A method for coronary artery calcium scoring using contrast-enhanced computed tomography

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BACKGROUND: Limitations to the coronary calcium score include its requirement for noncontrast imaging and radiation exposure that approaches current methods for contrast-enhanced CT angiography.

OBJECTIVES: We sought to derive and validate a method of measuring the coronary artery calcium score (CACS) from standard contrast-enhanced CT, obviating the need for a second non-contrast calcium scan.

METHODS: The volume of intramural calcium of >320 HU in major coronary vessels was measured in 90 contrast-enhanced and traditional non-contrast calcium scan pairs. An empiric conversion factor was derived to convert the small voxel contrast-enhanced calcium volume to an Agatston calcium score. The accuracy of this technique was then prospectively validated in 120 consecutive patients undergoing clinical calcium scans and contrast-enhanced coronary CT. Eleven patients were excluded from analysis because of the prespecified criteria of excessive noise in the contrast-enhanced CT or total coronary artery occlusion.

RESULTS: The Pearson correlation of the contrast scan-derived calcium score with the measured CACS was \( r^2 = 0.99 \). With standard CACS risk bands, agreement of the contrast-enhanced calcium score estimate with the measured CAC by quadratic weighted \( \kappa \) was 0.96. The 95% limits of agreement (Agatston units) were given by \( 6(\pm3.2+0.14 \times \text{CACS}+4.44 \times \sqrt{\text{CACS}}) \). Inter-observer and intra-observer reliability with the intraclass correlation was 0.99.

CONCLUSION: The calcium score can be accurately measured from contrast-enhanced cardiac CT scans with the use of a Hounsfield unit threshold of 320.

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Introduction

Coronary artery calcium measurement, determined with non-contrast CT, is a powerful predictor of future cardiovascular risk which provides information supplemental to traditional Framingham risk assessment. When mild or
moderate atherosclerotic disease is detected in the context of contrast-enhanced coronary CT angiography, the calcium score provides a well-validated quantification of future cardiovascular risk which allows reasoned selection of further treatment and follow-up. However, although the radiation dose of contrast-enhanced cardiac CT has diminished rapidly in recent years because of ongoing technologic developments, the radiation dose of calcium score evaluation is largely fixed because of protocol constraints. In some cases, scans for the measurement of calcified plaque now equal or exceed the radiation dose of contrast-enhanced CT coronary angiography.4

Previous attempts to measure coronary calcified plaque from contrast-enhanced coronary CT5 have either been unable to separate intracoronary contrast from intramural calcium6 or have been unable to adequately measure lower density coronary calcium that is often present in persons with lower coronary calcium scores.7

We demonstrate a novel method for the estimation of calcium scores from contrast-enhanced CT, without the need for additional radiation incurred by supplemental non-contrast scanning. We performed a prospective diagnostic accuracy study, comparing calcium estimation from contrast-enhanced coronary CT with the reference standard of non-contrast cardiac CT. We present the results of the validation and reliability assessments for this new technique.

Methods

The study was approved by the local ethics review committee, and the methods and reporting were designed to conform with published standards.8 The validation study, including design, recruitment criteria, and end points, were preregistered with Australia and New Zealand Clinical Trials registry (ANZCTR: 12610000354088).

Derivation study and conversion factor determination

We analyzed contrast-enhanced CT scans to assess the ability of plaque quantification tools to estimate intramural coronary calcium as measured by the method originally described by Agatston and colleagues. Initial investigations indicated that intramural calcium could be measured from contrast-enhanced CT, but the correlation between mural elements above the lower Agatston threshold of 130 HU and either the non-contrast calcium score or traditional calcium volume measurement were poor. We found that at an imaged voxel size of 0.5 mm³, noncalcified mural elements often occupy the Hounsfield range between 130 HU and ~200 HU, whereas true calcified plaques generally greatly exceed 300 HU.5 After investigating a range of potential Hounsfield thresholds, 320 HU was selected as a more appropriate threshold for calcium quantification because it excluded noncalcified mural elements and small areas of contrast inclusion while capturing lower density calcium that may be found in early calcification of the coronary arteries. Calcium volume measurements that used this threshold appeared robust irrespective of contrast attenuation, kilovolt levels, and motion artifact.

Because smaller voxel size tends to somewhat increase the coronary artery calcium score (CACS) by the Agatston method10 and higher Hounsfield unit calcium threshold values greatly reduce measured calcium volume,11 a means of converting the small voxel, high threshold calcium quantification to standard CACS was required. We therefore randomly selected 90 historical clinical contrast-enhanced coronary CT scans and calcium score pairs to determine an appropriate conversion factor.

Clinical scan protocol

All scans were performed with a 320-detector row Aquilion One CT scanner (Toshiba Medical Systems, Tokyo, Japan) and were acquired during single breathhold. Standardized calcium scores were obtained with beam energy of 120 kV, full rotation time of 350 milliseconds, and tube current of 300 mA, and nonoverlapping 3-mm slice thickness and a standard FC12 reconstruction kernel. Scans were electrocardiogram (ECG)–gated and were triggered at either 40% or 75% phase contingent on heart rate.

Contrast-enhanced coronary CT was performed on the same day according to clinical protocols at either 100, 120, or 135 kV with the x-ray tube current (in mA) and contrast volume adjusted to body habitus. Most scans were obtained during a single gantry rotation of 0.35–0.4 seconds. The reconstructed slice thickness was 0.5 mm, and the optimal cardiac phase for reconstruction was selected by visual inspection of available data. A standard FC03 reconstruction kernel was used for contrast CT image reconstruction.

Coronary artery calcium score measurement

Coronary artery calcium scores that used the Agatston method were performed by an experienced cardiac radiographer with the use of commercial software (Vitrea FX v2.1; Toshiba Medical Systems). A focus of calcification was defined as 2 contiguous pixels of >130 HU with the quantification method as has been previously described.12 The CACS was verified and adjusted, if necessary, by a certified cardiologist.

Contrast-enhanced CT calcium volume measurement

Coronary artery calcium was identified by appropriate windowing and examination of each axial slice in minimal slice thickness, thicker maximum intensity projection, and curved multiplanar reconstruction views. If no calcium
could be visualized on the contrast scan, the estimated calcium was recorded as 0. If an area of possible arterial calcification was seen, the calcium-containing arterial segment was selected in curved multiplanar view with the use of a commercial plaque quantification software tool (SurePlaque; VitreaFX v3.1; Toshiba Medical Systems). To minimize potential contrast contamination of the arterial wall region of interest, care was taken to avoid the selection of major arterial branch points unless they contained discernable atherosclerotic disease. The automated arterial edge detection was visually examined in arterial cross-section reconstructed at 1-mm intervals along the arterial segment and was manually adjusted, if necessary, to include the calcium deposits within the vessel wall and to exclude luminal contrast (Fig. 1). The software tool was adjusted to quantify the volume of high-intensity voxels exceeding 320 HU within the selected areas.

**Statistical derivation of the calcium conversion coefficient**

Regression analysis with suppressed constant was used to assess the relation between the contrast scan–measured calcium volume and the calcium score in each pair. The relation between the contrast scan–measured calcium volume and the Agatston score was found to be linear. The regression coefficient of the calcium volume in the linear regression equation with Agatston score as the dependent variable was then used as the final conversion factor required to transform the high-resolution, high Hounsfield elements of the contrast scan to the lower threshold and larger voxel–derived calcium score.

**Validation study**

**Study population**

We prospectively assessed the derived technique of calcium score estimation in 120 consecutive patients who underwent both non-contrast coronary artery calcium scoring and clinical contrast-enhanced coronary CT angiography and scoring during the period of May to September 2010. The validation cohort was entirely separate from the derivation study. Scans took place at a tertiary referral hospital in Sydney, Australia, and comprised inpatients and outpatients of both sexes. All scans from patients undergoing both clinical CT angiography and calcium score measurement were included unless they met prespecified exclusion criteria, namely ascending aortic contrast level >600 HU, contrast CT scan noise, as indicated by an ascending aorta Hounsfield unit SD > 35, or the presence of a totally occluded coronary artery because these factors may affect automated plaque volumetric analysis and centerline detection (Fig. 2). Patients with atrial fibrillation and patients receiving wide volume scanning to encompass the thoracic aorta were not excluded from analysis.

**Scan protocol**

Non-contrast and contrast-enhanced CT were performed according to standard protocols, as described above for the derivation cohort. Contrast-enhanced scan parameters used within the validation cohort are listed in Table 1.

**Coronary artery calcium analysis**

Readers blinded to the traditional calcium score, previous calcium measurements, and any prior calcium score
estimation performed analysis of the contrast-enhanced coronary scan. The readers were also blinded to the clinical history, reason for referral, and risk factors for cardiovascular disease. The volume of coronary artery calcium was converted to the corresponding CACS by multiplication with the predetermined, empirically derived conversion coefficient to generate the calcium score estimate.

Reliability assessment

The first 50 consecutive calcium scores in the validation set were independently assessed by 2 blinded readers (J.O. and D.B.) to assess inter-reader reliability. Intrareader reliability was assessed by repeat reading of 50 scans by a blinded reader (J.O.) after an interval of 3 months.

Statistical analysis

The agreement for the CACS between the non-contrast and the contrast scan was examined with a Bland-Altman analysis. Because the difference in 2 calcium score measurements varies according to the amount of coronary calcium present, we used the half-normal regression method proposed by Bland and Altman (11) to obtain limits of agreement within a fractional polynomial model. This method has previously been used to generate the confidence intervals of calcium score measurements. We also tested whether the mean difference in measurements varied by kilovolt and aorta contrast density by including terms for kilovolt and aorta contrast density in the regression of the mean difference against the average score. We also tested whether the limits of agreement varied by kilovolt and aorta contrast density by including these factors in the regression models.

The ability of the novel calcium score estimation method to accurately classify patients into the standard calcium score risk bands (very low, 0; low, 1–10; moderate, 10–100; moderate-high,100–400; high, >400) was calculated with the quadratic weighted $\kappa$ statistic.

Inter-observer and intra-observer reliabilities were assessed with the intraclass correlation. STATA version 10 (StataCorp LP, College State, TX) was used for statistical analysis.

Results

Derivation study

The CACS within the derivation cohort ranged from 0 to 1990 (mean ± SD, 210 ± 377). Despite the density-dependent cofactors inherent in the Agatston method, the correlation ($R^2$) with the measured calcium volume with the use of a single linear regression coefficient of 3.13 Agatston units/mm$^3$ calcium (95% CI, 3.04–3.22) was 0.98. This empiric calcium score conversion factor of 3.13 Agatston units/mm$^3$ calcium was then used prospectively in the validation study.

Validation study

Study population

Eleven patients (9%) met predefined exclusion criteria and were not included in the validation analysis. Two patients were excluded because of complete occlusion of a coronary artery. Nine patients were excluded because of suboptimal CT quality as defined by a noise SD of >35 HU within the ascending aorta.

The included cohort consisted of a broad range of body structures and underlying cardiac risk factors (Table 2). In 50 patients (46%), the primary reason for undergoing CT angiography was risk evaluation because of standard cardiovascular risk factors or positive or equivocal prior cardiac investigations. Forty-one subjects (38%) were evaluated primarily for chest pain, whereas the remaining 18 patients (16%) were investigated because of arrhythmias.

<table>
<thead>
<tr>
<th>Table 1 CT scan parameters</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Mean heart rate at scan, beats/min</td>
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<td>Single beat acquisition, n (%)</td>
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<tr>
<td>Two/three beat acquisition, (%)</td>
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<td>Minimal (350 ms) acquisition window, %</td>
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<td>X-ray tube voltage, %</td>
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<td>135 kV</td>
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<td>Total protocol radiation dose*, mean, mSv</td>
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<td>Contrast scan radiation dose*, mean, mSv</td>
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<td>Calcium score scan*, mean, mSv</td>
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*Conversion factor was 0.014 mSv/dose-length product.
presurgical planning, or for other reasons. Ten patients (8%) were in atrial fibrillation at the time of the study. All 109 (91% of the intention-to-analysis) included patients who received traditional calcium scoring were able to have the calcium estimate calculated with the described technique.

Agreement between methods

The relation between the calcium score estimate and the traditional calcium score measurement is displayed in Figure 3. The resultant coefficient of determination ($R^2$) of the 2 measurements was 0.99. The Bland-Altman plot of the difference in scores (derived score – Agatston score) against their average is shown in Figure 4, along with the expected difference (in scores and limits of agreement). The expected difference in scores ($\hat{D}$) is given by $\hat{D} = 3.109 - 0.034 \times A$, where $A$ is the average score ($P$ for linear term = 0.80, based on 107 measurements). Therefore, $\hat{D}$ may be assumed to be constant once the 2 values of high leverage are excluded. In addition no evidence was found that the mean difference ($\hat{D}$) was significantly different from zero ($P = 0.53$, based on 109 measurements.). The 95% limits of agreement can, therefore, be closely approximated by $6(3.2 + 0.14 \times \text{CAC} + 4.44 \times \sqrt{\text{CACS}})$ Agatson units, where CACS is the traditionally measured calcium score. For example, in a patient with a traditionally measured calcium score of 400, the contrast-enhanced estimate would be expected to lie within the range of 252–548 Agatson units 95% of the time. For 4 measurements (3.7%) within the validation cohort, the measurements lay outside the limits of agreement (3 of the 4 measurements were greater than the upper limit of agreement). There was no evidence that mean difference varied by aorta contrast density ($P = 0.43$) or kilovolt ($P = 0.72$). No evidence showed that the limits of agreement varied by aorta contrast density ($P = 0.85$) or kilovolt ($P = 0.75$).

The ability of the contrast-enhanced CT–derived calcium estimate to correctly categorize each patient in the appropriate calcium score risk band was assessed with the quadratic weighted $\kappa$ statistic. The $\kappa$ value (Table 3) was 0.96. In all but 2 cases reclassification was by one risk category only. Of the exceptional cases, in one, calcium measuring an equivalent of 12 Agatson units was not seen on the calcium score scan. In the other, calcium measuring 18 Agatson units, although in retrospect clearly visible, was not measured because of human error.

$A^* = A + 0.001007$. In this equation, $A^*$ may be replaced by $A$ with minimal difference. There were two average scores $> 4000$ Agatson units that were of extremely high leverage; when excluded, there was no indication of any association between the difference and average score ($P$ for linear term = 0.80, based on 107 measurements). Therefore, $\hat{D}$ may be assumed to be constant once the 2 values of high leverage are excluded. In addition no evidence was found that the mean difference ($\hat{D}$) was significantly different from zero ($P = 0.53$, based on 109 measurements.). The 95% limits of agreement can, therefore, be closely approximated by $6(3.2 + 0.14 \times \text{CAC} + 4.44 \times \sqrt{\text{CACS}})$ Agatson units, where CACS is the traditionally measured calcium score. For example, in a patient with a traditionally measured calcium score of 400, the contrast-enhanced estimate would be expected to lie within the range of 252–548 Agatson units 95% of the time. For 4 measurements (3.7%) within the validation cohort, the measurements lay outside the limits of agreement (3 of the 4 measurements were greater than the upper limit of agreement). There was no evidence that mean difference varied by aorta contrast density ($P = 0.43$) or kilovolt ($P = 0.72$). No evidence showed that the limits of agreement varied by aorta contrast density ($P = 0.85$) or kilovolt ($P = 0.75$).

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Both the inter-reader and intrareader reliability, as assessed by the intraclass coefficient, were 0.99. The corresponding Bland-Altman plots are shown in Figures 5 and 6.

**Post hoc analysis**

In a post hoc analysis, we examined the accuracy of calcium score estimation in the 9 patients excluded because of excessive contrast CT scan noise. In general, this cohort was more obese than the included cohort (body mass index: range, 29–45 kg/m²; mean, 33 kg/m²). In one patient, the corresponding calcium score was unable to be interpreted because of severe noise. In the remaining 8 patients despite obesity and image quality issues, all estimated calcium scores lay within the 95% confidence intervals established in low-noise CT scans.

**Effect on radiation dose**

Aside from z-axis coverage, the parameters of calcium scoring are largely fixed by parameter constraints. Calcium score radiation dose in the studied population ranged from 1.5 to 2.3 mSv (mean, 2.2 mSv). Over the entire study population the calcium score represented 33% of the received radiation dose. The relative contribution of the calcium score to the total received dose and thus the potential dose reduction of the new technique varied according to the kilovolts used. For 100-kV scans the calcium score dose represented 44% of the total dose (range, 14%–73%) and for 120-kV scans, 29% (range, 10%–46%) and for 135-kV scans, 22% (range, 12%–33%).

**Discussion**

The novel technique presented for calcium score estimation from contrast-enhanced CT, compared with the reference standard of coronary artery calcium quantification from non-contrast CT that used the Agatston method, performed well with high accuracy and reliability. The technique appears valid across a broad range of patient types and scan parameters, and the tools required are readily available within commercial software packages. The described technique therefore appears suitable to replace traditional calcium scoring in combined calcium scoring and contrast-enhanced coronary CT protocols.

It should be noted that the difference between the calcium score estimate and the traditional calcium score value in the current study is because of both the error of estimation of the new test and the imperfect repeatability inherent in traditional calcium score measurement. Indeed, imperfect repeatability of a reference test imposes fundamental limits on the assessed accuracy of any comparator test. The 95% confidence intervals of the contrast scan–derived calcium score estimate appears similar to the published repeatability limits of traditional calcium score measurement across all Agatston ranges and indicates that most, although not all, of the error of measurement results from the imperfect repeatability of traditional calcium score measurement.
Radiation dose minimization

Although coronary calcium scoring provides useful information, the process of acquiring the calcium score currently necessitates an additional non–contrast-gated cardiac CT scan, increasing the total scan time and total protocol radiation doses. The radiation dose component of calcium scoring comprised only a small fraction of older, retrospectively gated coronary CT protocols. Recent developments in CT technology enable prospective CT coronary angiography, without calcium scoring, at doses of ≤1 mSv,18 and the expected dose of standard prospective coronary CT is now in the order of ≤4 mSv.19 Further minimization of the total radiation dose of complete cardiac protocols, however, may be limited by the process of calcium score evaluation.

Traditional calcium scoring, although requiring only low tube current, is based on a fixed 120-kV tube voltage irrespective of body habitus. The associated radiation of calcium scoring is between 0.8 and 2.5 mSv for modern generation CT scanners20 and may therefore exceed the total dose of contrast-enhanced CT angiography. Although the dose of each scan is small, given the large and growing number of cardiac CT examinations, from a population perspective, the ionizing radiation of calcium scoring is not insignificant. In our cohort the calcium score constituted 33% of the median radiation dose, and, had traditional calcium scoring comprised only a small fraction of older, retrospectively gated coronary CT protocols. Recent developments in CT technology enable prospective CT coronary angiography, without calcium scoring, at doses of ≤1 mSv,18 and the expected dose of standard prospective coronary CT is now in the order of ≤4 mSv.19 Further minimization of the total radiation dose of complete cardiac protocols, however, may be limited by the process of calcium score evaluation.

Calcium score estimation from contrast-enhanced CT

Although the goal of calcium score measurement from contrast-enhanced CT has previously been sought, past studies have highlighted the difficulty of separating intramural calcium deposits from the high Hounsfield contrast-filled coronary lumen and the overlap of Hounsfield values in the 2 areas. Because of this, approaches that use axial images of contrast-enhanced scans require manual segmentation and have been largely unsuccessful because of the inability to separate contrast-filled lumen and extraluminal calcium6 or non-linear correlation with traditional calcium scores.21 Other techniques have attempted to use high calcium detection thresholds (>600 HU) to isolate high-density calcium from contrast material.7 However, although high density calcium correlates well with calcium scores overall, the technique ignores lower density calcium associated with early calcification and less extensive disease.

The current generation of cardiac CT scanners now possesses sufficient spatial resolution, low-contrast definition, scan quality, and software tools to achieve the aim of allowing clear separation of contrast-filled lumen and coronary vessel in most cases. By creating regions of interest coaxial to the coronary vessel, excluding the coronary lumen, we were able to minimize contrast contamination of intramural calcium quantification.

Study and technique limitations

Although no patients were excluded for excessive intravascular contrast in this validation study, during algorithm development we felt that contrast densities of >600 HU may make identification of coronary artery calcium difficult in some cases. Patients were excluded if the noise at the level of the ascending aorta, immediately above the aortic valve was >35 HU. As a group, these subjects were more obese than the remainder, so that the very obese may be less well represented in the validation cohort than the available population. Post hoc analysis, however, suggests that calcium score estimation within this group matches the expected accuracy of calcium scoring. Future studies are needed to evaluate accuracy in these patients.

The technique is also dependent on high-quality images, with high spatial resolution and minimal motion artefact. The general quality of the 320 detector row scans is excellent and the interpolated resolution is <0.5 mm³. Although the technique is directly applicable to other CT manufacturers and designs, the calcium score conversion factor is likely to differ slightly with voxel volume size. Furthermore, the plaque quantification tools currently available provide disparate measurements and may not be directly comparable.22 A limitation of this study, therefore, is that the results obtained may not be applicable to other CT scanner models or different analysis software. Although a fully automated technique is feasible, in its current form the technique depends on manual adjustment of the automated plaque, which takes ~5 minutes, although more for complex cases. Although inter-reader correlation is excellent, operator technique may cause a small degree of bias in calcium measurements.

Conclusion

We have demonstrated a new technique to accurately measure coronary artery calcium from contrast-enhanced cardiac CT scans which has excellent concordance with traditional calcium scoring, minimal bias, and excellent interobserver and intra-observer reliabilities. Further development of this technique could eliminate the need for separate non-contrast and contrast-enhanced CT scans within standard cardiac CT protocols and thus spare radiation exposure.

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