blinded readers using the method described by Agatston using the Aquarius iNtuition software.

Statistical analysis

Statistical analyses were performed using SAS (version 9.2, SAS Institute, Inc., Cary, NC, USA). Statistical significance was defined as P < 0.05. Continuous variables were expressed as means with SDs. Categorical variables were expressed as frequencies with percentages. To generate the correction factor, the ability for CCTA to predict the Agatston score (AS) was evaluated using a linear regression model.

To measure reliability of continuous data, intra-observer and inter-observer reliability for Standard-CAC and CCTA-CAC measures were assessed using intra-class correlation coefficients (ICC). The reliability between Standard-CAC and CCTA-CAC was also evaluated graphically using a Bland–Altman plot which demonstrates both the overall degree of agreement and whether the agreement is related to the underlying value of the item. The agreement between categorical Standard-CAC and CCTA-CAC measures of calcium in the validation cohorts.

Results

A total of 92 patients (age 61.1 ± 9.6 years, 69.2% men) were analysed in the derivation cohort (Table 1) with an additional 47 consecutive patients analysed in a validation cohort. The derivation and validation cohorts were well matched with regards to the presence of risk factors and indications for the study. Using a linear regression model, the correlation between Standard-CAC and CCTA-CAC was excellent (r = 0.96, Figure 1). Using the line of best fit (with the intercept set through 0), a correction factor was calculated enabling the conversion of CCTA-CAC results to a Standard-CAC AS, derived from the slope (CCTA-CAC corrected = 2.74 × CCTA-CAC score).

Inter-observer variability for both Standard-CAC and CCTA-CAC was excellent (ICC = 0.99 and 0.97, respectively). Inter-observer agreement for CCTA-CAC corrected was excellent (kappa = 0.92; 95% CI: 0.86–0.98) with 93.5% of scores read within the same Agatston scoring category. Only one patient had a CAC score of 7 on Standard-CAC, which was scored as 0 on CCTA-CAC.
Discussion

Although quantification of coronary artery calcification has prognostic value, it is calculated using an unenhanced contrast CT and thus cannot be used to assess obstructive CAD. Patients undergoing cardiac CT often require two separate scans thereby increasing radiation exposure. Quantifying CAC from a single CCTA study would thus be desirable. The results of our study suggest that CCTA images can be used to reliably estimate patient CAC with very good accuracy and agreement.

While CAC scoring is commonly performed in patients prior to CCTA via a separate protocol and scan, the two are potentially used for different patient populations. For example in asymptomatic patients with multiple risk factors for CAD, a CAC score is used to identify CAD, and to estimate prognosis while potentially influencing medical therapy. On the other hand, a CCTA is obtained in symptomatic patients at risk for CAD in whom the physician desires anatomical delineation of the potential cause of the patient’s symptoms. However in combination, one may evaluate the burden of CAC prior to CCTA scanning. Hence, if CAC is extensive precluding accurate coronary artery luminal investigation, further testing with CCTA can be forfeited thus saving the patient from both contrast administration and additional contrast. In a study by Hadamitzky et al., CCTA alone improved prediction of cardiac events over traditional risk scoring and CAC scoring. Similarly, Hou et al. demonstrated that CAC scoring in addition to traditional risk factors improved the prognostic value over traditional risk factors alone, with the addition of CCTA data to the CAC score and risk factors yielding the highest prognostic information.

Advances in CCTA protocols have resulted in significant reductions in radiation dose with many new scanners able to perform <1 mSv prospectively ECG-triggered studies. Although recent studies have shown that non-contrast CT for CAC may be feasible using radiation reduction strategies, it has not been widely adopted. Currently, standard-CAC scanning has remained relatively...
unchanged with a standard 120 kVp for all patients irrespective of the body size. As a result, the addition of standard-CAC imaging in addition to CCTA may account for a significant proportion of radiation for a cardiac study and in some cases exceed the CCTA dose. In our study, the elimination of the standard-CAC would reduce radiation exposure by ~2.0 mSv, while maintaining our ability to quantify CAC and evaluate patients for coronary artery stenoses.

When calculating the individualized calcium attenuation thresholds, 2 SD above the mean attenuation in the aorta was selected as it was considered to accurately represent selection of CAC while excluding noise. A study by Raggi et al.13 suggested the utilization of 3 SD above the average soft tissue attenuation threshold for CAC detection using electron beam computed tomography (EBCT). However, as acknowledged by the authors, scatter and noise is an issue with EBCT due to lower energy flux, which is potentially mitigated by multidetector computed tomography (MDCT). Thus, it was felt that using 3 SD above the mean attenuation in the aorta could possibly result in exclusion of lower attenuating calcific plaque and hence underestimation of CAC with MDCT. Similarly, Otton et al.14 published a method for CAC scoring using contrast-enhanced computed tomography. The authors set the threshold of calcium detection at 320 HU in all CCTA studies in an attempt to exclude non-calcified elements and luminal contrast, while still registering calcific plaque of lower density. This is in contrast to our study where we utilized a ‘patient-specific’ threshold of detection based on the average attenuation of the ascending aorta in individual CCTA scans. We found the average attenuation of the ROI placed in the ascending aorta was 462 HU. Thus, using a fixed threshold may not be feasible at all centres given variations in the protocol (e.g. contrast infusion rate, contrast volume, kVp) and the lumen with higher attenuation values. However, regardless of the technique employed, both our study and that of Otton et al. demonstrated that the quantification of CAC using CCTA is feasible and accurate.

A recent study by Bischoff et al. investigated the quantification of CAC using contrast CTA

| Table 3 Agreement between standard non-contrast Coronary Artery Calcium Agatston Score (Standard-CAC) and Corrected Contrast-enhanced-derived Calcium Score (CCTA-CACcorrected)* in the derivation cohort (n = 92) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Standard-CAC**               | **CCTA-CACcorrected** |
|                                 | 1–100           | 101–400         | >400            |
| 1–100                           | 24              | 9               | 0               |
| 101–400                         | 2               | 32              | 4               |
| >400                            | 0               | 1               | 20              |

Weighted Kappa = 0.78 (95% CI: 0.69–0.88).
HU, Hounsfield units; SD, standard deviation.
*CCTA-CACcorrected = 2.74 × (CCTA-CAC).

Figure 2 Bland–Altman plot comparing Standard Coronary Artery Calcium Score (Standard-CAC) and corrected contrast-enhanced CCTA-derived Coronary Artery Calcium Score (CCTA-CACcorrected).
ones proposed in our study. However, in contrast to our method, 120–160% of the mean CT attenuation value inside of the ascending aorta was used to determine the optimal threshold of calcium detection for each patient. Similarly, a ‘calibration factor’ was calculated using the slope of the regression line from an initial cohort of 100 patients, which was subsequently applied to a validation cohort. Nevertheless, given the differences in methodology, the authors found excellent correlation between standard-CAC and CCTA-CAC ($r = 0.95$) with 90% of patients correctly classified in risk categories by CCTA-CAC in comparison with Standard-CAC. This may indicate that a dynamic, ‘patient specific’, threshold of CAC detection using the mean attenuation of the aorta, may provide a more accurate means of quantifying CAC in contrast-enhanced CCTA rather than a static threshold.

Limitations
The use of CCTA may result in the inability to differentiate between the luminal contrast and coronary calcification (especially if the calcification is of similar attenuation as luminal contrast). Therefore, it would be important to optimize window width and level to improve visual differentiation of calcium and luminal contrast (Figure 3). In our study, based upon the mean attenuation of the ascending aorta, the mean threshold for calcium quantification with CCTA-CAC was 537 HU. A recent publication comparing plaque composition using 64-MDCT and intravascular ultrasound showed that CT attenuation values for calcific plaques was $772 \pm 251$ HU suggesting that calcific plaques typically have much higher attenuation values than luminal contrast. Using the Agatston method, it is accepted that plaque $\geq 130$ HU represents calcium on non-contrast CT. This study also showed that the non-calcified fibrous plaque had attenuation values ranging from 24 to 154 HU which may suggest that the 130 HU threshold may overestimate calcification. However, this lower threshold (130 HU) of Standard-CAC may be appropriate when reconstructing at 2.5–3 mm slice thickness because it potentially accounts for partial volume. Since CCTA-CAC studies were reconstructed using 0.625 mm slice thickness, the partial volume in the $z$-plane may be minimized thereby permitting a more accurate delineation of calcific plaque and thus the use of a higher threshold (Figure 4).

Another potential limitation is that CCTA-CAC studies were not acquired with a set tube potential (kVp) as in Standard-CAC. Tube potential is often tailored according to the body size, with larger patients receiving 120 kVp and smaller patients receiving 100 kVp. By decreasing the kVp from 120 to 100, contrast and calcium will have higher attenuation values, thus potentially affecting the threshold of detection (especially if using a ‘fixed threshold’). However, our method provides a dynamic threshold, which is individually calculated for each study using attenuation measures from the ascending aorta. Thus, the impact of different tube potentials would be minimized because the impact of tube potential would be similar in the aorta and calcific plaque and the ability for internal calibration.

Table 4  Agreement between standard non-contrast Coronary Artery Calcium Score (Standard-CAC) and Corrected Contrast-enhanced-derived Calcium Score (CCTA-CAC$_{\text{corrected}}$) in the validation cohort ($n = 47$)

<table>
<thead>
<tr>
<th>Standard-CAC</th>
<th>CCTA-CAC$_{\text{corrected}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1–100</td>
<td>9</td>
</tr>
<tr>
<td>101–400</td>
<td>0</td>
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<td>&gt;400</td>
<td>0</td>
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</tbody>
</table>

Weighted Kappa = 0.93 (95% CI: 0.86–0.99).
HU, Hounsfield units; SD, standard deviation.
CCTA-CAC$_{\text{corrected}}$ = 2.74 × (CCTA-CAC).

Figure 3  A 65-year-old male referred for CT coronary angiography. (A) The standard non-contrast-enhanced CT calcium scan (Standard-CAC) is shown displaying coronary artery calcification. (B) The contrast-enhanced CCTA is shown for comparison (W:1000, L:200). (C) Manual selection of CAC.
This was a single centre study and the results of our technique may not uniformly apply to all centres. Since there are variations in contrast and institutional image acquisition protocols, variations in luminal attenuation would be expected. As such, derivation of a ‘site-specific’ correction factor may be necessary for accurate CAC quantification from CCTA studies. Our proposed technique could be applicable to other centres and would avoid the potential limitations of a fixed threshold. Likewise the current study represents a single centre experience using 92 patients obtained through retrospective analysis of randomly selected cases. Larger multicentre studies will additionally be necessary to confirm our findings using the described methodology.

With raising the attenuation threshold of CAC detection, a concern is that some calcific plaques may be missed, but likely of significant concern in those with minimal CAC. In our cohort, only one patient was incorrectly identified as having no CAC while having an A5 of 7. However, this limitation may be partially overcome by the fact that CCTA has the added ability to identify non-calcific plaque.

Conclusion
The quantification of CAC using contrast-enhanced CTA is feasible using a systematic approach with very good reliability and accuracy compared with Standard-CAC. Larger-scale validation studies are needed to determine whether the use of Standard-CAC can be eliminated in favour of CCTA-CAC.

Conflict of interest: None declared.

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